Nasal Cavity and Paranasal Sinuses

2

Antonio Cardesa, Llucia Alos, Alfons Nadal,
and Alessandro Franchi

Contents

A. Cardesa, MD, PhD • L. Alos, MD, PhD
A. Nadal, MD, PhD
Department Anatomia Patológica, Hospital Clínic,
University of Barcelona, Villarroel 170, Barcelona 08036, Spain
e-mail: acardesa@clinic.ub.es; lalos@clinic.ub.es;
anadal@clinic.ub.es

A. Franchi, MD
Section of Anatomic Pathology, Department of Surgery and
Translational Medicine, University of Florence,
Largo Brambilla 3, 50134 Florence, Italy
e-mail: franchi@unifi.it

A. Cardesa et al. (eds.), *Pathology of the Head and Neck*, DOI 10.1007/978-3-662-49672-5_2

2.1 Introduction

The nasal cavity and paranasal sinuses occupy the top of the upper respiratory tract and form pneumatic spaces connected with the atmosphere. They are located immediately beneath the base of the cranium, where vital structures are harbored. From this region, very much exposed to airborne agents, arise some of the more complex and rare benign and malignant lesions seen in humans, whose difficulties in interpretation make this remarkable territory one of the most challenging in the practice of surgical pathology. Knowledge of the embryology, anatomy, and histology of the nasal cavity and paranasal sinuses is therefore an essential prerequisite for the precise understanding of the pathology of the lesions that develop in this unique region.

2.1.1 Embryology

The midface, or area between the upper lip and forehead, develops between 4 and 8 weeks of gestation [1]. The frontal prominence forms during the 4th postovulatory week and gives rise to the superior and middle portions of the face. The maxillary and nasal swellings form beneath the frontal prominence. At the end of the 4th week, two surface thickenings of the nasal swellings form the nasal placodes, which are of ectodermal origin and give rise to the epithelial lining of the nasal cavity and paranasal sinuses. The placodes invaginate, producing the nasal pits that become the anterior nares (nostrils) and, more deeply, the primitive posterior choanae. The medial nasal and frontal processes give rise to the nasal septum, frontal bones, nasal bones, ethmoid sinus complexes, and upper incisors. The lateral nasal and maxillary processes fuse to form the philtrum and columella. The cartilaginous nasal capsule forms deep to the nasal and frontal bones from the chondrocranium (skull base) during the 7th and 8th postovulatory weeks. The paranasal sinuses develop from the lateral nasal walls at the sixth fetal week, and their growth continues after birth, throughout childhood and adolescence. The maxillary sinus is the first to develop, starting approximately at the 70th day of gestation from the lateral wall of the nasal cavities. The frontal sinuses derive from the region of the frontal recess of the nose, and the ethmoid sinuses originate as multiple separate evaginations from the nasal cavities, while the sphenoid sinuses take origin as evaginations from the posterior nasal capsule reaching the sphenoid bone.

2.1.2 Anatomy

The nasal cavities are separated by the nasal septum and limited by a roof which is centrally formed by the cribriform plate of the ethmoid (horizontal part), anteriorly by the frontal and nasal bones, and posteriorly by the body of the sphenoid. The floor is formed by the hard palate, which comprises the palatine process of the maxillary bone and the horizontal plate of the palatine bone [2]. The lateral walls have three turbinates or conchae and three horizontal spaces, or meatii, on each side. The nasolacrimal duct opens in the inferior meatus, whereas the middle meatus receives drainage from the frontal, anterior ethmoid, and maxillary sinuses. Below the superior turbinate is the sphenoethmoid recess, with the openings of the sphenoid and posterior ethmoid sinuses. Each nasal cavity communicates posteriorly with the nasopharynx through the choanae and anteriorly with the nostril. The dilatation formed inside the aperture of each nostril is known as the vestibule. The columella separates medially both vestibules. The paranasal sinuses are a group of cavities within the corresponding craniofacial bones (maxilla, sphenoid, ethmoid, and frontal) which communicate with the nasal cavities through an ostium.

2.1.3 Histology

The nasal vestibule shares similar histology with the skin. At the level of the limen nasi, the boundary between the osseous and cartilaginous walls of the nasal cavity, the keratinizing squamous epithelium gradually changes first to cuboidal or columnar epithelium and then to ciliated respiratory-type epithelium, which lines most of the nasal cavity and all the paranasal sinuses, with the exception of the roof [2]. Numerous goblet cells are interspersed in the respiratory-type epithelium. The lamina propria contains several seromucous glands, lymphocytes, monocytes, and a well-developed vascular network, particularly evident in the inferior and middle turbinate. The olfactory mucosa lines the horizontal part of the roof of the nasal cavity. The olfactory epithelium is predominantly made of columnar non-ciliated sustentacular cells, intermingled with scattered bipolar sensory neurons and basal cells; the olfactory serous glands of Bowman are located in the lamina propria.

2.2 Acute and Chronic Rhinosinusitis

2.2.1 Acute Rhinosinusitis

Definition Rhinosinusitis is an inflammatory condition of the nasal and paranasal sinus mucosa. Acute rhinosinusitis (ARS) is usually infectious and can be clinically characterized by purulent (not clear) nasal drainage (anterior, posterior, or both) lasting up to 4 weeks, accompanied by nasal obstruction, facial pain-pressure-fullness, or both [3]. In the

immunocompetent patient, the etiology is predominantly viral or bacterial and less often fungal, whereas in immunocompromised patients, acute fungal sinusitis may occur.

Synonyms Acute sinusitis and acute rhinitis

Epidemiology The true incidence and prevalence of ARS are unknown, because a significant number of cases do not come usually to medical attention. However, the prevalence of rhinosinusitis in the general population is considered to be high, and it is estimated that more than 24 million cases of acute bacterial rhinosinusitis occur annually in the United States [4]. ARS is more common in children than adults. The prevalence of this disease is increased in women. It is generally thought that the process starts in the nasal mucosa and spreads through the ethmoidal prechambers to the frontal and maxillary sinuses.

Etiology and pathogenesis Infectious rhinitis is typically viral and is often referred to as "common cold." It is more common in children than in adults, and the most frequently identified agents are rhinovirus, myxovirus, coronavirus, and adenovirus [3]. Swelling of the mucosa may cause obstruction of a sinus ostium, with subsequent secondary bacterial infection (acute bacterial sinusitis). The most commonly involved agents are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [5, 6]. Allergic rhinitis (hay fever) is part of an inherited syndrome which also may manifest as atopic eczema and asthma. In allergic rhinitis, airborne particles, such as grass pollens, molds, and animal allergens, are deposited on the nasal mucosa giving rise to acute and chronic reactions. Allergens combine with the IgE antibodies produced by the plasma cells of the nasal mucosa which are avidly bound to the Fc-epsilon receptors on mast cells. This triggers degranulation of mast cells and releases the inflammatory mediators of the type I hypersensitivity reaction, causing rhinorrhea and nasal obstruction.

A further type of rhinitis is the non-allergic form (non-allergic rhinitis, NAR), which is defined by exclusion as a chronic nasal inflammation which is not caused by systemic IgE-dependent mechanisms [7]. Nasal cytology has allowed the distinction of different NAR types on the basis of the inflammatory infiltrate, which include the non-allergic rhinitis with eosinophils (NARES), the non-allergic rhinitis with neutrophils (NARNE), the non-allergic rhinitis with mast cells (NARMA), and the non-allergic rhinitis with eosinophils and mast cells (NARESMA). Their recognition is important in order to choose the appropriate treatment.

Macroscopy The mucosa is thickened and edematous, and there is a prominent exudate, which is purulent in bacterial forms. Necrotic tissue is obtained from debridement procedures in case of acute fungal sinusitis.

Microscopy In ARS, histopathologic examination is rarely requested. The sinonasal mucosa demonstrates extensive inflammation, with neutrophil-rich infiltrate. In some cases, hemorrhage and necrosis may also be noted. In acute fungal sinusitis, fungal hyphae can be recognized with appropriate staining methods. The fungus has a tendency to invade blood vessels causing thrombosis and may spread through the perineural spaces [8]. The affected tissues exhibit coagulative necrosis and hemorrhage, while the inflammatory reaction is scant [9]. In allergic rhinitis, the nasal mucosa shows numerous eosinophils, abundant plasma cells, and in some cases increased number of mast cells. There is goblet cell hyperplasia of the respiratory epithelium, and the basement membrane, which is destroyed in the acute phase, appears considerably thickened in the chronic phase.

Differential diagnosis Clinical data are usually sufficient to separate ARS from other inflammatory conditions. Histochemical stainings for fungi are helpful to recognize acute fungal sinusitis.

Treatment and prognosis The treatment of ARS is medical and depends upon the viral or bacterial etiology. Acute bacterial rhinosinusitis usually resolves with antibiotic therapy. Complications are rare and include contiguous infectious involvement of the orbit or central nervous system and can be potentially life-threatening. They include epidural abscess, subdural empyema, and cerebral abscess. The incidence of these complications seems to peak in early adolescence. Acute fungal sinusitis is lethal in most cases.

2.2.2 Chronic Rhinosinusitis

Definition Chronic rhinosinusitis (CRS) comprises a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration [10].

Synonyms Chronic sinusitis and chronic rhinitis

Epidemiology CRS is a common disease, but the true incidence is difficult to ascertain, mainly due to the lack of uniformly accepted criteria for the diagnosis. However, it is estimated that in the United States, the prevalence of CRS is 14 % of the global population [11, 12].

Children are more prone to suffer of CRS than adults [12]. The prevalence of the disease is higher in women than in men [13].

Incidence of atrophic rhinitis has markedly decreased in the last century, and nowadays most cases are secondary to trauma, surgery, granulomatous diseases, infection, and radiation exposure [14].

Pathogenesis Local predisposing factors include sinus ostia blockage, repeated episodes of common cold or acute sinusitis determining obstruction of sinus ostia, reduction of ciliary activity (immotile cilia syndrome), and cystic fibrosis. Multiple factors may be involved in the pathogenesis of atrophic rhinitis, including chronic bacterial infections and nutritional deficiencies.

Some patients with predisposing conditions, such as allergy, asthma, transplant, or AIDS, develop CRS more often [12].

Sinonasal infections are frequently observed in HIV patients; they are often asymptomatic and tend to be recurrent or refractory [15]. They are due to various pathogens including cytomegalovirus [16], *Staphylococcus aureus*, fungi (*Aspergillus* sp.) [17], and parasites (*Microsporidia, Cryptosporidium*) [18].

Variants of CRS Atrophic rhinitis is a chronic inflammation of the nasal mucosa of unknown etiology characterized by progressive nasal mucosal atrophy and by a thick, dense secretion, with fetid smelling and crusting [14]. Hypertrophic rhinitis is characterized by thickening of the sinonasal mucosa resulting from chronic inflammatory diseases [10, 19]. Frequently these patients have undergone several sinus operations, each time with limited success and subsequent recurrence. Recurrent nasal polyposis is often associated.

Macroscopy The mucosa is thickened, edematous, and gray white in color. In atrophic rhinitis, the mucosa becomes atrophic.

Microscopy The mucosal changes observed are variable and include basement membrane thickening, goblet cell hyperplasia, mucous gland hyperplasia, edema of varying extent, inflammation (mostly lymphocytes, plasma cells, and eosinophils), and polypoid change of the mucosa. The histopathological patterns do not always correlate with the clinical features although in atrophic rhinitis the nonspecific chronic inflammatory infiltrate goes with squamous metaplasia of the surface epithelium and of glandular excretory ducts and atrophy of seromucous glands [20, 21].

Differential diagnosis The differential diagnosis is with chronic inflammatory processes, including granulomatous infections, granulomatosis with polyangiitis (Wegener's), Churg-Strauss disease, and other noninfectious midline granulomas.

Treatment and prognosis Medical treatment (decongestants, antihistamines, topical steroids) is recommended for most forms of CRS. Surgery is indicated in case of persistence of symptoms despite medical therapy, for correction of anatomic deformities believed to be contributing to persistence of disease and for debulking of advanced nasal polyposis. CRS may relapse and eventually complicate in sinonasal inflammatory polyposis and mucocele formation.

2.3 Sinonasal Polyps

Definition Sinonasal polyps are nonneoplastic pedunculated swellings of the sinonasal mucosa. When multiple, they are referred as polyposis. The majority of them are inflammatory allergic. Other polyps are of infective, chemical, or familial etiology. The histological appearances of nasal polyps do not always correlate well with their etiology.

2.3.1 Inflammatory Allergic Polyps

Definition Inflammatory allergic polyps (IAPs) are those inflammatory swellings of the sinonasal mucosa of allergic origin.

Synonym Inflammatory polyp

Epidemiology IAPs develop in patients of all ages, being most commonly seen over 20 years of age. They arise most frequently from the upper part of the lateral nasal wall and from the ethmoidal region. Nasal cavities and paranasal sinuses may be simultaneously involved, either unilateral or bilateral.

Etiology and pathogenesis IAPs are due to allergens that trigger the path of the hypersensitivity reaction type I (see Sect. 2.2.1).

Macroscopy IAPs are grapelike formations of soft consistency and glassy appearance, measuring from a few millimeters to several centimeters.

Microscopy IAPs are made up largely of myxoid edematous tissue with pseudocysts containing eosinophilic proteinaceous fluid and infiltrates of inflammatory cells usually exhibiting heavy infiltration by eosinophils (Figs. 2.1 and 2.2), being accompanied by variable number of plasma cells and some mast cells [22]. They are covered by respiratory epithelium with goblet cell hyperplasia, squamous metaplasia, and thickening of the basement membrane. Seromucous glands with mucin-containing cysts may also occur (Fig. 2.3). Epithelial dysplasia may be present in rare cases. Granulomas may be seen in polyps treated with intranasal injection, application of steroids, or other oily medications. Atypical fibroblasts with abundant cytoplasm, poorly defined cell borders, and large pleomorphic nuclei are present in a small proportion of cases [23]. These atypical cells occur individually and are more frequently found close to blood vessels

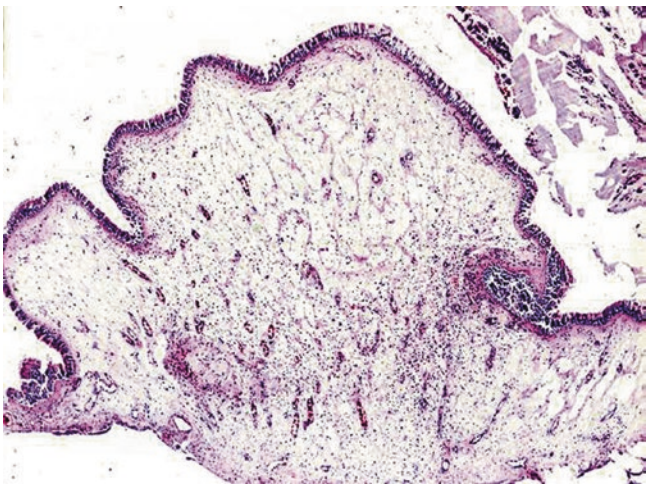

Fig. 2.1 Allergic polyp made up largely of edematous stroma containing proteinaceous fluid and infiltrate of inflammatory cells

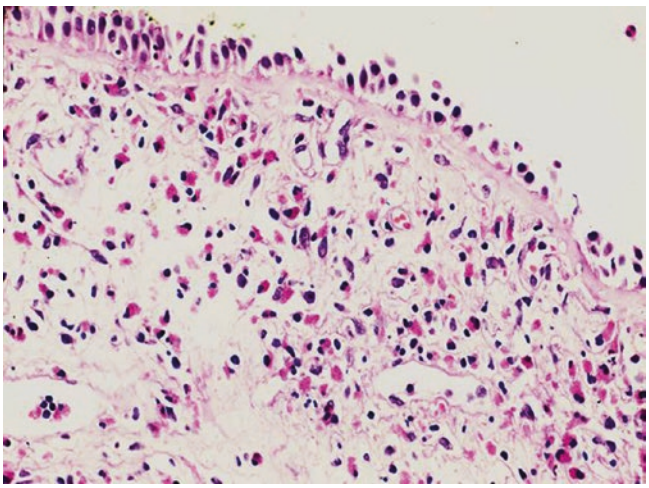

Fig. 2.2 Allergic polyp with marked stromal edema and heavy infiltration by eosinophils

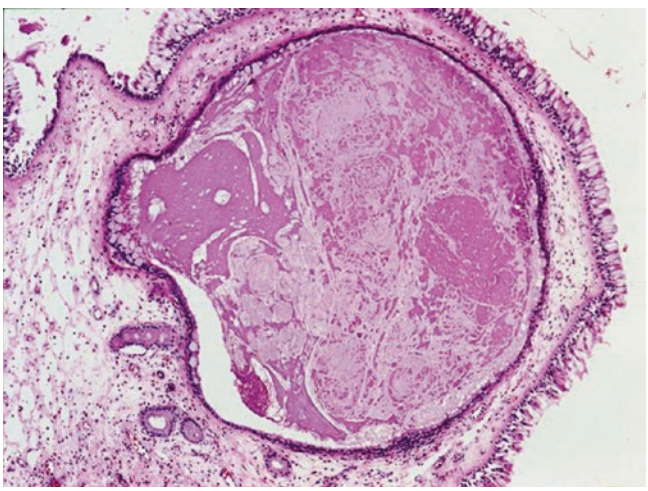

Fig. 2.3 Allergic polyp containing a cystic seromucinous gland

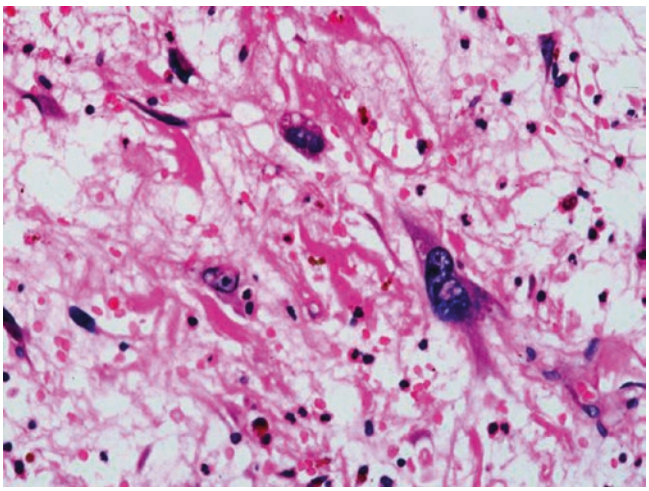

Fig. 2.4 Atypical fibroblasts in an inflammatory allergic polyp: enlarged fibroblasts with bizarre nuclei and occasional prominent nucleoli appear interspersed in granulation tissue

(Fig. 2.4) or near the epithelial surface. Such stromal atypia is a reactive phenomenon that should not be mistaken for sarcoma.

Treatment and prognosis Complete excision is curative, although recurrences may occur if exposure to allergens persists.

2.3.2 Other Polyps

2.3.2.1 Antrochoanal Polyp

Definition Antrochoanal polyps (ACPs) are single polyps that arise in the maxillary sinus, also known as antrum, and extend into the middle meatus projecting posteriorly through the ipsilateral choana [24]. Those polyps that arise in the maxillary antrum and extend into the middle meatus projecting anteriorly are known as antronasal polyps. Killian polyp is a synonym of ACP commonly used by rhinologists.

Epidemiology ACPs account for about 5 % of all sinonasal polyps. Patients with ACP are younger than those with IAPs.

Macroscopy ACP is characterized by a long and thin stalk which originates in the maxillary mucosa.

Microscopy Typically ACPs are devoid of the marked eosinophilic infiltrate of IAPs and have sparser content in mucous glands than the latter. ACPs usually have a prominent fibrous stroma which surrounds thick-walled blood vessels (Fig. 2.5) [25]. In addition, scattered, enlarged, stromal cells with hyperchromatic nuclei are not an

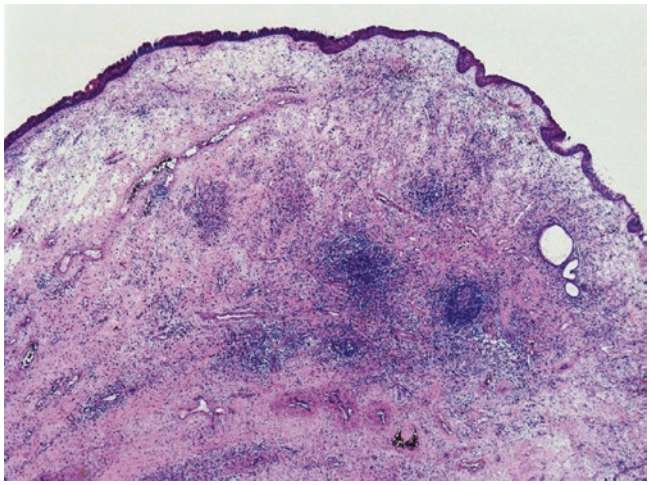

Fig. 2.5 Antrochoanal polyp with conspicuous fibrous stroma surrounding the wall of blood vessels and lack of significant eosinophilic infiltrate

uncommon finding in ACPs that should not be confused with sarcoma [26].

Differential diagnosis ACP must be differentiated from juvenile angiofibroma, as well as from low-grade sarcoma.

Treatment and prognosis Complete resection, stalk included, is curative.

2.3.2.2 Polyposis in Cystic Fibrosis

Definition Sinonasal polyps occurring in the context of cystic fibrosis (CF).

Synonym Polyposis in mucoviscidosis

Pathogenesis CF is an autosomal disorder affecting children with the presence of thick mucus, which obstructs, among other ducts, the lumina of the airways and impairs mucociliary function. CF is due to mutations of the *CFTR* gene located at 7q31.2 [27].

Microscopy Nasal polyps in mucoviscidosis show cystic glands filled with inspissated mucoid material and thickening of the basement membranes that surround the glands [28, 29].

2.3.2.3 Polyposis in Immotile Cilia Syndrome and Kartagener Syndrome

Immotile cilia syndrome (or primary ciliary dyskinesia) is a genetic disease affecting ciliary movement and resulting in respiratory infections and male infertility. Situs inversus may be associated (Kartagener syndrome). About 15 % of patients develop nasal polyps histologically indistinguishable from other nasal polyps. Ultrastructural analysis of nasal biopsies is needed to identify the alterations in the architecture of the cilium in immotile cilia syndrome [30]. Mutations have been detected in the following genes: *DNAI1*(7p21), *DNAH5* (5p14-5p15), and *DNAH11*(7p21) [31].

2.3.2.4 Angiomatoid Sinonasal Polyp

Definition Angiomatoid sinonasal polyps (ASNPs) are characterized by the conspicuous proliferation of small blood vessels, mostly capillaries, occurring within the myxoid background of conventional sinonasal polyps [32].

Epidemiology and etiology ASNP is a rare complication of IAPs and ACPs that may be due to trauma or be iatrogenic.

Microscopy The angiomatoid changes seen in ASNPs are characterized by the proliferation of numerous small blood vessels within a myxoid background. Thrombotic phenomena with heavy fibrin deposition are seen in nearly 50 % of cases. Necrosis is always present if thoroughly searched. Cellular atypia can be prominent but mitosis are rare and atypical mitosis are absent [32].

Differential diagnosis ASNP must be differentiated from angiosarcoma. Although cellular atypia can be prominent in ASNP, malignancy is ruled out by the scarce number of mitotic figures and the absence of atypical mitoses [33].

Treatment and prognosis Complete excision is curative.

2.4 Sinonasal Heterotopias and Hamartomas

2.4.1 Heterotopic Neuroglial Tissue and Encephalocele

2.4.1.1 Heterotopic Neuroglial Tissue

Definition Heterotopic neuroglial tissue (HNGT) is a mass of displaced mature neuroglial tissue presenting intranasally, in the adjacent nasal subcutaneous tissue or in both.

Synonyms Glial heterotopia and nasal glioma, although the latter is a misnomer

Epidemiology HNGT mostly occurs in young children.

Etiology and pathogenesis Usually, HNGT is the result of a congenital abnormality related to a variant of meningoencephalocele in which connection with the intracraneal central nervous system is lost [34, 35]. The lesion mainly arises at the base of the nose or in the upper part of the nasal cavity.

Macroscopy HNGT may be polypoid and rarely measures more than 2 cm.

Microscopy Histologically, HNGT is mostly composed of a mixture of astrocytes, glial fibers, and fibrous connective tissue. Multinucleated glial cells are not infrequently found (Fig. 2.6). Some glial cells can have large nuclei resembling nerve cells. A few true nerve cells or even ependymal elements can rarely be identified. Mitoses are not found. Bona fide gliomas may occur in association with HNGT [36].

Immunohistochemistry Staining for S-100 protein and glial fibrillary acidic protein is positive, the latter being a helpful diagnostic adjunct.

Treatment and prognosis Complete surgical excision is curative. Recurrence may follow incomplete resection.

2.4.1.2 Encephalocele

Definition Nasal encephalocele (EC) is the result of the herniation of brain tissue and its leptomeningeal covering through an osseous defect of the nasal roof.

Synonym Meningoencephalocele

Epidemiology EC mainly occurs in older children and also in adults.

Etiology and pathogenesis An osseous defect at the base of the skull, usually due to trauma, surgery, or infections, facilitates the herniation of the brain.

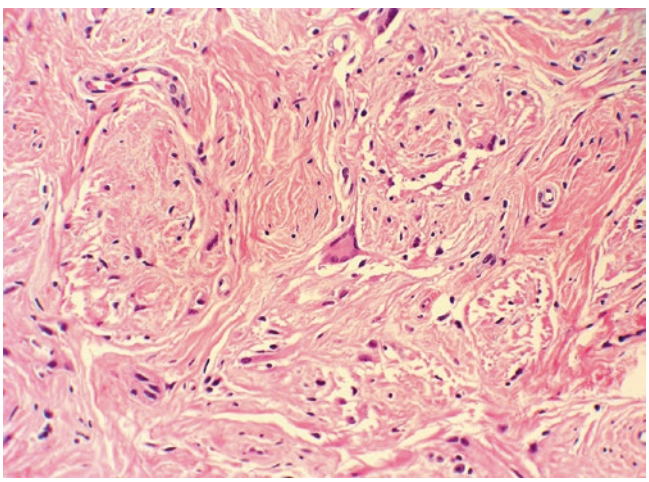

Fig. 2.6 Heterotopic glial tissue composed of a mixture of astrocytes, glial fibers, and fibrous connective tissue. A multinucleated glial cell is seen at the center

Microscopy EC displays a mixture of neural, glial, and leptomeningeal elements.

Differential diagnosis In contrast to heterotopias, encephaloceles are communicated with the central nervous system, and tissues are fairly organized although they can show dysplastic changes [37]. In addition EC has to be distinguished from glioma and teratoma.

Treatment and prognosis Complete resection of EC with repair of the osseous defect at the base of the skull is mandatory to achieve cure.

2.4.2 Hamartomas

Definition Benign polypoid overgrowths in which well-developed epithelial and mesenchymal sinonasal tissues are present with variable participation [38]. Three types are recognized: respiratory epithelial adenomatoid hamartoma, chondro-osseous and respiratory epithelial hamartoma, and nasal chondromesenchymal hamartoma.

2.4.2.1 Respiratory Epithelial Adenomatoid Hamartoma

Definition Respiratory epithelial adenomatoid hamartoma (REAH) is a benign polypoid lesion with well-developed branching glands covered with ciliated respiratory epithelium [38].

Epidemiology REAH occurs in adults and is equally frequent in men and women [39].

Etiology and pathogenesis The cause is unknown. REAH may be the result from an exuberant hyperplastic reaction within an inflammatory context, as most of cases develop in association to nasal polyposis [39].

Molecular genetics The molecular profile of REAH shows tumor suppressor gene alterations with a mean fractional allelic loss of 31 %, an unusually high percentage for a non-neoplastic entity, suggesting the possibility that may be a benign neoplasm rather than a hamartoma [40].

Macroscopy Polypoid formations of soft consistency measuring up to several centimeters.

Microscopy The seromucous epithelium of the deep mucosal glands in REAHs is characteristically replaced by ciliated respiratory epithelium admixed with goblet cells accompanied by thick bands of fibrous stroma in the underlying supportive tissue (Figs. 2.7 and 2.8). When the deep glandular component

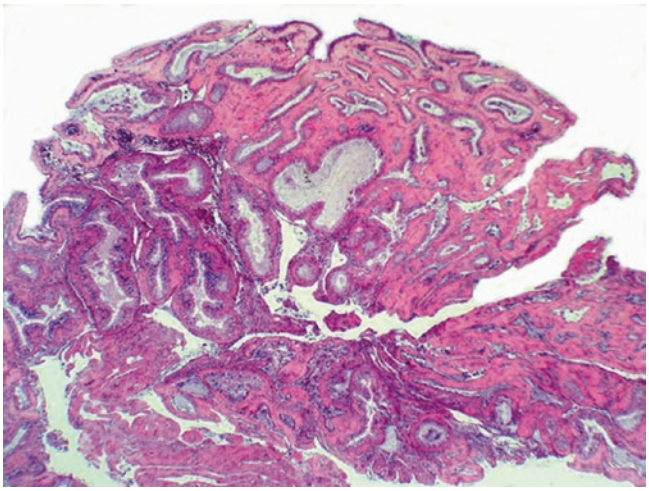

Fig 2.7 Respiratory epithelial adenomatoid hamartoma: polypoid formation with glandular-like spaces lined by respiratory epithelium and supported by fibrous stroma

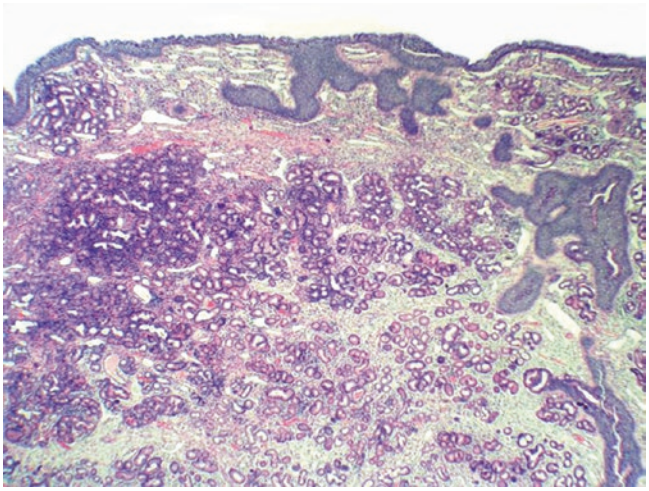

Fig 2.9 Seromucinous glandular hamartoma: abundant lobular aggregates of modified seromucous glands supported by slightly edematous stroma

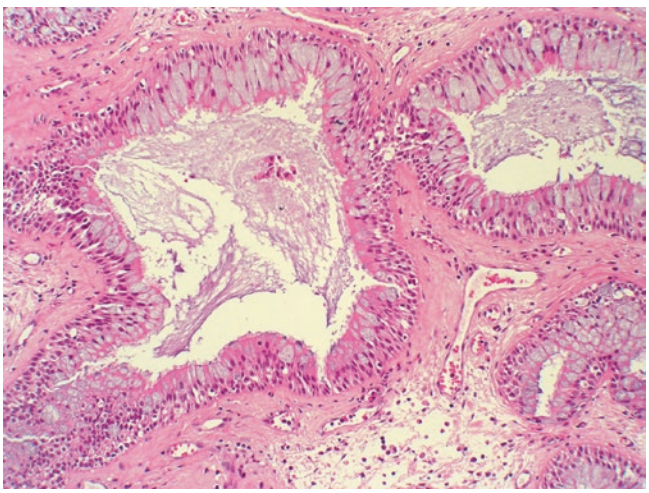

Fig 2.8 Respiratory epithelial adenomatoid hamartoma: glandular-like spaces lined by respiratory epithelium surrounded by fibrous stroma

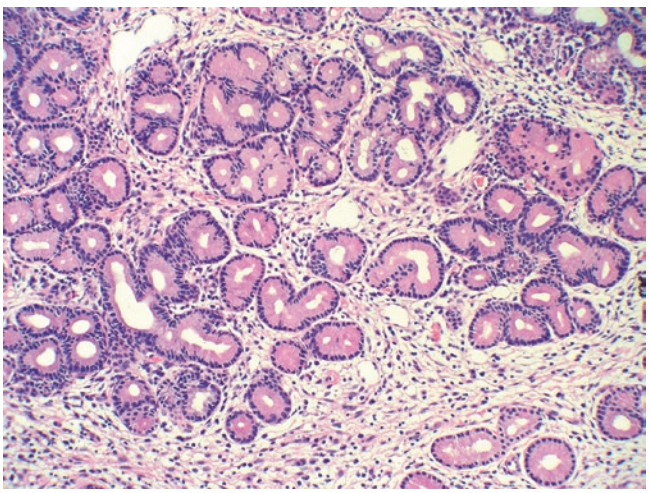

Fig 2.10 Seromucinous glandular hamartoma: disorderly placed seromucous glands, devoid of surrounding myoepithelial cells

is maintained and the overgrowth mainly consists of disorderly placed seromucinous glands, lacking myoepithelial cells, the term "seromucinous glandular hamartoma" (SMGH) is used [41, 42] (Figs. 2.9 and 2.10).

Differential diagnosis REAH and SMGH must be differentiated from sinonasal polyps, inverted papilloma, and the various types of low-grade adenocarcinomas [43]. The latter may show CK20 or CDX2 immunohistochemical expression, not reported in hamartomatous lesions [44].

Treatment and prognosis Conservative complete excision is curative [45].

2.4.2.2 Chondro-osseous and Respiratory Epithelial Hamartoma

Definition Chondro-osseous and respiratory epithelial hamartoma (COREH) combines the features of REAH with juxtaposed cartilaginous and osseous structures.

Epidemiology etiology, and pathogenesis: Similar to REAH

Macroscopy COREH is similar in shape to REAH but has harder consistency and abundant cystic formations on the cut section (Fig. 2.11).

Microscopy Immature to mature benign chondral and osseous trabeculae appear juxtaposed with gland-like formations

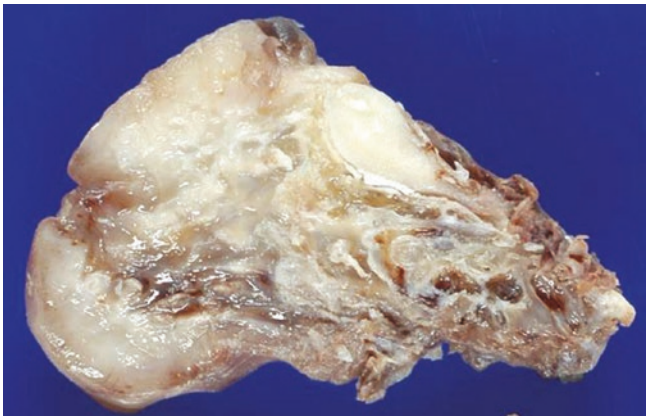

Fig 2.11 Chondro-osseous and respiratory epithelial hamartoma: chondro-osseous septation involving cystic spaces

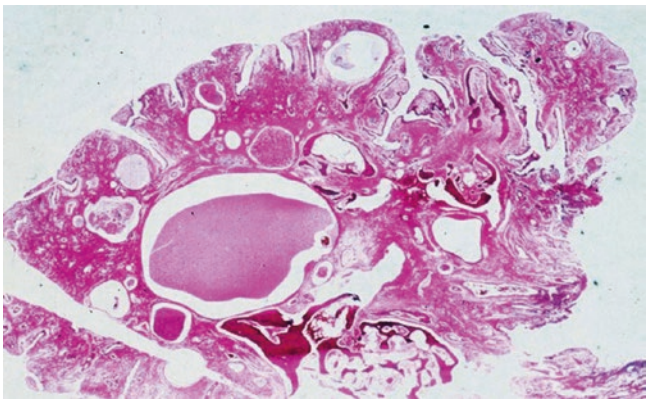

Fig 2.12 Chondro-osseous and respiratory epithelial hamartoma: osseous septa partially divide wide areas containing ducts and cysts lined by respiratory epithelium (Courtesy of Prof. M. Pfalz, Zurich, Switzerland)

covered with respiratory epithelium and supportive fibrous stroma (Fig. 2.12) [46].

Differential diagnosis COREH must be mainly distinguished from nasal chondromesenchymal hamartoma. The latter mostly occurs in children and the former in adults.

Treatment and prognosis As in REAH, conservative complete resection is curative.

2.4.2.3 Nasal Chondromesenchymal Hamartoma

Definition Nasal chondromesenchymal hamartoma (NCMH) is a benign pseudotumoral overgrowth composed of an admixture of chondroid, stromal, and cystic spaces.

Epidemiology and pathogenesis NCMH is a rare lesion mostly occurring in male newborns under 3 months of age [47, 48]. Very rare examples occur later in life. Although NCMHs are more frequent in nasal cavities, they can also arise from the nasopharynx and paranasal sinuses [41]. The cause is unknown. The occurrence of NCMH as initial lesion in children with pleuropulmonary blastoma predisposition syndrome has been reported [49]. In this disorder, NCMH arises secondary to germline and somatic mutations of the gene *DICER1*.

Macroscopy NCMH can reach up to 8 cm in size [48].

Microscopy NCMH consists of irregular nodules of mature hyaline cartilage in lobular arrangement. The chondroid nodules are surrounded by stroma that may be loose and myxoid or dense and collagenous. Blood-filled cystic spaces with features similar to aneurysmal bone cyst, as well as microcysts, within the myxoid areas can be seen. Ossicles, trabeculae of immature bone, osteoclast-like giant cells, and foci of mature adipose tissue can be found occasionally. The stromal spindle cells usually are positive for smooth muscle actin and the chondroid cells for S-100 protein.

Differential diagnosis NCMH needs to be distinguished from COREH, chondrosarcoma, mesenchymal chondrosarcoma, and chondroblastoma, entities that are exceedingly rare in newborns. The ectomesenchymal chondromyxoid tumor, although sharing certain similarities with NCMH, only occurs in the oral cavity.

Treatment and prognosis Combined intranasal and neurosurgical approach may be required to achieve complete resection, which is curative [48].

2.5 Pseudotumors

2.5.1 Mucocele

Definition Mucocele is a cyst filled with mucous that develops within a sinus cavity as the result of occlusion of the ostium.

Epidemiology The most common sites of occurrence are the frontal and the sphenoidal sinuses.

Etiology and pathogenesis Most commonly is due to infection but also may result from trauma or be congenital [50]. Retained secretions cause expansion of the sinus and bone erosion.

Microscopy The cyst is lined by respiratory epithelium that shows prominent goblet cell hyperplasia [51, 52]. Expansion of the cyst may cause atrophy and metaplasia of the epithelium.

Treatment and prognosis Surgical evacuation of the involved sinus by removal of the occlusion achieves excellent results.

2.5.2 Necrotizing Sialometaplasia

Definition Necrotizing sialometaplasia (NSM) is a reactive change of seromucous glands that undergo squamous metaplasia.

Etiology and pathogenesis Etiology relates to an ischemic event. Trauma has been claimed also as a cause of these lesions.

Clinical aspects It presents as a localized swelling that becomes ulcerated.

Microscopy Glandular lobular architecture is preserved, with squamous metaplasia of ducts and acini and glandular infarction. Mucin spillage elicits inflammation. The overlying epithelium can show pseudoepitheliomatous hyperplasia.

Differential diagnosis The most important entities to be considered are squamous cell carcinoma (SCC) and mucoepidermoid carcinoma. Proliferation in NSM is usually low, a feature that can be helpful in the distinction.

Treatment and prognosis Healing occurs spontaneously; therefore, surgical treatment is not necessary [53].

2.5.3 Organizing Hematoma

Definition Sinonasal organizing hematoma (OH) is a mass of hemorrhage in the nose and paranasal sinuses.

Synonyms "Cholesterol granuloma" and "rhinitis caseosa"

Etiology and pathogenesis OH is in most cases the result of occult submucosal hemorrhage in the maxillary sinus due to external trauma or tooth extraction. Resolution of the hematoma produces the formation of cholesterol granulomas [54].

Macroscopy A sessile mass is seen, consisting of dark-red hemorrhagic areas admixed with pale "cheesy" zones composed of cholesterol.

Microcopy In OH, large areas of degenerated blood and deposits of fibrin predominate, which are being organized by granulation tissue. Resolution of the hematoma produces the formation of cholesterol granulomas and fibrosis, simulating a foreign body reaction. Often, there are areas of irregular blood vessels, occasionally lined by bizarre endothelial cells, which may be mistaken for a malignant vascular tumor [55].

Differential diagnosis OH must be mainly differentiated from angiosarcoma.

Treatment and prognosis Surgical removal of the mass is curative.

2.5.4 Amyloidosis

Epidemiology Isolated amyloid deposition in the sinonasal mucosa is a rare event, with about 20 cases reported in the English literature [56, 57].

Macroscopy Grossly, the lesion appears as a friable to hard tumorlike mass, with frequent hemorrhage.

Microscopy Histologically, there is a deposition of intensely eosinophilic material in the stroma, around blood vessels and around ducts of seromucous glands, which is often associated with diffuse chronic inflammation and foreign body granulomatous reaction. Amyloid stains orange with Congo red and is apple-green birefringent at polarized light examination. Immunohistochemistry may help to identify the type of amyloid deposition. In the head and neck, most cases are of the primary (AL) type; therefore, they show immunoreactivity with AL (kappa or lambda light chain amyloid) [58].

Treatment and prognosis Surgical removal has a palliative purpose.

2.5.5 Myospherulosis

Definition Myospherulosis is characterized by the presence of cyst-like spaces lined by flattened histiocytes and containing clusters of brownish spherules resembling fungi [59–61].

Epidemiology Myospherulosis is a rare entity, with less than 200 cases reported [62].

Etiology and pathogenesis The lesion is usually found in patients who have had previous operations [63]. It is now recognized that the spherules are extravasated red cells that have been altered by interaction with traumatized fat or petrolatum-based ointments and gauzes used in surgical procedures.

Microscopy The spherules lie loosely or within sacs formed by thin refractile membranes. The brownish spherules do not

stain with PAS or Gomori methenamine silver, and their morphology does not correspond with any known fungus [64]. They are found within fibrous granulation tissue which may show a foreign body reaction.

Treatment and prognosis Surgical removal produces excellent results.

2.5.6 Eosinophilic Angiocentric Fibrosis

Definition Eosinophilic angiocentric fibrosis (EAF) is a disorder that compromises the airways due to progressive obstruction.

Etiology and pathogenesis Recent findings support that EAF is part of the spectrum of IgG4-related systemic diseases [65, 66].

Epidemiology EAF is a rare, chronic, benign, condition of the upper respiratory tract occurring predominantly in adult women [67, 68].

Microscopy Initially, the histologic picture is characterized by non-necrotizing eosinophilic vasculitis involving capillaries and venules of the sinonasal mucosa, accompanied by an inflammatory infiltrate with lymphocytes, plasma cells, histiocytes, and occasional neutrophils (Fig. 2.13). In late lesions, there is a characteristic obliterative perivascular onionskin fibrosis, while the inflammatory infiltrate is less dense (Fig. 2.14) [67].

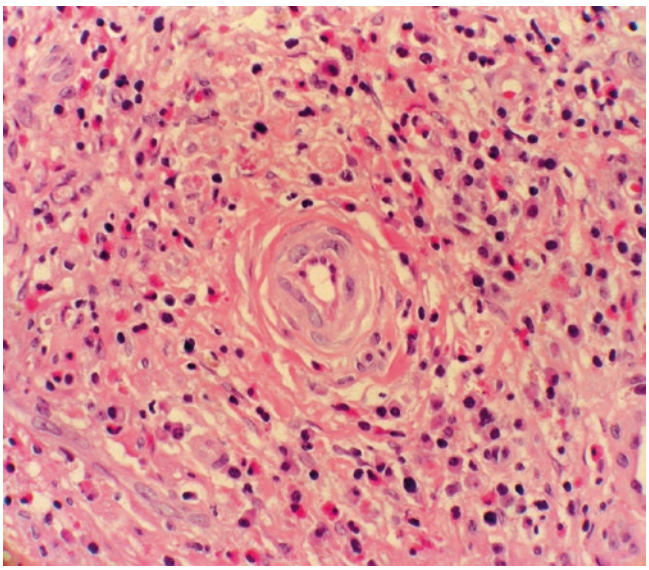

Fig. 2.13 Eosinophilic angiocentric fibrosis: initial lesion with non-necrotizing eosinophilic vasculitis involving capillaries and venules (Courtesy of Dr. F. Garcia-Bragado, Pamplona, Spain)

The differential diagnosis includes reactive processes of the sinonasal mucosa, like granulomatosis with polyangiitis (Wegener's), Churg-Strauss disease, Kimura disease, angiolymphoid hyperplasia with eosinophilia, and IgG4-associated disease.

Treatment and prognosis Surgery offers palliation of the nasal obstruction.

2.5.7 Surgical Ciliated Cyst of the Maxilla

Definition Surgical ciliated cyst of the maxilla is a locally aggressive lesion that develops mainly as a complication of surgery in the maxillary sinus region [69, 70].

Synonyms Postoperative maxillary cyst and paranasal cyst

Epidemiology and pathogenesis The incidence is variable. It represents 19.5 % of all oromaxillary cystic lesions in the Japanese population [69], while it is rare in Europe and the United States. It occurs in adult subjects, with a mean age of 52 years [71]. There is no significant gender predilection [70, 71]. This cyst usually arises in the lateral wall of the maxilla and expands toward the canine fossa or toward the nasal wall or sphenopalatine wall of the sinus. Some lesions may be more aggressive and occupy the orbit floor or ethmoidal air cells (Fig. 2.15). There are also reports of mandibular localization. The lesion is likely to be caused by sinus or nasal mucosa entrapment in the bone healing process after an osteotomy in these sites.

Macroscopy Surgical ciliated cyst is usually unilocular, but multilocular lesions have also been observed. The wall

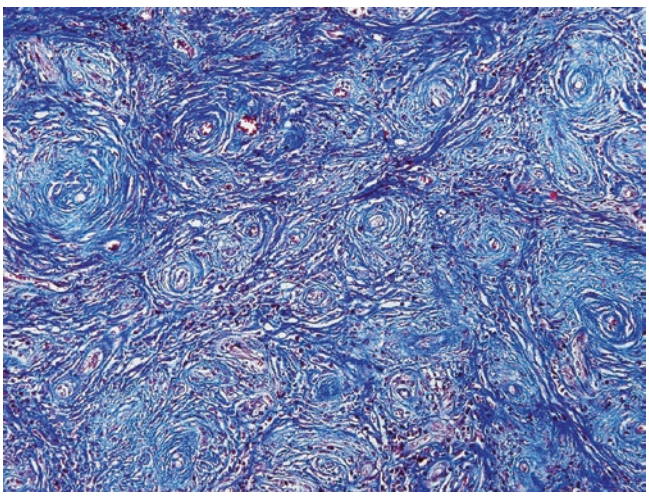

Fig. 2.14 Eosinophilic angiocentric fibrosis: late lesion with obliterative perivascular onionskin fibrosis. Masson's trichrome

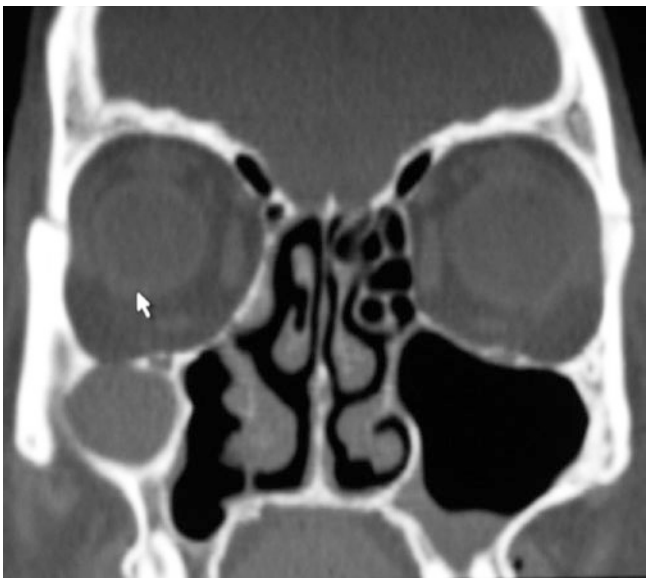

Fig 2.15 Surgical ciliated cyst of the maxilla: CT scan depicts a cyst in the lateral wall of the maxilla that expands to contact with the floor of the orbit (Courtesy of Dr. P. Claros, Barcelona, Spain)

shows variable thickness, and the content is brown mucinous, more rarely serous. Purulent fluid and cholesterol crystals are frequently seen [70].

Microscopy The wall of the cyst characteristically displays a fibrous connective tissue band, often with mild-to-moderate inflammatory infiltrate, which appears entrapped between the osseous wall and the overlying mucosa (Fig. 2.16). The mucosa is lined by an epithelium, which is pseudostratified ciliated in two-thirds of the cases, transitional in 28 % and squamous in 6 %. Goblet cells are also present, and their number increases with local infiltration of inflammatory cells into the cyst wall [71]. Epithelial dysplasia has been rarely observed [70].

Differential diagnosis Surgical ciliated cyst should be differentiated from mucocele of the maxillary sinus, which presents as a cyst containing mucoid or gelatinous material, lined by pseudostratified ciliated epithelium, sometimes with areas of squamous metaplasia. However, the main difference with surgical ciliated cyst is that paranasal sinus mucocele is not found in intraosseous location. Odontogenic cysts, including radicular cysts and keratocyst, may also occasionally present areas of ciliated epithelium. The clinical history of previous surgery of the maxillary sinus (Caldwell-Luc procedure) and the radiological aspect of the lesion are helpful in the distinction [72].

Treatment and prognosis Treatment consists of surgical removal of the lesion. Removal of the lesion is curative.

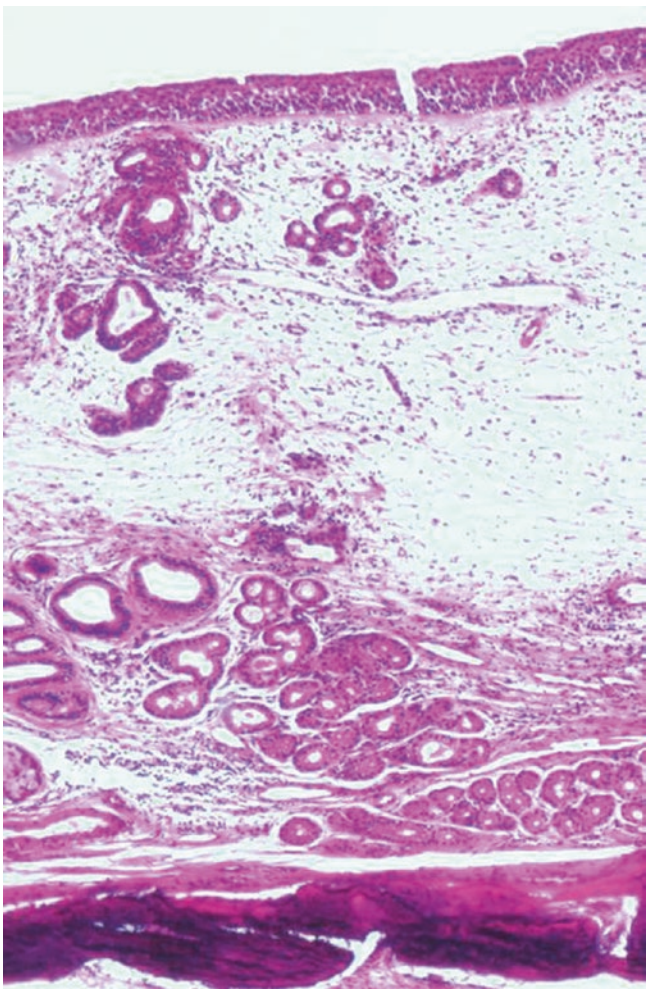

Fig 2.16 Surgical ciliated cyst of the maxilla: notice at the bottom the characteristic band of periosteal fibrous thickening between the calcified osseous wall and the lower part of the lamina propria of the respiratory mucosa

2.6 Fungal Diseases

Sinonasal fungal diseases are clinically classified as non-invasive allergic, non-invasive fungus ball or mycetoma, invasive chronic indolent, and invasive acute fulminant or angioinvasive (Table 2.1). The correct distinction between these four entities sometimes requires histologic, clinical, and radiologic correlations.

2.6.1 Allergic Fungal Rhinosinusitis

Definition The allergic form of fungal rhinosinusitis (FRS) is a non-invasive form of fungal infection, due to a localized hypersensitivity response to fungal growth that arises in areas of compromised mucus drainage.

Synonym Eosinophilic fungal sinusitis

Table 2.1 Fungal diseases of sinonasal tract

Non-invasive rhinosinusitis	Tissue-invasive rhinosinusitis
Allergic fungal sinusitis	Invasive indolent
Fungus ball	Invasive fulminant

Epidemiology Allergic FRS is the most common of all fungal sinusitis and accounts for between 5 and 10% of all chronic rhinosinusitis cases [73]. It most commonly affects adolescents and young adults (mean age at diagnosis 21.9 years) [74]. There is no significant gender predilection. The maxillary, ethmoid, and sphenoid sinuses are most commonly involved. Unilateral involvement may occur in some cases [74]. It is associated with nasal polyps, atopy, asthma, and elevated serum IgE [75].

Etiology In the first description of this disease, *Aspergillus* sp. was recognized as the primary causative fungus [76], but subsequent reports have evidenced that fungi of the dematiaceous family (*Alternaria* sp., *Bipolaris* sp., *Curvularia* sp., and others) are implicated in the majority of the cases [77].

Macroscopy At the time of surgery, allergic fungal mucin is recognized as thick and highly viscous in consistency, varying in color from light tan to brown, black, or dark green.

Microscopy The histological features necessary for the diagnosis of allergic FRS are detected in the mucin, rather than in paranasal sinus mucosa, which shows the changes of a nonspecific inflammatory condition, without involvement by fungi. The hallmark of the disease is the production of allergic mucin in which mucous material alternates with cell debris conferring a wavy appearance (Fig. 2.17). With hematoxylin and eosin stain, the mucin has a basophilic background and contains a mixed inflammatory cell infiltrate with a predominance of eosinophils, necrotic cell debris, and Charcot-Leyden crystals (Fig. 2.18). Fungal hyphae are rare, scattered, and fragmented and can be identified within the mucin with histochemical stainings (Fig. 2.19), including Grocott and Gomori methenamine silver [76, 78]. When fungal hyphae are not identified, the term sinonasal allergic mucinosis is applied.

Differential diagnosis Allergic FRS must be differentiated from other sinonasal fungal diseases, particularly from invasive forms, including indolent, granulomatous, and fulminant variants [9]. These are rare diseases in which fungi are found in the mucosa, soft tissues, and bone [76]. Chronic non-invasive fungal sinusitis, also known as fungus balls or mycetomas, is recognized as self-limited collections of matted fungal hyphae confined most commonly to the maxillary sinus.

Treatment and prognosis To prevent recurrences, a combination of conservative surgery and adjunctive medical

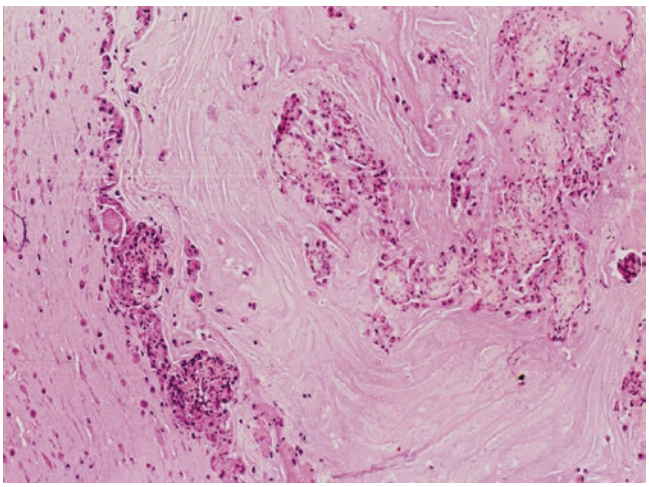

Fig. 2.17 Allergic mucinosis: basophilic pools of mucin alternate with dense aggregates of eosinophilic leukocytes conferring a wavy appearance

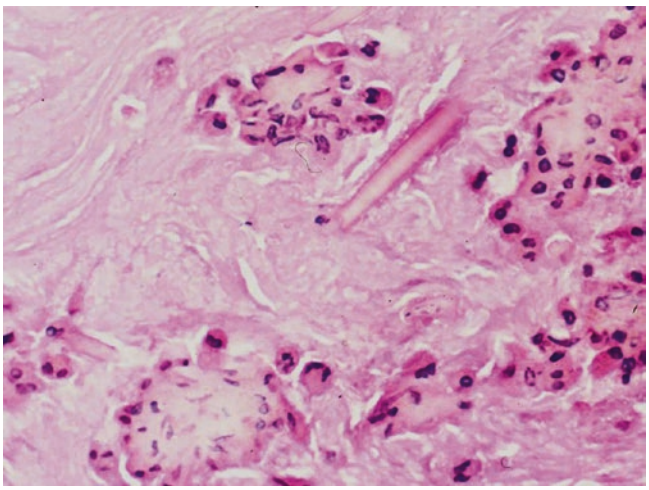

Fig. 2.18 Allergic mucinosis: a Charcot-Leyden crystal between lakes of mucin and aggregates of eosinophilic leukocytes

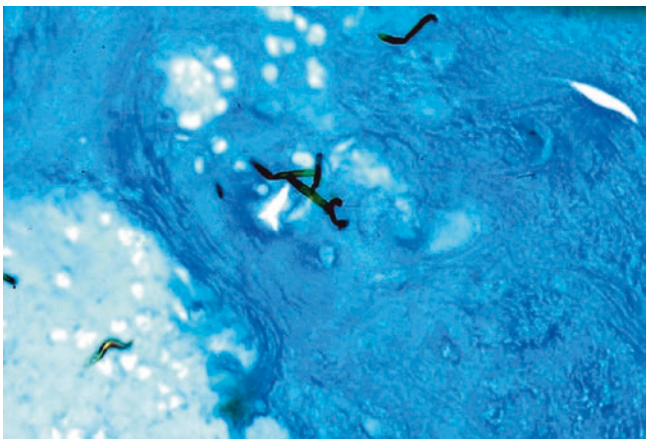

Fig. 2.19 Allergic fungal sinusitis, scarce fungal hyphae in a lake of mucin. Gomori methenamine silver

treatments, including systemic and/or topical corticosteroids, and immunotherapy to pertinent fungal and nonfungal antigens is recommended [75, 79].

2.6.2 Non-invasive Fungal Rhinosinusitis

Definition Non-invasive FRS is a mycotic infection characterized by the presence of a fungus ball in the sinus lumen, without involving the adjacent tissues.

Synonyms Mycetoma, fungus ball, and extramucosal fungal sinusitis

Epidemiology The maxillary sinus is the most commonly involved. Ethmoid, frontal, and sphenoid sinuses are affected less often.

Etiology and pathogenesis Non-invasive FRS occurs in immunocompetent patients, being mainly caused by *Aspergillus* sp. Other fungi are less common.

Macroscopy The consistency of the fungus ball may vary from soft to hard with focal central calcification.

Microscopy As a non-invasive disease, the fungal mass is present in the lumen of the sinus. Usually, the neighboring mucosa shows mild chronic inflammation. In sections stained with PAS-diastase or Gomori methenamine silver, the *Aspergillus* sp. hyphae appear as dichotomously, acute-angle branching septate hyphae 6–8 μm wide (Fig. 2.20).

Differential diagnosis Allergic FRS and invasive forms of fungal sinusitis must be ruled out.

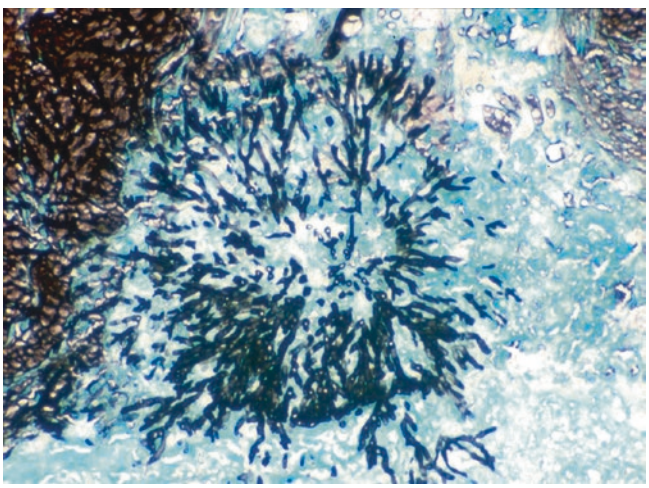

Fig. 2.20 Non-invasive fungal sinusitis: densely packed branching hyphae of *Aspergillus* forming a fungus ball. Gomori methenamine silver

Treatment and prognosis Evacuation of the sinus with removal of the fungus ball by endoscopic surgery is the recommended option. Antifungal medication is not required.

2.6.3 Invasive Fungal Rhinosinusitis

The spectrum of invasive FRS covers the chronic indolent invasive and the acute fulminant forms [9, 75]. The first form is found in immunologically competent patients and the latter is restricted to immunocompromised patients.

2.6.3.1 Chronic Invasive Fungal Rhinosinusitis

Definition Chronic invasive FRS is an uncommon form of sinusitis characterized by a protracted clinical course despite the finding of fungal tissular invasion. Chronic indolent invasive fungal sinusitis is a synonymous.

Epidemiology Two forms of chronic invasive FRS are recognized: the nonspecific chronic invasive fungal sinusitis and the granulomatous chronic invasive fungal sinusitis [80].

Etiology and pathogenesis Both of these conditions are thought to be due to *Aspergillus* sp. and both occur in immunologically competent patients.

Microscopy Fungi are found in the mucosa, soft tissues, and bone. The presence of a granulomatous reaction, the recognition of which is strictly a function of histopathology, is currently the sole means of identifying this category [75]. At present, there is no histopathologic hallmark diagnostic of nonspecific chronic invasive FRS, which may be better labeled as "nongranulomatous chronic invasive" FRS.

Treatment and prognosis Surgical debridement and drainage are required. Systemic antifungal drugs may not be necessary to achieve favorable response to treatment.

2.6.3.2 Fulminant Invasive Fungal Rhinosinusitis

Definition Invasive fulminant FRS is an acute, rapidly progressive, and life-threatening fungal infection characterized by destructive tissue invasion with or without obvious vascular invasion.

Epidemiology Invasive fulminant FRS is most commonly seen in adult immunocompromised patients.

Etiology and pathogenesis Invasive fulminant FRS has been traditionally associated with *Mucor* sp. and poorly controlled diabetics [81], but currently, invasive fulminant FRS also encompasses *Aspergillus* sp., as well as dematiaceous and non-dematiaceous fungi, with a strong association with immunodeficiencies [75].

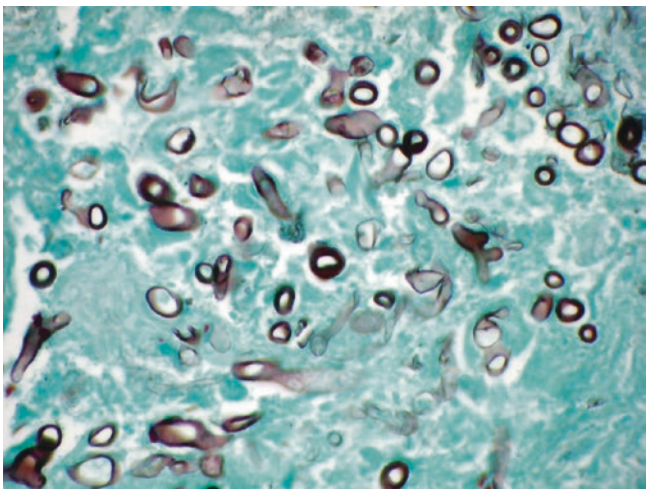

Fig. 2.21 Invasive fulminant fungal sinusitis: necrotic background with wide nonseptated hyphae of *Mucor* species. Gomori methenamine silver (Courtesy of Prof. J. Ramirez, Barcelona, Spain)

Microscopy Invasive fulminant FRS causes destructive inflammation of the sinonasal tissues featured by a combination of necrotic debris and tissue invasion with or without obvious vascular invasion [75, 82]. Fungi are found in the mucosa, soft tissues, and bone [76]. The fungus invasion of the blood vessels causes thrombosis, and the surrounding affected tissues may exhibit coagulative necrosis and hemorrhage, while the inflammatory reaction is scant. Although the architecture of the surrounding tissues may fade away, the fungi can often be recognized (Fig. 2.21). In tissue sections stained with PAS-diastase or Gomori methanamine silver, the *Mucor* sp. fungi are seen as 10- to 20-μm-wide nonseptate hyphae, usually branching at right angles, whereas *Aspergillus* sp. hyphae appear as dichotomously, acute-angle branching septate hyphae 6–8 μm wide.

Differential diagnosis Invasive fulminant FRS must be differentiated from other types of fungal sinusitis, as well as from other midfacial destructive and granulomatous lesions.

Treatment and prognosis The therapy for patients with acute fungal sinusitis is multimodal and involves surgery and antibiotic therapy. Aggressive surgical debridement and drainage and systemic antifungal drugs are mandatory. A quick histological recognition of the fungi is of paramount importance in the proper management of invasive fulminant FRS. A frozen section may be required from the pathologist, as fungal cultures are often negative and an early diagnosis and treatment improves survival rates and lowers morbidity [8].

2.6.4 Rhinosporidiosis

Definition Rhinosporidiosis (RSP) is a special form of chronic invasive granulomatous fungal disease that follows a protracted course, growing in the form of polyps involving the upper respiratory tract, principally the nasal cavity [83, 84].

Epidemiology Most cases of RSP occur in India and Sri Lanka and less frequently in Brazil. Although very rarely, RSP may be seen in any country.

Etiology and pathogenesis RSP is caused by the endosporulating fungus *Rhinosporidium seeberi*. It affects immunocompetent patients through endospores contaminating water or soil.

Macroscopy RSP lesions may look alike allergic sinonasal polyps.

Microscopy In RSP the mucosal and submucosal involvement is characterized by the presence of thick-walled sporangia measuring 50–350 μm in diameter and containing numerous mucicarminophilic spores. They are associated with a heavy chronic inflammatory reaction with occasional foci of suppuration and foreign body giant cell reaction. Sporangia also stain with PAS-diastase and Gomori methenamine silver.

Differential diagnosis Sinonasal polyps and papillomas, as well as coccidiomycosis

Treatment and prognosis Surgical removal of the lesions. Recurrence rate is low.

2.7 Midfacial Destructive Granulomatous Lesions

2.7.1 Granulomatosis with Polyangiitis

Definition Granulomatosis with polyangiitis (GPA) is an immunologically mediated inflammatory disease characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. Variable degrees of disseminated vasculitis involving both small arteries and veins may also occur.

Synonym Wegener's granulomatosis

Epidemiology GPA lesions in the upper respiratory tract are ulcerative and destructive and occur mainly in the nasal cavity and paranasal sinuses. At the time of initial presentation, the full clinical picture of the disease is rarely seen.

Clinical aspects A high percentage of patients develop elevated c-ANCA as well as elevated proteinase 3 (PR3).

Microscopy The hallmarks of GPA are the presence of geographic necrosis surrounded by palisaded histiocytes, granulomas and scattered giant cells, vasculitis with fibrinoid necrosis or infiltration of vessel walls by inflammatory cells, neutrophilic microabscesses, and a mixed inflammatory infiltrate with variable fibrosis (Figs. 2.22 and 2.23) [85–90].

Differential diagnosis The classic histological features of GPA are not present in many biopsy specimens. Repeat biopsies and clinical correlations are often essential for early diagnosis. In the early stages, when GPA is restricted to the upper respiratory tract and ear, the diagnosis can be quite difficult [90]. Stains for acid-fast bacilli and fungi are negative. GPA must be differentiated from allergic granulomatosis and vasculitis (AGV) also known as Churg-Strauss disease, in which, besides vasculitis and poorly formed granulomas, eosinophils predominate with formation of eosinophilic microabscesses [89]. In AGV, c-ANCA may be occasionally elevated but PR3 is absent. NK-/T-cell lymphoma and diffuse large B-cell lymphoma are other differential diagnoses. Increased IgG4-positive cells can be seen in sinonasal, orbital, and periorbital biopsies of GPA that could induce a wrong diagnosis of IgG4-related disease [66].

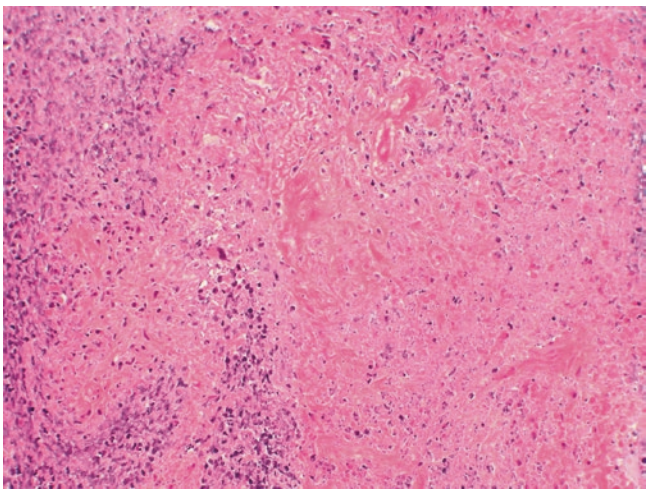

Fig. 2.22 Granulomatosis with polyangiitis: presence of geographic necrosis surrounded by granulomas and scattered giant cells

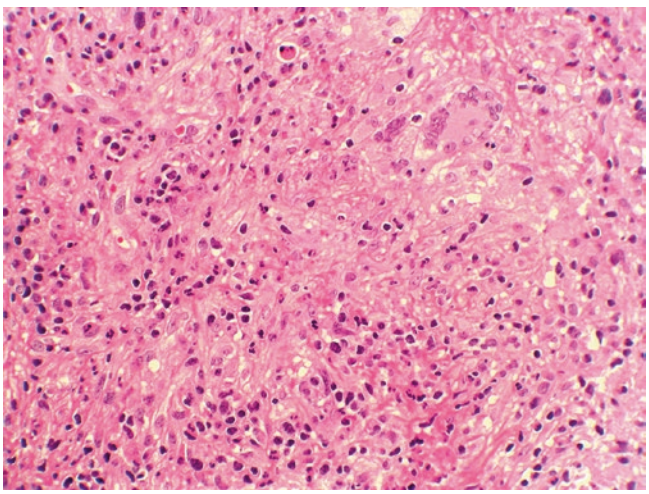

Fig. 2.23 Granulomatosis with polyangiitis: vasculitis with fibrinoid necrosis, infiltration of vessel walls by inflammatory cells, giant cells, and occasional epithelioid cells

Treatment and prognosis Concomitant administration of cyclophosphamide and prednisone is recommended [90].

2.7.2 Leprosy

Definition Leprosy is a chronic infection caused by *Mycobacterium leprae* that depending on the immunoreactivity of the patients presents three clinical forms: lepromatous, tuberculoid, and indeterminate.

Epidemiology and pathogenesis *Mycobacterium leprae* affects principally the cooler parts of the body as the upper respiratory tract and especially the sinonasal region [91, 92].

Microscopy Lepromatous leprosy is the most frequent form of this disease involving the nasal cavity [93]. It is characterized by nodular masses of foamy macrophages (Virchow lepra cells) in which large numbers of acid-fast bacilli (*Mycobacterium leprae*) are demonstrable by the Fite-Faraco stain, a modified Ziehl-Neelsen method. Tuberculoid leprosy is characterized by non-caseating granulomas and the indeterminate variant by a nonspecific chronic inflammatory reaction; acid-fast bacilli are seldom demonstrable in these types.

Treatment Combination of rifampicin, dapsone, and clofazimine

2.7.3 Tuberculosis

Definition Tuberculosis (TBC) is a chronic granulomatous infection caused by *Mycobacterium tuberculosis*.

Epidemiology Tuberculosis (TBC) of the head and neck occurs infrequently, and involvement of the nose is rare, representing in most cases a secondary event to pulmonary involvement [94].

Macroscopy In most cases, there is a polyp of the nasal septum or an ulcerated granular lesion.

Microscopy TBC is characterized by caseating and confluent granulomas with surrounding epithelioid cells palisading

and Langhans-type giant cells. Lack of caseation is uncommon. Histologically, acid-fast bacilli may be occasionally identified by the Ziehl-Neelsen stain. The definitive diagnosis is made by isolating *Mycobacterium tuberculosis* by culture and/or PCR from tissue removed during biopsy.

Differential diagnosis It includes all other granulomatous diseases, mainly those with caseating type of necrosis. The presence of intracranial extension may lead to a clinical diagnosis of malignancy [95].

Treatment and prognosis Administration of tuberculostatic drugs is usually curative.

2.7.4 Sarcoidosis

Definition Sarcoidosis is a chronic multisystem, non-caseating granulomatous disorder of unknown etiology. The upper aerodigestive tract is occasionally involved.

Epidemiology Besides the lung, hilar and mediastinal lymph nodes, skin, liver, and other systems and organs, several head and neck territories may be affected. The sinonasal mucosa is rarely involved, and most patients have generalized disease [96–99].

Microscopy Discrete non-caseating and non-confluent granulomas are a distinguishing feature. Sarcoid granulomas are composed predominantly of epithelioid histiocytes with multinucleated giant cells and a peripheral rim of lymphocytes. Asteroid bodies and Schaumann's conchoid calcium concretions may be found in the cytoplasm of the giant cells. Stains for acid-fast bacilli and for other infectious agents are negative. Although no microorganisms are found in sarcoid granulomas, cell wall-deficient forms of mycobacteria have been detected by PCR [100].

Differential diagnosis Includes other granulomatous disorders, like tuberculosis, leprosy, granulomatosis with polyangiitis, inhalant granulomatous processes, and cholesterol granuloma [85].

Treatment and prognosis Corticosteroids are recommended for treatment of clinically active disease. Outcome is usually favorable. Low-dose corticosteroid treatment may be required to maintain remission and prevent fibrosis.

2.7.5 Rhinoscleroma

Definition Rhinoscleroma (RNS) is a chronic bacterial infection caused by *Klebsiella rhinoscleromatis*.

Epidemiology RNS is most prevalent in Russia, Belarus, Poland, and central European countries. Central and upper South American countries are also endemic areas [101].

Etiology *Klebsiella rhinoscleromatis* is a capsulated gram-negative bacillus [83, 101].

Macroscopy Large nodular tumorlike masses are found in the nasal cavity (Hebra nose). Less often, RNS nodules are found in other parts of the upper respiratory tract.

Microscopy RNS nodules contain large macrophages with abundant clear or vacuolated cytoplasm, known as Mikulicz cells (Fig. 2.24). The causative organism may be seen within these cells by the H&E stain; however, they are better identified by the Warthin-Starry staining method or by immunostaining for the *Klebsiella* capsular antigen. In addition, there is fibrosis and heavy infiltration by chronic inflammatory cells, mainly plasma cells showing numerous Russell bodies. The mucosal epithelium may show squamous metaplasia and occasionally prominent pseudoepitheliomatous hyperplasia. Exceptional examples of squamous cell carcinoma have been reported, in association with RNS [83, 101–103].

Differential diagnosis RNS must be ruled out from leprosy, syphilis, yaws, TBC, leishmaniasis, rhinosporidiosis, and paracoccidioidomycosis [101]. Another entity to be distinguished from RNS is Rosai-Dorfman disease.

Treatment and prognosis Prolonged treatment by tetracycline and ciprofloxacin is recommended. Surgery may be used for debulking the obstruction.

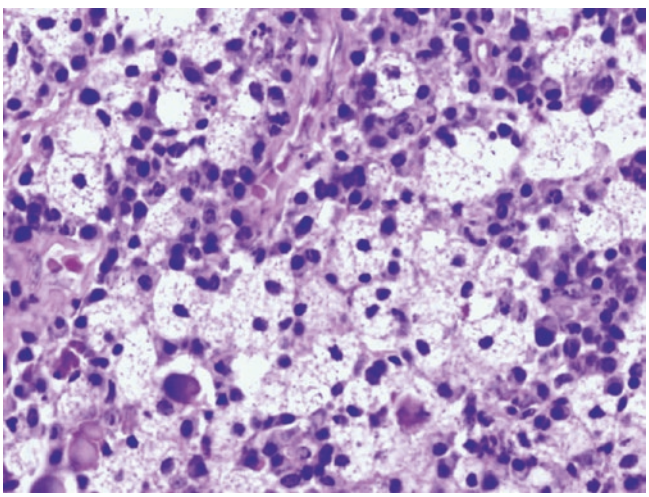

Fig. 2.24 Rhinoscleroma: large macrophages with abundant clear or vacuolated cytoplasm (Mikulicz cells) and heavy infiltration by chronic inflammatory cells (Courtesy of Prof. Y. Rogov, Minsk, Belarus)

2.7.6 Leishmaniasis

Definition Cutaneous leishmaniasis is an infection of the skin by a protozoan of the genus *Leishmania*. It comprises three different entities: localized cutaneous leishmaniasis, also known as "oriental sore" or "tropical sore," mucocutaneous leishmaniasis, and disseminated anergic cutaneous leishmaniasis [104].

Epidemiology Leishmaniasis of the nasal region when seen in Mediterranean and Oriental countries is mostly in the form of "oriental sore" caused by *Leishmania tropica*. In Central and South America, leishmaniasis is mostly seen in the form of mucocutaneous leishmaniasis caused by *Leishmania braziliensis* [105, 106].

Disseminated anergic cutaneous leishmaniasis develops in hosts lacking specific cell-mediated immune responses to the distinct species of *Leishmania*. The parasites are transmitted through the bites of blood-sucking female sand flies of the genus *Phlebotomus* [104].

Microscopy The protozoan parasite (amastigote) is seen in the cytoplasm of histiocytes or, extracellularly, measures 1.5–3.0 μm in maximum dimension and has a nucleus and a rod-shaped kinetoplast which stains positively with Giemsa. The kinetoplast is more readily identified in Giemsa-stained smears of exudates or scrapings than in paraffin sections. The lesions, commonly found in the nasal mucosa and facial skin, are associated with chronic inflammatory reaction and granuloma formation. They are in general circumscribed and self-involutive in the case of the "oriental sore" and disfiguring with marked destruction of the nasal septum in mucocutaneous leishmaniasis. In anergic cutaneous leishmaniasis, the nodules show enormous amounts of histiocytes repleted with leishmania [104].

Differential diagnosis Nasal leishmaniasis must be differentiated from other granulomatous diseases such as rhinoscleroma, paracoccidioidomycosis, yaws, leprosy, syphilis, TBC, and histoplasmosis.

Treatment and prognosis Antimonial compounds remain the treatment of choice. Prognosis is good in oriental sore, resistant to healing in the mucocutaneous form, and unfavorable in anergic leishmaniasis.

2.7.7 Cocaine Abuse

Cocaine abuse (snorting) may be associated with severe nasal necrotizing inflammation [107]. Endoscopically, there is atrophy of the inferior and middle turbinates and ulceration of the nasal septum. Histologically, areas of necrosis are admixed with acute and chronic inflammation; giant cells embracing birefringent foreign body particles are often present; however, vasculitis is minimal or absent. The lesion may be confused with granulomatosis with polyangiitis (Wegener's).

2.7.8 Local Steroid Injections

A granulomatous lesion of the nasal mucous membranes occurs in patients treated with injections of steroid preparations [108]. There is a central deposition of amorphous material bordered by histiocytes and foreign body giant cells. Occasional particles of birefringent crystalline material may be present. Special stains should be performed to exclude the presence of microorganisms.

2.8 Benign Epithelial Neoplasms

2.8.1 Sinonasal Papillomas

Sinonasal papillomas are usually divided into squamous cell papilloma of the nasal vestibule and Schneiderian papillomas of the nasal cavity and paranasal sinuses (Table 2.2). The first are covered by the epithelium of the skin surface. The latter are lined by the respiratory mucosa of the nasal cavity and paranasal sinuses (referred to as the Schneiderian membrane) and comprise three histopathological types: exophytic, inverted,

Table 2.2 Sinonasal papillomas

	Squamous	Everted	Inverted	Oncocytic
Location	Vestibule	Nasal septum	Lateral wall and sinuses	Lateral wall and sinuses
Growth	Exophytic	Exophytic	Endophytic-exophytic	Exophytic-endophytic
Epithelium	Keratinizing squamous	Non-keratinizing squamous and ciliated	Non-keratinizing squamous and ciliated	Oncocytic columnar
Intraepithelial mucin cysts	–	+	+	+++
Recurrence	Unusual	Usual[a]	Usual[a]	Usual[a]
Malignancy	Unusual	Unusual	10 %	<10 %

Modified from Wenig [567]
[a]If incomplete excision

and oncocytic. The histopathologic features that clearly differentiate between the three types of Schneiderian papillomas have been well documented [109]. Human papillomavirus (HPV) types 6 and 11 are involved in the pathogenesis of exophytic papillomas but not so consistently in the other two variants of Schneiderian papillomas [110–112]. All oncocytic papillomas examined have been HPV negative [110, 112, 113].

2.8.1.1 Squamous Cell Papilloma of the Nasal Vestibule

Definition A benign proliferative lesion composed of delicate stromal papillae covered by squamous epithelium. Squamous cell papillomas (SCPs) located in the nasal vestibule are formed by keratinizing stratified squamous epithelium of the skin surface [114].

Microscopy SCPs are exophytic and consist of a thickened layer of differentiated squamous epithelium without evidence of atypia or mitoses which is supported by arborescent stalks of fibrovascular stroma. Varying degrees of keratinization are present and hyperkeratosis, parakeratosis, or both may be seen (Fig. 2.25).

Differential diagnosis SCP of the nasal vestibule must be distinguished from exophytic papilloma of the Schneiderian mucosa. The keratinizing nature of the squamous epithelium in the former and the presence of mucous epithelial cells in the latter are the key differentiating features.

Treatment and prognosis SCPs of the nasal vestibule are benign, rarely recur after simple excision, and in general are not associated with HPV.

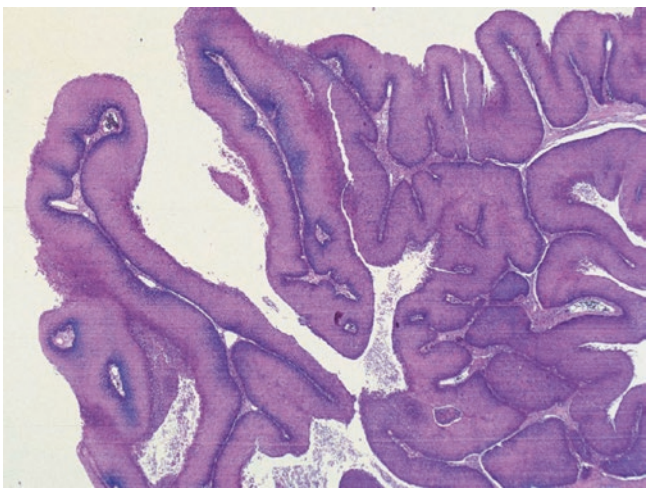

Fig. 2.25 Squamous cell papilloma of nasal vestibule: thickened layer of benign squamous epithelium is supported by arborescent stalks of fibrovascular stroma

2.8.1.2 Everted (Schneiderian) Papilloma

Definition Everted (Schneiderian) papilloma (ESP) is composed of papillary fronds with delicate fibrovascular cores covered by multiple layers of epithelial cells.

Synonyms ESP is also known as exophytic, fungiform, septal, and transitional cell papilloma among other terms [115]

Epidemiology ESPs arise most frequently at the nasal septum and only very rarely in the lateral nasal walls or in paranasal sinuses [115]. Males are predominantly affected. Patients tend to be younger than with other types of Schneiderian papillomas. ESPs are almost always unilateral [116]. No side is preferred and bilaterality is exceptional.

Macroscopy ESP is a single, warty tumor measuring up to 1.5 cm in diameter.

Microscopy ESP is composed of branching papillary structures, with papillae covered by stratified non-keratinizing squamous epithelium, admixed with intermediate or transitional cells and with ciliated respiratory epithelium that contains interspersed mucin-secreting cells (Fig. 2.26). The supporting stroma is fibrovascular.

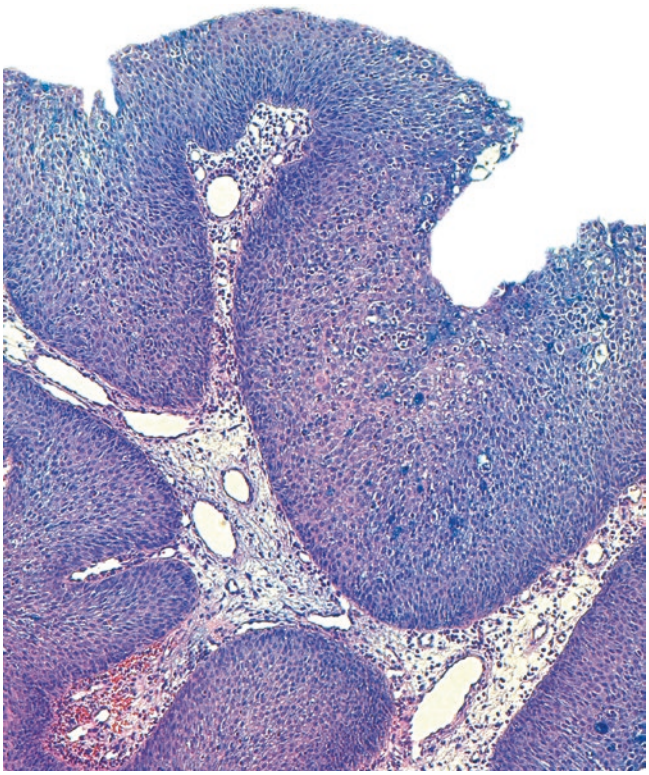

Fig. 2.26 Exophytic papilloma: branching papillary structures mainly covered by stratified non-keratinizing squamous epithelium that contains interspersed mucin-secreting cells. Alcian blue stain

Differential diagnosis The two main differential diagnoses of ESP are inverted papilloma and oncocytic papilloma. Neither the invaginated pattern of growth of inverted papillomas nor the oncocytic columnar epithelium of oncocytic papilloma is found in exophytic papilloma [109]. Non-keratinizing squamous cell carcinoma can be easily ruled out by the lack of atypia and invasion.

Treatment and prognosis Wide surgical excision is the best choice of treatment to avoid recurrences. Recurrences occur in about 20–40 % of cases, which is less than in inverted papillomas. Malignant transformation almost never occurs in ESP.

2.8.1.3 Inverted (Schneiderian) Papilloma

Definition Inverted (Schneiderian) papilloma (ISP) is a papilloma in which the epithelium invaginates and proliferates inward the underlying stroma.

Synonyms Inverting papilloma [115]

Epidemiology and pathogenesis ISP is the most common type of Schneiderian papilloma and accounts for about 60 % of them [117]. This lesion occurs almost exclusively in the lateral wall of the nasal cavity and in the paranasal sinuses, although on rare occasions, it may also arise on the nasal septum [115]. Patient's age ranges between 30 and 50 years and the male to female ratio is 3:1 [118]. Molecular studies show supportive evidence of clonality in ISPs [119].

Macroscopy ISPs frequently have a polypoid appearance and may be grossly indistinguishable from nasal polyps of the common type.

Microscopy ISPs are characteristically composed of invaginating crypts, cords, and nests covered by non-keratinizing squamous epithelium, which alternates with columnar ciliated respiratory epithelium and with intermediate or transitional epithelium. This newly formed duct system is similar to the embryonic development of the nasal mucosa [120]. The multilayered epithelium typically contains mucous cells and mucin-filled microcysts. The invagination of the mucosa may result in the presence of apparently discontinuous cell masses lying deep to the epithelial surface, but the basement membrane is intact and may be shown in continuity with that of the surface epithelium [121]. An inverted growth is the hallmark of inverted papilloma, but varying degrees of papillary growth may be seen at the surface (Fig. 2.27) [116]. The surface is characteristically lined by respiratory type of epithelium; nevertheless, foci of surface keratinization are occasionally present [114]. A few regular mitoses may be found in the basal and parabasal layers. Although the nuclei may show mild nuclear irregularities and hyperchromatism, no disturbances of the cellular polarity are found. An abundant and edematous connective tissue stroma is a common feature of inverted papillomas. It usually contains macrophages and neutrophils, but eosinophils may also be present. This inflammatory infiltrate may also be present between the epithelial cells, within the dilated lumens of invaginated crypts and within the numerous microcysts that usually occur in the respiratory epithelium (Fig. 2.28). Seromucinous glands are absent, but branching gland ducts are often present. The tumor grows by extension to involve the contiguous sinonasal epithelium [122].

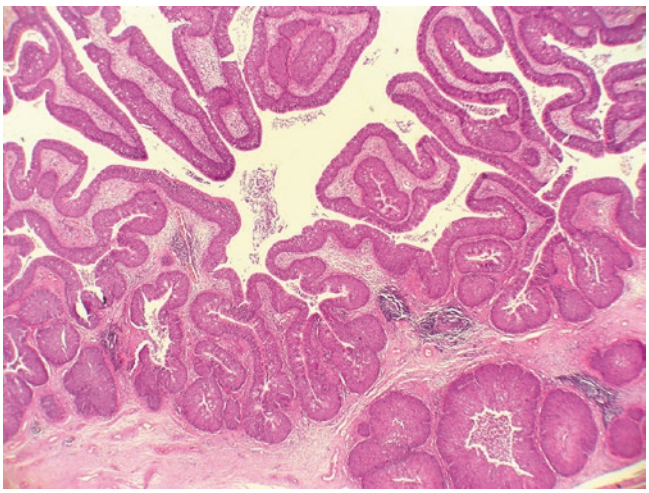

Fig. 2.27 Inverted papilloma: inverted growth is the hallmark of inverted papilloma, but varying degrees of papillary growth may be seen at the surface

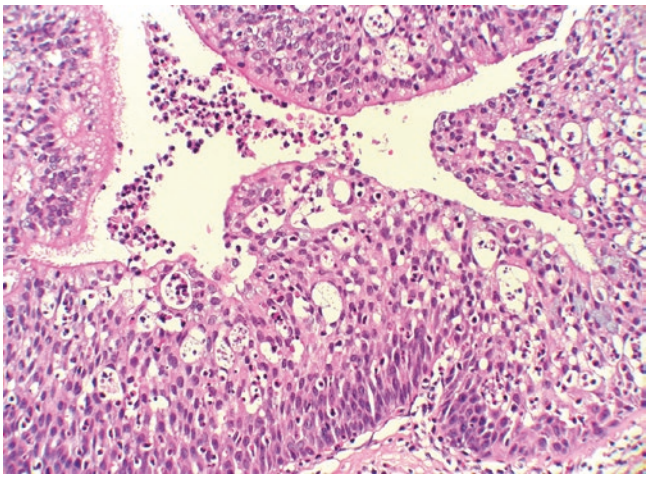

Fig. 2.28 Inverted papilloma: inflammatory infiltrate is present between the epithelial cells, within the dilated lumens of invaginated crypts, and within the numerous microcysts of the respiratory epithelium

Differential diagnosis ISPs must be distinguished mainly from REAH and from squamous cell carcinoma with basaloid features.

Treatment and prognosis If treated only by local surgical excision, recurrence occurs in up to 75% of cases. Therefore, lateral rhinotomy and medial maxillectomy are advisable for tumors of the lateral nasal wall [123]. Carcinoma develops in about 10–15% of inverted papillomas [114, 123, 124]. Carcinoma may coexist with inverted papilloma at the initial presentation or originate subsequently [114, 122, 125–127]. According to the experience of Michaels and Hellquist [128], carcinoma does not usually develop in the course of recurrences of inverted papilloma. The presence of severe atypia or marked keratinization in an inverted papilloma is always suspicious of malignant transformation. In these instances, the entire specimen should be thoroughly examined to exclude an associated carcinoma. Most associated carcinomas are squamous and less often undifferentiated (Figs. 2.29 and 2.30) [129]; other types may also occur such as verrucous carcinoma [130]. Carcinoma associated with ISP has a 60% 10-year survival rate [131].

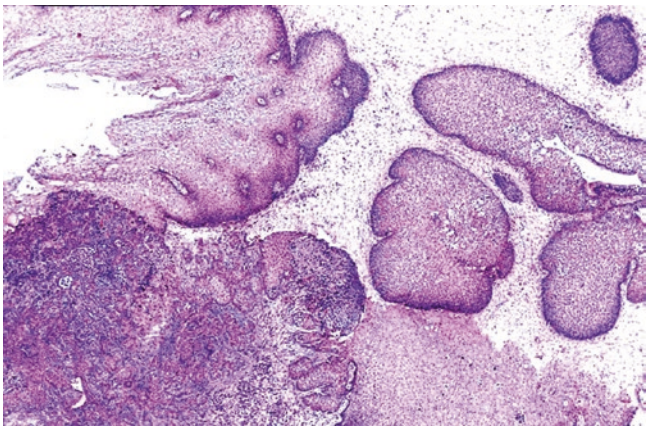

Fig. 2.29 Squamous cell carcinoma ex-inverted papilloma: cords and nests of infiltrating squamous epithelium are seen at the *lower left* (Courtesy of Prof. C. Ereño, Bilbao, Spain)

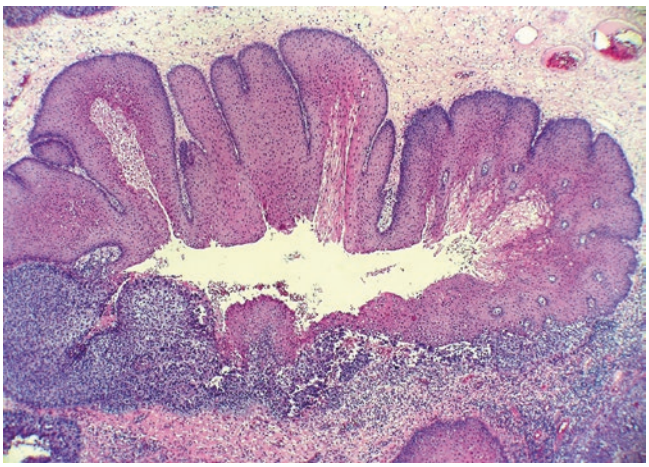

Fig. 2.30 Undifferentiated carcinoma ex-inverted papilloma: confluent nests of undifferentiated carcinoma originate from inverted papilloma at the bottom. The characteristic edematous stroma of inverted papilloma is seen at the *top* (Courtesy of Prof. C. Ereño, Bilbao, Spain)

2.8.1.4 Oncocytic (Schneiderian) Papilloma

Definition Oncocytic (Schneiderian) papilloma (OSP) is papilloma composed of both exophytic fronds and endophytic invaginations lined by multiple layers of columnar cells with oncocytic features.

Synonyms OSP is also known as "columnar" or "cylindrical" cell papilloma [115]

Epidemiology OSP is the least common type of Schneiderian papillomas. It comprises less than 5% of all sinonasal papillomas [109, 114, 132–135]. Both sexes are equally affected. Bilaterality has not been documented.

Macroscopy Tumors are in general small, although occasionally may reach various centimeters in greatest dimension.

Microscopy OSPs are composed of exophytic fronds and endophytic invaginations lined by pseudostratified or multilayered columnar cells with prominent oncocytic features. The cells have uniform hyperchromatic nuclei and abundant eosinophilic, occasionally granular cytoplasm that contains abundant mitochondria and stains for the mitochondrial enzyme cytochrome C oxidase [136]. Goblet cells are not found. Cilia may be occasionally encountered on the superficial epithelial layer. Intraepithelial microcysts containing mucin and neutrophils are usually present. These microcysts are larger than the similar structures also seen in inverted papilloma. The tumor resembles inverted papilloma in its sites of occurrence, the lateral wall of the nasal cavity and the maxillary antrum.

Differential diagnosis OSP must be distinguished from low-grade mucoepidermoid adenocarcinoma and other low-grade adenocarcinomas of the sinonasal tract. Rhinosporidiosis is the main entity to rule out in endemic countries like India and South America, as sporangia of *Rhinosporidium seeberi* may mimic the microcysts of OSP.

Treatment and prognosis The same treatment principles apply for OSP as for ISP [134]. The rate of recurrence of OSP is considered to be 36%, which is slightly lower than in inverted papilloma. The low frequency of these tumors makes it difficult to evaluate its true malignant potential, which seems to be similar to that of inverted papilloma [133]. Atypical hyperplasia and carcinoma in situ changes can be occasionally found (Fig. 2.31). Surgical excision with wide margins is the treatment of choice. Invasive squamous cell carcinoma, high-grade mucoepidermoid carcinoma, and undifferentiated carcinoma have been reported in association with oncocytic papilloma [114, 132, 137–139].

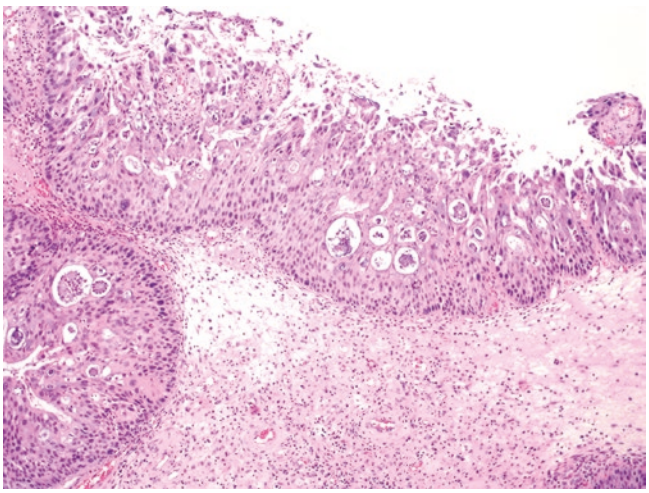

Fig. 2.31 Oncocytic papilloma with atypical cells: papillary fronds formed by columnar cells with frequent atypical nuclei, oncocytic cytoplasm, and presence of microcysts

2.8.2 Salivary Gland-Type Adenomas

2.8.2.1 Pleomorphic Adenoma

Definition Pleomorphic adenoma is a tumor composed of epithelial and modified myoepithelial cells variably mixed with mucoid, myxoid, or chondroid ground substance. Pleomorphism is architectural while cells are monomorphic.

Synonym Mixed tumor

Epidemiology Pleomorphic adenoma is the most frequent benign glandular tumor of the sinonasal region. Most of them arise on the nasal septum and the rest on the lateral nasal wall or turbinates. Origin from the maxillary antrum is rare. Most patients are between 20 and 60 years of age [140, 141].

Macroscopy Tumors are usually polypoid and may measure up to 5 cm.

Microscopy They are unencapsulated. Myoepithelial cells, often of the plasmacytoid hyaline type, tend to predominate over the glands [141].

Differential diagnosis Myoepithelioma is the main type of tumor to differentiate from pleomorphic adenoma.

Treatment and prognosis Wide surgical excision is recommended. The recurrence rate of sinonasal pleomorphic adenoma is much lower than for its counterpart in the major salivary glands [140, 142].

2.8.2.2 Other Salivary Gland-Type Adenomas

Rare examples of sinonasal oncocytoma have been reported, most arise from the nasal septum, although they may also arise from the maxillary sinus [143, 144]. Those examples that have behaved aggressively are more appropriately considered low-grade adenocarcinomas rather than adenomas [141]. Intranasal basal cell adenoma has been also documented [145]. In addition, myoepithelioma [146] and one case of sinonasal myoepithelioma transformed into myoepithelial carcinoma following multiple recurrences were reported [147].

2.8.3 Pituitary Adenomas

Definition Pituitary adenomas are benign tumors expressing the phenotype of cells of the anterior pituitary gland.

Epidemiology The rare pituitary adenomas of the sinonasal region are in most instances extensions from intrasellar tumors [148, 149]. Very unusually, they arise from ectopic pituitary tissue as tumors from the sphenoid sinus or the nasal cavity [150, 151].

Microscopy Extrasellar pituitary adenomas are histologically similar to tumors within the sella [148, 149]. The main growth patterns are diffuse, ribbonlike, papillary, and pleomorphic. Most consist of chromophobe cells (Fig. 2.32). Immunohistochemistry is required for classification according to the hormones produced [152].

Differential diagnosis Main pitfalls to avoid in pituitary adenomas presenting as sinonasal tumors include carcinoma, melanoma, paraganglioma, and olfactory neuroblastoma [152, 153].

Treatment and prognosis Complete surgical removal of pituitary adenomas is mandatory. Radiotherapy is required in incomplete resections as well as an optional dopamine agonist.

2.8.4 Primary Sinonasal Ameloblastoma

Definition Ameloblastoma (AMB) primary of the sinonasal tract is a tumor derived from remnants of odontogenic epithelium, having similar features to its gnathic counterparts (see Chap. 4) and devoided of significant osseous involvement [154].

Epidemiology Primary sinonasal AMBs are rare tumors that present in the nasal cavity and in the maxillary sinus [154–159]. The mean age of patients at presentation is about 60 years; the rate of men versus women is of 4 to 1 [154].

Macroscopy Frequently presents as a polypoid mass of variable size and rubbery consistence.

Microscopy AMB consists of centrally placed islands and nests of epithelial stellate reticulum cells, surrounded by columnar ameloblastic epithelium. The columnar epithelium presents a characteristic nuclear palisading with reverse

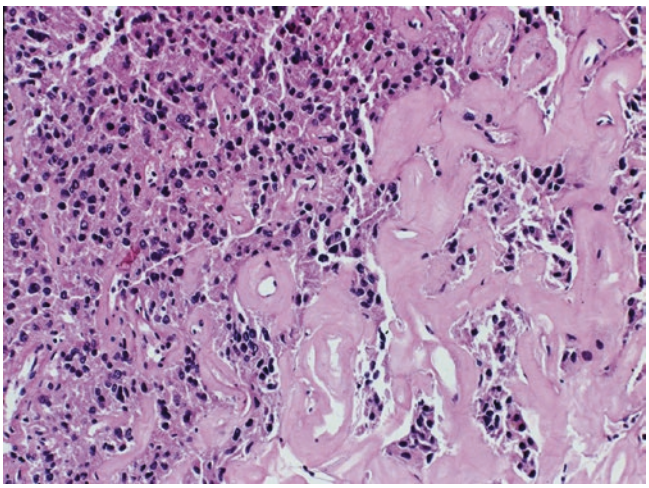

Fig. 2.32 Ectopic pituitary adenoma: cords and nests of chromophobe cells often surrounded by strands of hyaline deposits. Immunohistochemistry was positive for prolactin

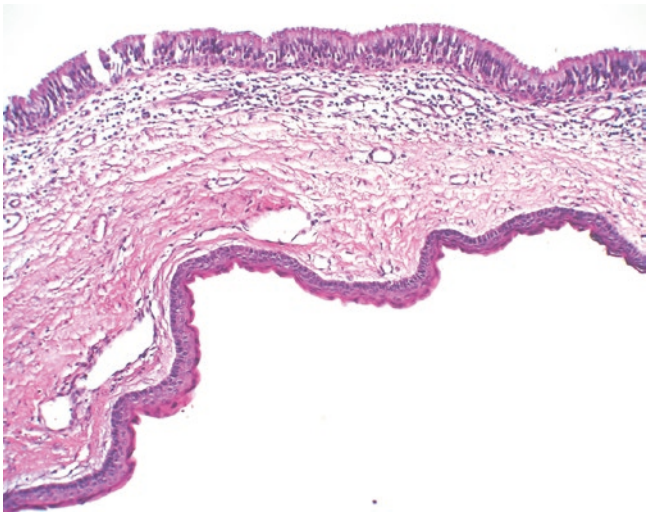

Fig. 2.33 Sinonasal odontogenic keratocyst: corrugated squamous epithelium with palisading of basal cell lines the inner surface of the cyst, while adjacent Schneiderian epithelium covers the lumen of the maxillary sinus

polarity, due to the presence of cytoplasmic subnuclear vacuoles that displace the nuclei away from the basement membrane toward the stellate reticulum. Occasional foci of squamous metaplasia may be found in the stellate reticulum. Immunostaining for calretinin is positive in over 90 % of AMB [160]. Remnant bands of covering respiratory epithelium may be found, which have been considered as a possible source of the tumor [154].

Differential diagnosis AMB must be distinguished mainly from basal cell adenoma, pleomorphic adenoma, basaloid squamous cell carcinoma, adenoid cystic carcinoma, and biphasic synovial sarcoma. Unicystic AMB must be told apart from odontogenic keratocyst (Fig. 2.33).

Treatment and prognosis Excellent results are usually achieved after surgical excision with margins free of tumor. Ameloblastoma is a benign, but locally aggressive tumor that requires long-term follow-up to control the risk of recurrence.

2.9 Benign Sinonasal Soft Tissue and Neural Neoplasms

2.9.1 Hemangiomas

Hemangiomas of the upper respiratory tract may be of the lobular capillary, cavernous or venous types [161].

2.9.1.1 Lobular Capillary Hemangioma

Definition Lobular capillary hemangioma (LCH) is a benign proliferation of capillary blood vessels adopting a lobular configuration [161].

Synonym Pyogenic granuloma.

Epidemiology and pathogenesis The sinonasal mucosa accounts for 29 % of the LCH of the upper aerodigestive tract. Although the cause of LCH is unknown, it has an association with trauma, pregnancy, and oral contraceptives [161].

Clinical features The nasal and the vestibular septum are typical sites for LCH. Nasal obstruction and epistaxis are the most common early symptoms.

Macroscopy LCHs present as red-colored polypoid formations with a collar-like invagination around its basis. They measure up to 1.5–2 cm.

Microscopy LCH consists of lobular arrangements of blood-filled capillaries separated by loose connective tissue. The blood supply is provided by a feeder vessel with branches ramifying to the lobules (Fig. 2.34). Nasal LCHs are covered often by squamous metaplastic epithelium. Superficial stromal edema and ulceration are common accompanying features. At the ulcerated zone, conventional granulation tissue may be found.

Differential diagnosis LCH should be distinguished mainly from conventional polypoid granulation tissue, which has a distinctive radial distribution of capillary blood vessels and lacks lobular arrangements. Other differential diagnoses include papillary endothelial hyperplasia, angiomatoid polyp, bacillary angiomatosis, glomangiopericytoma, Kaposi's sarcoma, and angiosarcoma.

Treatment and prognosis After complete excision, recurrences of LCH are rare.

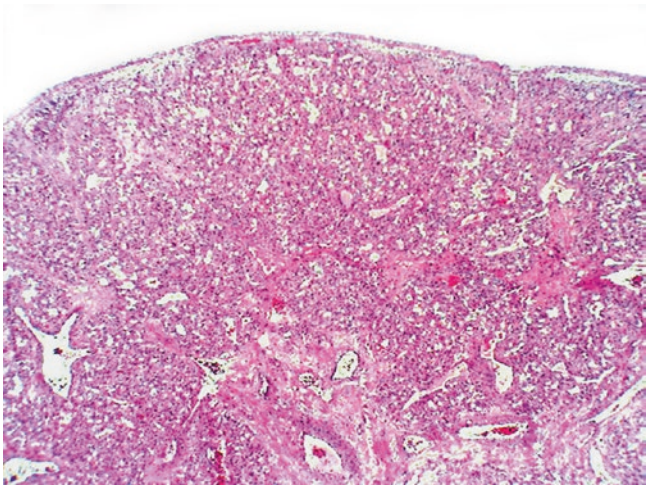

Fig. 2.34 Lobular capillary hemangioma: lobular arrangements of blood-filled capillaries separated by loose connective tissue. The blood supply is provided by a feeder vessel at the base of the lesion

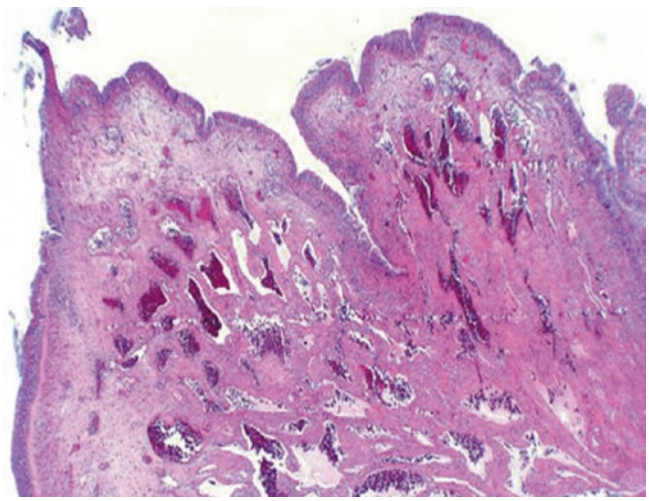

Fig. 2.35 Cavernous hemangioma: multiple, thin-walled, markedly dilated blood vessels separated by fibrous stroma

2.9.1.2 Cavernous Hemangioma

Definition Cavernous hemangiomas are neoplastic proliferations of thin-walled blood vessels with marked luminal dilatation.

Epidemiology Cavernous hemangiomas of the sinonasal tract are commonly intraosseous or involve the turbinates or the lateral nasal wall. They occur mainly in men in the fifth decade of life [163].

Microscopy As elsewhere in the body, they are composed of multiple, large thin-walled, dilated blood vessels separated by fibrous stroma (Fig. 2.35).

Differential diagnosis Cavernous hemangioma of the sinonasal tract has to be distinguished from venous hemangioma, a rare vascular tumor in this location being composed of thick-walled veins with abundant smooth muscle. Other differential diagnoses include sporadic telangiectasia, hereditary telangiectasia (Osler-Weber-Rendu syndrome), vascular malformations, angiomatoid polyps, and papillary endothelial hyperplasia.

Treatment and prognosis Complete removal is the treatment of choice whenever possible. Recurrences occur after incomplete resection.

2.9.2 Fibroma and Fibrous Histiocytoma

2.9.2.1 Fibroma

Definition Sinonasal fibroma is a benign nodular proliferation composed of fibroblasts and collagen.

Epidemiology and pathogenesis Sinonasal fibromas are uncommon lesions, mainly seen in the nasal cavity. Their distinction from reactive fibrosis may be controversial. A few true examples reported in the past [164] continue to be recognized as such nowadays [165].

Macroscopy Sinonasal fibromas are small nodules of polypoid configuration that may measure up to 1 cm.

Microscopy They consist of a proliferation of fibroblastic spindle cells intermingled with bands of collagen. Cytoplasms are inconspicuous and nuclei are bland, although on occasions may depict slight pleomorphism. Mitoses are minimal or absent (Fig. 2.36).

Differential diagnosis Sinonasal fibromas must be distinguished from other benign sinonasal myofibroblastic proliferations. True sinonasal fibromas are only immunoreactive for vimentin.

Treatment and prognosis Complete removal is curative.

2.9.2.2 Fibrous Histiocytoma

Definition Benign fibrous histiocytoma (BFH) is a benign nodular proliferation composed of fibrohistiocytes and collagen.

Epidemiology Since the advent of immunohistochemistry, tumors typed as sinonasal BFHs have become an exceedingly rare entity.

Clinical features BFH presents as a yellow-tan nodule or polyp, most commonly causing nasal obstruction or bleeding [165].

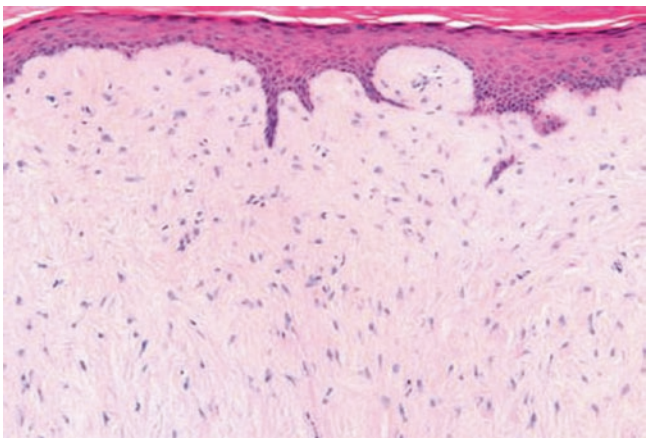

Fig. 2.36 Fibroma of the nasal vestibule: fibroblastic dermal proliferation covered by hyperplastic squamous epithelium

Microscopy BFH is composed of spindle-shaped cells arranged in a storiform pattern admixed with histiocytic cells and multinucleated giant cells.

Differential diagnosis The distinction from other benign sinonasal spindle cell proliferations is largely based on the immunohistochemical findings. BFH is immunoreactive for vimentin and for markers of macrophages such as CD68.

Treatment and prognosis Benign fibrous histiocytoma may recur if incompletely excised.

2.9.3 Leiomyoma and Myofibroma

2.9.3.1 Leiomyoma

Definition Leiomyoma is a benign nodular proliferation composed of smooth muscle cells.

Epidemiology Sinonasal leiomyomas are rare tumors. They occur in adults and preferentially involve the nasal cavities [166].

Clinical features Nonspecific symptoms of nasal obstruction [166]

Microscopy Their morphologic and immunohistochemical profiles are identical to those of leiomyomas of other sites. An origin from blood vessel walls has been postulated. Leiomyomas usually express smooth muscle actin, muscle-specific actin, and desmin.

Differential diagnosis The distinction of leiomyoma from myofibroma is mainly based on immunohistochemical features and on the presence in the latter of a hemangiopericytoma-like vascular network, which is lacking in the former (see also Sect. 2.9.3.2). The distinction of leiomyoma from leiomyosarcoma is based on the absence of atypia and mitoses in the former.

Treatment and prognosis Complete removal of leiomyomas is curative. Huang and Antonescu have proposed to separate a category of smooth muscle tumors of uncertain malignant potential, characterized by the presence of 1–4 mitotic figures/10 high-power fields, which tend to pursue a more aggressive behavior than leiomyoma [167].

2.9.3.2 Myofibroma

Definition Myofibromas are solitary nodular proliferations composed of benign myofibroblasts. Myofibromatosis is the term for the presence of multiple myofibromas.

Epidemiology Most myofibromas are seen in young children. Sinonasal myofibromas are very rare [168].

Microscopy Myofibromas are made up of interlacing fascicles of plump spindle cells, with weakly eosinophilic cytoplasm and bland, round to oval nuclei. The cellular density may vary between the different areas. In the densely cellular areas, the blood vessels may show hemangiopericytoma-like features [169]. Myofibromas express smooth muscle actin and muscle-specific actin and are usually negative for desmin and other markers [170].

Differential diagnoses Sinonasal myofibromas must be differentiated from leiomyomas, as well as from glomangiopericytoma and low-grade myofibroblastic sarcoma.

Treatment and prognosis Complete excision of myofibromas is the recommended treatment. Incompletely removed tumors may recur.

2.9.4 Schwannoma, Neurofibroma, and Neurothekeoma

2.9.4.1 Schwannoma

Definition Schwannoma is a benign tumor, composed of differentiated, neoplastic Schwann cells [162].

Synonym Neurilemmoma

Epidemiology About 4 % of schwannomas of the head and neck region arise in the sinonasal tract [163]. Schwannomas of the sinonasal mucosa are usually not associated with type 2 neurofibromatosis.

Clinical aspects They usually present as polypoid lesions involving the nasal cavity and/or a paranasal sinus, with nonspecific symptoms of obstruction, compression, or extension in the surrounding structures [162].

Microscopy Histologically, the tumor is composed of elongated wavy-shaped monomorphic spindle cells, with eosinophilic cytoplasm and oval nucleus. Antoni type A and type B areas usually coexist within the lesion, and nuclear palisading may be present. Focal degenerative nuclear atypia has been described, while mitotic activity is absent to low. A consistently reported feature of sinonasal schwannomas is the lack of tumor encapsulation which determines an apparently infiltrative growth pattern. Immunohistochemically, sinonasal schwannoma is intensely reactive for S-100 protein and also for vimentin [171].

Differential diagnosis It includes neurofibroma and other spindle cell lesions of the sinonasal mucosa, like angiofibroma, solitary fibrous tumor, and leiomyoma. Particular care should be taken in evaluating cellular schwannomas with a predominance of Antoni type A areas, which should not be confused with malignant spindle cell neoplasms, like malignant peripheral nerve sheath tumor, fibrosarcoma, leiomyosarcoma, and spindle cell melanoma.

Treatment and prognosis Complete removal of sinonasal schwannomas is curative.

2.9.4.2 Neurofibroma

Definition Neurofibroma is a benign tumor of peripheral nerve sheath phenotype with mixed cellular components including Schwann cells, perineural hybrid cells, and intraneural fibroblasts [162].

Epidemiology Neurofibromas of the sinonasal mucosa are rare, usually solitary, and sporadic, not associated with multiple neurofibromatosis, type 1 (von Recklinghausen's disease).

Etiology and pathogenesis Experimental induction of peripheral nerve sheath tumors of the Gasserian ganglion and the orbital and maxillary regions has been achieved after prenatal and postnatal exposure to ethylnitrosourea [172].

Microscopy Neurofibromas appear as unencapsulated lesions composed of a mixture of Schwann cells and fibroblasts embedded in a predominately myxoid stroma. Residual neurites may be found at the center of the lesion [162, 173].

Differential diagnosis Due to the overlap of the histological features, it may be difficult to differentiate neurofibroma from schwannomas of the sinonasal mucosa. Neurofibroma should be distinguished also from myxoma, which is S-100 protein negative.

Treatment and prognosis Complete removal is the treatment of choice for solitary neurofibroma.

2.9.4.3 Neurothekeoma

Definition Neurothekeoma is a rare benign neoplastic proliferation derived from nerve sheaths and arranged in lobules separated by fibrous septa.

Epidemiology The tumor may be seen anywhere in the body. One neurothekeoma of the paranasal sinuses has been reported in a 3-year-old boy [174].

Microscopy A syncytium of spindle and epithelioid-like cells often admixed with osteoclastoid cells and occasional myxomatous areas appears surrounded by fibrous septations that confer the lobular pattern. Tumor cells are usually positive for vimentin and glial fibrillary acidic protein, while reactivity for S-100 protein is variable. Cytokeratin markers are constantly negative.

Treatment and prognosis Complete resection is curative.

2.9.5 Meningioma

Definition Meningioma is a tumor derived from meningothelial cells.

Epidemiology Meningiomas of the sinonasal tract may extend directly from the central nervous system or arise from ectopic extracranial tissue. Although rare, they are more commonly seen in the orbit, ear, and skin of the head and neck than in the sinonasal tract. Sinonasal meningiomas tend to occur in younger patients than intracranial meningiomas [162, 175].

Microscopy Histologically, they are similar to meningiomas elsewhere, being the meningothelial type the most frequent. Aggressive variants of meningioma may be seen mainly within the group of primary intracranial sinonasal meningiomas.

Treatment and prognosis Surgical removal with margins free of tumor is mandatory. Extracraneal sinonasal meningiomas have usually an excellent prognosis. Primary intracranial sinonasal meningiomas require aggressive surgery [176].

2.9.6 Juvenile Angiofibroma

Definition Juvenile angiofibroma (JAF) is a benign and richly vascularized fibrous neoplasm that arises in the posterior nasal cavity and neighboring nasopharynx in young males [177].

Synonym Nasopharyngeal angiofibroma

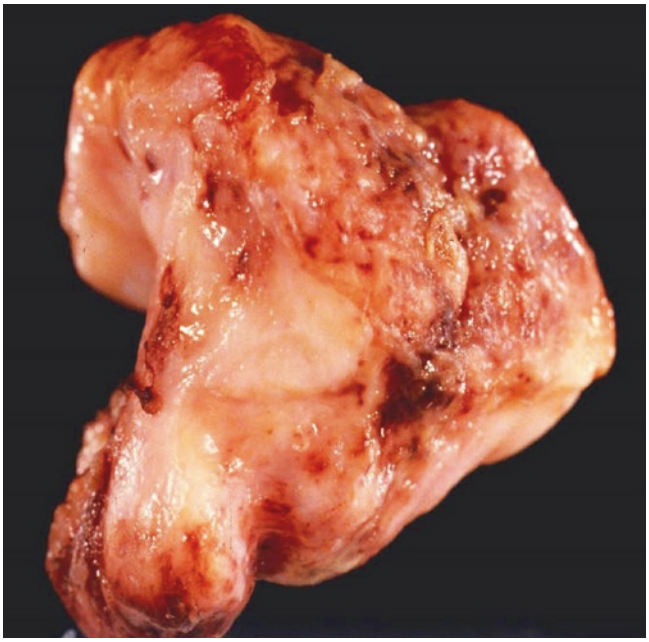

Fig. 2.37 Juvenile angiofibroma: well-demarcated polypoid formation with white-red cut surface and a lobulated contour

Epidemiology JAF arises in the confluence of the posterolateral nasal wall and the lateral nasopharynx and occurs nearly always in young males [177, 178]. Although JAFs almost invariably arise in the nasopharynx and often extend secondarily to the sinonasal region, about 1.5 % of angiofibromas involve the nasal cavity alone [179].

Clinical aspects Although benign JAF has a tendency to recur and is locally destructive, causing pressure necrosis of adjacent soft tissue and bone, it may occasionally extend into paranasal sinuses, into the orbit, and intracranially.

Macroscopy JAFs are sessile or polypoid lobulated formations of rubbery consistency, well demarcated but devoid of a capsule (Fig. 2.37). The cut surface is whitish and a rich vascularization is not always apparent.

Microscopy JAFs are composed of vascular and fibrous elements in varying proportions. The vessels in the superficial portions of the tumor are mainly gaping capillaries which may become compressed with increasing stromal fibrosis. Thick-walled vessels without elastic membranes and with irregular, incomplete, or absent muscle coats and focal intimal thickenings are usually present in the deeper portions of the tumor. These vessels resemble those normally seen in the submucosa of the nasal conchae. The vascular elements are embedded in fibrous tissue which varies in cellularity and collagenization. Stellate fibroblast-like cells are often present close to the blood vessels. The tumor cells express vimentin and the vascular endothelial cells CD31 and CD34. Pericytes

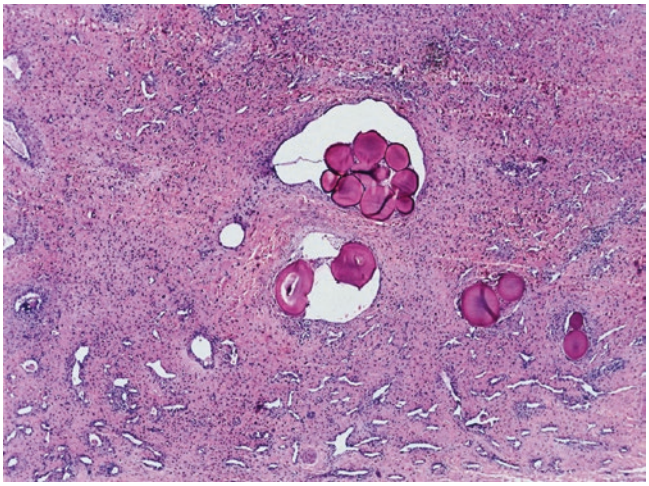

Fig. 2.38 Juvenile angiofibroma: blood vessels embedded in fibrous tissue showing intravascular microembolization, a therapeutic procedure before surgery

that surround parts of small blood vessels stain for smooth muscle actin. The nuclei of fibroblastic cells of juvenile angiofibroma are strongly positive for testosterone receptors [180]. Ultrastructurally the nuclei of angiofibroma contain characteristic dense granules [181]. Occasionally, the fibroblasts may exhibit cytologic atypia, and some of these cells may be multinucleated, but mitosis are rare. Mast cells may be numerous. There may be focal thrombosis, hemorrhage, and chronic inflammatory reaction. With the advent of preoperative selective embolization, iatrogenic emboli may be encountered in resected specimens (Fig. 2.38) [182]. For further reading on this tumor, see Chap. 6.

2.10 Borderline Soft Tissue Neoplasms

2.10.1 Glomangiopericytoma

Definition Glomangiopericytoma (GPC) is a sinonasal tumor with perivascular myoid phenotype, showing features of glomus and pericytes [183, 184]. It is characterized by the proliferation of oval, polyhedral, or spindle-shaped cells arranged about vascular channels provided with a single layer of endothelial cells [185, 186].

Synonyms Hemangiopericytoma-like tumor, sinonasal hemangiopericytoma, and sinonasal glomus tumor

Epidemiology GPCs arise in the nasal cavity as well as in the paranasal sinuses. They show a slight predilection for females. Most of them develop in the seventh decade of life.

Clinical features Nasal obstruction, epistaxis, and difficulty of breathing are usual presenting symptoms. A rare association with osteomalacia has been recently reported [187, 188].

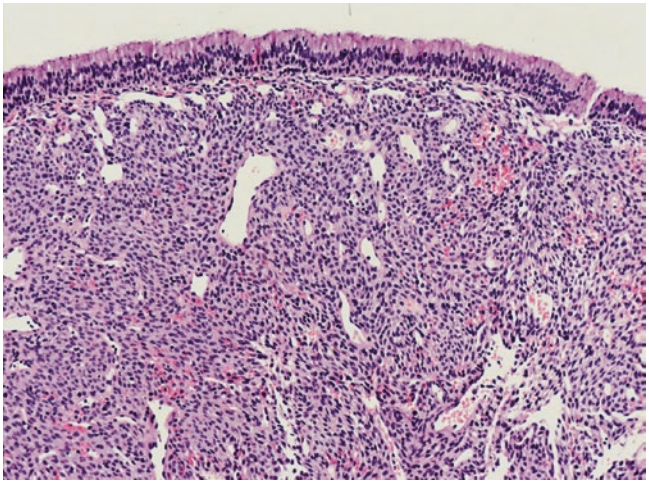

Fig. 2.39 Glomangiopericytoma: rich interconnection of thin-walled blood vessels surrounded by uniform spindle-shaped cells with oval or elongated bland nuclei and pale cytoplasm

Macroscopy GPCs are usually polypoid measuring in average 3 cm and may reach up to 8 cm in size [189].

Microscopy GPC contains numerous thin-walled blood vessels that often may adopt a staghorn configuration and on occasions are surrounded by prominent hyalinization. The tumor cells, typically arranged around the blood vessels, are of uniform size with regular oval or elongated nuclei and pale cytoplasm; mitoses are very rare and without atypia (Fig. 2.39). The cells may also be arranged in short haphazard fascicles or in sheets of closely packed cells containing compressed capillaries. Areas of poor cellularity, myxoid change, and fibrosis are not uncommon. The tumor cells are enmeshed by collagen type IV fibers and entirely situated outside the capillaries which are lined by a single-layer of normal-looking endothelium.

Immunohistochemistry GPCs show diffuse reactivity for actins, factor XIIIA, and vimentin, lacking diffuse staining for other markers. GPC vessels stain for muscle-specific actin [184].

Differential diagnosis It includes lobular capillary hemangioma, solitary fibrous tumor, leiomyoma, myofibroblastic low-grade sarcoma, synovial sarcoma, and leiomyosarcoma [184]. In GPC the tumor cells are enmeshed by collagen type IV fibers; this feature, well shown by reticulin stain or by anti-collagen IV antibodies, helps to distinguish the tumor from angiosarcoma [184]. In due clinical settings, other differential diagnoses to consider are Kaposi's sarcoma and phosphaturic mesenchymal tumor.

Treatment and prognosis Complete surgical removal is the recommended treatment for GPCs achieving an overall 5-year survival of about 90 %; recurrence may occur many years after initial surgery and may rarely metastasize [184, 189]. Aggressive GPCs (malignant glomangiopericytomas) are very uncommon and often show size larger than 5 cm, bone invasion, nuclear atypia, necrosis, increased mitotic number, and proliferation index higher than 10 % [184, 189, 190].

2.10.2 Desmoid-Type Fibromatosis

Definition Desmoid-type fibromatosis (DTF) is a nonmetastasizing unencapsulated myofibroblastic proliferation that has a tendency for local invasion and recurrence.

Synonyms Desmoid tumor, extra-abdominal fibromatosis, and aggressive fibromatosis

Epidemiology DTF rarely arises in the sinonasal tract [164, 191].

Microscopy DTF is composed of interlacing fascicles of bland spindle-shaped myofibroblasts, in a collagenous background of parallel-running fibers. Focal myxoid areas may be found. Immunohistochemistry: Actins and vimentin are positive while desmin only occasionally. Beta-catenin presents intranuclear localization [192].

Differential diagnosis DTF must be distinguished from fibrosarcoma, solitary fibrous tumor, fibroma, and reactive types of fibrosis.

Treatment and prognosis Complete surgical removal is the treatment of choice; positive or close (<1 mm) resection margins are predictive of recurrences [193]. DTFs of the sinonasal tract tend to have lower recurrence rates than those arising in other locations [164].

2.10.3 Solitary Fibrous Tumor

Definition Solitary fibrous tumor (SFT) of the nose and paranasal sinuses is a fibroblastic proliferation with variable cellularity and vascularity having features identical to those of SFT of the pleura [194–196].

Epidemiology The sinonasal region is the second most common location for SFTs of the upper aerodigestive tract, only preceded by the oral cavity. SFTs mainly develop in adults, with slight predominance in women [194–198].

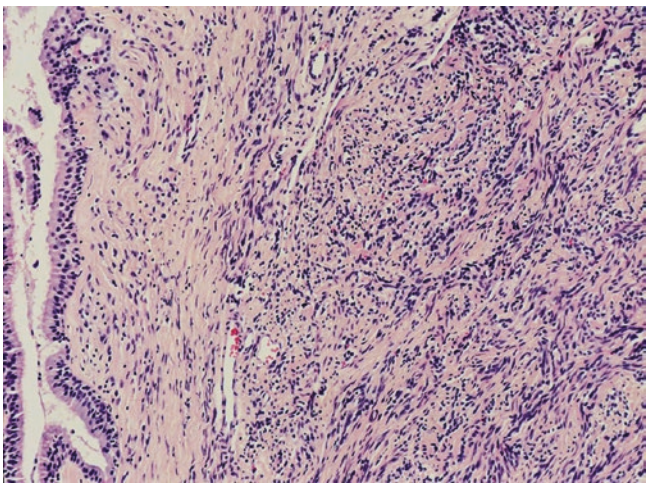

Fig. 2.40 Solitary fibrous tumor: fibroblastic proliferation, collagen production, and variably dilated blood vessels. Identical features to the pleural counterpart

Clinical features Nasal obstruction is the most common presenting symptom.

Macroscopy Sinonasal SFTs are polypoid to nodular formations of firm consistency that usually measure several centimeters [199].

Microscopy SFTs are characterized by a disorderly proliferation of small spindle cells with bland nuclei and inconspicuous cytoplasms that produce abundant amounts of collagen (Fig. 2.40). The proportion of cells and collagen may vary considerably between the different areas. Mitoses are quite uncommon; growth is slow and expansile. Usually vascularization is prominent with blood vessels forming thick collagenized walls; in other areas hemangiopericytoma-like vessels may be found. Mucosal ulceration, necrosis, and invasion are usually absent. Nevertheless, recent examples of malignant SFTs of the upper aerodigestive tract have been reported [200].

Immunohistochemistry SFTs are immunoreactive for CD34, BCL2, CD99, and vimentin [195].

Differential diagnosis The main differential diagnoses of SFT are sinonasal glomangiopericytoma and juvenile angiofibroma. Also, other benign and malignant spindle cell tumors must be distinguished from SFT.

Treatment and prognosis Fully excised SFTs with free margins do not recur. This is the case for sinonasal polypoid SFTs. Broad-based SFTs are difficult to remove and prone to recur. Progression of recurrences is in most cases very slow [199]. The very rare examples of malignant SFT behave aggressively [200].

2.11 Malignant Neoplasms

Malignant sinonasal tumors comprise less than 1 % of all cancers seen in humans and represent about 3 % of all malignancies of the head and neck region [201, 202]. Despite the low rate of malignancy arising in the sinonasal tract, a great variety of histological types of tumors may be found [121, 122]. The advent of electron microscopy and the more recent advances in immunohistochemistry, and in gene technologies, have further refined the criteria for their correct recognition [203], which recent comprehensive publications have made available worldwide [204, 205].

Geographical differences in the relative frequency of certain histological types of malignant sinonasal tumors may be related to variations in the exposure to carcinogens [206]. In Table 2.3, the histological types of malignant sinonasal tumors collected at the Hospital Clinic of the University of Barcelona from 1976 to 2005 are presented in decreasing order of frequency. Keratinizing squamous cell carcinoma, undifferentiated carcinoma, non-keratinizing squamous cell carcinoma, malignant lymphoma, malignant mucosal melanoma, intestinal-type adenocarcinoma, adenoid cystic carcinoma, low-grade adenocarcinomas, and olfactory neuroblastoma are the most frequent histological types. Most common sinonasal carcinogens in humans are cigarette smoking, high-risk HPV, radiation therapy, nickel, chromates, wood dust, boot and shoe dusts, and isopropyl alcohol.

A practical way to start typing malignant sinonasal tumors is to separate them into large and small cell categories. Among the large cell malignant tumors, the most common types are squamous cell carcinoma, non-keratinizing squamous cell carcinoma, malignant mucosal melanoma, intestinal-type adenocarcinoma, and low-grade adenocarcinomas. Sinononasal undifferentiated carcinoma, malignant lymphoma, adenoid cystic carcinoma, and olfactory neuroblastoma are among the most common small cell tumors. Large cell tumors account for approximately 75 % of the malignant sinonasal tumors and the small cell tumors for the remaining 25 %.

For staging of malignant sinonasal tumors, Ref. [207] is recommended, as well as Tables 13 and 14 in Chap. 17.

2.11.1 Keratinizing Squamous Cell Carcinoma

Definition Keratinizing squamous cell carcinoma (KSCC) is a malignant epithelial neoplasm originating from the mucosal epithelium of the nasal cavities or paranasal sinuses with histological evidence of squamous differentiation and keratin production.

Table 2.3 Malignant sinonasal tumors at the Hospital Clínic, University Barcelona Medical School

Histological	Frequency		Men		Women		Mean	Age
Type of tumor	Nr %		Nr %		Nr %		Age	Range
Keratinizing SCC	54	27	38	70	16	30	64	39–87
Undifferentiated carcinoma	26	13	19	73	7	27	60	41–87
Non-keratinizing SCC	19	9.5	15	79	4	21	59	26–84
Malignant lymphoma	19	9.5	15	79	4	21	59	9–89
Malignant melanoma	14	7	7	50	7	50	69	56–89
High-grade adenocarcinoma	13	7	10	77	3	23	59	16–81
Adenoid cystic carcinoma	11	5	7	64	4	36	58	22–69
Low-grade adenocarcinoma	10	5	4	40	6	60	64	28–92
Olfactory neuroblastoma	7	3	3	43	4	57	36	2–67
Mucoepidermoid carcinoma	4	2	3	75	1	25	55	50–61
Malignant fibrous histiocytoma	4	2	3	75	1	25	56	35–65
Plasmacytoma	4	2	3	75	1	25	51	50–65
Rhabdomyosarcoma	4	2	2	50	2	50	30	8–51
Malignant schwannoma	3	1.5	1	33	2	67	57	27–70
Adenosquamous carcinoma	2	1	2	100	–	–	66	61–71
Myoepithelial carcinoma	2	1	2	100	–	–	47	29–66
Kaposi's sarcoma	2	1	2	100	–	–	37	34–40
Teratocarcinosarcoma	1	0.5	1	100	–	–	76	–
Ewing's sarcoma (PNET)	1	0.5	–	–	1	100	23	–
Total	200	100	137	69	63	31	58	2–92

Synonyms Conventional squamous cell carcinoma and squamous cell carcinoma NOS

Epidemiology At the nasal vestibule, KSCC is the most common malignancy [208–210]. Due to early recognition and easy access to treatment, they usually have more favorable prognosis than their counterpart of the sinonasal region.

Sinonasal KSCC comprises up to 45–50 % of the malignant tumors of this region in several series [211, 212]. They predominate in males and the great majority are seen in patients aged over 50 years. The maxillary antrum, the lateral nasal wall, and the ethmoid sinuses are the most common sites (Fig. 2.41) [213]. Other locations such as the nasal septum and the nasal floor are less usual; the frontal and sphenoid sinuses are rarely involved. These tumors grow by local extension, infiltrating the neighboring structures, but lymph node metastases are rare [214].

Etiology and pathogenesis The occupational epidemiology of KSCC has been strongly related to exposure to nickel [215–218] and to a lesser extent to chromium, isopropyl alcohol, and radium [219]. As in other territories of the respiratory tract, a definite association between sinonasal KSCC and cigarette smoking has been documented [220, 221]. Chronic sinonasal inflammation is considered as a predisposing factor. A case of carcinoma of the maxillary antrum after thorotrast exposure has been reported [222].

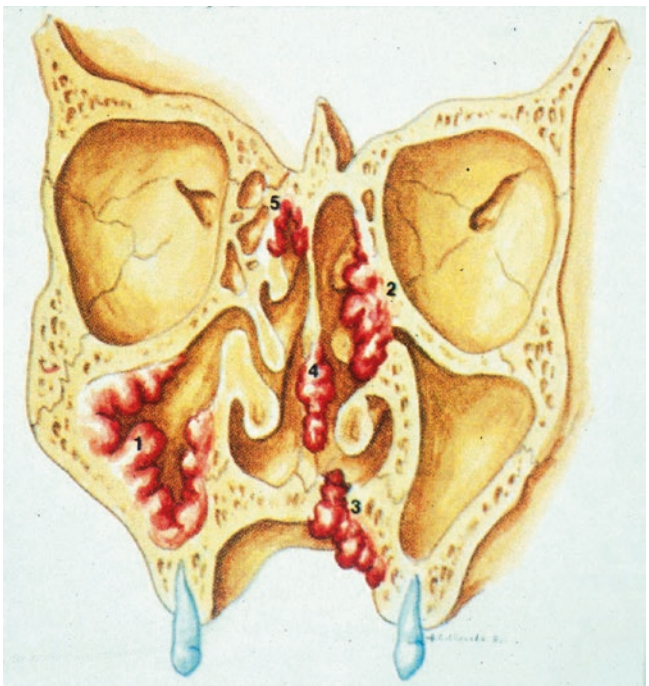

Fig. 2.41 Main locations of sinonasal malignant tumors: *1* maxillary sinus, *2* ethmoid and lateral wall, *3* nasopalatine septum, *4* nasal septum, and *5* roof of the nasal cavity (Courtesy of Prof. J Traserra, Barcelona, Spain. Ref: [213])

Nitrosamines and to a lesser extent formaldehyde are strong nasal carcinogens in laboratory rodents [223, 224].

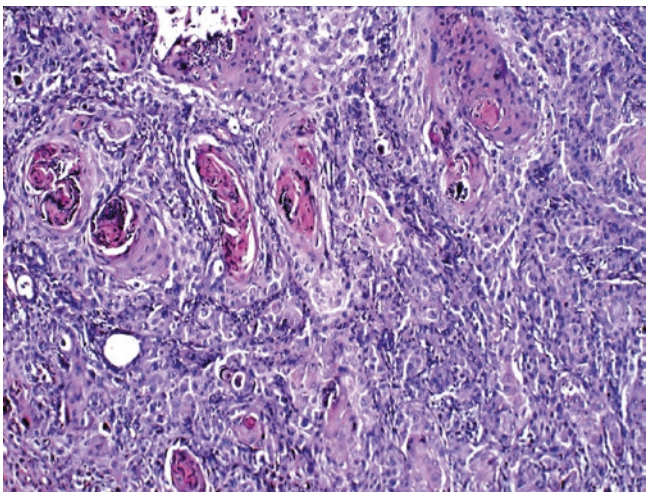

Fig. 2.42 Keratinizing squamous cell carcinoma: proliferation of malignant squamous cells with keratin pearls

Macroscopy Sinonasal KSCCs display gross features similar to those of other upper aerodigestive tract territories.

Microscopy KSCCs originate in the respiratory sinonasal mucosa from areas of preexisting squamous metaplasia and manifest the same range of histological appearances as those arising in other sites. They are characterized by the proliferation of malignant squamous epithelial cells with keratin production and intercellular bridges (Fig. 2.42). Malignancy is graded according to the degree of differentiation, cellular pleomorphism, and mitotic activity. They are divided into well-differentiated, moderately differentiated, and poorly differentiated forms. Most KSCC of the sinonasal tract present as moderately or poorly differentiated tumors. Special types of squamous cell carcinoma (SCC), such as verrucous carcinoma [225], spindle cell carcinoma [226, 227], basaloid squamous cell carcinoma [228, 229], and adenosquamous carcinoma [230, 231], are occasionally found in the sinonasal tract.

Immunohistochemistry and in situ hybridization The prototypical KSCC is p53 positive, p16 negative, and high-risk HPV negative.

Differential diagnosis KSCC has to be mainly differentiated from NKSCC and from other special types of SCC. Well-differentiated carcinomas are uncommon in this territory and when encountered need to be differentiated from pseudoepitheliomatous types of hyperplasia and from verrucous carcinoma.

Treatment and prognosis Complete surgical resection combined with radiotherapy and optional chemotherapy is recommended [232, 233]. Regional lymph node involvement is seen in about 17 % of sinonasal squamous cell carcinomas and distant metastases in about 1.5 % [214]. For neoplasms circumscribed to the nasal cavity, the 5-year survival is slightly above 50 % [234], whereas in neoplasms of the maxillary antrum, the 5-year survival may be as low as 25 % [220].

2.11.2 Non-keratinizing Squamous Cell Carcinoma

Definition Non-keratinizing squamous cell carcinoma (NKSCC) is a malignant epithelial neoplasm originating from the mucosal epithelium of the nasal cavities or paranasal sinuses with squamous differentiation and lack of histological evidence of keratin production.

Synonyms Cylindrical cell carcinoma, transitional cell carcinoma, and Schneiderian carcinoma. The name cylindrical cell carcinoma was first coined by Ringertz in 1938 [235]; it was the preferred term in the 1991 WHO classification [121], until the 2005 WHO classification recommended non-keratinizing squamous cell carcinoma as the most appropriate term [202]

Etiology and pathogenesis NKSCC is etiopathogenetically related with HPV [236–238]. In SCC with biologically active HPV, inactivation of the Rb protein by the HPV E7 protein leads to p16 overexpression because Rb normally represses the transcription of p16. HPV-positive HNSCC also expresses the oncoprotein E6 that binds and degrades wild-type p53 protein [238]. Unlike carcinomas of the uterine cervix, where HPV infection and *TP53* mutations are mutually exclusive events, HPV infection and *TP53* overexpression sometimes occur together in HNSCC, but disruptive *TP53* gene mutations are not encountered in HPV-positive carcinomas [239, 240].

Epidemiology NKSCC affects males more often than women, at younger ages than keratinizing carcinoma, between 40 and 60 years of age, in patients that usually do not drink alcohol nor smoke tobacco [241, 242]. Twenty percent of sinonasal SCC is HPV positive and shows non-keratinizing histological features [236–238]. Eighty-two percent of them were type 16, 12 % types 31/33, and 6 % type 18 [243].

Macroscopy The tumors grow in most cases as exophytic masses showing either corrugated or smooth surface. They may arise from the antrum, the lateral nasal wall, or the ethmoid, being the antrum the most frequent site. They may occur concomitantly with other nonneoplastic polypoid formations.

Microscopy Main histological features of NKSCC are the presence of islands and interlaced cords of squamous epithelial cells with the lack of maturation, absence of keratinization, and moderate to significant degree of atypia (Fig. 2.43).

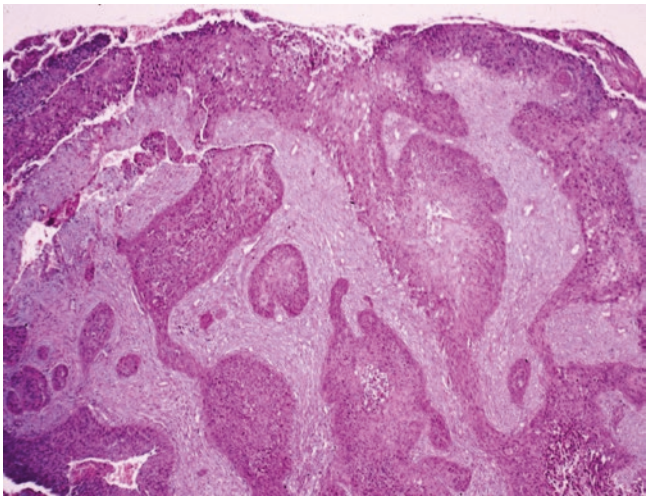

Fig. 2.43 Non-keratinizing squamous cell carcinoma: islands and interlaced cords of squamous epithelial cells with poor maturation, absence of keratinization, and moderate to significant atypia

The tumor invades into the underlying fibrosed tissue with an expanding, smooth and lobulated, generally well-delineated border, although foci of infiltration by irregular small nests or strands may be seen. NKSCC is usually moderately or poorly differentiated, being in the latter case difficult to recognize as SCC. Occasionally, some degree of keratinization may be seen. When keratinization is conspicuous, there may be microscopic overlap with KSCC [202]. Some of these tumors may also overlap with the papillary, basaloid SCC, adenosquamous [244], and lymphoepithelial-like types of SCC.

The papillary variant of NKSCC is composed of papillary fronds, thick ribbons, and polystratified masses of commonly cylindrical cells that give rise quite often to invaginations of the surface epithelium [245]. The tumor cells have a tendency to form palisade arrangements perpendicular to the underlying basement membrane (Fig. 2.44). The nuclei are atypical and show increased mitotic activity, as well as abnormal mitotic figures. The basement membrane remains in most cases conspicuous, despite stromal infiltration, which should not be regarded as carcinoma in situ. Recent studies have shown that not only the papillary type but most of the variants of head and neck SCC may be associated with high-risk HPV [244, 246–248].

Immunohistochemistry HPV-positive NKSCCs are immunohistochemically positive for p16 protein in a diffuse and intense fashion (Fig. 2.45). Positivity must be nuclear, although cytoplasmic positivity is also seen [236–238].

Molecular diagnosis HPV detection may be achieved through various techniques [203], such as DNA-PCR [236] or DNA-ISH (Fig. 2.46) [237], as well as mRNA-PCR [238] or mRNA-ISH assays [249]; the latter have gained increasing relevance as it is not the presence of the virus alone but its transcriptional activity what confers pathogenicity. For a more detailed description of these methods, the reader is referred to Chap. 6.

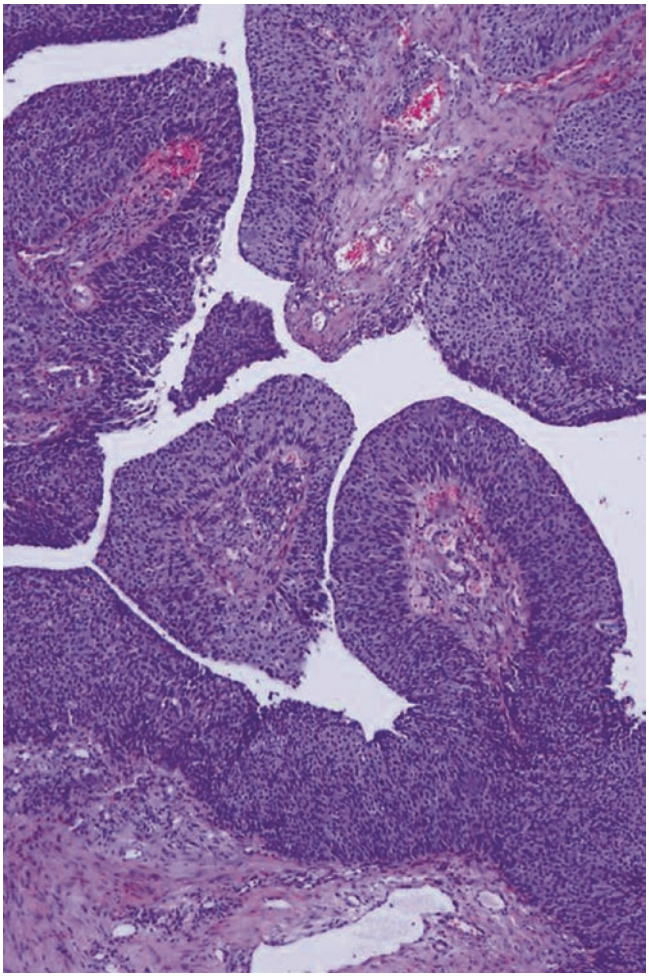

Fig. 2.44 Papillary non-keratinizing squamous cell carcinoma: papillary fronds usually composed of cylindrical cells, with tendency to form palisade arrangements perpendicular to the basement membrane

Differential diagnosis In addition to rule out KSCC and the different sinonasal SCCs that are negative for HPV, it includes the Schneiderian papillomas of the inverted and oncocytic types, especially when they have concomitant carcinomatous changes. Both types of papilloma lack the atypical cellularity constantly seen in NKSCC. When Schneiderian papillomas coexist with NKSCC, or with other types of carcinoma, the two components appear usually demarcated one from the other although in contiguity. When the invaginating crypts of an inverted papilloma are filled with the cords and ribbons of a keratinizing or non-keratinizing SCC, the lesion represents a conventional squamous cell carcinoma arising in an inverted papilloma, which implies a worse prognosis than that of NKSCC.

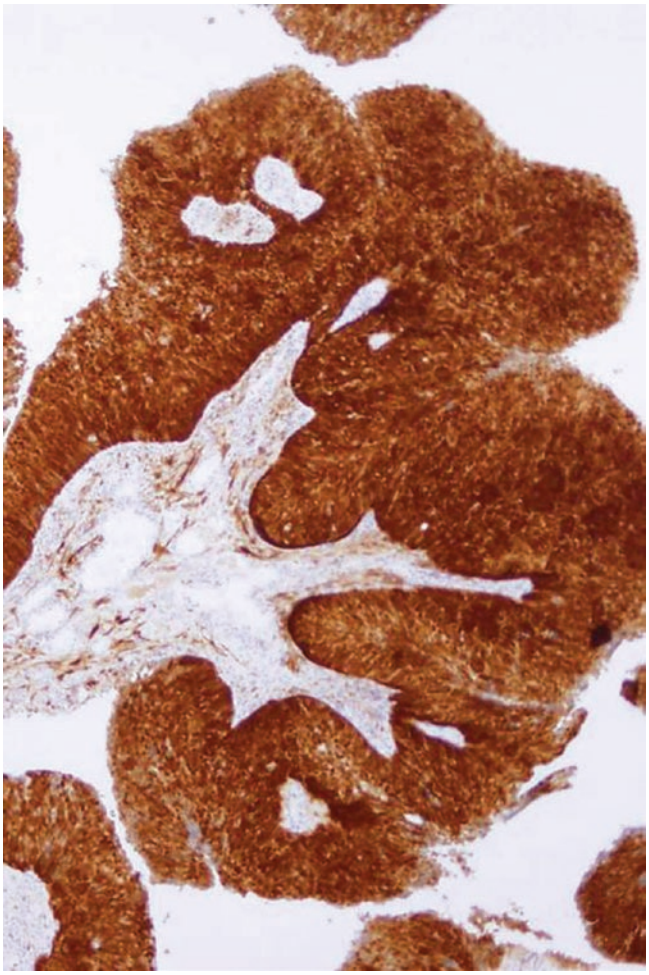

Fig. 2.45 Exophytic non-keratinizing squamous cell carcinoma: diffuse and intense positive immune reaction for p16 protein

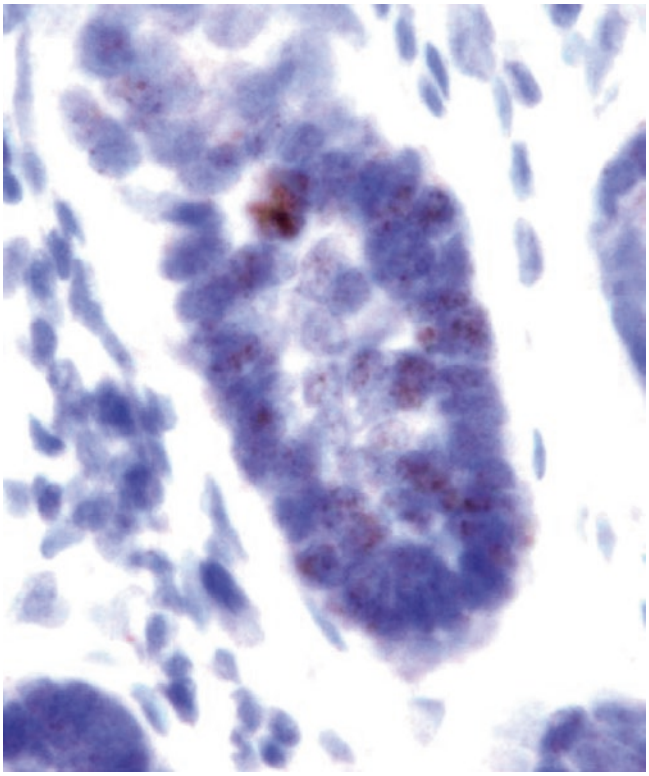

Fig. 2.46 Non-keratinizing squamous cell carcinoma: intranuclear detection of HPV 16 DNA by in situ hybridization

An unusual variant of HPV-related carcinoma with adenoid cystic-like features arising in the sinonasal tract was recently described because of immunohistochemical p16 protein expression. It was characterized by a nested growth with a prominent basaloid component showing myoepithelial differentiation, microcystic spaces, and even ductal structures. Evidence of squamous differentiation, when present, was restricted to the surface epithelium [243]; more experience with this type of tumor may be needed to clearly separate it from the HPV-related basaloid SCC. A unique example of low-grade papillary Schneiderian carcinoma has been very recently reported [250].

Treatment and prognosis NKSCC behaves as locally aggressive tumor, and the recommended treatment is complete surgical excision followed by radiotherapy. NKSCC bears a better prognosis than conventional squamous cell carcinomas [236, 237, 251]. The mechanisms underlying this favorable outcome may involve the combined effects of immune surveillance to viral-specific tumor antigens, an intact apoptotic response to radiation, and absence of widespread genetic alterations associated with smoking [252–255].

2.11.3 Sinonasal Undifferentiated Carcinoma

Definition Sinonasal undifferentiated carcinoma (SNUC) is a high-grade malignant epithelial neoplasm of the nasal cavity and paranasal sinuses, composed of small- to medium-sized cells, lacking evidence of squamous or glandular differentiation, as well as of rosette formation [256–258].

Epidemiology etiology, and pathogenesis SNUC occurs in both sexes over a wide age range, with a median in the sixth decade of life. Cigarette smoking [257] and nickel exposure [218] have been associated with SNUC. Epstein-Barr virus (EBV) and the deletion of the retinoblastoma gene have been ruled out as factors involved in the development of this tumor (Table 2.4). Ionizing radiation is another etiologic factor, for radiotherapy either for retinoblastoma or for nasopharyngeal carcinoma has been associated with SNUC [259]. High-risk HPV has been recently related to SNUC [260].

Clinical aspects The most common symptoms are nonspecific and include nasal obstruction, proptosis, cranial nerve

Table 2.4 Immunohistochemical and molecular features of SNUC

CK	++
EMA	+
NSE	–
Synaptophysin	–
Chromogranin	–
S-100 protein	–
HR-HPV	+/–
EBV	–
del 13q14	–
Other markers	–

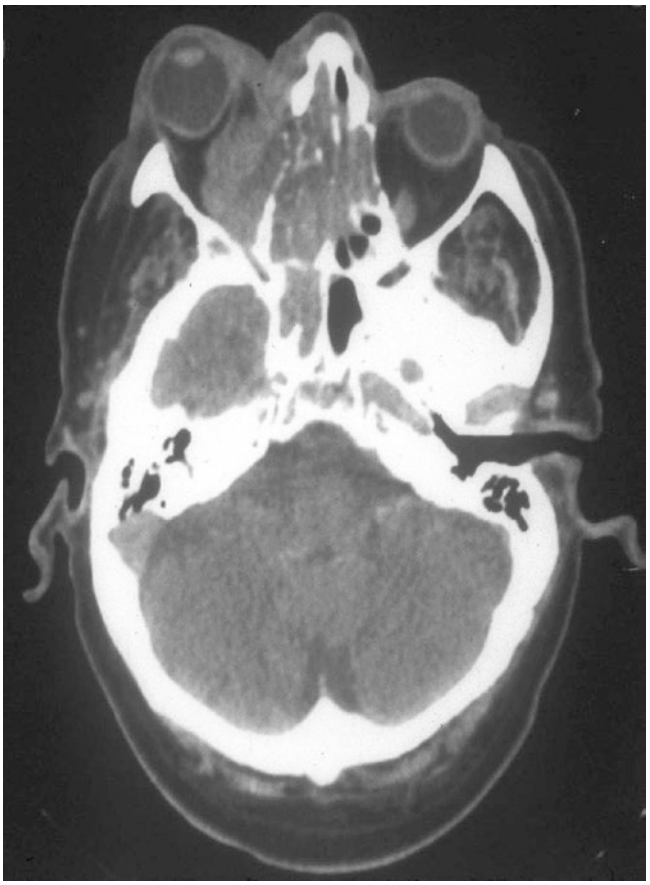

Fig. 2.47 Sinonasal undifferentiated carcinoma: CT scan demonstrating bilateral occupation of the nasal cavity, perforation of the nasal septum, extensive involvement of paranasal sinuses, including left sphenoid and also the left orbit (Courtesy of Prof. J. Traserra, Barcelona, Spain)

palsies, periorbital swelling, diplopia, epistaxis, and periorbital pain [257]. Most tumors present in advanced stage with involvement of multiple paranasal sinuses and invasion of adjacent structures, including the orbit, the cranial cavity and the nasopharynx (Fig. 2.47).

Macroscopy The tumors are often extensive lesions.

Microscopy SNUC is composed of small- to medium-sized, undifferentiated cells, which arise via dysplastic changes from the basal cells of the surface epithelium. The cells are polygonal with distinct borders, showing round to oval, hyperchromatic or vesicular nuclei, with either inconspicuous or slightly prominent nucleoli, surrounded by moderate amount of either amphophilic or eosinophilic cytoplasm. Mitotic figures are common (Fig. 2.48). The tumor forms nests, cords, and sheets of cells that show frequent areas of central necrosis and tendency to vascular and perineural invasion (Fig. 2.49).

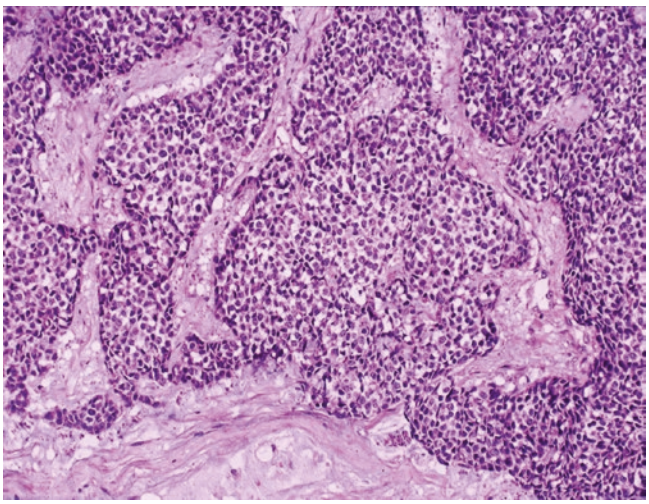

Fig. 2.48 Sinonasal undifferentiated carcinoma: interconnected nests of small- to medium-sized, polygonal undifferentiated epithelial cells with distinct borders. They show round to oval, hyperchromatic, or vesicular nuclei, surrounded by moderate amount of cytoplasm

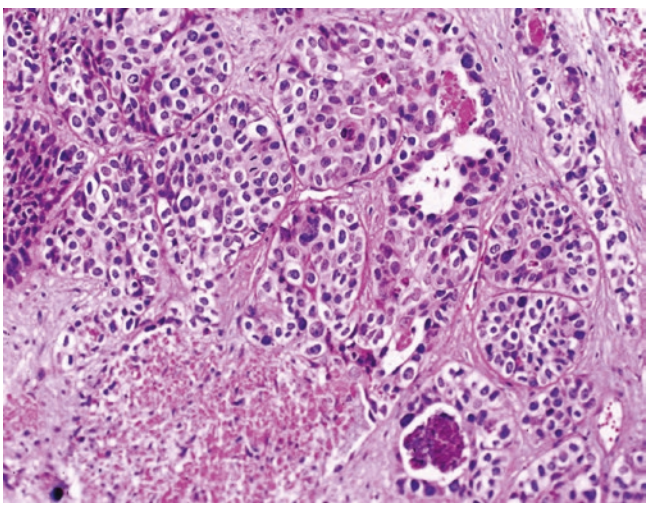

Fig. 2.49 Sinonasal undifferentiated carcinoma: nests of small to intermediate epithelial cells showing pleomorphic atypical nuclei, with either inconspicuous or slightly prominent nucleoli, mitosis, and areas of necrosis

Immunohistochemistry SNUCs are immunoreactive with epithelial markers, such as simple epithelium-type cytokeratins (Fig. 2.50) [261] and epithelial membrane antigen (EMA). Synaptophysin, chromogranin, and other neuroendocrine markers are negative [262]. In a recent report, up to 47 % of SNUCs have been found positive for high-risk HPV [260]. EBV is negative [256, 259] (Table 2.4).

Electron microscopy Ultrastructural studies demonstrate poorly formed desmosomes in quite a number of cells, while the presence of tiny bundles of tonofilaments is very rare. Neurosecretory granules are either absent or very rarely found (Fig. 2.51).

Genetics Few cases of SNUC have been examined cytogenetically, and they showed a complex karyotype [263]. Activating genomic mutations of clinically relevant genes, including *AKT*, *BRAF*, *CDK4*, *CTNB1*, *EGFR*, *FBXW7*, *JAK2*, *c-KIT*, *KRAS*, *PDGFR*, *PI3K*, and *VEGF*, have not been detected [264, 265].

Differential diagnosis The three main differential diagnoses of SNUC are small cell neuroendocrine carcinoma (SCNC), large cell neuroendocrine carcinoma (LCNC), and high-grade olfactory neuroblastoma (ONB). All four entities may share some overlapping clinical and light microscopic features. However, SNUC, SCNC, and LCNC show a marked immunoreactivity for cytokeratins that is not seen in ONB, and on the other hand, SNUC lacks the marked neuroendocrine immunoreactivity seen in SCNC, LCNC, and ONB (Table 2.5). Most lesions categorized in the past as grade IV ONB are now considered to be either SNUC or SCNC. This is important because SNUC, SCNC, and LCNC have worse prognosis than ONB. The recently described NUT carcinoma can be separated from SNUC based on the presence of *NUTM1* gene rearrangement or NUT immunohistochemical positivity. Notably, in the past, NUT carcinomas arising in the sinonasal tract may have been diagnosed as SNUC [266].

In addition, SNUC needs to be distinguished from other primary sinonasal tumors, such as solid adenoid cystic carcinoma, microcytic malignant melanoma, NKSCC, primary sinonasal nasopharyngeal-type undifferentiated carcinoma, lymphoma, and others.

Treatment and prognosis SNUCs are very aggressive tumors, with frequent local recurrence and spread to lymph node and distant sites. In most instances, the tumor is so large and the infiltration is so extensive that complete surgical resection cannot be achieved. Neck involvement in advanced local disease is considered a poor prognostic sign [267]. Combined treatments, including surgery and adjuvant radiotherapy, or surgery, radiotherapy, and chemotherapy,

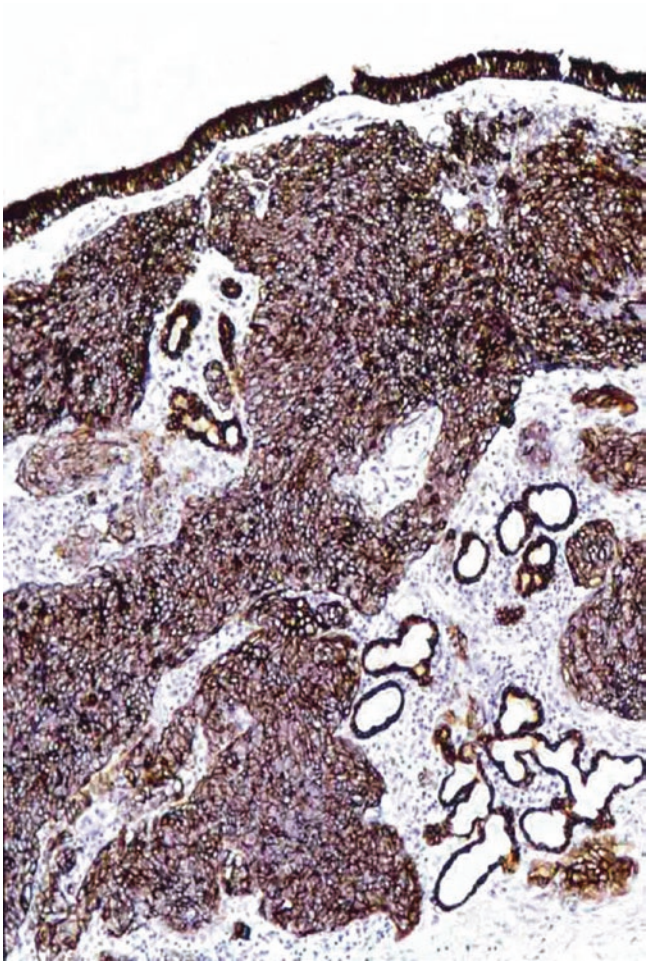

Fig. 2.50 Sinonasal undifferentiated carcinoma: strong immune reaction of the tumor cells with the marker of low molecular weight cytokeratins CAM 5.2

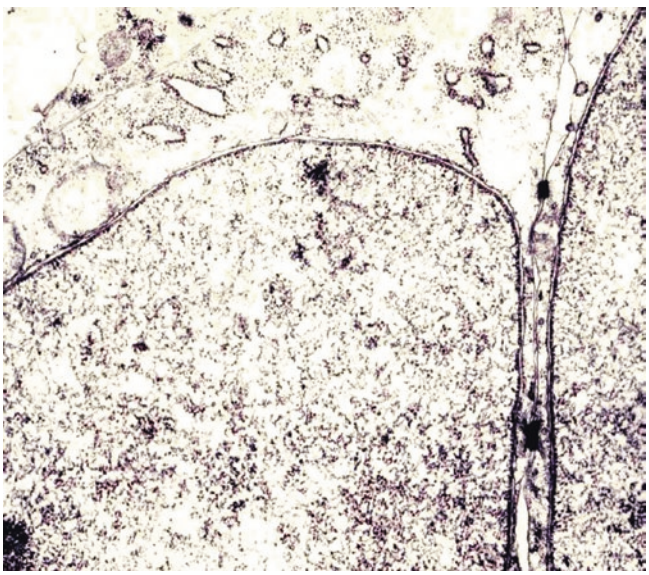

Fig. 2.51 Sinonasal undifferentiated carcinoma: ultrastructurally, poorly formed desmosomes are seen joining the cells (Courtesy of Prof. J.A. Bombi, Barcelona, Spain)

Table 2.5 Summary of the immunohistochemical and molecular features of selected sinonasal round cell tumors

Entity	CK	SYN	CHR	CD56	S100	HMB45	CD45	CD99	Desmin	P63	Calretinin	EBV	Molecular diagnostics
Sinonasal undifferentiated carcinoma	7+, 8 + 5/6–, 13–	– (focal +)	– (focal +)	–	–	–	–	–	–	Rarely +	–	–	–
Nasopharyngeal-type undifferentiated carcinoma	Pan +, 5/6 +, 13 +	–	–	–	–	–	–	–	–	+	–	+	–
Neuroendocrine carcinoma	Pan +, 5/6 –	+	+	+	–	–	–	–	–	–	–	–	–
Basaloid squamous cell carcinoma	Pan+, 5/6+	–	–	–	–	–	–	–	–	+	–	–	–
NUT carcinoma	Pan+, 7+	–	–	–	–	–	–	–	–	+	ND	–	t(15;19)
Ectopic pituitary adenoma	Pan+	+	+	+	–	–	–	+	–	–	+	–	–
Olfactory neuroblastoma	–	+	+	+	Sustentacular cells	–	–	–	–	–	+	–	–
Melanoma	– (rarely +)	– (rarely +)	– (rarely +)	– (rarely +)	+	+	–	–	– (rarely +)	–	– (rarely +)	–	–
Lymphoma	–	–	–	+ in NK/T cell	–	–	+	–[a]	–	–	–	+ in NK/T cell	–
Rhadomyosarcoma	– (rarely +)	– (rarely +)	–	– (rarely +)	–	–	–	– (rarely +)	+	–	ND	–	t(2;13) alveolar
Ewing's sarcoma	– (rarely +)	– (focal +)	–	– (focal +)	– (focal +)	–	–		–	–	–	–	t(11;22)
Metastatic neuroblastoma	–	+	+	+	–	–	–	–	–	–	–	–	*MYCN*

CK cytokeratins, *SYN* synaptophysin, *CHR* chromogranin, *ND* not determined

[a]Lymphoblastic lymphoma and anaplastic large cell lymphomas are positive for CD99

seem to offer the best chance of cure compared with either modality alone [268, 269]. High-dose chemotherapy and autologous bone marrow transplantation have been considered as a form of treatment [270]. Prognosis of SNUC is dismal, with a median survival of 4 months to 1 year [257, 258]. In a recent meta-analysis of outcome, 26.3 % of patients were alive with no evidence of disease, 21.0 % were alive with disease, and 52.7 % were dead of disease [267].

2.11.4 Primary Sinonasal Nasopharyngeal-Type Undifferentiated Carcinoma

Definition A poorly differentiated squamous cell carcinoma or histologically undifferentiated carcinoma accompanied by a prominent reactive lymphoplasmacytic infiltrate, morphologically similar to nasopharyngeal carcinoma, that originates in the sinonasal tract.

Synonym Sinonasal lymphoepithelioma.

Although nasopharyngeal carcinoma (NPC) almost invariably arises in the nasopharynx [271], "bona fide" primary sinonasal nasopharyngeal-type undifferentiated carcinomas (PSNPC) have been recently reported [259]. Due to the undifferentiated appearance of cells in NPC and PSNPC, these tumors may be lumped together with SNUC if unaware of their differences [256, 259, 261]. SNUC does not arise in the nasopharynx, but bulky lesions may extend into this region. Also NPC may extend from the nasopharynx into the sinonasal region. The distinction between these tumors can generally be made on purely histological grounds, since SNUC lacks the lymphoplasmacytic cell infiltrate seen in most cases of NPC and PSNPC. Immunohistochemistry and in situ hybridization are of great help in difficult cases. All three, NPC, PSNPC, and SNUC, react positively for low molecular weight cytokeratins and EMA. In contrast, NPC and PSNPC are positive for EBV, whereas SNUC is negative. Until very recently, confusion of NPC and PSNPC with SNUC has led to the belief that some SNUCs were related to EBV. The sharp distinction of these entities is crucial because NPC and PSNPC have a better prognosis and are more responsive to radiation therapy than SNUC. HPV-related lymphoepithelial-like NKSCC is another entity to be distinguished from PSNPC.

2.11.5 Neuroendocrine Neoplasms

Sinonasal neuroendocrine carcinomas are rare neoplasms accounting for about 5 % of all tumors in this region. Like in the lungs, they encompass four entities: carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma, and large cell neuroendocrine carcinoma [272]. For a detailed discussion of neuroendocrine neoplasms, the reader is referred to Chap. 11.

2.11.5.1 Carcinoid

Definition Sinonasal carcinoids are very rare well-differentiated neuroendocrine neoplasms that present bland cytology, lack of necrosis, and have <2 mitoses per 10 high-power fields [272].

Differential diagnosis, treatment, and prognosis are similar to carcinoids in other territories of the respiratory tract.

2.11.5.2 Atypical Carcinoid

Definition Sinonasal atypical carcinoids are moderately differentiated neuroendocrine carcinomas that present generally mild cytologic atypia, can have patchy necrosis, and have mitotic activity between 2 and 10 per high-power field. Although very rarely seen, a tumor with low mitotic activity, <2 per 10 high-power fields, that has bona fide necrosis is also considered atypical carcinoid [272].

Differential diagnosis, treatment, and prognosis are similar to those of atypical carcinoids in other territories of the respiratory tract.

2.11.5.3 Small Cell Neuroendocrine Carcinoma

Definition Small cell neuroendocrine carcinoma (SCNC) of the sinonasal tract is a high-grade, poorly differentiated, malignant epithelial tumor with histological features similar to small cell carcinoma of the lung [121].

Synonyms Small cell carcinoma, oat cell carcinoma, and poorly differentiated neuroendocrine carcinoma

Epidemiology This type of tumor has been well documented in various head and neck territories, mainly in the parotid gland and in the larynx. In the sinonasal tract, where they are distinctly uncommon, SCNC mainly arises from the ethmoid and maxillary sinuses and from the nasal cavity [273–277]. They may occur in pediatric age after treatment of retinoblastoma [278].

Etiology and pathogenesis Sinonasal SCNC is considered to derive from cells with neuroendocrine differentiation occasionally found in the seromucous glands.

Microscopy SCNC gives rise to nests, cords, and sheets of small undifferentiated cells, with molded nuclei and scanty cytoplasm (Fig. 2.52). More often than not, there is ulceration of the mucosa, but sometimes SCNC exclusively infiltrates beneath the surface epithelium. Foci of necrosis may be found and mitotic figures are frequently seen. Occasionally

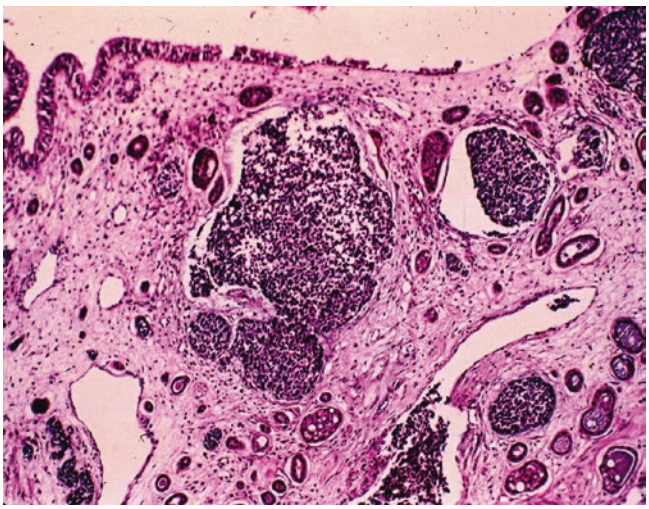

Fig. 2.52 Small cell neuroendocrine carcinoma: nests, cords, and islands of small undifferentiated cells, with compact nuclei and scanty cytoplasm, are seen to infiltrate beneath the surface epithelium. They appear interspersed in the lamina propria with the seromucous glands of a low-grade adenocarcinoma

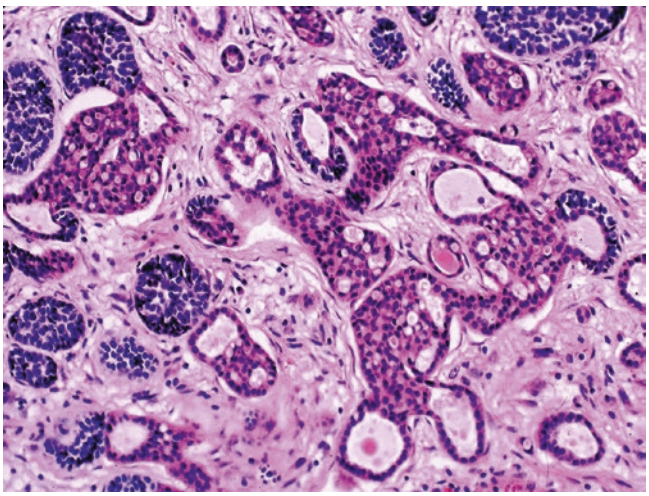

Fig. 2.53 Small cell neuroendocrine carcinoma: cords and nests of a small undifferentiated carcinoma, with molded nuclei and scanty cytoplasm, are seen in continuity with the seromucous glands of a low-grade adenocarcinoma, as if the former tumor was originating from the latter

the tumor grows surrounding the seromucous glands of the lamina propria, as if it was originating from them (Fig. 2.53). We have observed one case of SCNC originating at the base of a papillary NKSCC (Fig. 2.54). Variable degrees of neuroendocrine differentiation may be demonstrable by electron microscopy or immunohistochemistry (Fig. 2.55) [279]. Before placing a tumor within this category, a primary tumor from the lung must be ruled out.

Immunohistochemistry SCNC exhibits positive reaction for low molecular weight cytokeratins and EMA, as well as

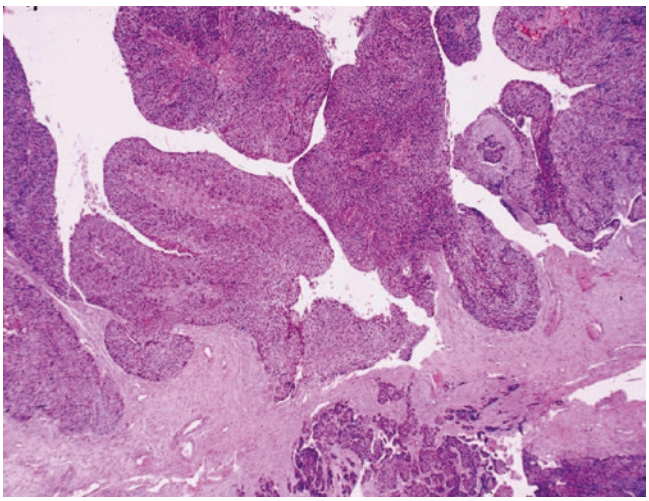

Fig. 2.54 Small cell neuroendocrine carcinoma: the tumor is at the base of a papillary non-keratinizing squamous cell carcinoma

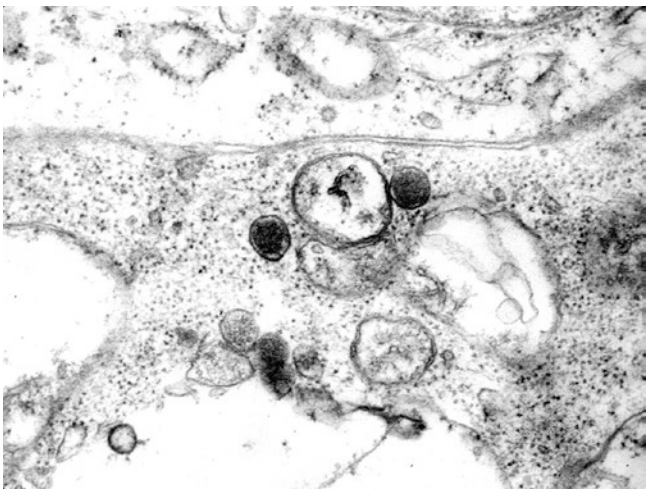

Fig. 2.55 Small cell neuroendocrine carcinoma: ultrastructurally, neurosecretory granules are found after diligent search (Courtesy of Prof. J.A. Bombi, Barcelona, Spain)

variable positivity for CD 56, synaptophysin, and chromogranin. At least two neuroendocrine markers should be positive [280].

Differential diagnosis Sinonasal SCNCs have been less precisely characterized than in other head and neck territories, and so far no unanimous consensus has been reached in regard to the way they have to be separated from other small cell tumors, either round or undifferentiated, occurring in this region [274–277, 281–284]. Table 2.5 provides the current criteria most widely accepted for their recognition. In addition, large cell neuroendocrine carcinoma has to be distinguished from SCNC [285, 286].

Treatment and prognosis Combination of surgery and radiotherapy, plus chemotherapy, is the treatment of

SCNC. Its prognosis seems to be somewhat better than for SNUC or for similar tumors of the lung.

2.11.5.4 Large Cell Neuroendocrine Carcinoma

Definition Large cell neuroendocrine carcinoma (LCNC) of the sinonasal tract is a high-grade, poorly differentiated, malignant epithelial tumor with histological features similar to its counterpart of the lung [272].

Epidemiology Only a few cases of LCNC have been reported in the sinonasal region [285, 286].

Microscopy LCNC is a tumor with high mitotic activity, but instead of having cells with high nuclear to cytoplasmic ratios, molding, and crush artifact, it has moderate to abundant cytoplasm.

Differential diagnosis Mitotic activity is the major histological feature that distinguishes LCNC from carcinoid and atypical carcinoid, >10 mitoses/10 HPFs in the former versus <10 mitoses/10 HPFs in the latter two.

Treatment and prognosis Surgery supplemented with postoperative radiotherapy and chemotherapy is the primary treatment for LCNC, which in general has the same poor prognosis as SCNC [272].

2.11.6 NUT Carcinoma

Definition NUT carcinoma is a rare, highly aggressive variant of poorly differentiated squamous cell carcinoma, which is defined by a rearrangement of the nuclear protein in testis (NUT) gene *NUTM1* on chromosome 15q14 [287].

Epidemiology It is a rare tumor, but the exact incidence is unknown, because most cases have gone unrecognized due to the lack of specific diagnostic features. In two recently published studies, it represented 18 % of poorly differentiated carcinomas of the upper aerodigestive tract [288] and 2 % of sinonasal carcinomas [266].

Clinical aspects NUT carcinoma can occur at all ages, but patients with sinonasal involvement are mainly young adults. Presenting symptoms are nonspecific and include nasal mass and pain, proptosis, and toothache. The tumors involved in most cases both the nasal cavities and the paranasal sinuses [266, 288].

Microscopy Histologically, NUT carcinoma is composed of undifferentiated basaloid cells, with monotonous appearance, round to ovoid nuclei, and often clear cytoplasm. Areas of abrupt squamous differentiation can be present, in which mature keratinizing cells are juxtaposed to undifferentiated neoplastic cells. In some instances, squamous differentiation may be more pronounced [289]. Areas of necrosis and the presence of neutrophilic infiltrate are commonly observed. The surface epithelium may show areas of squamous metaplasia, but no evidence of dysplastic changes has so far been reported [266, 288].

Immunohistochemistry A monoclonal antibody to NUT for use in immunohistochemistry is currently available [290], which may help to separate NUT carcinoma from other poorly differentiated sinonasal carcinomas. This antibody is considered to be enough sensitive and specific, so that the demonstration of the *NUTM1* rearrangement is no longer considered necessary [291]. Other immunohistochemical markers, which are consistently positive in NUT carcinoma, are cytokeratins, EMA, and p63, while no or limited immunoreactivity has been observed with muscle, neuroendocrine, and melanocytic markers. The presence of HPV and EBV infection has never been identified, either using immunohistochemistry, in situ hybridization, or polymerase chain reaction [292].

Genetics NUT carcinoma is characterized by a translocation involving the *NUTM1* gene on chromosome 15q14 and, in most cases, the *BRD4* gene on chromosome 19p13.1 [293]. The remaining cases either present a *BRD3-NUTM1* fusion [t(9;15)(q34.2;q14)] or a yet uncharacterized fusion (so-called NUT-variant). The fusion gene encodes for a protein which is thought to be involved in a block of epithelial differentiation and squamous maturation [294].

Differential diagnosis It is difficult if not impossible to separate NUT carcinoma from other poorly differentiated carcinomas on pure morphological grounds. It has been suggested that some features that may support the inclusion of NUT carcinoma in the differential diagnosis are neoplastic cells with monotonous appearance, which vary in size from small to medium but are not large, and the presence of areas of focal "abrupt" keratinization [291]. The differential diagnosis in the sinonasal tract includes SNUC, poorly differentiated squamous cell carcinoma, basaloid squamous cell carcinoma, and neuroendocrine carcinoma. Among non-epithelial neoplasms, olfactory neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma (RMS), and hematolymphoid tumors can be considered in the differential diagnosis. The diagnosis of NUT carcinoma requires either the immunohistochemical demonstration of nuclear reactivity for NUT, which has a characteristic speckled pattern [290], or the demonstration of *NUTM1* rearrangement by FISH or PCR. Other markers that may be useful in the differential diagnosis with the abovementioned entities are p63, which is diffusely positive in NUT carcinoma, but not in SNUC and neuroendocrine carci-

noma, and neuroendocrine markers, which are not expressed or only focally expressed by NUT carcinoma.

Treatment and prognosis NUT carcinoma has an extremely aggressive clinical course with short survival periods. According to a recent report, intensive local therapy, with complete surgical resection and radiation, seems to be associated with improved progression-free and overall survival. The type of translocation does not seem to affect prognosis [295].

2.11.7 SMARCB1–Deficient Sinonasal Basaloid Carcinoma

Recently, some tumors initially diagnosed as SNUCs as well as NKSCCs and myoepithelial carcinomas of the sinonasal tract have been shown to share a common alteration resulting in inactivation of the *SMARCB1* (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1, also *INI-1*) tumor suppressor gene along with rhabdoid features, whether in isolated cells or in confluent sheets of polygonal cells with a plasmacytoid appearance. SMARCB1 deficiency can be easily identified through immunohistochemistry. Although the number of cases reported of these aggressive basaloid carcinomas is limited, it is likely that they represent a distinctive type of sinonasal carcinoma [296, 297].

2.11.8 Sinonasal Adenocarcinomas

Sinonasal adenocarcinomas comprise a wide spectrum of glandular tumors accounting for approximately 20 % of all sinonasal malignancies [298]. They show a remarkable wide range of histological appearances, and they arise both from mucosal seromucous glands and surface epithelium. The 2005 WHO classification recognizes three major adenocarcinoma subtypes: intestinal type, non-intestinal type, and salivary gland type.

2.11.8.1 Intestinal-Type Adenocarcinoma

Definition Intestinal-type adenocarcinoma (ITAC) is a tumor with histological features resembling colorectal dysplastic adenoma or adenocarcinoma [299, 300]. It is considered to originate through intestinal metaplasia of the ciliated respiratory cells lining the Schneiderian membrane. Metastasis from gastrointestinal adenocarcinoma should be ruled out before a tumor is labeled as a primary of this region.

Epidemiology and etiology ITAC is the most common type of sinonasal adenocarcinoma representing about 6–13 % of malignancies developing in the sinonasal tract [301–303]. It is strongly associated with exposure to different types of dust, mainly hardwood but also softwood dusts, as well as leather dust [304–310]. About 20 % of sinonasal ITACs seem to be sporadic, without evidence of exposure to industrial dusts [298, 305]. The incidence has remained relatively stable in the last decades, although recently a decrease in the incidence of sinonasal adenocarcinomas has been observed in males [298, 311]. Males are more frequently affected than females, and the peak age is in the fifth and sixth decades, for both sexes. The most common location is the ethmoidal region [312], followed by the nasal cavities and other sinuses.

Macroscopy ITACs have a fungating appearance with either polypoid or papillary features. Occasionally, they may have a gelatinous consistency resembling a mucocele.

Microscopy Histologically, ITAC is mainly composed of columnar mucin-secreting cells and of goblet cells [312]. Some well-differentiated tumors may also contain resorptive cells, argentaffin cells, and Paneth cells (Fig. 2.56). Endocrine-amphicrine enteric differentiation may occasionally be found [313]. Metaplastic and atypical changes have been observed in adjacent preneoplastic epithelium [314]. These tumors depict different histological patterns that may be predominantly (a) papillary, (b) glandular, (c) compact, (d) mucinous, and (e) mixed [312, 315]. Papillary tumors mainly consist of elongated outgrowths lined by intestinal-type cells with markedly atypical pseudostratified nuclei (Fig. 2.57). Although most of them are high-grade tumors, low-grade forms mimicking colonic villous adenoma may occasionally occur (Fig. 2.58) [316]. The glandular pattern resembles common-type intestinal adenocarcinoma (Fig. 2.59). Compact or solid forms show poorly differentiated nests of cells in which glandular formation is rarely seen. In the mucinous pattern, more than 50 % of the tumor is composed of dilated mucin-filled glands lined by columnar mucin-secreting epithelium and lakes of mucin containing fragmented epithelial elements (Fig. 2.60). Other mucinous tumors show mucin-filled cells with the pattern of "signet ring" cell carcinoma. Various attempts have been made to correlate histopathological grading and typing with clinical behavior [317–319].

In rare instances, ITAC may be combined with small cell neuroendocrine carcinoma. In these cases, the two components are distinct and differ morphologically and immunohistochemically [320].

Immunohistochemistry and electron microscopy Both technologies have confirmed the enteric differentiation of the tumor cells [321]. Wide-spectrum cytokeratin markers are positive, whereas CEA is only occasionally positive

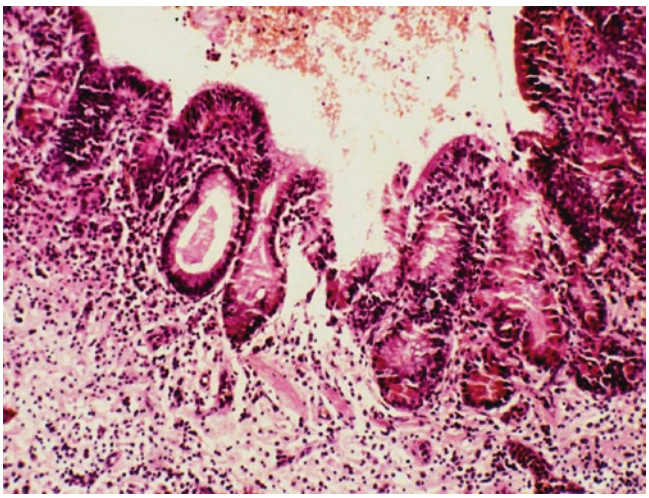

Fig. 2.56 Intestinal-type adenocarcinoma: in situ adenocarcinoma with abundant presence of Paneth cells

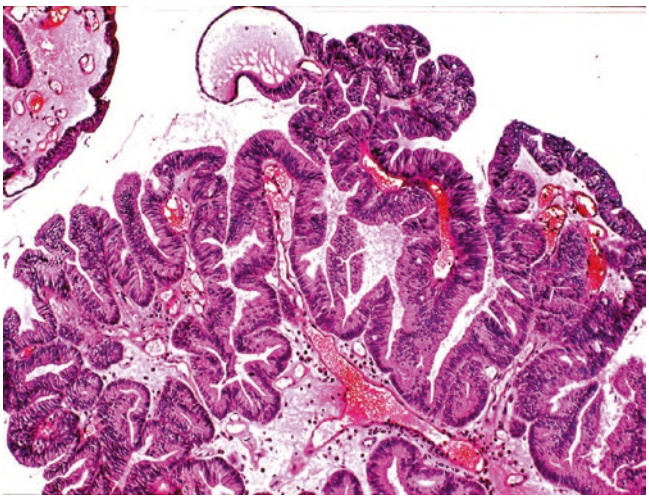

Fig. 2.58 Intestinal-type adenocarcinoma: low-grade variant mimicking villous adenoma. Notice the presence of small intestine-type resorptive cells at the *left*

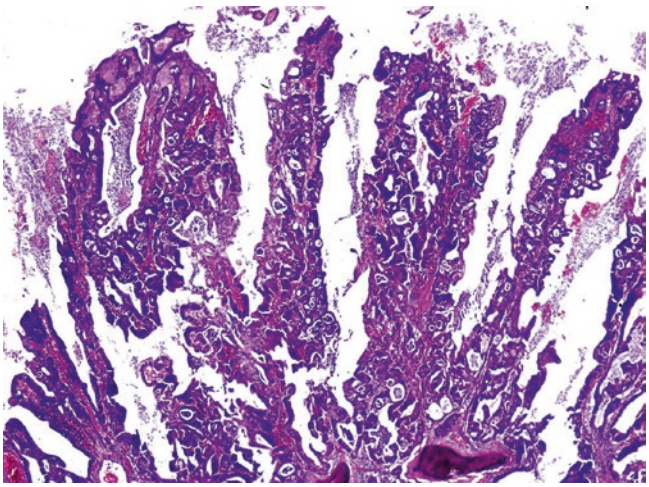

Fig. 2.57 Intestinal-type adenocarcinoma: high-grade variant of papillary outgrowth of intestinal-like malignant epithelium. Destruction of sinonasal bone at the *bottom*

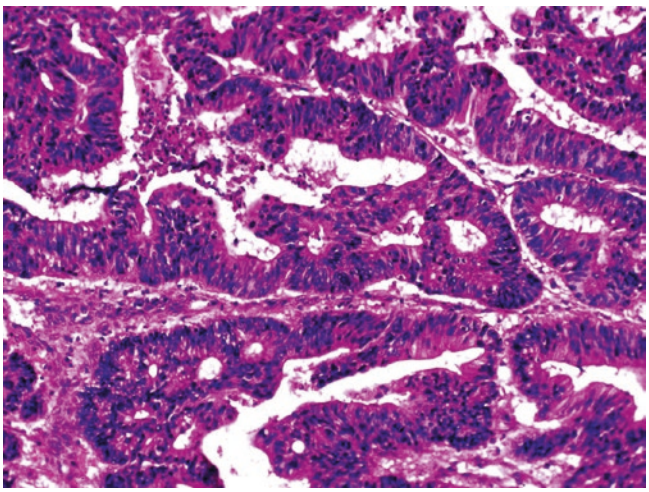

Fig. 2.59 Intestinal-type adenocarcinoma: the glandular pattern resembles common-type intestinal adenocarcinoma

[322]. Cytokeratin 7 is frequently but not constantly positive, while most ITACs express cytokeratin 20 and CDX2, two markers related to intestinal differentiation [323]. Villin is another marker of enteric differentiation which is positive in these tumors [280]. Neuroendocrine markers, including chromogranin and synaptophysin, are frequently detected in individual cells or small clusters of cells, representing interspersed neuroendocrine or amphicrine cells [322, 324].

Genetics The genotypic features of ITAC show a significant overlap with those present in colorectal adenocarcinoma, particularly with colorectal adenocarcinomas developing through the MSI-negative pathway [325]. Commonly altered genes include *TP53*, *CDKN2A*, and deleted in colon cancer (*DCC*), while, at variance with colorectal adenocarcinoma, the APC-beta-catenin pathway is likely to have a marginal involvement in the development of ITAC. In addition, activating *KRAS* mutations occur at a lower frequency (10–13%) than in colorectal cancer [326, 327]. The epidermal growth factor receptor (EGFR) is overexpressed in approximately 15% of ITACs, and most of these cases show either chromosome 7 polysomy or *EGFR* gene amplification by FISH analysis [328]. Conversely, activating mutations of *EGFR* and *BRAF* genes are rare or absent.

Differential diagnosis ITAC can be differentiated from other adenocarcinomas on the basis of histological morphology and with the help of immunohistochemical markers of intestinal differentiation. These markers are characteristically expressed by ITACs but not by sinonasal non-intestinal-type adenocarcinomas.

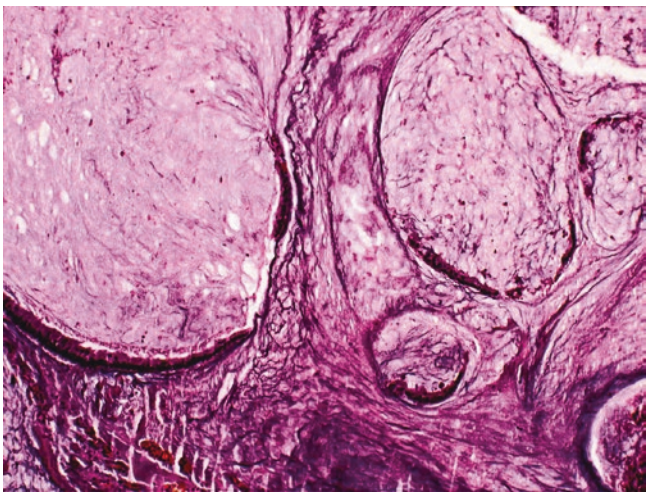

Fig. 2.60 Intestinal-type adenocarcinoma: dilated glands lined by columnar mucin-secreting epithelium, containing lakes of mucin and fragmented epithelial elements. A mucocele was clinically suspected

Features such as cytologic atypia, high mitotic rate, and areas of necrosis, which are common findings in most ITACs, help to distinguish the high-grade variants from rare low-grade ITACs and from mucoceles. The lack of epidermoid and squamous differentiation separates these tumors from mucoepidermoid and adenosquamous carcinomas.

In rare occasions, adenocarcinomas originating in the gastrointestinal tract may metastasize to the sinonasal region, and this is usually a late event in the clinical course of the tumor. In these cases, the differential diagnosis with primary ITAC is mainly based on the clinical history, because no histological or immunohistochemical feature is distinctive enough to allow separation.

Treatment and prognosis Treatment of choice is complete surgical resection followed by radiotherapy. A good response to chemotherapy has been observed in some cases. Interestingly, chemotherapy was highly effective in tumors bearing wild-type or a still-efficient p53 protein, but ineffective in those carrying a disabled p53 protein, indicating that p53 status represents a promising predictive biomarker to chemotherapy in ITAC [329]. Prognosis of ITAC is generally poor and largely depends on T stage. Recurrences and subsequent deeply invasive local growth are frequent; however, lymph node and distant metastases are rare [310, 312, 318].

2.11.8.2 Non-intestinal-Type Adenocarcinomas

Sinonasal non-intestinal-type adenocarcinomas (non-ITAC) are an uncommon and heterogeneous group of tumors defined, by exclusion, as glandular malignancies that do not show signs of intestinal differentiation and do not resemble any salivary gland tumor type. Possibility of a metastatic adenocarcinoma should also be ruled out. They can be further distinguished in high- and low-grade subtypes.

High-Grade Non-intestinal-Type Adenocarcinomas

Definition High-grade non-ITACs are characterized by neoplastic non-intestinal and non-salivary type of glands showing moderate to marked cell pleomorphism, high number of mitotic figures, and foci of necrosis.

Epidemiology High-grade non-ITACs are rare tumors that develop more commonly in men, and, although they occur over a wide age range, they are much more common in older individuals [330].

Macroscopy They arise more often in the nasal cavity and maxillary sinus and appear as large destructive tumor masses, with areas of necrosis and hemorrhage.

Microscopy High-grade non-ITACs appear as poorly differentiated tumors, with predominantly solid growth pattern, and poorly formed gland structures. They show a great deal of heterogeneity, and different patterns have been recognized. The blastomatous pattern resembles primitive gland differentiation seen in teratocarcinosarcoma, with ribbons and trabeculae of neoplastic cells with numerous rosette-like gland structures sometimes containing mucus. In the apocrine subtype, the infiltrating glands resemble those of ductal carcinoma of the breast or high-grade salivary duct carcinoma. The oncocytic/mucinous can be associated with oncocytic Schneiderian papilloma and is formed by oncocytic and mucinous cells, growing as solid sheets and sometimes showing extracellular mucus accumulation [330]. The poorly differentiated/undifferentiated adenocarcinomas are predominantly solid with occasional cribriform nests and papillary structures.

Immunohistochemistry These tumors are consistently positive for cytokeratin cocktails and cytokeratin 7, while cytokeratin 20 and CDX2 are negative. Occasional cases have shown focal positivity for synaptophysin, S-100 protein, and p63.

Differential diagnosis High-grade non-ITAC can be distinguished from low-grade non-ITAC for the presence of prominent cytologic atypia, brisk mitotic activity, and/or necrosis. ITAC can be ruled out based on the lack of morphological resemblance to colorectal adenocarcinoma and for the absence of positivity to intestinal markers, such as cytokeratin 20, CDX2, and villin. Other poorly differentiated high-grade neoplasms to be considered in the differential diagnosis include salivary duct carcinoma and teratocarcinosarcoma.

Treatment and prognosis Although definitive specific treatment recommendations are lacking due to the rarity of this type of tumors, complete surgical excision is the treatment of choice, which may be followed by radiotherapy [331]. The prognosis, however, remains poor, with most patients experiencing local recurrence and death from disease.

Low-Grade Non-intestinal-Type Adenocarcinomas

Definition Low-grade non-intestinal-type adenocarcinomas (low-grade non-ITACs) are characterized by neoplastic non-intestinal and non-salivary type of glands showing absence or minimal cell pleomorphism, absence or minimal number of mitotic figures, and absence of necrosis.

Epidemiology Low-grade non-ITACs occur over a wide age range, with a mean of 60 years. There is no significant gender predilection. No relation with occupational activities has been documented in these tumors. The nasal cavity is the most commonly affected site, followed by the ethmoid sinus.

Macroscopy Given their rarity, precise data are not available.

Microscopy Different histological patterns may be recognized: papillary, tubular, tubulopapillary, glandular, mucinous, trabecular, cribriform, psammomatous, and clear cell. The papillary pattern is characterized by complex papillary fronds lined by bland columnar cells (Fig. 2.61). They may occasionally mimic oncocytic (columnar) cell papilloma. Recognition of invasion may be difficult in these cases. Quite similar tumors also develop in the nasopharynx [332]. The tubulopapillary carcinoma consists of a proliferation of cuboidal to columnar of epithelial cells, forming tubules at the center and papillae at the surface [333]; it has to be differentiated from the terminal tubulus adenocarcinoma of the nasal seromucous glands (Fig. 2.62) [334]. Tumors with glandular pattern may simulate adenoma; nevertheless, the presence of closely packed glands, forming back-to-back arrangements, indicates the true malignant nature of the lesion [335]. Papillary structures may be occasionally noted within dilated glandular structures. In a recent report, one-third of the cases were associated with respiratory epithelial adenomatoid hamartoma, but the significance of this finding is yet to be determined [336]. The clear cell pattern is best exemplified by the nasal renal cell-like adenocarcinoma, which consists of cuboidal to polyhedral cells with abundant clear cytoplasms, forming either solid or glandular patterns that mimic clear cell renal carcinoma [337].

Immunohistochemistry Neoplastic cells are positive for broad-spectrum cytokeratins and cytokeratin 7, but not for cytokeratin 20, CDX2, MUC2, or villin. S-100 protein can also be detected [336]; positivity for myoepithelial markers has been reported in a few cases [338].

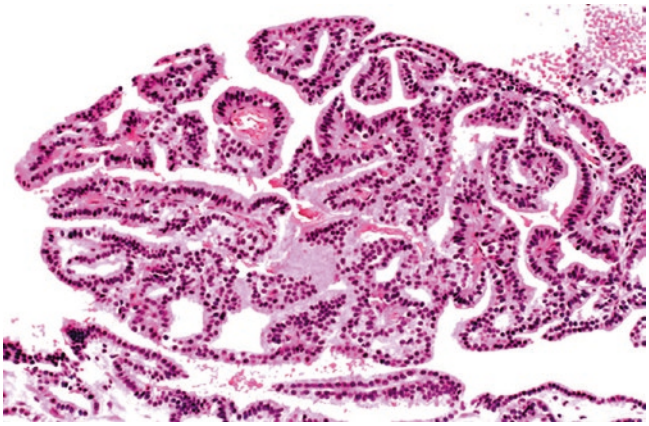

Fig. 2.61 Low-grade non-intestinal-type adenocarcinoma: the papillary variant is made up of cuboidal to columnar epithelial cells, forming papillae supported by delicate fibrovascular stalks

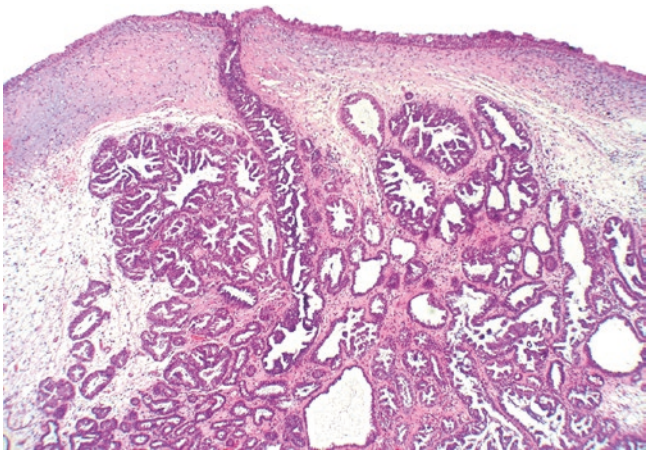

Fig. 2.62 Low-grade non-intestinal-type adenocarcinoma: the terminal tubulus variant shows tubulopapillary glands in continuity with a duct that drains into the luminal surface

Genetics There are only sporadic reports of genetic analysis in these tumors. *TP53* gene was not mutated in two cases examined by Franchi et al. [338].

Differential diagnosis *L*ow-grade non-ITACs have to be distinguished both from benign and malignant lesions (Table 2.6). The main differential diagnosis is with sinonasal seromucinous hamartoma. The lack of lobular architecture; presence of epithelial tufting and papillae, "back-to-back" glands, areas with cribriform or trabecular pattern; and invasion of normal structures support the diagnosis of low-grade non-ITAC [42]. Respiratory epithelial adenomatoid hamartoma is characterized by gland-like structures lined by ciliated respiratory-type epithelium that originate from the

Table 2.6 Differential features of selected glandular lesions of the sinonasal tract

Lesion	Clinical features	Salient histopathologic features	Immunohistochemistry
Respiratory epithelial adenomatoid hamartoma (REAH)	Polypoid lesion; posterior nasal septum, ethmoid sinus, nasopharynx; wide age range, male predominance	Back-to-back glands lined by ciliated columnar cells, periglandular hyalinization; occasional mucinous change of proliferating epithelium	CK7+, CK20–, CDX2–, p63+ in the basal compartment, S100-
Seromucous hamartoma	Polypoid lesion; posterior nasal septum, nasopharynx; wide age range, slight male predominance	Lobular growth of small serous glands, uncommon mucinous glands; areas resembling REAH occasionally seen	S100+, CK7+, CK20–, CDX2–, myoepithelial markers -
Intestinal-type adenocarcinoma (ITAC)	Exophytic lesions, often with necrotic-hemorrhagic or mucoid appearance; ethmoid sinus, nasal cavity; adult subjects, male predominance; association with woodworking and leatherworking	Columnar cells, goblet cells, signet ring cells; papillary, glandular, solid, and alveolar-mucinous architecture	CK20+, CK7 variably positive, CDX2+
Low-grade non-ITAC	Papillary/exophytic lesions; nasal cavities and ethmoid sinus; wide age range, predominantly adult patients, no gender predilection	Different growth patterns, more frequently tubulopapillary, cribriform, clear cell; back-to-back glands, mild atypia, low mitotic activity, infiltration of the mucosa and bone	CK7+, CK20–, CDX2–, myoepithelial markers occasionally +
High-grade non-ITAC	Large destructive lesions, with exophytic appearance; hemorrhage and necrosis often present; nasal cavities and maxillary sinus; adult patients	Predominantly solid growth pattern, poorly formed glands, marked atypia, pleomorphism, necrosis, brisk mitotic activity	CK7+, CK20–, CDX2–

surface epithelium of the sinonasal tract. In addition, mucinous tumors have to be distinguished from mucoceles [339, 340]. Low-grade non-ITAC can be separated from high-grade non-ITAC based on the lack of marked cellular pleomorphism, necrosis, and brisk mitotic activity. Tubulopapillary ITAC can be ruled out with the help of immunohistochemistry for markers of intestinal differentiation, including cytokeratin 20, CDX2, MUC2, and villin. Salivary-type adenocarcinomas to be ruled out include acinic cell carcinoma [341] and low-grade salivary duct carcinoma of salivary glands [342]. The renal cell-like adenocarcinoma has to be separated from the salivary-type tumors with clear cells and from metastatic renal carcinoma [337, 343] and from the very rare clear cell variant of olfactory neuroblastoma, another mimicker of renal cell carcinoma [344]. Immunohistochemistry may help in this latter distinction, because vimentin and RCC are usually positive in clear cell renal carcinoma, while both markers are negative in sinonasal renal cell-like adenocarcinoma [337, 343].

Treatment and prognosis The main treatment is surgery, but radiotherapy has been employed in some cases, especially in case of positive margins [331]. Low-grade non-ITACs tend to recur locally, but distant metastases are rare. Only few deaths from disease have been recorded [336].

2.11.8.3 Salivary-Type Adenocarcinomas

A wide range of salivary gland-type tumors may occur in the sinonasal region (see Chap. 5). However, with the exception of adenoid cystic carcinoma, they are quite rare, and most of them have been reported as single cases. They derive from the seromucous glands of the Schneiderian mucosa. Most sinonasal salivary-type tumors are malignant and account for 8–10 % of all malignancies in this territory [345].

Adenoid Cystic Carcinoma

Definition Adenoid cystic carcinoma (AdCC) is a malignant small cell tumor composed of ductal epithelial cells surrounded by modified myoepithelial cells, giving rise to tubular, cribriform, and solid patterns.

Epidemiology AdCC is the most common malignant salivary type of tumor of the upper respiratory tract and comprises 5–10 % of all sinonasal malignancies [302, 346, 347]. AdCC is most common in the maxillary antrum, followed by the nasal cavity [348], although ethmoid, sphenoid, and frontal sinuses may also be involved [142, 349, 350]. Invasion of the skull base by an AdCC has been recently documented [351].

Macroscopy AdCCs present as unencapsulated masses of white to gray color and variable size.

Microscopy Sinonasal AdCC is identical to that arising at other head and neck sites (Fig. 2.63). Over 50 % present a cribriform growth pattern and less often solid or tubular growths [352]. Perineural growth and bone invasion are frequently observed (Fig. 2.64). Rarely, sinonasal AdCC may arise in a preexisting pleomorphic adenoma [353]. Examples of so-called dedifferentiated AdCC have also been reported in the sinonasal region [354]. These tumors consist of a con-

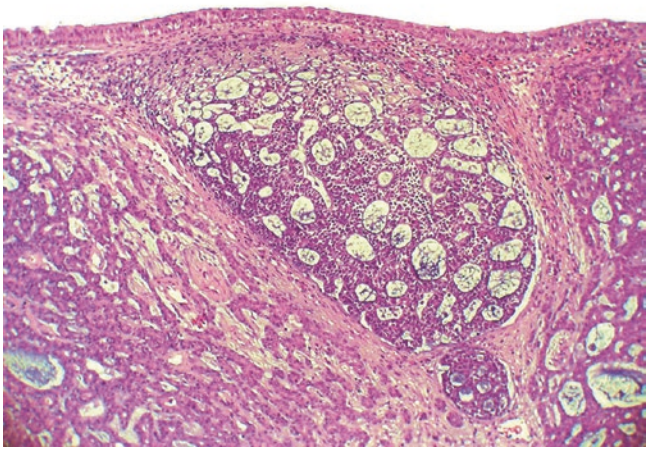

Fig. 2.63 Adenoid cystic carcinoma: typical cribriform growth pattern is seen infiltrating beneath the respiratory mucosa

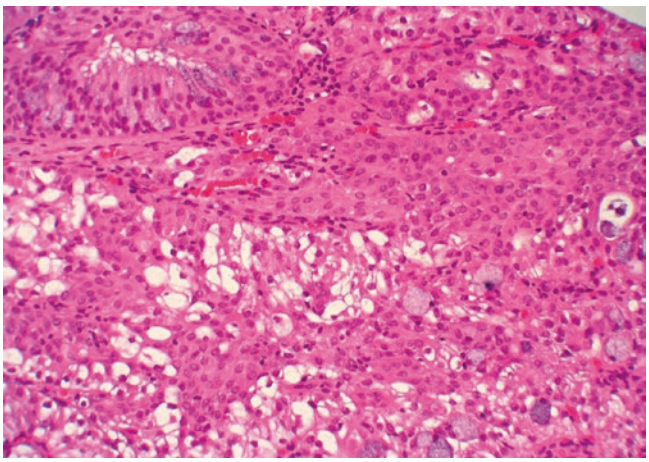

Fig. 2.65 Mucoepidermoid carcinoma: mucous-secreting cells, clear cells, and intermediate cells are the main components. At the *upper left*, entrapped respiratory epithelium is seen

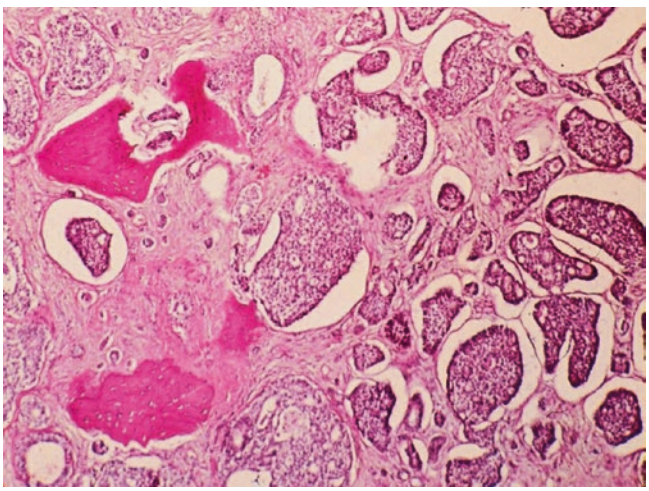

Fig. 2.64 Adenoid cystic carcinoma: the tumor invades and destroys adjacent bone

ventional low-grade AdCC component, with tubular or cribriform architecture, which is clearly separated from a high-grade undifferentiated or poorly differentiated carcinoma component.

Differential diagnosis Sinonasal AdCC must be mainly distinguished from other salivary gland-type tumors which occur in this territory, particularly pleomorphic adenoma, polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma, and basaloid squamous cell carcinoma with cribriform pattern.

Treatment and prognosis Wide surgical resection is the usual treatment, which may be followed by radiotherapy. AdCC follows a protracted but relentless course, which at the outset may be silent. The majority of patients present with locally advanced disease; lymph node and distant metastases are a rare late event. The overall 5-year survival is around 60 %, but the 10–20-year survival is poorer [355]. Patients with cribriform pattern may have a longer survival than patients with solid-type tumors [352]. Spontaneous regression of an AdCC of the nasal cavity has been recently reported [356].

Mucoepidermoid Carcinoma

Definition Mucoepidermoid carcinoma (MEC) is a malignant glandular tumor characterized by mucous, intermediate, and epidermoid cells. They are subdivided in low- and high-grade categories.

Epidemiology Sinonasal MEC is rare, representing less than 1 % of all sinonasal carcinomas [357, 358]. Patients are usually adult, and there is no gender predilection [359]. The majority of tumors arise in the nasal cavity, followed by the maxillary sinus.

Microscopy The diagnosis of sinonasal MEC requires the identification of mucous, squamous, and intermediate cells (Fig. 2.65). Infiltration of the mucosa and bone is usually identifiable. The presence of cystic spaces is a frequent feature, while necrosis and atypical mitotic figures are rarely seen. The majority of tumors are in the low-grade category [359] although high-grade MEC may be encountered in the sinonasal tract [360].

Differential diagnosis In the sinonasal tract, the differential diagnosis of MEC includes mainly squamous cell carcinoma and adenosquamous carcinoma. Non-intestinal-type adenocarcinomas with clear cells and/or mucous production should also be ruled out.

Treatment and prognosis Most tumors present in low stage and recurrences develop in about one-third of patients after surgical resection [359].

Acinic Cell Carcinoma

Definition Acinic cell carcinoma (ACC) is a low-grade malignant neoplasm composed of cells with serous acinar differentiation.

Epidemiology ACC is uncommon in the sinonasal tract, and only a small number of cases have been documented in the nasal cavity [341, 361–365] and in the maxillary sinuses [366–368]. Most of them are single case reports.

Microscopy ACC is composed of four cell types, acinar, vacuolated, clear, and nonspecific glandular. They may give rise to the following main patterns: solid, microcystic, papillary cystic, and follicular [369].

Differential diagnosis The main tumors to distinguish from ACC are oncocytoma (Figs. 2.66 and 2.67), all the clear cell salivary-type tumors that may arise in the sinonasal tract and metastatic renal cell carcinoma [345]. Although mammary analogue secretory carcinoma (MASC) should be considered another differential diagnosis in cases of non-parotid ACCs, the single potential ethmoidal case so far studied was negative for the *ETV6-NTRK3* translocation, which excluded MASC, and showed PAS-diastase-resistant zymogen granules typical of ACC [370].

Treatment and prognosis Surgical resection alone gives in most cases excellent results.

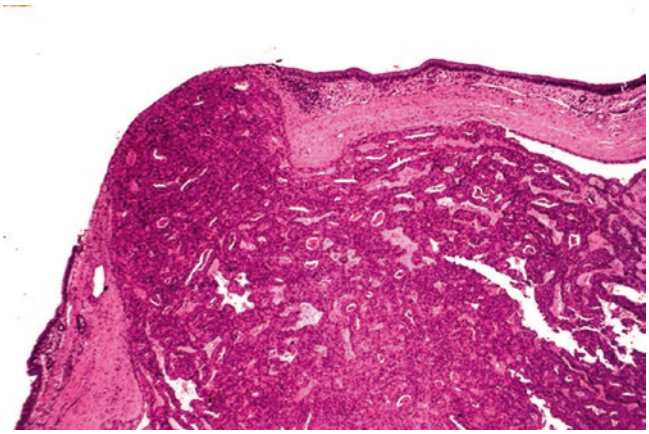

Fig. 2.66 Low-grade oncocytic carcinoma: the tumor infiltrates the sinonasal mucosa just beneath the epithelium which is focally eroded (Courtesy of Prof. H. Ostertag, Hannover, Germany)

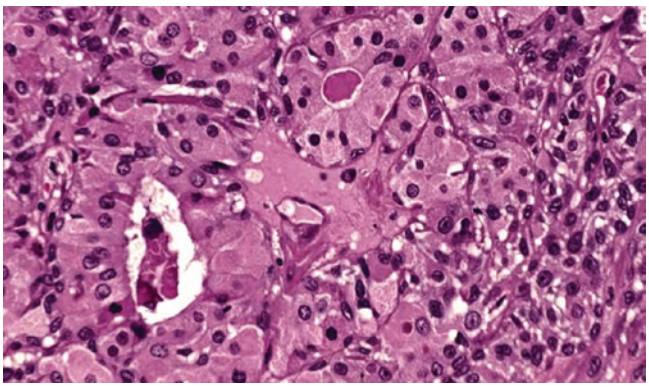

Fig. 2.67 Low-grade oncocytic carcinoma: the oncocytes form glands and cords and contain nuclei with conspicuous nucleoli and discrete atypia (Courtesy of Prof. H. Ostertag, Hannover, Germany)

Epithelial-Myoepithelial Carcinoma

Definition Epithelial-myoepithelial carcinoma (EMC) is a low-grade malignant tumor composed of variable proportions of two cell types which typically form duct-like structures. There is an inner layer of duct lining cells and an outer layer of clear cells [339].

Epidemiology EMC is quite rare in the sinonasal tract. Cases have been reported to involve the nasal cavity and maxillary sinus [371–377].

Microscopy The inner layer of the duct-like structures consists of small dark-staining cuboidal cells. The outer clear cells stain strongly for glycogen and are also positive for p63, vimentin, and smooth muscle actin; the inner luminal ductal cells are positive for cytokeratin cocktails and also for CK 19. There is considerable variation in the proportion of duct lining cells and clear cells, and not uncommonly, the latter are the predominant feature, forming sheets or nests of clear cells rather than ductal structures. The tumor is cytologically bland and mitoses are rare. Perineural and vascular invasion may be present and recurrence and metastases may develop.

Differential diagnosis Main differential diagnoses of EMC are myoepithelioma, pleomorphic adenoma, myoepithelial carcinoma, and adenoid cystic carcinoma.

Treatment and prognosis Wide surgical resection and adjuvant radiotherapy currently achieve excellent results in patients with EMC.

Other Salivary-Type Adenocarcinomas

Carcinoma ex pleomorphic adenoma [142, 378], myoepithelial carcinoma [147, 379], polymorphous low-grade adenocarcinoma (Figs. 2.68, 2.69, and 2.70) [380], and basal cell adenocarcinoma [381] have been reported in the sinonasal

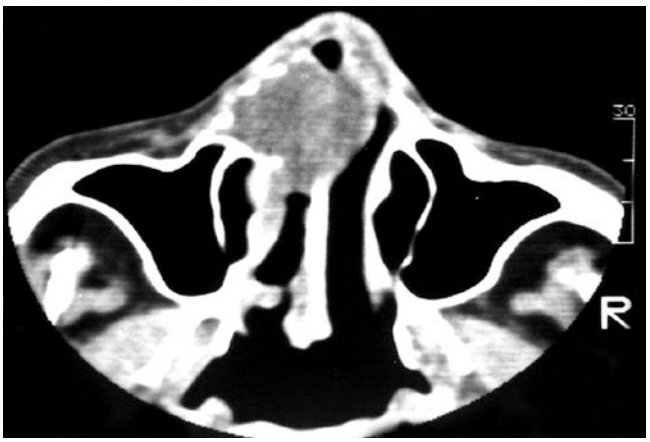

Fig. 2.68 Polymorphous low-grade adenocarcinoma: CT scan showing an irregularly nodular lesion destroying the anterior nasal septum

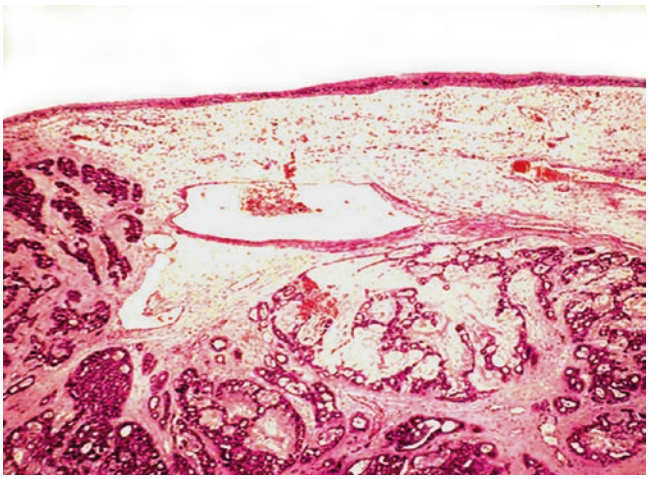

Fig. 2.69 Polymorphous low-grade adenocarcinoma: variegated glandular arrangements composed of tubules with bland cellularity are seen beneath the respiratory epithelium

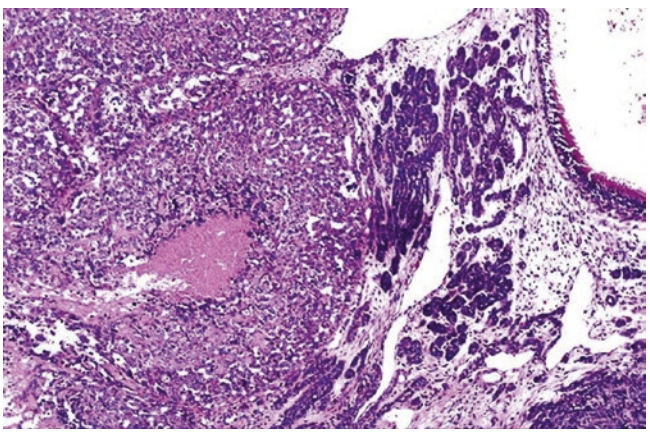

Fig. 2.70 Polymorphous low-grade adenocarcinoma with high-grade component: an undifferentiated carcinoma with a focus of central necrosis is seen in the immediate neighborhood of the usual low-grade component (Courtesy of Prof. J. Lloreta, Barcelona, Spain)

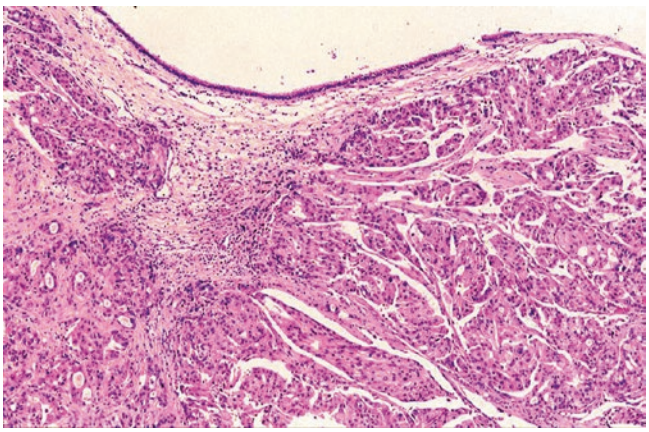

Fig. 2.71 Salivary duct carcinoma: markedly atypical glandular growth beneath the respiratory epithelium

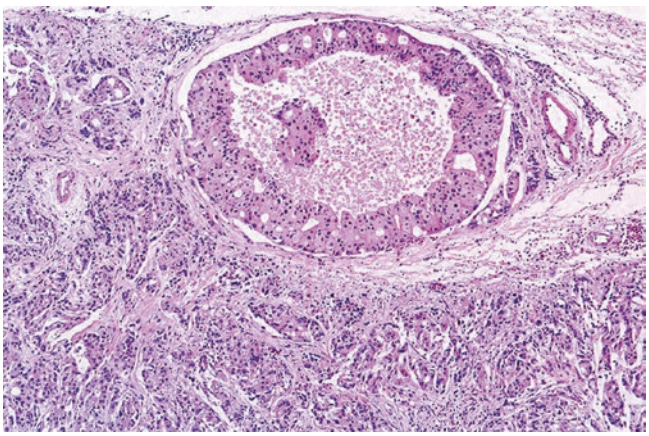

Fig. 2.72 Salivary duct carcinoma: the ductal pattern, with comedo type of necrosis, was convincingly evident in the metastasis to a submandibular lymph node

tract. Two to 10% of salivary duct carcinomas (SDCs) arise from the seromucous glands of the upper respiratory tract [382]. We have seen one example of SDC originating in the maxillary sinus, in which the characteristic ductal pattern, with comedo type of necrosis, was only evident in the metastases to the submandibular lymph nodes. The primary tumor was initially classified as adenocarcinoma NOS (Figs. 2.71 and 2.72).

2.11.9 Primary Malignant Mucosal Melanoma

Definition Primary malignant mucosal melanoma (PMMM) of the sinonasal tract is a neoplasm derived from the melanocytes in the Schneiderian mucosa [383–385].

Epidemiology The head and neck region is the most commonly involved site in which PMMMs develop, being the sinonasal tract its most frequent location [386, 387]. Sinonasal PMMMs account for less than 1 % of all melanomas and for less than 5 % of all sinonasal malignancies [386–389]. Although most series report a similar gender distribution, others indicate a slightly increased incidence in males [390, 391]. The tumors develop primarily between the fifth and eighth decades of life with a median age of presentation at approximately 60 years [391, 392]. They originate from melanocytes present in the mucosa of the respiratory tract (Fig. 2.73) [384, 385, 388]. In our experience, it is not uncommon to see melanoma arising in an area of squamous metaplasia (Fig. 2.74). In contrast to Caucasian, black Africans often show visible pigmentation at sites corresponding with the common locations of intranasal melanomas, for which they have a higher incidence [393].

Clinical aspects The signs and symptoms of presentation of sinonasal PMMMs are not specific. Epistaxis and nasal obstruction are frequent when located in the nasal cavity. PMMMs of the head and neck occur most frequently in the nasal cavity, where the lateral nasal wall and nasal septum are the most common sites of origin of the sinonasal tract. Melanomas arising from the lateral nasal wall account for almost half of the total. Middle and inferior turbinates and nasal vestibule are other possible sites. The maxillary sinus is the most commonly affected paranasal cavity, followed by the ethmoid, frontal, and sphenoid sinuses. Concurrent nasal and paranasal lesions are infrequent. The sinonasal PMMMs are usually advanced at presentation and the precise site of origin may be difficult to localize. Sinonasal PMMMs metastasize less frequently to lymph nodes but more frequently to the lungs and brain [390, 391, 394].

Etiology Unlike cutaneous melanomas, sinonasal PMMMs are not clearly related to ultraviolet radiation. Inhaled and ingested carcinogens, particularly products of smoking and formaldehyde, have been implicated in the pathogenesis, similar to other malignancies of the nasal cavity [395, 396].

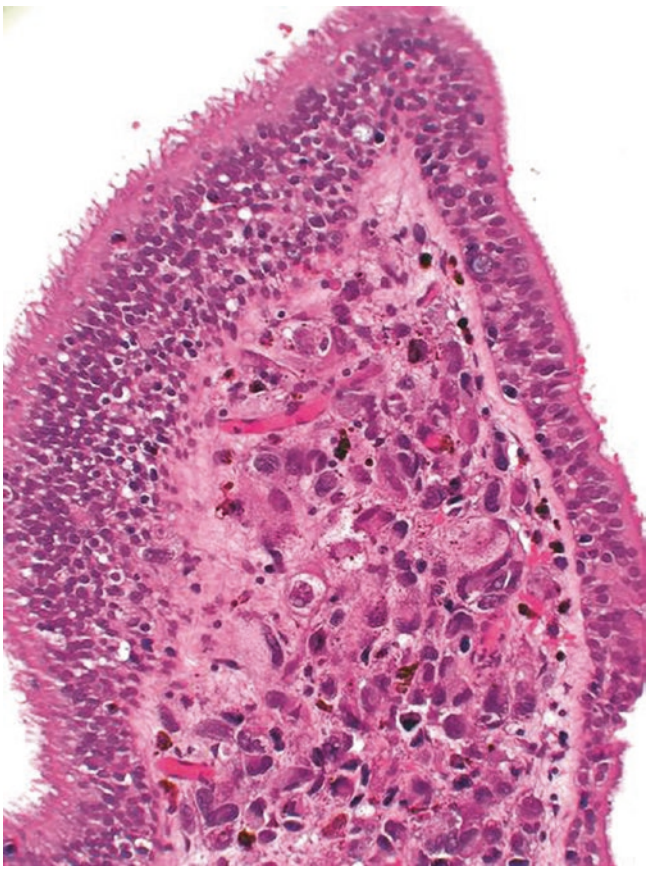

Fig. 2.73 Malignant mucosal melanoma: sheet of pigmented malignant melanocytes distributed in the lamina propria underneath ciliated respiratory epithelium

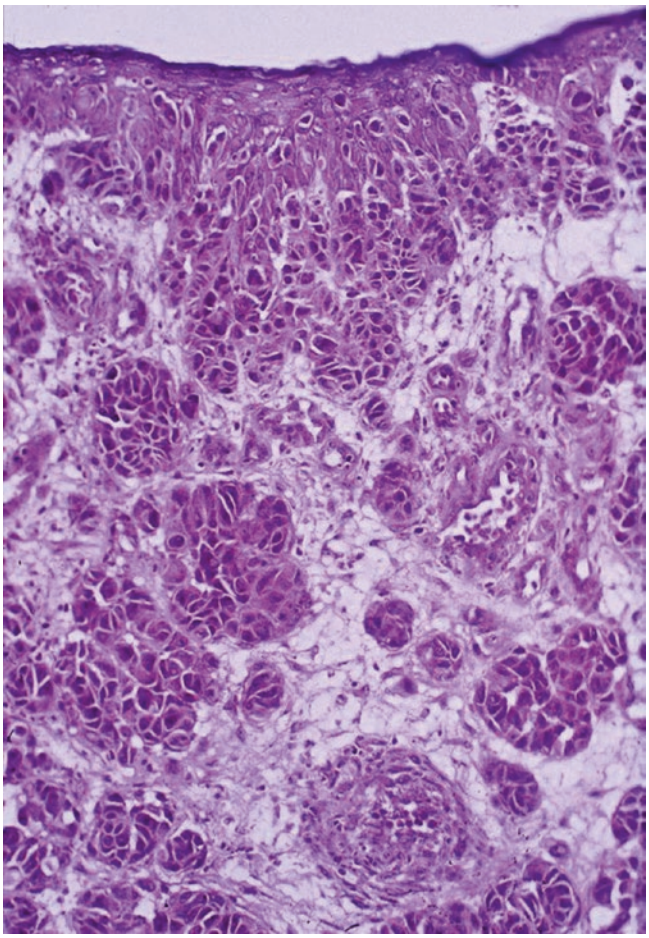

Fig. 2.74 Malignant mucosal melanoma: nests of nonpigmented, downward invasive malignant melanocytes arising from metaplastic squamous epithelium showing junctional activity

Genetics An increased frequency of c-KIT (CD117) aberrations has been observed in PMMMs, while this is not the case in cutaneous melanomas [397]. Conversely, *BRAF* mutations that are increased in cutaneous melanomas are uncommon in PMMMs [398, 399]. Recently, it has been reported that in sinonasal PMMMs *NRAS* mutations and *CCDN1* amplification are more frequent than *KIT* or *BRAF* mutations [398]. Loss of p16 expression, *CDKN2A* mutations, and loss of heterozygosity are observed in up to 50 % of PMMMs [400, 401].

Macroscopy Sinonasal malignant melanomas are either pigmented (black-brown) or nonpigmented (pink-tan) lesions. In the nasal cavity, they commonly arise in the anterior portion of the septum and present as tan-brown polypoid formations, with occasional ulcerated and hemorrhagic areas (Fig. 2.75). When arising within sinuses, they present as extensive and widely infiltrative tumors. The development of intranasal malignant melanoma in inverted papilloma has been reported [402].

Microscopy The histological features of sinonasal melanomas may be as polymorphic as in their cutaneous counterpart. Metastatic disease needs to be ruled out, before they are labeled as primary tumors. Primary melanomas may be recognized by the presence of junctional activity or by the finding of an intraepithelial component in the adjacent mucosa; nevertheless, these features are usually lost in sinonasal mucosa because of the thinness of the surface epithelium and frequent ulceration in advanced stages of the disease. Melanomas are composed of medium- to large-sized cells that may be polyhedral, round, fusiform, pleomorphic, microcytic, or a mixture of them. Usually, they have finely granular cytoplasm and nuclei with one or more eosinophilic nucleoli. Mitotic activity is prominent. A rare balloon cell variant with clear cytoplasm may mimic the various sinonasal salivary gland-type clear cell tumors. Osteocartilaginous differentiation has also been observed [403]. The cells of sinonasal melanoma grow in either solid, loosely cohesive, storiform, pseudo-alveolar, or organoid patterns [388]. Two-thirds of sinonasal melanomas contain some intracytoplasmic brown pigment [388], which has to be confirmed as melanin (Fig. 2.76). In the sinonasal tract, nonpigmented melanomas are not uncommon; in our series in Barcelona, up to 40 % of the sinonasal melanomas are amelanotic (Fig. 2.77). When melanin is scarce or is not found, diagnosis may be difficult, and special techniques are mandatory. Electron microscopy reveals the presence of premelanosomes and/or melanosomes (Fig. 2.78).

Immunohistochemistry The cells of melanotic and amelanotic malignant melanomas are negative for cytokeratin and positive for vimentin, S-100 protein, Melan-A, HMB-45, tyrosinase, microphthalmia-associated transcription factor

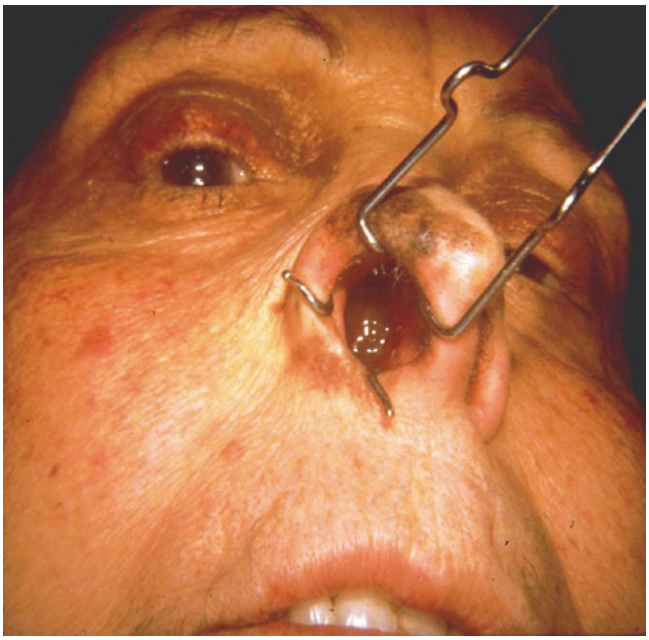

Fig. 2.75 Malignant mucosal melanoma: darkly pigmented polypoid lesion of the anterior nasal cavity in contiguity with a similarly pigmented lesion of the nasal skin (Courtesy of Prof. J. Trasserra. Barcelona, Spain)

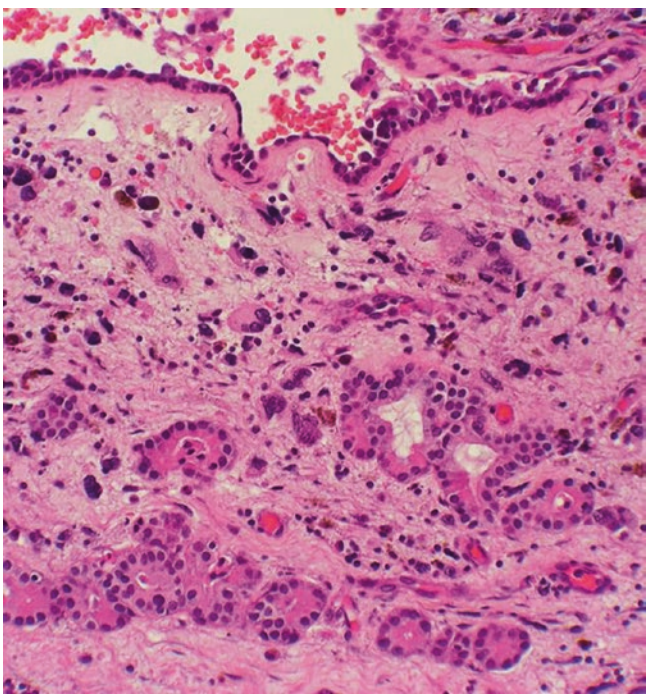

Fig. 2.76 Malignant mucosal melanoma: the tumor grows in the lamina propria beneath the respiratory epithelium and between seromucous glands. The presence of intracytoplasmic brown pigment is recognized

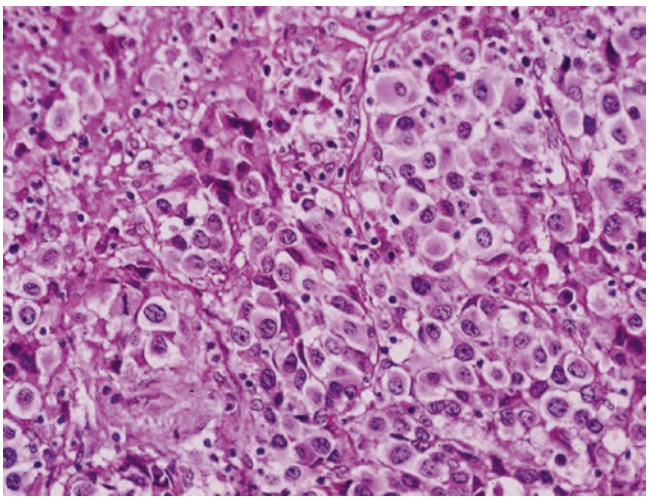

Fig. 2.77 Malignant mucosal melanoma: diffuse growth of nonpigmented malignant melanocytes with delicate fibrous septa forming theca arrangements. This pattern should not be mistaken for non-keratinizing squamous cell carcinoma

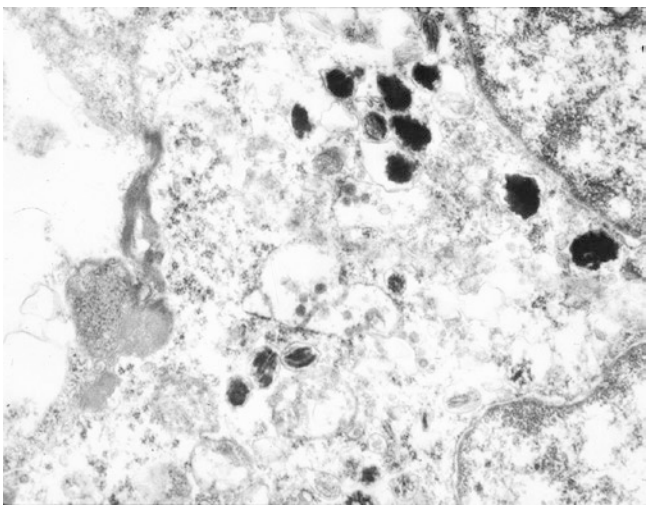

Fig. 2.78 Malignant mucosal melanoma: the ultrastructural hallmark is the presence of melanosomes and premelanosomes in the cytoplasm. The former appear near the nuclear membrane and the latter more peripherally. Desmosomes and tonofilaments are absent (Courtesy of Prof. Bombi, Barcelona, Spain)

(MITF), and SOX10 [404–408]. Loss of p16 expression is seen in 74 % of sinonasal melanomas [409].

Differential diagnosis The recognition of amelanotic malignant melanoma of the sinonasal tract requires ruling out a large list of entities. Epithelioid melanomas have to be mainly distinguished from non-keratinizing squamous cell carcinoma, but also from clear cell carcinomas as well as from epithelioid malignant schwannoma [410] and from metastatic renal cell carcinoma. Microcytic melanoma may mimic SNUC and other small round cell tumors (Table 2.5). Spindle cell melanoma may be mistaken for a variety of spindle cell sarcomas.

Treatment and prognosis The mainstay of treatment is radical surgical resection. Adjuvant radiotherapy seems to improve locoregional control but does not improve overall survival. Systemic therapy should be considered only for patients with metastatic or unresectable locoregional disease [394]. Patients with primary nasal melanomas had significantly better 5-year survival than do patients with melanomas from other head and neck sites [411]. The prognostic significance of the level of local invasion, as established for cutaneous melanomas, does not apply to mucosal melanomas because of the absence of histological landmarks analogous to the papillary and reticular dermis; nevertheless, invasion deeper than 0.5 mm is associated with decreased survival [388].

Although many of the patients do not show initial lymph node involvement or disseminated metastases [388, 412, 413] and have stage I disease at the time of initial diagnosis, the prognosis is bad due to high recurrence rate [389]. This recurrence appears to be related to multicentricity of the tumors and to the anatomic characteristics of the region that preclude adequate resection, which is the treatment of choice [414, 415]. Patients with lower Ki-67 scores showed better survival than those with higher Ki-67 scores [416]. The utility of radiotherapy is controversial but it can be of use in unresectable cases or to control recurrences [415, 417]. Immunotherapy and chemotherapy are also used for metastatic disease [414]. Five-year survival of sinonasal PMMM ranges reportedly between 17 and 47 % [389, 394, 414, 415, 418]. In our series in Barcelona, the 5-year survival is of 35 %, which is similar to that of sinonasal SCC.

2.11.10 Olfactory Neuroblastoma

Definition Olfactory neuroblastoma (ONB) is a malignant tumor unique to the nasal cavity composed of neuroblasts derived from the olfactory mucosa that share neuroepithelial and neuroendocrine features [419–422].

Synonyms Esthesioneuroepithelioma, esthesioneurocytoma, and esthesioneuroblastoma

Epidemiology ONB is an uncommon malignant tumor representing about 2–3 % of all sinonasal neoplasms [383]. ONB can affect patients of all ages and both sexes are equally involved [423]. Although a bimodal age presenta-

tion has been previously suggested, recent reports show an even incidence across all ages with peaks in the fifth and sixth decades [272]. This is clearly different from adrenal neuroblastoma, with most cases arising in children under 4 years of age.

Clinical aspects Nasal obstruction, rhinorrhea, and epistaxis are the most common presenting symptoms. The site of origin of ONB is confined to the olfactory mucosa that lines the upper part of the nasal cavity [424]. Occasionally ONB involves predominantly the superior aspect of the cribriform plate and grows as an intracranial tumor [425, 426]. Ectopic foci of the olfactory mucosa, the Jacobson's or vomeronasal organ, sphenopalatine ganglion, ganglion of loci, and autonomic ganglia of the nasal mucosa are very rare potential sites of origin of ONB [427]. Before establishing a diagnosis of "ectopic" ONB, an extremely rare entity that implies absence of involvement of the olfactory membrane, other sinonasal small round cell tumors have to be carefully ruled out (Table 2.5).

Genetics ONB is characterized by a marked genomic instability with frequent chromosomal losses and gains [428]. ONB lacks the t(11;22) translocation characteristic of PNET [429]. It also lacks the molecular genetic changes of adrenal neuroblastoma, which, in children, may metastasize to the sinonasal region.

Macroscopy ONBs are often unilateral, presenting as smooth polypoid or fungating masses of fleshy consistency and yellow to pink color (Fig. 2.79).

Microscopy ONBs exhibit one of two main patterns of growth that bear diagnostic and prognostic implications [344]. This pattern approach is a valuable complement of the initial scheme proposed by Hyams et al. [114] to grade ONB in four groups (Table 2.7). The low-grade pattern comprises grades I–II of Hyams and the high-grade pattern grades III–IV. The low-grade pattern is seen most often, and it presents lobular arrangements with well-defined groups of tumor cells separated by abundant edematous and variably vascularized stroma (Fig. 2.80). Prominent vascularization may cause bleeding at the time of biopsy. The neoplastic neuroblasts are typically small, showing round to oval nuclei with stippled chromatin, absent or small nucleoli, and minimal cytoplasm; occasionally clear cell type cytoplasms may be found. Neuroblasts are commonly separated by a neurofibrillary matrix formed by neuronal cell processes, in which axons may be demonstrable (Fig. 2.81). This background, seen in about 85 % of ONB, is the most helpful diagnostic feature. Homer Wright pseudorosettes are quite characteristic of ONB; however, they are less commonly seen. They form when the tumor cells surround the neurofibrillary matrix in collar-like arrangements. Perivascular pseudorosettes, formed by tumor cells arranged around capillaries, are of no diagnostic value, for they may be found in several types of neoplasms.

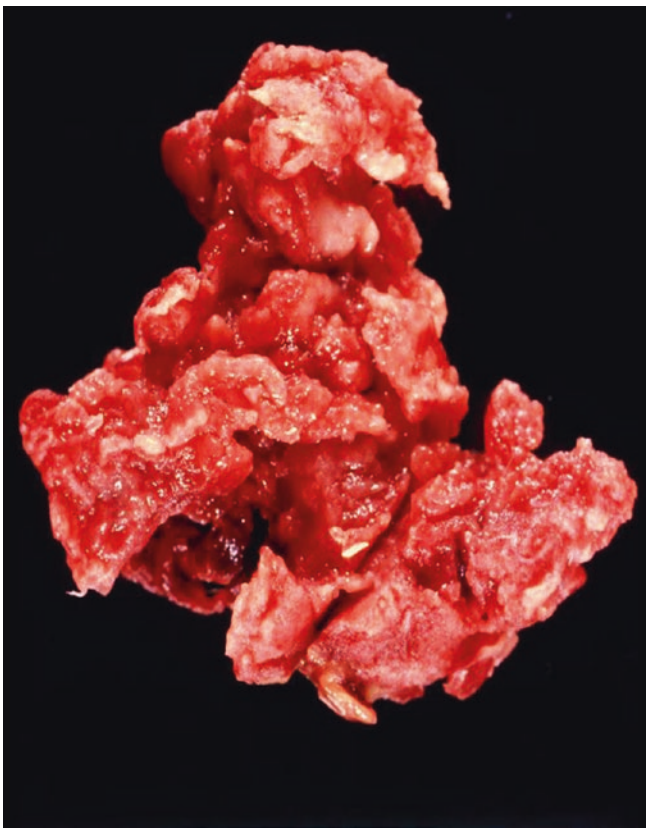

Fig. 2.79 Olfactory neuroblastoma: polypoid mass of fleshy consistency and pink color

Table 2.7 Olfactory neuroblastoma

Histological grades	I	II	III	IV
Lobular architecture	Present	Present	±	±
Mitotic activity	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Moderate	Prominent	Marked
Fibrillary matrix	Prominent	Moderate	Slight	Absent
Rosettes	H-W ±	H-W ±	Flexner ±	Absent
Necrosis	Absent	Absent	Occasional	Common
Calcification	±	±	Absent	Absent

Hyams grading scheme

H-W Homer Wright rosettes, ± present or absent

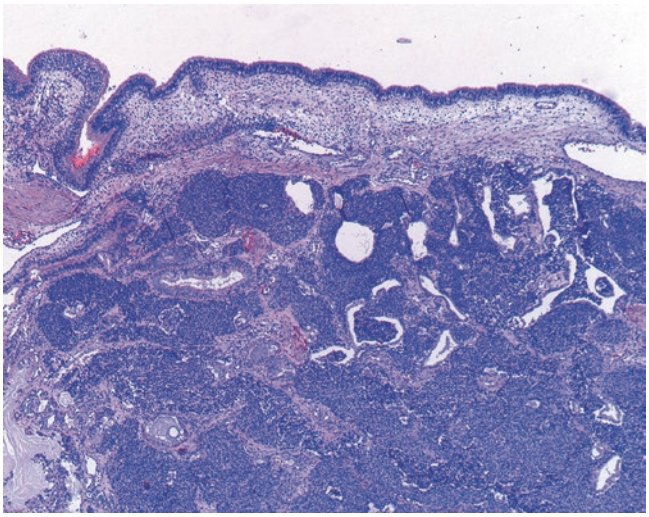

Fig. 2.80 Olfactory neuroblastoma: beneath an intact olfactory mucosa, the low-grade pattern displays well-defined lobular arrangements of tumor cells separated by edematous and variably vascularized stroma

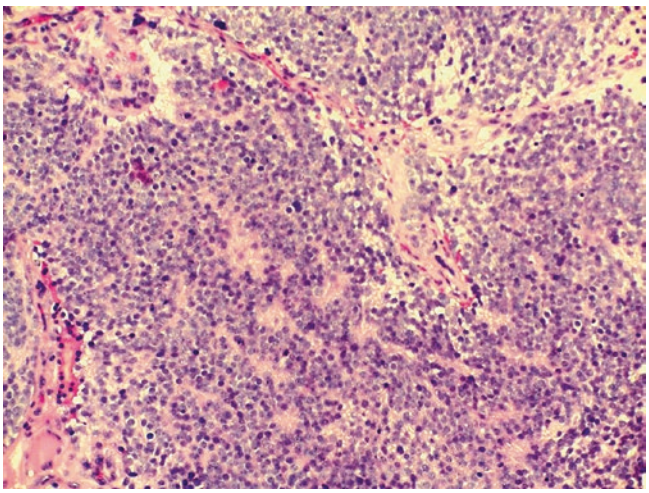

Fig. 2.82 Olfactory neuroblastoma: the high-grade pattern presents diffuse sheets of cells, often with irregular nuclei and compact chromatin. The stroma is scant but well vascularized

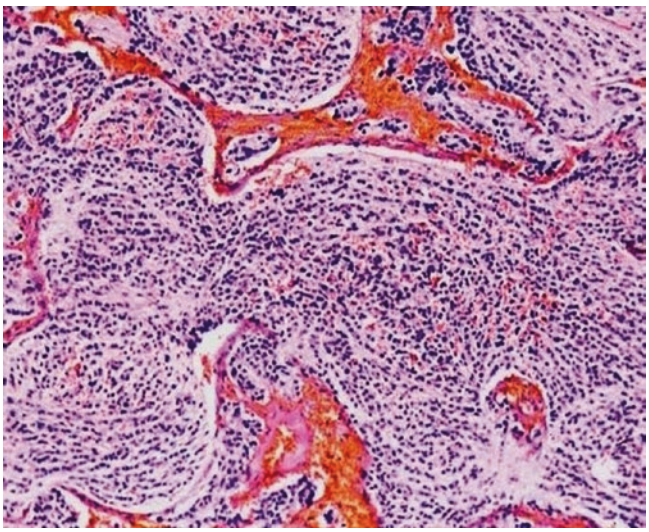

Fig. 2.81 Olfactory neuroblastoma: the neuroblasts appear separated by a neurofibrillary matrix formed by neuronal cell processes

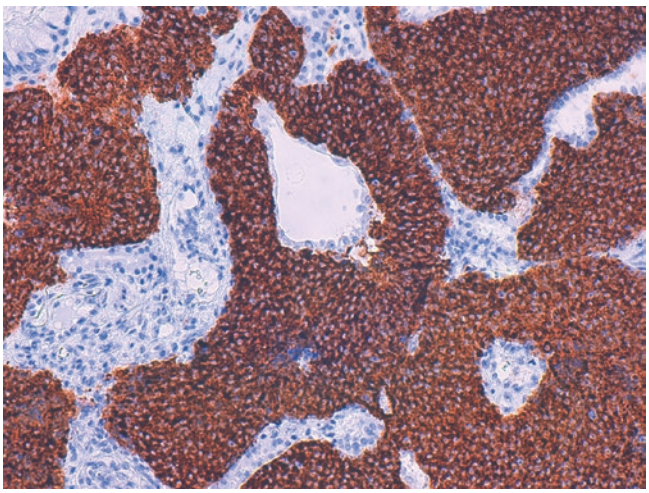

Fig. 2.83 Olfactory neuroblastoma: the neuroblasts that surround entrapped glands show strong and diffuse positivity for synaptophysin

Less frequently seen is the high-grade pattern of ONB, in which the tumor grows as diffuse sheets of cells with presence of foci of necrosis and scanty but highly vascular stroma (Fig. 2.82). True olfactory Flexner-Wintersteiner rosettes are only seen in grade III ONBs; this uncommon type of rosettes depicts well-defined lumina lined by columnar cells resembling olfactory epithelium. These cells generally have basally located nuclei and merge with the adjacent neuroblasts without any intervening basal lamina. Grade IV ONBs are anaplastic tumors and usually show pleomorphic nuclei, prominent eosinophilic nucleoli, increased mitotic rate, and conspicuous necrosis [427]. Very rarely, ONB may exhibit melanocytic or rhabdomioblastic differentiation [430–432]. Exceptional examples of mixed ONB and carcinoma have also been reported [433].

Immunohistochemistry and electron microscopy ONB shows diffuse positivity for synaptophysin, CD56, and NSE (Fig. 2.83). Chromogranin is less often positive. In tumors with a nesting pattern, S-100 protein is positive in the peripheral sustentacular cells. Cytokeratin is generally negative, although in ONB with nesting pattern, a few tumors may exhibit focal staining for low molecular weight CKs. EMA is negative. Neurofilament protein and other markers of neural

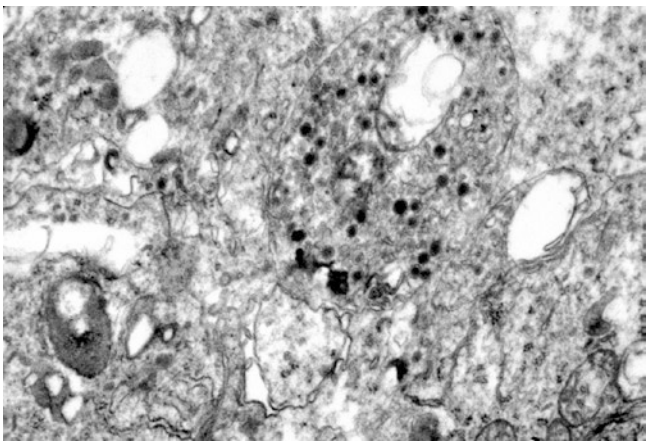

Fig. 2.84 Olfactory neuroblastoma: ultrastructural presence of neuroblastic differentiation, with neuritic processes, neurotubules, and membrane-bound dense-core granules, is seen (Courtesy of Prof. J. A. Bombí, Barcelona, Spain)

Table 2.8 Olfactory neuroblastoma

Kadish* – Morita** Staging		
Stage	Distribution (%)	5-year survival (%)
A* Confined to the nasal cavity	18	90
B* Involves the nasal cavity and paranasal sinuses	32	70
C* Beyond sinonasal cavities	50	40
D** Cervical lymphadenopathy and distant metastasis		<40

differentiation are more often expressed in tumors with diffuse, sheetlike pattern [421, 434–436]. Electron microscopy shows evidence of neuroblastic differentiation, demonstrating neuritic processes, neurotubules, and membrane-bound dense-core granules (Fig. 2.84) [437–439]. The human analogue of achaete-scute gene *HASH1*, expressed in immature olfactory neurons, is also expressed in olfactory neuroblastoma [440]. Conversely the olfactory marker protein [441], expressed exclusively in mature olfactory neurons, is not. ONB lacks CD 99 (MIC-2) expression [429, 442]. In a recent study, intense expression of olfactory-specific sensory transduction proteins was found in ONB, indicating that ONB and olfactory sensory neurons share the same lineage and that the detected transduction proteins could serve as specific tumor markers [443].

Differential diagnosis ONB must be distinguished from a wide variety of small round cell tumors arising in the sinonasal region (Table 2.5). While the diagnosis of low-grade ONBs is usually straightforward, particular care has to be taken before diagnosing high-grade ONBs, as glands of sinonasal non-intestinal-type adenocarcinomas should not be mistaken for the Flexner-Wintersteiner rosettes of ONB grade III; likewise the diffuse sheets of cells seen in either sinonasal undifferentiated carcinoma or in small cell neuroendocrine carcinoma may mimic grade IV ONB. Furthermore, ONBs with rhabdomyoblastic differentiation or mixed with carcinoma have to be differentiated from teratocarcinosarcoma and those with melanocytic differentiation from malignant mucosal melanoma [444].

Treatment and prognosis Complete surgical excision with cribriform plate resection, often followed by radiation therapy and/or chemotherapy, seems to be the treatment of choice [419, 445, 446]. In advanced ONB, high-dose chemotherapy and autologous bone marrow transplantation have been used [447, 448]. Staging of ONB is based on the Kadish system [449], in which stage A disease is confined to the nasal cavity, stage B is confined to the nasal cavity and paranasal sinuses, and stage C shows local or distant spread beyond the nasal cavity or sinuses; most tumors present in stage C. This correlates with survival, which is about 90 % for stage A, 70 % for stage B, and 40 % for stage C [449]. Recognizing the poor prognostic implications of regional and distant metastatic disease, adding cervical lymphadenopathy and distant metastasis as a fourth, stage D category was suggested [445], which showed a worse disease-free survival specifically for the D category [450] (Table 2.8). Necrosis is the single histological feature that seems to correlate with poor survival [420]. About two-thirds of recurrences are in the form of local disease, whereas locoregional recurrences, with intracranial extension or involvement of cervical lymph nodes, represent about 20 %, and distant metastases account for the rest [423, 451]. Distant metastases mainly involve the bone and lung [448].

2.11.11 Ewing's Sarcoma/Primitive Neuroectodermal Tumor (EWS/PNET)

Definition An exceedingly rare sinonasal tumor composed of poorly differentiated small round cells that shows varying degrees of neuroectodermal differentiation and originates from a pluripotential neuroectodermal cell progenitor [452, 453].

Epidemiology Approximately 9 % of extraosseous EWS/PNETs arise in the head and neck region [279], and about 20 % of them develop in the sinonasal tract, being the most common site the maxillary sinus, followed by the nasal cavity (Fig. 2.85) [453–455].

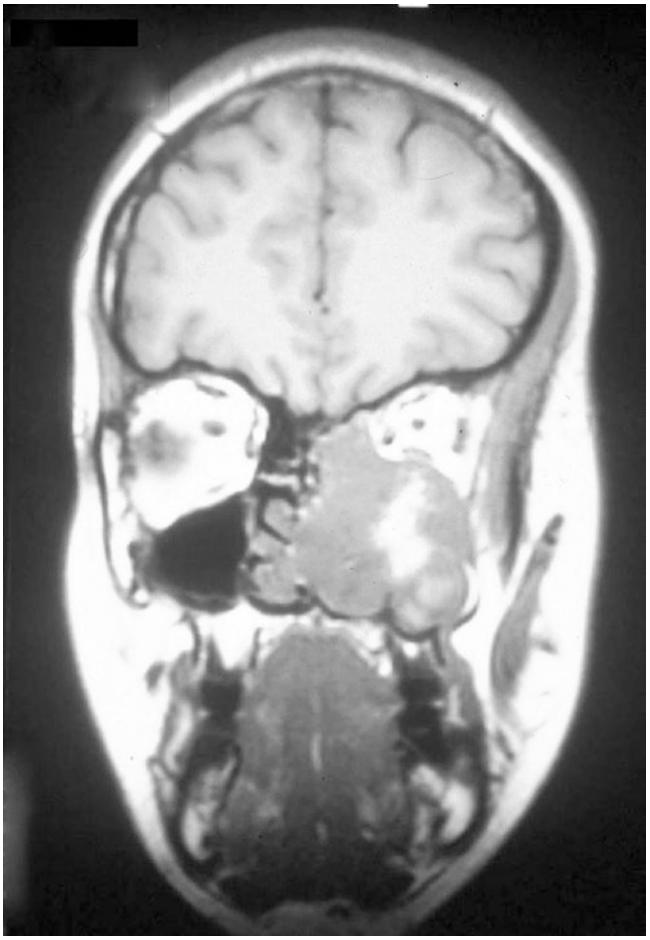

Fig. 2.85 Primitive neuroectodermal tumor: MRI displaying a destructive mass involving the right maxillary sinus, expanding to the orbit and to both sides of the nasal cavity

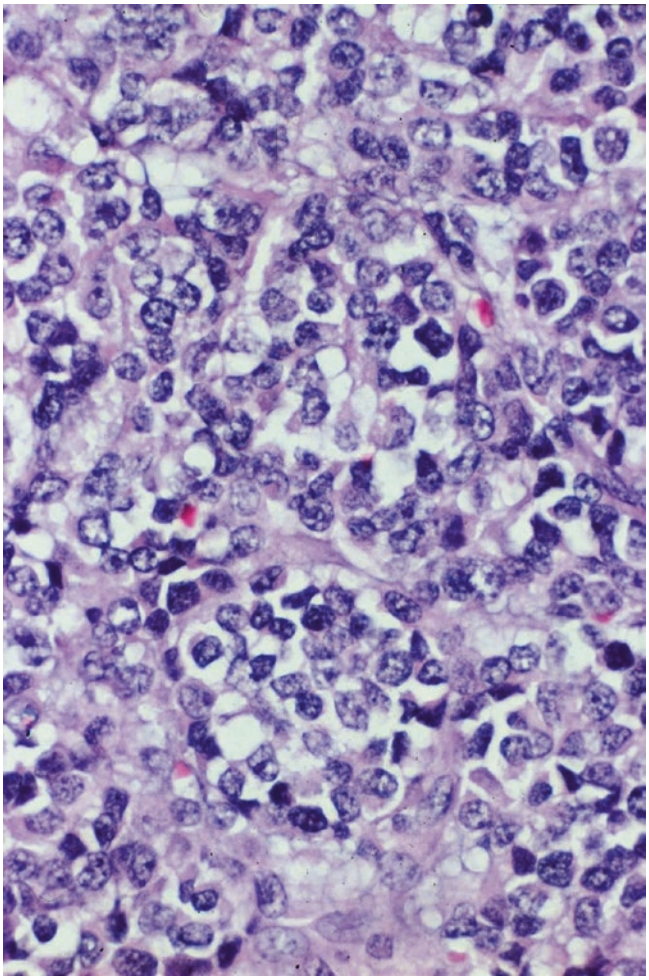

Fig. 2.86 Primitive neuroectodermal tumor: monotonous proliferation of small, round, undifferentiated cells requiring immunohistochemistry for correct typing

Etiology EWS/PNET has been reported following radiotherapy for retinoblastoma [456–458].

Macroscopy Sinonasal EWS/PNET may present as a soft polypoid mass.

Microscopy EWS/PNET is composed of uniform, small, undifferentiated, primitive neuroectodermal cells (Fig. 2.86) [459]. Unusually, pseudorosettes and true rosettes may be found in these tumors.

Electron microscopy EWS/PNET displays rudimentary neuritic differentiation, as well as scanty microtubule formation; dense-core granules are much less abundant than in olfactory neuroblastoma (Fig. 2.87).

Immunohistochemistry The great majority of EWS/PNET will react strongly with antibodies against CD99 (Fig. 2.88). This marker is of considerable value but it is by no means specific. A growing number of other neoplasms expressing

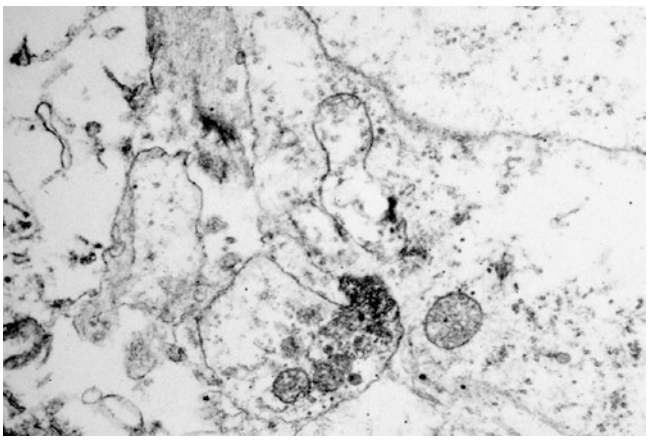

Fig. 2.87 Primitive neuroectodermal tumor: ultrastructurally, a rudimentary neuritic differentiation is seen with scanty microtubule formation. Dense core granules are much less abundant than in olfactory neuroblastoma (Courtesy of Prof. J. A. Bombí, Barcelona, Spain)

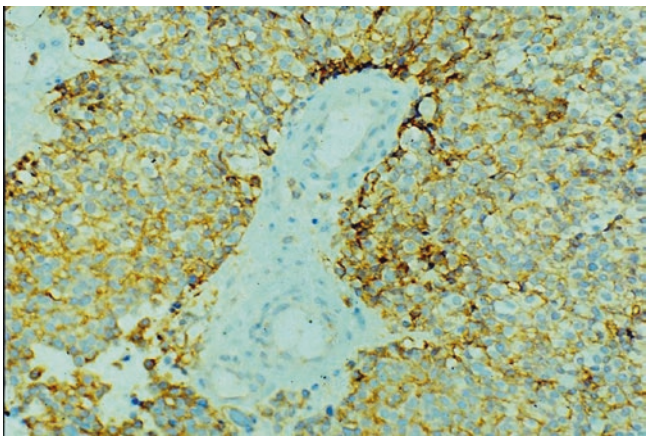

Fig. 2.88 Primitive neuroectodermal tumor: CD99-positive immune reaction seen at the cellular membrane. Molecular study confirmed diagnosis

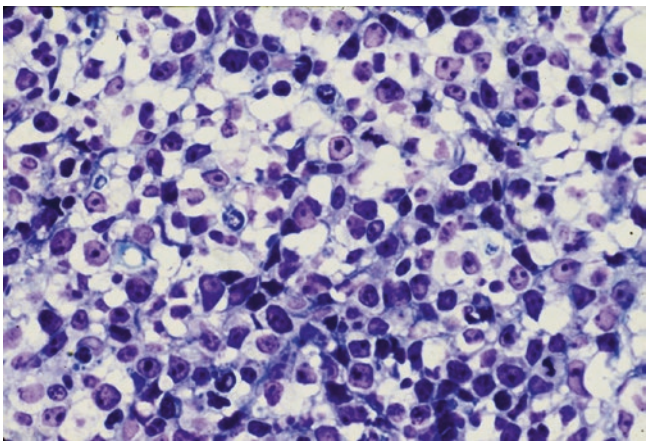

Fig. 2.89 Malignant lymphoma: diffuse large B-cell lymphoma proliferation. Giemsa stain

this protein have been documented. Among these are T-cell lymphomas [442].

Genetics The standard translocation t(11; 22) (q24; q12) of PNET [460] results in the fusion of the *EWS-FLI1* genes. The detection of the chimeric transcript by techniques of molecular biology confirms the diagnosis [461–463].

Differential diagnosis Olfactory neuroblastoma, sinonasal undifferentiated carcinoma, lymphoma, rhabdomyosarcoma, and primary malignant mucosal melanoma are the main entities to rule out [262]. We have seen one example of EWS/PNET arising from the maxillary antrum, which ultrastructurally showed rudimentary neuritic differentiation, as well as scanty microtubule formation. This raised the differential diagnostic dilemma of "ectopic olfactory neuroblastoma"; nevertheless, the tumor cells were CD99 positive and showed the t(11;22)(q24;q12) translocation, findings that are characteristically negative in ONB [429].

Treatment and prognosis Multimodal therapy, which includes chemotherapy, radiotherapy, and surgery, offers the best results. Head and neck EWS/PNET has better prognosis than tumors of other sites. The overall 5-year survival rates reach between 60 and 70 % [453].

2.11.12 Malignant Lymphomas

Definition Malignant lymphomas are small round cell tumors with phenotypic features of B/T cells and variable differentiation.

Epidemiology Sinonasal malignant lymphomas (SNML) account for approximately 13 % of all upper aerodigestive tract lymphomas [205] and for 6 % of all sinonasal malignancies [464]. In our own series, they account for 9.5 % (Table 2.3). In western countries, about 50 % of SNML are of B-cell-type and the other 50 % mostly shows NK-/T-cell lineage [465], whereas other reports point to more variable rates [466–469]. Differently, in oriental populations, most primary lymphomas of the nasal cavity and nasopharynx are of NK-/T-cell lineage [470–473].

Microscopy Sinonasal B-cell lymphomas are in general composed of a diffuse proliferation of large lymphoid cells or of a diffuse mixed pattern of small and large cells (Fig. 2.89). They infiltrate and expand the subepithelial soft tissue and may extend into the underlying bone. Sinonasal B-cell lymphomas lack epitheliotropism, polymorphous cell infiltrate, angiocentricity, prominent necrosis, and fibrosis. They are usually positive for B-cell markers (CD20 and CD79a) and negative for NK-/T-cell markers. κ-light chain restriction is seen more often than λ restriction. EBV markers are often negative.

Sinonasal NK-/T-cell lymphomas were labeled in the past decades with terms such as "lethal midline granuloma," "polymorphic reticulosis," and angiocentric T-cell lymphoma, among others. Patients may present either with an obstructive mass or with midfacial destructive lesions. Histologically, an angiocentric and angiodestructive infiltrate with extensive necrosis and epitheliotropism is frequently seen. In extranodal NK-/T-cell lymphoma, cells may be small, medium sized, large, or anaplastic and may show a conspicuous admixture of inflammatory cells (Fig. 2.90). Pseudoepitheliomatous hyperplasia of the covering epithelium may occur, and when exaggerated, it should not be confused with squamous cell carcinoma [471]. Extranodal NK-/T-cell lymphoma is almost always associated with EBV positivity. The most typical immunophenotype is CD2+, CD56+, surface CD3−, and cytoplasmic CD3ε+. Most cases

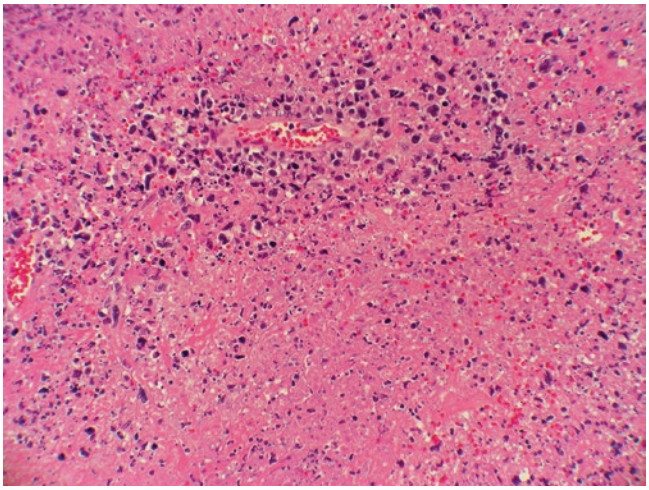

Fig. 2.90 Malignant lymphoma: NK-/T-cell lymphoma nasal type with angiocentric infiltrate of atypical lymphocytes and extensive necrotic areas

are also positive for cytotoxic granule associated proteins (granzyme B, TIA-1, and perforin). Other T- and NK-cell-associated markers are usually negative. Sinonasal lymphomas demonstrating CD3ε+, CD56−, cytotoxic molecule+, and EBV+ are also included within the NK/T category. No specific cytogenetic abnormalities have been identified [474].

Differential diagnosis SNML of either B-cell or T-cell derivation needs a careful distinction of other small round cell tumors (Table 2.5) and with extramedullary plasmacytoma [475, 476], as well as with extramedullary tumors composed of myeloid or lymphoid blasts [477].

Treatment and prognosis Radiotherapy and chemotherapy CHOP regime has been the standard treatment for advanced sinonasal diffuse large B-cell lymphomas [478]. The addition of the anti-CD20 monoclonal antibody Rituximab® has led to a marked improvement in survival [479].

The treatment and prognosis of nasal NK-/T-cell lymphoma are variable. Initial treatment with radiotherapy alone or combined with multiagent chemotherapy is used. Some patients respond well to therapy and others die of disease despite aggressive therapy [472]. In recent years, the survival has improved with more intensive therapy [480]. For a detailed discussion of lymphoid lesions, the reader is referred to Chap. 13.

2.11.13 Extraosseous Plasmacytoma

Definition A mass-forming lesion of monoclonal plasma cells that occurs outside the bone and bone marrow, without evidence of underlying multiple myeloma [481].

Epidemiology More than 80 % of extraosseous plasmacytomas develop in the head and neck region, and 44 % of them involve the sinonasal region [482].

Clinical aspects Full examination of the patient is required to exclude disseminated disease.

Microscopy Plasmacytoma of the sinonasal tract usually appears as a diffuse infiltration of mature plasma cells of the mucosa; occasionally, tumor cells are less differentiated, and diagnosis may be difficult exclusively on histologic basis [475, 476, 483, 484].

Immunohistochemistry Staining for CD138 and κ and λ chains may be helpful. CD19 is nearly always negative and CD56 and CD117 are often aberrantly expressed.

Differential diagnosis Mucosal lymphomas with plasmacytic differentiation, particularly extranodal marginal zone (MALT) lymphoma, may be misinterpreted as extramedullary plasmacytoma.

Treatment and prognosis Most extraosseous plasmacytomas are cured with local radiation therapy. Regional recurrences occur in one-fourth of patients; distant extraosseous metastasis may occasionally occur [482].

2.11.14 Malignant Soft Tissue Tumors

Malignant soft tissues tumors of the sinonasal tract are very rare neoplasms and account for about 5 % of all the malignancies in this territory (Table 2.3). Only the most salient of these entities are covered here. For a detailed discussion of soft tissue tumors, the reader is referred to Chap. 12.

2.11.14.1 Fibrosarcoma

Definition A malignant mesenchymal tumor composed of fibroblast with variable collagen production and in prototypical cases a herringbone pattern [485].

Synonym Adult fibrosarcoma.

Epidemiology Most of head and neck fibrosarcomas occur in the sinonasal tract and are seen across a wide age range [486–489]. They are considered the second most common soft tissue sarcoma after rhabdomyosarcoma in the head and neck [490].

Clinical aspects Fibrosarcomas most commonly cause obstruction and epistaxis [163]. An ethmoid sinus fibrosarcoma arising as a frontal sinus mucocele has been reported [491].

Microscopy The histological appearance is that of a spindle cell lesion, with fascicles or bundles of neoplastic cells intersecting at various angles, sometimes with a herringbone pattern. Most sinonasal fibrosarcomas have a low-grade appearance, with moderate cellularity and low mitotic rate [492]. In accordance, the behavior is more often characterized by repeated local recurrences, while distant metastases are rare.

Differential diagnosis It includes desmoid-type fibromatosis, leiomyosarcoma, nerve sheath tumors, spindle cell carcinoma, and desmoplastic melanoma.

Treatment and prognosis Surgery is the recommended treatment, often followed by radiotherapy [490].

2.11.14.2 Undifferentiated Pleomorphic Sarcoma

Definition The name undifferentiated pleomorphic sarcoma (UPS) has nowadays replaced the until recently used term malignant fibrous histiocytoma (MFH), which was commonly employed as a diagnosis of exclusion for sarcomas mainly composed of myofibroblasts or undifferentiated mesenchymal cells [490].

Epidemiology : A considerably decrease in the frequency of the diagnosis of MFH has occurred following the advent of immunohistochemistry. About 3 % of MFH develop in the head and neck, and 30 % of these arise in the sinonasal region. They most often are seen in adulthood [490].

Etiology MFH represents the most common post-radiation sarcoma, although they are predominantly sporadic.

Microscopy MFH is a high-grade sarcoma, histologically consisting of a proliferation of spindle cells arranged in storiform pattern, intermixed with atypical pleomorphic, often multinucleated giant cells. In the sinonasal tract, it presents as a highly aggressive and destructive lesion, with bone invasion and extension in adjacent structures [166].

Differential diagnosis Before a diagnosis of malignant fibrous histiocytoma is rendered, other pleomorphic malignant tumors, like leiomyosarcoma, osteosarcoma, and sarcomatoid carcinoma, should be excluded by means of immunohistochemical or ultrastructural analysis.

Treatment and prognosis Complete surgical resection is the recommended treatment, often followed by radiotherapy. Prognosis is related to the extension of the tumor.

2.11.14.3 Leiomyosarcoma

Definition Leiomyosarcoma (LMS) of the sinonasal tract is an extremely rare malignant neoplasm, with identical histological and immunophenotypic appearance to its soft tissue counterpart [166].

Epidemiology Sinonasal LMS accounts for less than 1 % of all soft tissue tumors in this region [490].

Microscopy As in other territories, LMS is composed of right-angle intersecting bundles of spindle cells with eosinophilic cytoplasm and "cigar-shaped" nuclei. Foci of necrosis, increased mitotic activity, and cellular atypia are present.

Immunohistochemistry Cells of LMS are reactive for smooth muscle and/or muscle-specific actin, desmin, h-caldesmon, and vimentin.

Differential diagnosis Sinonasal LMS must be distinguished from leiomyoma, glomangiopericytoma, and other spindle cell malignant tumors.

Treatment and prognosis Sinonasal leiomyosarcoma can be regarded as a locally aggressive neoplasm with limited metastatic potential that should be treated by surgery alone if the tumor is limited to the nasal cavity [493]. Adjuvant radiochemotherapy may be used in advanced tumors.

2.11.14.4 Rhabdomyosarcoma

Definition Rhabdomyosarcoma (RMS) is a malignant mesenchymal tumor of skeletal muscle phenotype [490].

Epidemiology RMS is the most common sinonasal malignancy of the pediatric age, [494, 495]. The most common histologic subtypes are the embryonal and the alveolar [494]. RMS is predominantly seen in children and young adults, but they may also occur in older adults, specially the alveolar subtype [490].

Macroscopy The botryoid variant of embryonal RMS has a characteristic grapelike or polypoid appearance, while the other subtypes/variants show an indistinct fish-flesh appearance.

Microscopy Embryonal RMS is characterized by the presence of small, eosinophilic polygonal, or spindled cells with hyperchromatic nuclei and occasional cytoplasmic cross striations; the cell population is usually dense or intermingled with myxoid stroma. Alveolar RMS has fibrous septa, separating clusters of loosely cohesive small round cells with hyperchromatic nuclei and scant eosinophilic cytoplasm; the presence of multinucleated giant cells is a typical feature (Fig. 2.91). Other variants of RMS include sclerosing, spindled, botryoid, and pleomorphic forms [490, 496].

Immunohistochemistry The diagnosis of RMS can be confirmed by immunostaining for myogenin and MyoD1,

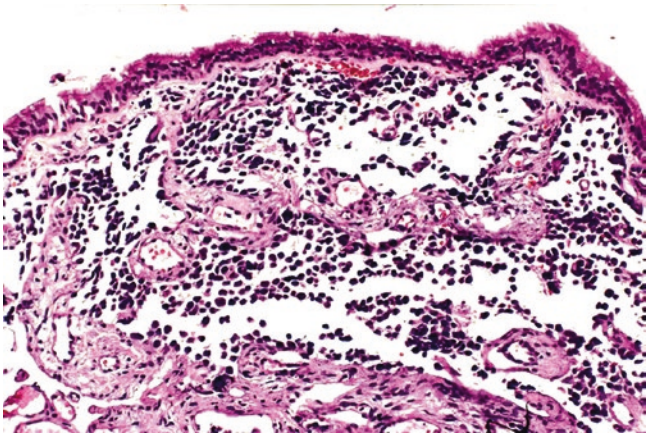

Fig. 2.91 Rhabdomyosarcoma: the alveolar variant depicts fibrous septa separating clusters of loosely cohesive small round cells with hyperchromatic nuclei and scant eosinophilic cytoplasm; notice the presence of multinucleated giant cells, another typical feature

which are nuclear markers with high specificity for skeletal muscle differentiation. Less specific are desmin, muscle-specific actin, and myoglobin.

Genetics Alveolar RMS typically harbors t(2;13) or t(1;13) translocations resulting in *PAX3-FOXO1A* or *PAX7-FOXO1A* gene fusions. Embryonal RMS harbors more complex genetic alterations, such as loss of the tumor suppressor *CDKN2A*, mutation/amplification of *FGFR4*, gain of *GLI1*, and mutations in the myogenic transcription factor *MYOD1* [497–499].

Differential diagnosis It includes all sinonasal undifferentiated small round cell tumors. Furthermore, it must be kept in mind that rhabdomyoblastic differentiation may be encountered in tumors other than RMS [444]. This fact is important because RMS is treated by specific chemotherapy protocols that may be different than those of other tumors in the differential diagnosis.

Treatment and prognosis Treatment includes a combination of radiotherapy and chemotherapy, with surgical resection reserved for residual disease. The risk for neck involvement is high. With the advent of more aggressive therapy, the overall 5-year survival has increased from 40 to 70 % [500]. Adult age and alveolar subtype are adverse prognostic factors in RMS.

2.11.15 Malignant Peripheral Nerve Sheath Tumors

Definition A malignant tumor of nerve sheath phenotype [490].

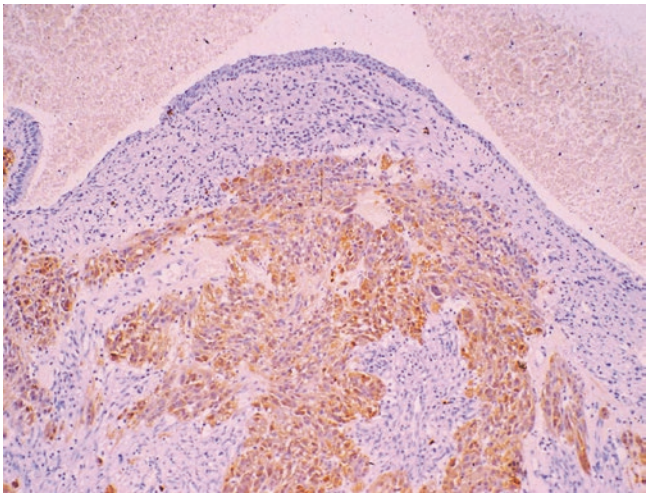

Fig. 2.92 Epithelioid MPNST marked S-100 protein positivity in a large cell malignant neoplasm, mimicking amelanotic melanoma. Additional immunohistochemistry and electron microscopy resulted confirmatory

Synonyms Neurofibrosarcoma, malignant schwannoma, and neurogenic sarcoma

Epidemiology The head and neck is one of the more common anatomic areas to be affected by malignant peripheral nerve sheath tumors (MPNSTs) [501]. MPNST of the sinonasal tract is a very rare neoplasm [502]. Most arise de novo or less often in the context of neurofibromatosis type 1 (NF1) [503–505]. There is female predominance for the novo sinonasal MPNST [492] and male predominance in NF1-associated MPNST [490, 506].

Etiology Radiation and immunosuppression may be causative agents of MPNSTs [507].

Microscopy MPNSTs typically grow in a herringbone-type fascicular pattern. MPNST is a highly cellular spindle cell proliferation and exhibits nuclear hyperchromasia, pleomorphism, elevated mitotic rates, and necrosis. Typically, dark hypercellular areas alternate with light, less cellular ones, conferring a so-called "marbleized" appearance [501]. Sinonasal MPNSTs are often low grade, in contrast to those arising at other sites [492]. In poorly differentiated MPNSTs, the diagnosis can be based on the identification of a preexisting neurofibroma. The epithelioid variant of MPNST has been described in the sinonasal tract and may mimic amelanotic malignant melanoma (Fig. 2.92) [410]. Some tumors may show morphological and immunohistochemical features of skeletal muscle differentiation and are designated as "malignant Triton tumor" [492, 508]. The majority of malignant Triton tumors occur in the setting of NF1. About a third of malignant Triton tumors involve the head and neck [444].

Immunohistochemistry In MPNSTs the nerve sheath markers S100 and SOX10 are positive, but usually have focal distribution; in contrast, epithelioid MPNSTs stain diffusely for S-100.

Genetics Both NF1 alleles are inactivated in MPNSTs ex neurofibroma associated with NF1.

Differential diagnosis It includes fibrosarcoma, leiomyosarcoma, synovial sarcoma, spindle cell carcinoma, and malignant melanoma. Furthermore, positivity for S-100 in a spindle cell sarcoma as present in MPNST may also be shown by the recently described sinonasal biphenotypic sarcoma, a low grade sarcoma that shows immunohistochemically demonstrable neurogenic and myogenic differentiation [509].

Treatment and prognosis Surgical removal is the mainstay treatment that may be followed by radio- and chemotherapy.

2.11.16 Biphenotypic Sinonasal Sarcoma

A new entity known as low-grade, biphenotypic, sinonasal sarcoma has been recently recognized [509]. In addition to distinguishing histological and immunohistochemical features, this tumor is often hallmarked by a recurrent *PAX3-MALM3* gene fusion [510]. It occurs in adults, predominantly women, being characterized by a submucosal proliferation of spindle cells with scant mitotic activity and concomitant neural and myogenic differentiation. Benign glandular proliferation is often present; the majority of glands are lined by respiratory type of epithelium, but areas of oncocytic and squamous metaplasia may be encountered. Hemangiopericytoma - like blood vessels are conspicuous. Focal rhabdomyoblastic differentiation may be seen. Bone invasion emphasizes the infiltrative nature of the lesion. Local recurrence rate approaches 45%, but no patient has developed metastases or died of disease.

2.12 Germ Cell Tumors

Teratoma is the principal benign germ cell tumor of the sinonasal region and shows histological features similar to its counterparts in the gonads and in other extragonadal locations. Malignant tumors with histological features similar to germ cell tumors of the gonads arise on rare occasions in the sinonasal tract. Immature teratomas and teratomas with malignant transformation are tumors of infancy and early childhood, whereas sinonasal endodermal sinus tumors and sinonasal teratocarcinosarcoma have only been documented in adults [511].

2.12.1 Dermoid Cyst

Definition A dermoid cyst is a developmental lesion histogenetically and histologically composed of ectoderm and mesoderm, but no endoderm [511].

Synonyms Nasal dermoid sinus cyst and cystic dermoid

Epidemiology Dermoid cysts of the nose comprise 3 % of all dermoids and 5.5–12 % of those of the head and neck region [512, 513]. A male predominance has been described for cystic dermoids. More than half are detected in children 6 years old or less, and approximately a third are present at birth [514]. Dermoid cysts of the head and neck are located more often in the subcutaneous tissue of the lateral supraorbital ridge and nose. In the nose, they occur most commonly in the bridge and always in the midline. The glabella, nasal tip, and columella are less common sites [512–515]. A few cases have been described as originating in the paranasal sinuses [516].

Etiopathogenesis The most likely explanation for the ontogeny of dermoid cysts is the retention of ectodermal tissue along the lines of closure at junctions of bones, soft tissues, and embryonic membranes [515].

Clinical features Nasal dermoid cysts manifest as a midline nasal pit, fistula, or subcutaneous infected mass. They may cause broadening of the nasal bridge and occasionally cellulitis or purulent discharge. On palpation, the cysts are soft to fluctuant with a pale yellowish-pink color noted beneath the thinned but intact epithelium; when keratin debris and sebum fill the lumen, they may have a doughy consistency [512–515]. Most patients do not have other malformations, but 6–41 % have associated congenital malformations [517, 518]. Computed tomography and magnetic resonance imaging scans are valuable in determining the intracranial and nasal components of a lesion and excluding encephalocele [512–516].

Macroscopy The cysts may range in size from a few millimeters to 12 cm in diameter. The lumen contains cheesy, yellow-white material.

Microscopy Dermoid cysts are lined with mature keratinizing squamous epithelium and frequently contain appendages of the skin in the cyst wall but no endoderm.

Differential diagnosis This lesion is differentiated from a teratoma by the limited variety of tissue types and the absence of endodermal components. Epidermal inclusion cysts may resemble cystic dermoids but do not contain adnexa. Epidermal inclusion cysts occur more frequently in

adults, in contrast to dermoids, which are more commonly found in children and young adolescents [514–516]. Dermoid cysts should be clinically differentiated from encephalocele, which occurs in the same anatomic area.

Treatment and prognosis Dermoid cysts are treated by complete surgical excision, regardless of the extent of the lesion. The recurrence rate has been reported to be less than 7 % [512–515].

2.12.2 Mature Teratoma

Definition Mature teratomas are tumors composed of a variety of mature tissues that are foreign to their sites of occurrence. There are typically tissues derived from two or three germ layers [511].

Synonyms Teratoid tumor, benign teratoma and mature cystic teratoma

Epidemiology Teratomas of the head and neck region account for only 6 % of all teratomas [519, 520]. Mature teratomas in the sinonasal tract are even more unusual [521]. The majority of sinonasal teratomas occur in neonates and infants, and an equal sex distribution has been reported [521, 522]. Stillbirth, prematurity, fetal malpresentation, dystocia, and maternal polyhydramnios are frequent accompaniments. The orbit, oropharynx, and neck are classic locations for mature teratomas of the head and neck, but these tumors have been found rarely in the sinonasal tract [521]. In the sinonasal tract, the maxillary antrum and nasal cavity are affected more often than is the sphenoid sinus [519, 523–525].

Etiopathogenesis The exact origin of teratomas is not yet known, although numerous theories have been presented. The most popular theories of their origin are that they derive from primordial germ cells or from primitive somatic cells that escaped the influence of organizers and inducers [520].

Clinical features Manifestations of teratomas depend on the specific location of the tumors. Signs and symptoms usually result from compression of adjacent organs and tissues. Facial deformity, nasal obstruction, and a nasal mass are common manifestations of sinonasal teratomas. The occasional calcifications seen in computed tomography and magnetic resonance imaging scan provide the most valuable aids in resolving the differential diagnosis [519, 521, 524]. Teratomas may be associated with other skull deformities, anencephaly, hemicrania, and palatal fissures [519].

Macroscopy The tumors are usually cystic, but they can be solid or multilocular. They are commonly encapsulated masses that measure up to 7 cm at their largest dimension.

Microscopy Teratomas are composed of varied admixtures of mature skin, appendages of the skin, fat, glial tissue, smooth muscle, cartilage, bone, minor salivary glands, and respiratory and gastrointestinal epithelium. Neural tissues may be seen more often in sinonasal teratomas than in other teratomas.

Differential diagnosis Although the variegated histological appearance of mature teratomas is usually diagnostic, nasal glial heterotopia and meningocele should be considered in the differential diagnosis. The presence of immature elements or any other germ cell tumor excludes mature teratoma.

Treatment and prognosis Complete surgical excision has been curative in the few cases of sinonasal mature teratomas reported in the literature.

2.12.3 Immature Teratoma

Definition Immature teratomas are composed of variable quantities of immature tissue elements, mostly neuroepithelial, that appear interspersed with mature tissues derived from the three embryonic germ layers [511].

Synonym Teratoma with immature elements

Epidemiology Immature teratomas are tumors of infancy and childhood [121].

Etiopathogenesis The histogenesis of this type of tumor remains unsettled, as it is the case for mature teratomas. Either the displaced, persistent germ cell theory or the possibility of an alternative progenitor cell has been discussed [526].

Clinical features Symptoms are not specific. Nasal discharge and airway obstruction are common. Imaging procedures show expansive growth without invasive destruction.

Macroscopy In contrast to mature teratomas that are usually cystic, immature teratomas tend to be either solid-nodular or a combination of solid and cystic tumor masses; however, this is not a consistent observation.

Microscopy The distinction between mature and immature teratomas is based on their microscopic appearances.

The tumor may contain cystic spaces lined by mature ciliated pseudostratified epithelium and immature areas with primitive neuroepithelial rosettes lined with multilayered neuroblasts. Mitotic figures are frequently present in the immature arrangements; however, cellular atypia is not found.

Differential diagnosis In infants and children, a teratoma with malignant transformation has to be excluded. In adult patients, thorough sampling of the specimen is mandatory to rule out teratocarcinosarcoma.

Treatment and prognosis Complete surgical excision is usually an effective treatment. Despite the immaturity of its tissue elements and of the presence of mitotic figures, immature teratomas rarely behave in a malignant fashion [526].

2.12.4 Teratoma with Malignant Transformation

Definition Teratoma with malignant transformation is a neoplasm containing benign tissue elements of all three germinal layers and, in addition, a specific type of malignant tumor [511].

Synonym Malignant teratoma

Epidemiology In the head and neck, malignant transformation of a teratoma is a distinctly uncommon observation. Involvement of the sinonasal tract by such a lesion is extremely rare. Kuhn et al. reported of a case of squamous cell carcinoma arising in a benign teratoma of the maxilla of a 13-month-old boy [527]. Petrovich et al. reported a nasal malignant teratoma in a 63-year-old man [528].

Clinical features A fluctuating left facial swelling occurred during a period of 9 months prior to the diagnosis. On computed tomography scans, thickened left maxillary sinus mucoperiostium and a soft tissue defect were observed over the alveolar ridge. Metastatic disease was not found.

Macroscopy A soft tissue mass of 2.0-cm diameter in the left maxillary alveolar ridge with displacement of unerupted teeth has been noted [527].

Microscopy The tumor was composed of variable mature tissue elements of ectodermal, mesodermal, and endodermal derivation consistent with extragonadal teratoma. An additional finding was the presence of an atypical squamous proliferation with the features of squamous cell carcinoma [527].

Differential diagnosis It includes immature teratoma with pseudocarcinomatous proliferation of the squamous epithelium and odontogenic cyst.

Treatment and prognosis The tumor reported by Kuhn et al. was locally aggressive and recurred after surgery. There was no evidence of further recurrence 2 years after chemotherapy [527].

2.12.5 Yolk Sac Tumor

Definition Yolk sac tumor (YST) of the sinonasal tract is a primary malignant neoplasm found to arise in this location that has histological features indistinguishable from yolk sac tumor of the gonads [511].

Synonyms Endodermal sinus tumor, yolk sac carcinoma, and orchioblastoma

Epidemiology Only 20 % of YSTs are extragonadal [529]. Head and neck YSTs are very rare, and similarly to the gonadal counterpart, they have two distinct peaks of incidence; the most common one is seen in the early years of life and the less frequent in adult age [526, 529–533].

Pathogenesis The development of a germ cell malignancy does not need always to be explained by the neoplastic transformation of a primordial germ cell. Alternatively, YSTs of the adult may evolve from precursor somatic neoplastic cells by a process of divergent differentiation toward structures resembling the fetal yolk sac [534].

Clinical aspects While the YSTs that develop in infancy and childhood may be associated or not to a teratoma, those occurring in adult patients may associate or not to a somatic carcinoma [534–538]. The two sinonasal YSTs reported in adults developed in men aged 43 and 59 years [534, 537]. Both tumors occupied the paranasal sinuses with focal orbital and cranial destruction. YSTs are known to secrete alpha-fetoprotein (AFP). A case of sinonasal YST admixed with choriocarcinoma has been documented [535].

Macroscopy YSTs tend to be gray white to yellow, focally hemorrhagic.

Microscopy The most characteristic pattern of growth of YSTs is composed of pseudopapillary structures with numerous glomeruloid or perivascular Schiller-Duval bodies and labyrinthine cavities and channels lined by flattened to cuboidal epithelium with various degrees of atypia (Fig. 2.93). Another common pattern is the reticular or microcystic, in which eosinophilic hyaline globules, PAS

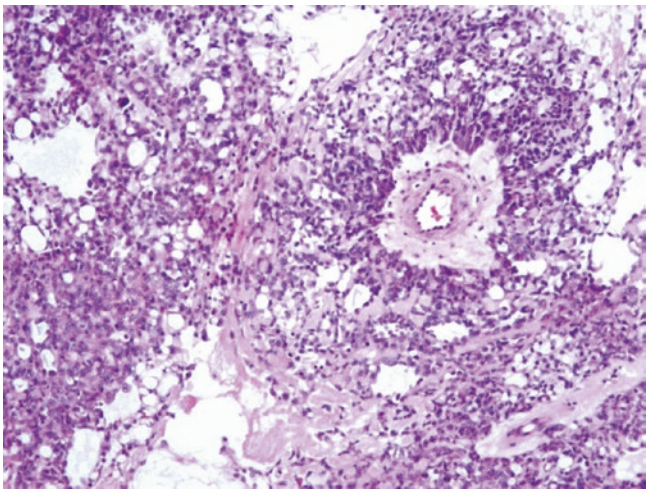

Fig. 2.93 Yolk sac tumor: perivascular Schiller-Duval body and pseudopapillary structures forming labyrinthine cavities and channels lined by flattened to cuboidal epithelium

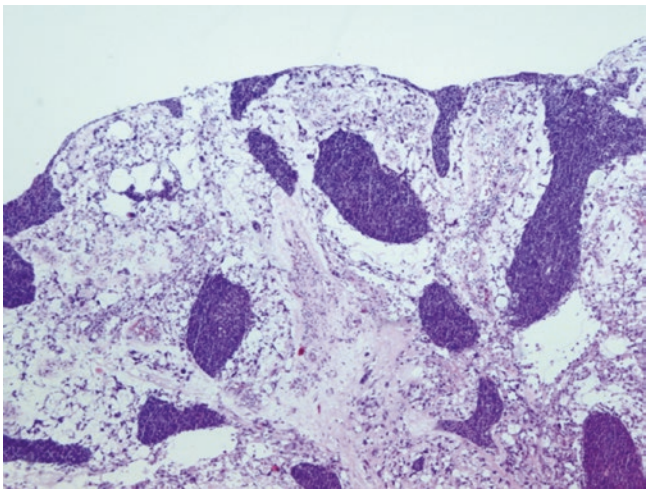

Fig. 2.94 Yolk sac tumor: nests and cords of immature cells displaying the solid pattern of growth are surrounded with reticular and microcystic structures (Courtesy of Dr. Prantl, Munich, Germany)

positive and diastase resistant, are found intracellularly and extracellularly. The solid pattern is composed of densely cellular nests and cords of immature elements that may differentiate into somatic endodermal derivatives (Fig. 2.94). Another pattern is the polyvesicular vitelline. Surrounding these tissue patterns, there are variable amounts of reactive stromal component.

Immunohistochemistry AFP is the characteristic marker of the pseudopapillary and reticular structures of YSTs. The solid pattern mainly immunoreacts with wide-spectrum cytokeratin cocktails and CK20. Beta-HCG is negative in pure YSTs, unless combined with choriocarcinoma [535].

Differential diagnosis Sinonasal YSTs must be distinguished from other germ cell tumors occurring in this region, mainly from teratocarcinosarcoma. The solid pattern of YSTs must be distinguished from somatic malignancies with undifferentiated carcinoma component and from basaloid non-keratinizing squamous cell carcinoma.

Treatment and prognosis Complete excision, whenever possible, followed with radiochemotherapy is the recommended treatment of YSTs. Owing to the aggressive behavior of these gonadal or extragonadal tumors in adult patients, platinum-based therapy should be added [533].

2.12.6 Teratocarcinosarcoma

Definition Sinonasal teratocarcinosarcoma (SNTCS) is a complex malignant sinonasal neoplasm combining features of teratoma and carcinosarcoma. Benign and malignant epithelial, mesenchymal, and neural elements are typically present, including immature tissue with blastomatous features [511, 539].

Synonyms Teratocarcinoma, teratoid carcinosarcoma. blastoma

Epidemiology SNTCS is very rare [540]. Patients are exclusively adults, with ages ranging from 18 to 79 years (mean 60 years) [539–544]. There is a marked male predominance. SNTCS almost exclusively arises in the ethmoid sinus and maxillary antrum, although it may arise in other head and neck territories [539, 545, 546].

Etiology and pathogenesis SNTCS is unlikely to be a germ cell tumor, but probably arises from pluripotent stem cells of the neuroepithelium that not only reproduce the neuroectodermal features of olfactory neuroblastoma but also have the capacity to differentiate into divergent types of somatic cells [543]. In contrast with malignant gonadal teratomas, which are frequently found in patients at younger age, SNTCS does not contain areas of embryonal carcinoma, choriocarcinoma, or seminoma as seen in many germ cell tumors [539].

Clinical aspects Patients present with a short history of nasal obstruction and epistaxis. Imaging studies reveal a nasal mass occasionally accompanied by opacification of the paranasal sinuses. Bone destruction may be seen [539].

Macroscopy Tumors are usually bulky, soft to rubbery, and red tan to purple. A mass filling the nose and projecting for about 3 cm from the naris has been documented [547].

Microscopy SNTCS is made up of multiple tissue types derived from two or three germ layers, often forming cystic spaces and exhibiting variable degrees of maturity and undifferentiated/primitive component (Fig. 2.95). In addition there are carcinomatous and sarcomatous components [540, 544]. The epithelial component includes keratinizing and non-keratinizing squamous epithelium, pseudostratified columnar ciliated epithelium, and glandular structures lined by either cuboidal or columnar cells that may show mucous differentiation (Fig. 2.96). Nests of immature squamous cells containing clear cells which are "fetal appearing" are a common finding and an important diagnostic clue [539]. The carcinomatous component is usually glandular, but sometimes squamous. Neuroepithelial elements with rosettes and neuroblastoma-like areas are in most instances present (Fig. 2.97). These epithelial and neuroepithelial elements occur in close relationship with each other and with mesenchymal elements. The most prominent mesenchymal elements are immature cells with oval or elongated nuclei. The mesenchymal cells may exhibit skeletal muscle differentiation with cross striations and bizarre formations (Fig. 2.98). Foci of cartilage, smooth muscle, adipose tissue, and fibrovascular tissues may also be present. There may be proliferation of small round cells that are difficult to classify. Mitotic activity and cytological features of malignancy are demonstrable in the undifferentiated areas of both the epithelial and mesenchymal elements [540].

Immunohistochemistry The undifferentiated/primitive component often shows positive immunoreaction for CD99 and occasionally for synaptophysin and S-100 protein [543]. The spindle cell component is consistently positive for vimentin and sometimes for desmin, myoglobin, and glial fibrillary acidic protein. The neuroepithelial component is positive for neuron-specific enolase and occasionally for chromogranin, alpha-fetoprotein, cytokeratin, and neurofilaments [540]. The epithelial component is positive for cytokeratins, epithelial membrane antigen, and occasionally S-100 protein and glial fibrillary acidic protein.

Differential diagnosis Small biopsies and/or inadequate sampling of SNTCS specimens may lead to erroneous diagnoses of olfactory neuroblastoma, squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma, malignant salivary gland-type tumors, and adenosquamous carcinoma [539].

Treatment and prognosis Aggressive initial therapy with a combination of surgical resection, radiotherapy, and chemotherapy is usually recommended [539]. SNTCSs are locally aggressive tumors, with rapid invasion of soft tissues and bone, and metastasize to regional lymph nodes and

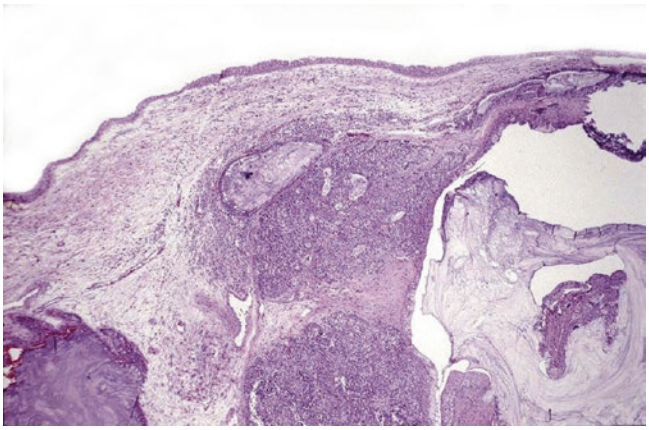

Fig. 2.95 Teratocarcinosarcoma: cystic spaces filled with mucin are partly covered by benign columnar epithelium and surrounded by immature blastematous tissue

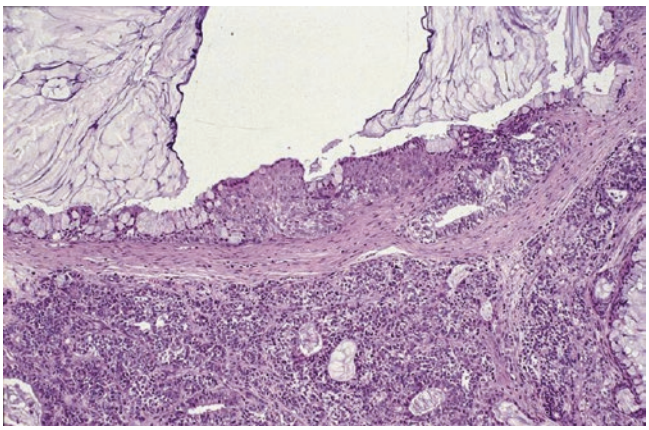

Fig. 2.96 Teratocarcinosarcoma: a mature cystic space covered by benign columnar mucous-secreting epithelium alternating with nests of mature squamous cells is seen in continuity with poorly differentiated glandular structures

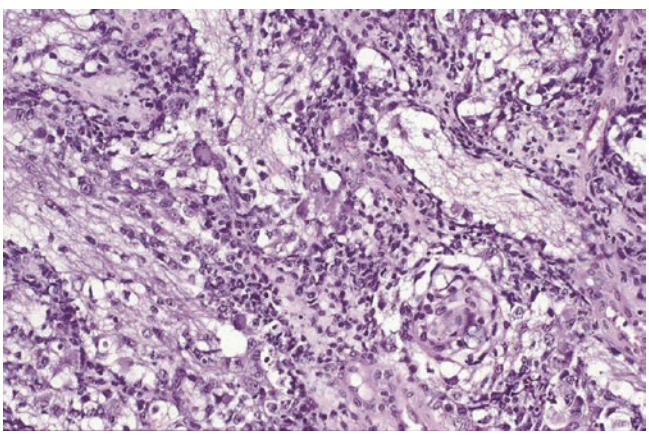

Fig. 2.97 Teratocarcinosarcoma: neuroepithelial elements with ganglion cells and neurofilaments depict neuroblastoma-like areas

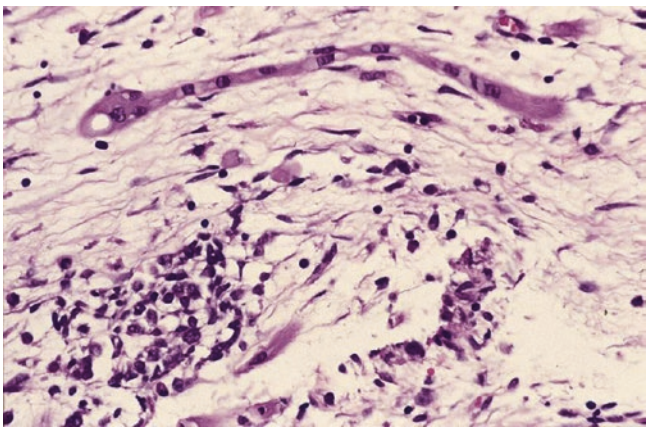

Fig. 2.98 Teratocarcinosarcoma: immature striated muscle cells, one of them displaying a snakelike configuration, are seen amid blastematous elements

sites, such as the lung. Craniospinal dissemination may occur [548]. The average survival of SNTCS is less than 2 years, with 60 % of the patients not surviving beyond 3 years [539]. Improved outcomes have been reported in more recent years [546].

2.12.7 Choriocarcinoma

Definition Choriocarcinoma is a malignant neoplasm composed of syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast [549].

Synonym Non-gestational choriocarcinoma

Epidemiology Sinonasal choriocarcinoma is an extremely rare entity. Of the two cases reported, one originated in the maxillary sinus, and the other affected the nasal cavity, ethmoid and sphenoid sinuses. Both patients were males, one 44 years of age and the other 49 year old [550].

Clinical features One patient presented with epistaxis and the other with nasal obstruction. Both had elevated beta-HCG in serum.

Macroscopy Tumors are soft and hemorrhagic.

Microscopy Tumors are composed of an admixture of small, round to polygonal cytotrophoblastic cells, forming fenestrated sheets or pseudopapillae, surrounded by large multinucleated syncytiotrophoblastic cells.

Immunohistochemistry All choriocarcinoma cells are positive for pancytokeratin and syncytiotrophoblast reacts with beta-HCG.

Differential diagnosis Before establishing a diagnosis of primary sinonasal choriocarcinoma, it is mandatory to rule out metastatic gestational or non-gestational disease [551, 552].

Treatment and prognosis Patients with primary sinonasal choriocarcinoma are tributary of the aggressive chemotherapy regimens for non-gestational choriocarcinoma. Gestational choriocarcinoma requires less aggressive therapy.

2.13 Metastatic Tumors

Definition Sinonasal metastatic tumors are secondary malignancies that derive from a noncontiguous neoplasm. Direct extension from an adjacent neoplasm and leukemia-lymphoma is excluded [553, 554].

Synonym Secondary tumors

Epidemiology Metastases to the nasal cavity and paranasal sinuses are rare [555, 556]. The median age of patients with sinonasal metastatic tumors is 57 years, range 3 months to 76 years, and about 60 % occur in males [557]. The most frequent primary sites of origin of the tumors are the kidney (40 %), lung (9 %), breast (8 %), thyroid (8 %), prostate (7 %), and miscellaneous (28 %) [556]. The most habitual anatomic sites involved by the metastases are maxillary (33 %), sphenoid (22 %), ethmoid (14 %), frontal (9 %), and multiple sinuses (22 %) [556, 558]. In 10–15 % of cases, the metastases are limited to the nasal cavity [553].

Clinical aspects Metastases of tumors to the sinonasal tract are hematogenous and may be solitary or multifocal [554]. Usually symptoms are indistinguishable from those of a primary sinonasal tumor. Epistaxis is particularly common in metastatic renal and thyroid carcinomas; other common symptoms are nasal obstruction, headache, facial pain, visual disturbances, exophthalmos, facial swelling, and cranial nerve deficits. Metastases may be the first manifestation of an otherwise clinically occult carcinoma [553].

Microscopy Often, metastatic tumors to the sinonasal tract reproduce the most common histological features depicted by the primary tumors, which facilitates their recognition. Most renal cell carcinomas are of the clear cell type, while other types are very rarely seen (Fig. 2.99) [556]. Thyroid carcinomas are usually of the papillary and follicular types [559, 560]. Examples of colonic adenocarcinoma and of hepatocellular carcinoma metastatic to the sinonasal tract have been reported (Fig. 2.100) [561–566].

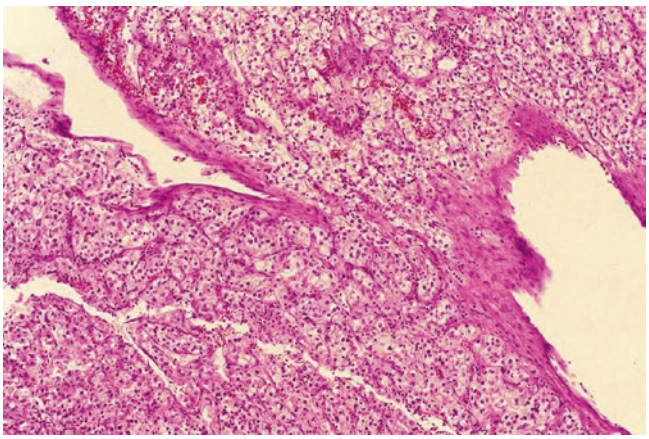

Fig. 2.99 Metastatic clear cell carcinoma of the kidney: the finding in a clear cell carcinoma of a rich network of well-formed mature blood vessels is highly suspicious of renal origin

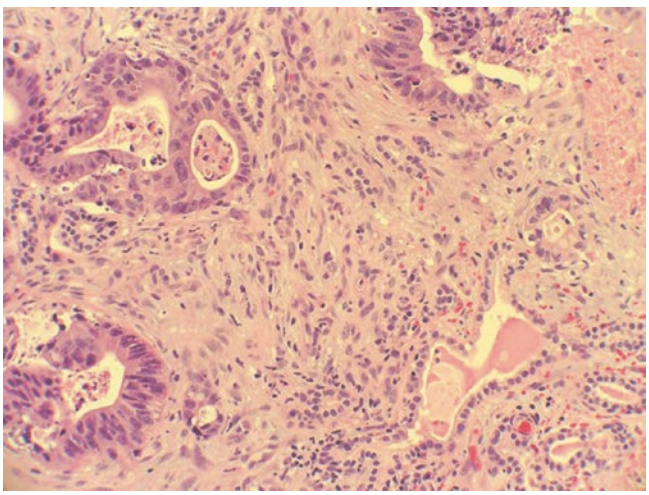

Fig. 2.100 Metastatic adenocarcinoma of the colon and rectum: in the sinonasal tract, the presence of intestinal-type adenocarcinoma with foci of necrosis and preservation of neighboring seromucous glands is quite suggestive of metastasis

Differential diagnosis Metastatic clear cell carcinomas have to be distinguished mainly from primary sinonasal clear carcinomas of minor salivary gland derivation [553]. Metastatic lung cell carcinomas, mainly those of small and intermediate cell type, have to be distinguished from their primary sinonasal counterparts [272]. Metastatic thyroid carcinomas have to be differentiated from primary sinonasal low-grade carcinomas tubulopapillary type [333]. Metastatic intestinal adenocarcinomas require precise distinction from primary ITAC [565]. Diagnostic difficulties usually arise with undifferentiated metastatic tumors, mainly those of unknown primary site of origin; clinical history, immunohistochemistry, and molecular techniques are in these instances of help.

Treatment and prognosis For metastatic sinonasal tumors, palliative therapy is in most instances recommended. However, prognosis may depend on whether the metastasis is isolated or part of widespread disseminated disease. If the sinonasal metastasis is localized and treated aggressively, the average survival following its discovery may be as long as 20–30 months [555].

References

1. Sadler T. Langman's medical embryology. Baltimore: Williams & Wilkins; 1985.
2. Ogle OE, Weinstock RJ, Friedman E. Surgical anatomy of the nasal cavity and paranasal sinuses. Oral Maxillofac Surg Clin North Am. 2012;24(2):155–66, vii.
3. Dykewicz MS, Hamilos DL. Rhinitis and sinusitis. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S103–15.
4. Anon JB. Upper respiratory infections. Am J Med. 2010;123(4 Suppl):S16–25.
5. Anon JB. Acute bacterial rhinosinusitis in pediatric medicine: current issues in diagnosis and management. Paediatr Drugs. 2003;5 Suppl 1:25–33.
6. Brook I, Frazier EH. Microbiology of recurrent acute rhinosinusitis. Laryngoscope. 2004;114(1):129–31.
7. Bousquet J, Fokkens W, Burney P, Durham SR, Bachert C, Akdis CA, et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. Allergy. 2008;63(7):842–53.
8. Taxy JB, El-Zayaty S, Langerman A. Acute fungal sinusitis: natural history and the role of frozen section. Am J Clin Pathol. 2009;132(1):86–93.
9. Das A, Bal A, Chakrabarti A, Panda N, Joshi K. Spectrum of fungal rhinosinusitis; histopathologist's perspective. Histopathology. 2009;54(7):854–9.
10. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg. 2003;129(3 Suppl):S1–32.
11. Kaliner MA, Osguthorpe JD, Fireman P, Anon J, Georgitis J, Davis ML, et al. Sinusitis: bench to bedside. Current findings, future directions. Otolaryngol Head Neck Surg. 1997;116(6 Pt 2):S1–20.
12. Van CP, Watelet JB. Epidemiology of chronic rhinosinusitis. Thorax. 2000;55 Suppl 2:S20–1.
13. Anand VK. Epidemiology and economic impact of rhinosinusitis. Ann Otol Rhinol Laryngol Suppl. 2004;193:3–5.
14. Moore EJ, Kern EB. Atrophic rhinitis: a review of 242 cases. Am J Rhinol. 2001;15(6):355–61.
15. Zurlo JJ, Feuerstein IM, Lebovics R, Lane HC. Sinusitis in HIV-1 infection. Am J Med. 1992;93(2):157–62.
16. Marks SC, Upadhyay S, Crane L. Cytomegalovirus sinusitis. A new manifestation of AIDS. Archi Otolaryngol Head Neck Surg. 1996;122(7):789–91.
17. Meyer RD, Gaultier CR, Yamashita JT, Babapour R, Pitchon HE, Wolfe PR. Fungal sinusitis in patients with AIDS: report of 4 cases and review of the literature. Medicine. 1994;73(2):69–78.
18. Dunand VA, Hammer SM, Rossi R, Poulin M, Albrecht MA, Doweiko JP, et al. Parasitic sinusitis and otitis in patients infected with human immunodeficiency virus: report of five cases and review. Clin Infect Dis. 1997;25(2):267–72.

19. Fang SY, Shen CL. Neuropeptide innervation and neuroendocrine cells in allergic rhinitis and chronic hypertrophic rhinitis. Clin Exp Allergy. 1998;28(2):228–32.
20. El-Barbary AE, Yassin A, Fouad H, Shennawy M. Histopathological and histochemical studies in atrophic rhinitis. J Laryngol Otol. 1976;84:1103–11.
21. Abdel-Latif SM, Baheeg SS, Aglan YI, Babin RW, Giltman LI. Chronic atrophic rhinitis with fetor (ozena): a histopathologic treatise. Rhinology. 1987;25(2):117–20.
22. Hellquist H. Nasal polyps update. Histopathology. Allergy Asthma Proc. 1996;17:237–42.
23. Nakayama M, Wenig BM, Heffner DK. Atypical stromal cells in inflammatory nasal polyps: immunohistochemical and ultrastructural analysis in defining histogenesis. Laryngoscope. 1995;105(2):127–34.
24. Hardy G. The choanal polyp. Ann Otol Laryngol Rhinol. 1957;66:306–26.
25. Aktas D, Yetiser S, Gerek M, Kurnaz A, Can C, Kahramanyol M. Antrochoanal polyps: analysis of 16 cases. Rhinology. 1998; 36:81–5.
26. Smith CJ, Echevarria R, McLelland CA. Pseudosarcomatous changes in antrochoanal polyps. Arch Otolaryngol. 1974;99(3):228–30.
27. Greger R, Mall M, Bleich M, Ecke D, Warth R, Riedemann N, et al. Regulation of epithelial ion channels by the cystic fibrosis transmembrane conductance regulator. J Mol Med (Berl). 1996;74(9):527–34.
28. Oppenheimer EH, Rosenstein BJ. Differential pathology of nasal polyps in cystic fibrosis and atopy. Lab Invest. 1979; 40(4):445–9.
29. Batsakis JG, El-Naggar AK. Cystic fibrosis and the sinonasal tract. Ann Otol Rhinol Laryngol. 1996;105(4):329–30.
30. Min YG, Shin JS, Choi SH, Chi JG, Yoon CJ. Primary ciliary dyskinesia: ultrastructural defects and clinical features. Rhinology. 1995;33(4):189–93.
31. Geremek M, Witt M. Primary ciliary dyskinesia: genes, candidate genes and chromosomal regions. J Appl Genet. 2004;45(3):347–61.
32. Hadravsky L, Skalova A, Kacerovska D, Kazakov DV, Chudacek Z, Michal M. Angiomatoid change in polyps of the nasal and paranasal regions: an underrecognized and commonly misdiagnosed lesion – report of 45 cases. Virchows Arch. 2012;460(2):203–9.
33. Heffner DK. Sinonasal angiosarcoma? Not likely (a brief description of infarcted nasal polyps). Ann Diagn Pathol. 2010;14(4):233–4.
34. Karma P, Rasanen O, Karja J. Nasal gliomas. A review and report of two cases. Laryngoscope. 1977;87(7):1169–79.
35. Patterson K, Kapur S, Chandra RS. "Nasal gliomas" and related brain heterotopias: a pathologist's perspective. Pediatr Pathol. 1986;5(3–4):353–62.
36. Chan JK, Lau WH. Nasal astrocytoma or nasal glial heterotopia? Arch Pathol Lab Med. 1989;113(8):943–5.
37. Heffner DK. Brain in the middle ear or nasal cavity: heterotopia or encephalocele? Ann Diagn Pathol. 2004;8(4):252–7.
38. Wenig BM, Heffner DK. Respiratory epithelial adenomatoid hamartomas of the sinonasal tract and nasopharynx: a clinicopathologic study of 31 cases. Ann Otol Rhinol Laryngol. 1995;104(8): 639–45.
39. Gauchotte G, Marie B, Gallet P, Nguyen DT, Grandhaye M, Jankowski R, et al. Respiratory epithelial adenomatoid hamartoma: a poorly recognized entity with mast cell recruitment and frequently associated with nasal polyposis. Am J Surg Pathol. 2013;37(11):1678–85.
40. Ozolek JA, Hunt JL. Tumor suppressor gene alterations in respiratory epithelial adenomatoid hamartoma (REAH): comparison to sinonasal adenocarcinoma and inflamed sinonasal mucosa. Am J Surg Pathol. 2006;30(12):1576–80.
41. Khan RA, Chernock RD, Lewis Jr JS. Seromucinous hamartoma of the nasal cavity: a report of two cases and review of the literature. Head Neck Pathol. 2011;5(3):241–7.
42. Weinreb I, Gnepp DR, Laver NM, Hoschar AP, Hunt JL, Seethala RR, et al. Seromucinous hamartomas: a clinicopathological study of a sinonasal glandular lesion lacking myoepithelial cells. Histopathology. 2009;54(2):205–13.
43. Aviles Jurado FX, Guilemany Toste JM, Alobid I, Alos L, Mullol J. The importance of the differential diagnosis in rhinology: respiratory epithelial adenomatoid hamartoma of the sinonasal tract. Acta Otorrinolaringol Esp. 2012;63(1):55–61.
44. Ozolek JA, Barnes EL, Hunt JL. Basal/myoepithelial cells in chronic sinusitis, respiratory epithelial adenomatoid hamartoma, inverted papilloma, and intestinal-type and nonintestinal-type sinonasal adenocarcinoma: an immunohistochemical study. Arch Pathol Lab Med. 2007;131(4):530–7.
45. Weinreb I. Low grade glandular lesions of the sinonasal tract: a focused review. Head Neck Pathol. 2010;4(1):77–83.
46. Roffman E, Baredes S, Mirani N. Respiratory epithelial adenomatoid hamartomas and chondroosseous respiratory epithelial hamartomas of the sinonasal tract: a case series and literature review. Am J Rhinol. 2006;20(6):586–90.
47. McDermott MB, Ponder TB, Dehner LP. Nasal chondromesenchymal hamartoma: an upper respiratory tract analogue of the chest wall mesenchymal hamartoma. Am J Surg Pathol. 1998;22(4):425–33.
48. Ozolek JA, Carrau R, Barnes EL, Hunt JL. Nasal chondromesenchymal hamartoma in older children and adults: series and immunohistochemical analysis. Arch Pathol Lab Med. 2005;129(11): 1444–50.
49. Stewart DR, Messinger Y, Williams GM,Yang J, Field A, Schultz KA, et al. Nasal chondromesenchymal hamartomas arise secondary to germline and somatic mutations of DICER1 in the pleuropulmonary blastoma tumor predisposition disorder. Hum Genet. 2014;133:1443–50.
50. Heffner DK. Problems in pediatric otorhinolaryngic pathology. I. Sinonasal and nasopharyngeal tumors and masses with myxoid features. Int J Pediatr Otorhinolaryngol. 1983;5:77–91.
51. Lund VJ, Milroy CM. Fronto-ethmoidal mucocoeles: a histopathological analysis. J Laryngol Otol. 1991;105(11):921–3.
52. Natvig K, Larsen TE. Mucocele of the paranasal sinuses. A retrospective clinical and histological study. J Laryngol Otol. 1978;92(12):1075–82.
53. Carlson DL. Necrotizing sialometaplasia: a practical approach to the diagnosis. Arch Pathol Lab Med. 2009;133(5):692–8.
54. Lee BJ, Park HJ, Heo SC. Organized hematoma of the maxillary sinus. Acta Otolaryngol. 2003;123(7):869–72.
55. Michaels L, Hellquist H. Organising haematoma. Ear, nose and throat histopathology. 2nd ed. Springer, London; 2001. p. 169–70.
56. Mufarrij AA, Busaba NY, Zaytoun GM, Gallo GR, Feiner HD. Primary localized amyloidosis of the nose and paranasal sinuses. A case report with immunohistochemical observations and a review of the literature. Am J Surg Pathol. 1990;14(4): 379–83.
57. Tsikoudas A, Martin-Hirsch DP, Woodhead CJ. Primary sinonasal amyloidosis. J Laryngol Otol. 2001;115(1):55–6.
58. Rauba D, Lesinskas E, Petrulionis M, Sukyte D, Valeviciene N, Palionis D, et al. Isolated nasal amyloidosis: a case report. Medicina (Kaunas). 2013;49(11):497–503.
59. Paugh DR, Sullivan MJ. Myospherulosis of the paranasal sinuses. Otolaryngol Head Neck Surg. 1990;103(1):117–9.
60. Rosai J. The nature of myospherulosis of the upper respiratory tract. Am J Clin Pathol. 1978;69:475–81.
61. Sindwani R, Cohen JT, Pilch BZ, Metson RB. Myospherulosis following sinus surgery: pathological curiosity or important clinical entity? Laryngoscope. 2003;113(7):1123–7.

62. Phillip V, Becker K, Bajbouj M, Schmid RM. Myospherulosis. Ann Diagn Pathol. 2013;17(4):383–9.
63. Kyriakos M. Myospherulosis of the paranasal sinuses, nose and middle ear. A possible iatrogenic disease. Am J Clin Pathol. 1977;67:118–30.
64. Shimada K, Kobayashi S, Yamadori I, Ohmori M. Myospherulosis in Japan. A report of two cases and an immunohistochemical investigation. Am J Surg Pathol. 1988;12(6):427–32.
65. Deshpande V, Khosroshahi A, Nielsen GP, Hamilos DL, Stone JH. Eosinophilic angiocentric fibrosis is a form of IgG4-related systemic disease. Am J Surg Pathol. 2011;35(5):701–6.
66. Chang SY, Keogh KA, Lewis JE, Ryu JH, Cornell LD, Garrity JA, et al. IgG4-positive plasma cells in granulomatosis with polyangiitis (Wegener's): a clinicopathologic and immunohistochemical study on 43 granulomatosis with polyangiitis and 20 control cases. Hum Pathol. 2013;44(11):2432–7.
67. Roberts PF, McCann BG. Eosinophilic angiocentric fibrosis of the upper respiratory tract: a mucosal variant of granuloma faciale? A report of three cases. Histopathology. 1985;9(11):1217–25.
68. Thompson LD, Heffner DK. Sinonasal tract eosinophilic angiocentric fibrosis. A report of three cases. Am J Clin Pathol. 2001;115(2):243–8.
69. Kaneshiro S, Nakajima T, Yoshikawa Y, Iwasaki H, Tokiwa N. The postoperative maxillary cyst: report of 71 cases. J Oral Surg. 1981;39(3):191–8.
70. Yamamoto H, Takagi M. Clinicopathologic study of the postoperative maxillary cyst. Oral Surg Oral Med Oral Pathol. 1986;62(5):544–8.
71. Maruyama M, Onodera K, Ooya K. A histopathological and lectin-histochemical study of the lining epithelium in postoperative maxillary cysts. Oral Dis. 2002;8(5):241–8.
72. Claros P, Claros A, Sarr M, Cardesa A. Post operative Caldwell-Luc procedure maxillary cyst: report of a case. Rev Laryngol Otol Rhinol. 2014;135(1):45–7.
73. Luong A, Marple BF. Allergic fungal rhinosinusitis. Curr Allergy Asthma Rep. 2004;4(6):465–70.
74. Hamilos DL. Allergic fungal rhinitis and rhinosinusitis. Proc Am Thorac Soc. 2010;7(3):245–52.
75. Taxy JB. Paranasal fungal sinusitis: contributions of histopathology to diagnosis: a report of 60 cases and literature review. Am J Surg Pathol. 2006;30(6):713–20.
76. Torres C, Ro JY, El-Naggar AK, Sim SJ, Weber RS, Ayala AG. Allergic fungal sinusitis: a clinicopathologic study of 16 cases. Hum Pathol. 1996;27(8):793–9.
77. Revankar SG. Dematiaceous fungi. Mycoses. 2007;50(2):91–101.
78. Granville L, Chirala M, Cernoch P, Ostrowski M, Truong LD. Fungal sinusitis: histologic spectrum and correlation with culture. Hum Pathol. 2004;35(4):474–81.
79. Marple B, Newcomer M, Schwade N, Mabry R. Natural history of allergic fungal rhinosinusitis: a 4- to 10-year follow-up. Otolaryngol Head Neck Surg. 2002;127(5):361–6.
80. Adelson RT, Marple BF. Fungal rhinosinusitis: state-of-the-art diagnosis and treatment. J Otolaryngol. 2005;34 Suppl 1:S18–23.
81. Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am. 2000;33:349–65.
82. Schwartz S, Thiel E. Clinical presentation of invasive aspergillosis. Mycoses. 1997;40 Suppl 2:21–4.
83. Batsakis JG, El-Naggar AK. Rhinoscleroma and rhinosporidiosis. Ann Otol Rhinol Laryngol. 1992;101(10):879–82.
84. Makannavar JH, Chavan SS. Rhinosporidiosis – a clinicopathological study of 34 cases. Indian J Pathol Microbiol. 2001;44(1):17–21.
85. Coup AJ, Hopper IP. Granulomatous lesions in nasal biopsies. Histopathology. 1980;4(3):293–308.
86. McDonald TJ, DeRemee RA, Kern EB, Harrison EG. Nasal manifestations of Wegener's granulomatosis. Laryngoscope. 1974;84(12):2101–12.
87. Devaney KO, Travis WD, Hoffman G, Leavitt R, Lebovics R, Fauci AS. Interpretation of head and neck biopsies in Wegener's granulomatosis. A pathologic study of 126 biopsies in 70 patients. Am J Surg Pathol. 1990;14(6):555–64.
88. Del Buono EA, Flint A. Diagnostic usefulness of nasal biopsy in Wegener's granulomatosis. Hum Pathol. 1991;22(2):107–10.
89. Olsen KD, Neel HB, III, DeRemee RA, Weiland LH. Nasal manifestations of allergic granulomatosis and angiitis (Churg-Strauss syndrome). Otolaryngol Head Neck Surg (1979). 1980;88(1):85–9.
90. Tsuzuki K, Fukazawa K, Takebayashi H, Hashimoto K, Sakagami M. Difficulty of diagnosing Wegener's granulomatosis in the head and neck region. Auris Nasus Larynx. 2009;36(1):64–70.
91. Binford CH, Meyers WM. Diseases caused by mycobacteria leprosy. In: Binford CH, Connor DH, editors. Pathology of tropical and extraordinary diseases. Washington, DC: AFIP; 1976. p. 205–25.
92. Bhat R, Sharma VK, Deka RC. Otorhinolaryngologic manifestations of leprosy. Int J Dermatol. 2007;46(6):600–6.
93. Gupta A, Seiden AM. Nasal leprosy: case study. Otolaryngol Head Neck Surg. 2003;129(5):608–10.
94. Singhal SK, Dass A, Mohan H, Venkataramana Y. Primary nasal tuberculosis. J Otolaryngol. 2002;31(1):60–2.
95. Batra K, Chaudhary N, Motwani G, Rai AK. An unusual case of primary nasal tuberculosis with epistaxis and epilepsy. Ear Nose Throat J. 2002;81(12):842–4.
96. Krespi YP, Kuriloff DB, Aner M. Sarcoidosis of the sinonasal tract: a new staging system. Otolaryngol Head Neck Surg. 1995;112(2):221–7.
97. Baughman RP, Lower EE, Tami T. Upper airway. 4: Sarcoidosis of the upper respiratory tract (SURT). Thorax. 2010;65(2):181–6.
98. Schwartzbauer HR, Tami TA. Ear, nose, and throat manifestations of sarcoidosis. Otolaryngol Clin North Am. 2003;36(4):673–84.
99. Shah UK, White JA, Gooey JE, Hybels RL. Otolaryngologic manifestations of sarcoidosis: presentation and diagnosis. Laryngoscope. 1997;107(1):67–75.
100. Popper HH, Winter E, Hofler G. DNA of Mycobacterium tuberculosis in formalin-fixed, paraffin-embedded tissue in tuberculosis and sarcoidosis detected by polymerase chain reaction. Am J Clin Pathol. 1994;101(6):738–41.
101. Hyams VJ. Rhinoscleroma. In: Binford CH, Connor DH, editors. Pathology of tropical and extraordinary diseases. Washington, DC: AFIP; 1976. p. 187–9.
102. Meyer PR, Shum TK, Becker TS, Taylor CR. Scleroma (rhinoscleroma). A histologic immunohistochemical study with bacteriologic correlates. Arch Pathol Lab Med. 1983;107(7):377–83.
103. Thompson LD. Rhinoscleroma. Ear Nose Throat J. 2002;81(8):506.
104. Connor DH, Neafie RC. Cutaneous leishmaniasis. In: Binford CH, Connor DH, editors. Pathology of tropical and extraordinary diseases. Washington, DC: AFIP; 1976. p. 258–64.
105. Lohuis PJ, Lipovsky MM, Hoepelman AI, Hordijk GJ, Huizing EH. Leishmania braziliensis presenting as a granulomatous lesion of the nasal septum mucosa. J Laryngol Otol. 1997;111(10):973–5.
106. Patuano E, Carrat X, Drouet Y, Barnabé D, Vincey P, Berthelot B. Mucocutaneous leishmaniasis in otorhinolaryngology. Ann Otolaryngol Chir Cervicofac. 1993;110(7):415–9.
107. Seyer BA, Grist W, Muller S. Aggressive destructive midfacial lesion from cocaine abuse. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94(4):465–70.
108. Wolff M. Granulomas in nasal mucous membranes following local steroid injections. Am J Clin Pathol. 1974;62:775–82.

109. Michaels L, Young M. Histogenesis of papillomas of the nose and paranasal sinuses. Arch Pathol Lab Med. 1995;119(9):821–6.
110. Buchwald C, Franzmann MB, Jacobsen GK, Lindeberg H. Human papillomavirus (HPV) in sinonasal papillomas: a study of 78 cases using in situ hybridization and polymerase chain reaction. Laryngoscope. 1995;105(1):66–71.
111. Fu YS, Hoover L, Franklin M, Cheng L, Stoler MH. Human papillomavirus identified by nucleic acid hybridization in concomitant nasal and genital papillomas. Laryngoscope. 1992;102(9):1014–9.
112. Judd R, Zaki SR, Coffield LM, Evatt BL. Sinonasal papillomas and human papillomavirus: human papillomavirus 11 detected in fungiform Schneiderian papillomas by in situ hybridization and the polymerase chain reaction. Hum Pathol. 1991;22(6):550–6.
113. Sarkar FH, Visscher DW, Kintanar EB, Zarbo RJ, Crissman JD. Sinonasal Schneiderian papillomas: human papillomavirus typing by polymerase chain reaction. Mod Pathol. 1992;5(3): 329–32.
114. Hyams VJ, Batsakis JG, Michaels L. Tumors of the upper respiratory tract and ear. Washington, DC: Armed Forces Institute of Pathology; 1988.
115. Barnes L, Tse LLY, Hunt JL. Schneiderian papillomas. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 28–32.
116. Christensen WN, Smith RR. Schneiderian papillomas: a clinicopathologic study of 67 cases. Hum Pathol. 1986;17(4):393–400.
117. Barnes L. Schneiderian papillomas and nonsalivary glandular neoplasms of the head and neck. Mod Pathol. 2002;15(3): 279–97.
118. Eggers G, Muhling J, Hassfeld S. Inverted papilloma of paranasal sinuses. J Craniomaxillofac Surg. 2007;35(1):21–9.
119. Califano J, Koch W, Sidransky D, Westra WH. Inverted sinonasal papilloma: a molecular genetic appraisal of its putative status as a Precursor to squamous cell carcinoma. Am J Pathol. 2000; 156(1):333–7.
120. Stammberger H. Neue Aspekte zur Genese des Invertierten Papilloms. Laryngol Rhinol Otol (Stuttg). 1983;62:249–55.
121. Shanmugaratnam K. WHO histological typing of tumors of the upper respiratory tract and ear. Berlin: Springer; 1991.
122. Slootweg PJ, Ferlito A, Cardesa A, Thompson LD, Hunt JL, Strojan P, et al. Sinonasal tumors: a clinicopathologic update of selected tumors. Eur Arch Otorhinolaryngol. 2013;270(1):5–20.
123. Smith O, Gullane PJ. Inverting papilloma of the nose: analysis of 48 patients. J Otolaryngol. 1987;16(3):154–6.
124. Ridolfi RL, Lieberman PH, Erlandson RA, Moore OS. Schneiderian papillomas: a clinicopathologic study of 30 cases. Am J Surg Pathol. 1977;1(1):43–53.
125. Woodson GE, Robbins KT, Michaels L. Inverted papilloma. Considerations in treatment. Arch Otorhinolaryngol. 1985; 111(12):806–11.
126. Batsakis JG, Suarez P. Schneiderian papillomas and carcinomas: a review. Adv Anat Pathol. 2001;8(2):53–64.
127. Sandison A. Common head and neck cases in our consultation referrals: diagnostic dilemmas in inverted papilloma. Head Neck Pathol. 2009;3(3):260–2.
128. Michaels L, Hellquist H. Ear, nose and throat histopathology. Berlin: Springer; 2001.
129. Phillips PP, Gustafson RO, Facer GW. The clinical behavior of inverting papilloma of the nose and paranasal sinuses: report of 112 cases and review of the literature. Laryngoscope. 1990;100(5):463–9.
130. Orvidas LJ, Lewis JE, Olsen KD, Weiner JS. Intranasal verrucous carcinoma: relationship to inverting papilloma and human papillomavirus. Laryngoscope. 1999;109(3):371–5.
131. Tanvetyanon T, Qin D, Padhya T, Kapoor R, McCaffrey J, Trotti A. Survival outcomes of squamous cell carcinoma arising from sinonasal inverted papilloma: report of 6 cases with systematic review and pooled analysis. Am J Otolaryngol. 2009;30(1): 38–43.
132. Barnes L, Bedetti C. Oncocytic Schneiderian papilloma: a reappraisal of cylindrical cell papilloma of the sinonasal tract. Hum Pathol. 1984;15(4):344–51.
133. Ward BE, Fechner RE, Mills SE. Carcinoma arising in oncocytic Schneiderian papilloma. Am J Surg Pathol. 1990;14(4):364–9.
134. Kaufman MR, Brandwein MS, Lawson W. Sinonasal papillomas: clinicopathologic review of 40 patients with inverted and oncocytic schneiderian papillomas. Laryngoscope. 2002; 112(8 Pt 1):1372–7.
135. Perez-Ordonez B. Hamartomas, papillomas and adenocarcinomas of the sinonasal tract and nasopharynx. J Clin Pathol. 2009;62(12):1085–95.
136. Cunningham MJ, Brantley S, Barnes L, Schramm VL. Oncocytic Schneiderian papilloma in a young adult: a rare diagnosis. Otolaryngol Head Neck Surg. 1987;97(1):47–51.
137. Weissler MC, Montgomery WW, Turner PA, Montgomery SK, Joseph MP. Inverted papilloma. Ann Otol Rhinol Laryngol. 1986;95(3 Pt 1):215–21.
138. Yang YJ, Abraham JL. Undifferentiated carcinoma arising in oncocytic Schneiderian (cylindrical cell) papilloma. J Oral Maxillofac Surg. 1997;55(3):289–94.
139. Kapadia SB, Barnes L, Pelzman K, Mirani N, Heffner DK, Bedetti C. Carcinoma ex oncocytic Schneiderian (cylindrical cell) papilloma. Am J Otolaryngol. 1993;14(5):332–8.
140. Compagno J, Wong RT. Intranasal mixed tumors (pleomorphic adenomas): a clinicopathologic study of 40 cases. Am J Clin Pathol. 1977;68(2):213–8.
141. Eveson JW. Salivary gland-type adenomas. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 34.
142. Heffner DK. Sinonasal and laryngeal salivary gland lesions. In: Ellis GL, Auclair PL, Gnepp DR, editors. Surgical pathology of salivary glands. Philadelphia: WB Saunders; 1991. p. 544–59.
143. Cohen MA, Batsakis JG. Oncocytic tumors (oncocytomas) of minor salivary glands. Arch Otorhinolaryngol. 1968;88(1):71–3.
144. Handler SD, Ward PH. Oncocytoma of the maxillary sinus. Laryngoscope. 1979;69:372–6.
145. Zarbo RJ, Ricci A, Kowalczyk PD, Cartun RW, Knibbs DR. Intranasal dermal analogue tumor (membranous basal cell adenoma). Ultrastructure and immunohistochemistry. Arch Otolaryngol. 1985;111(5):333–7.
146. Begin LR, Rochon L, Frenkel S. Spindle cell myoepithelioma of the nasal cavity. Am J Surg Pathol. 1991;15:184–90.
147. Alos L, Cardesa A, Bombi JA, Mallofre C, Cuchi A, Traserra J. Myoepithelial tumors of salivary glands: a clinicopathologic, immunohistochemical, ultrastructural and flow-cytometric study. Semin Diagn Pathol. 1996;13:138–47.
148. Davis JM, Weber AL. Pituitary adenoma presenting as a sphenoid sinus lesion. Ann Otol Rhinol Laryngol. 1980;89(5 Pt 1): 483–4.
149. Lloyd RV, Chandler WF, Kovacs K, Ryan N. Ectopic pituitary adenomas with normal anterior pituitary glands. Am J Surg Pathol. 1986;10(8):546–52.
150. Gondim JA, Schops M, Ferreira E, Bulcao T, Mota JI, Silveira C. Acromegaly due to an ectopic pituitary adenoma in the sphenoid sinus. Acta Radiol. 2004;45(6):689–91.
151. Hori E, Akai T, Kurimoto M, Hirashima Y, Endo S. Growth hormone-secreting pituitary adenoma confined to the sphenoid sinus associated with a normal-sized empty sella. J Clin Neurosci. 2002;9(2):196–9.

152. Mills SE, Stelow EB, Hunt JL. Ectopic pituitary tissue and pituitary adenoma. Tumors of the upper respiratory tract and ear. AFIP atlas of tumor pathology. Silver Spring: ARP Press; 2013. p. 176–81.
153. Luk IS, Chan JK, Chow SM, Leung S. Pituitary adenoma presenting as sinonasal tumor: pitfalls in diagnosis. Hum Pathol. 1996;27(6):605–9.
154. Schafer DR, Thompson LD, Smith BC, Wenig BM. Primary ameloblastoma of the sinonasal tract: a clinicopathologic study of 24 cases. Cancer. 1998;82(4):667–74.
155. Bray D, Michael A, Falconer DT, Kaddour HS. Ameloblastoma: a rare nasal polyp. J Laryngol Otol. 2007;121(1):72–5.
156. Ereno C, Etxegarai L, Corral M, Basurko JM, Bilbao FJ, Lopez JI. Primary sinonasal ameloblastoma. APMIS. 2005;113(2):148–50.
157. Pantoja E, Kopp EA, Beecher TS. Maxillary ameloblastoma: report of a tumor originating in the antrum. Ear Nose Throat J. 1976;55(11):358–61.
158. Press SG. Odontogenic tumors of the maxillary sinus. Curr Opin Otolaryngol Head Neck Surg. 2008;16(1):47–54.
159. Wenig BL, Sciubba JJ, Cohen A, Goldstein A, Abramson AL. An unusual cause of unilateral nasal obstruction: ameloblastoma. Otolaryngol Head Neck Surg. 1985;93(3):426–32.
160. Altini M, Coleman H, Doglioni C, Favia G, Maiorano E. Calretinin expression in ameloblastomas. Histopathology. 2000;37(1):27–32.
161. Mills SE, Cooper PH, Fechner RE. Lobular capillary hemangioma: the underlying lesion of pyogenic granuloma. A study of 73 cases from the oral and nasal mucous membranes. Am J Surg Pathol. 1980;4(5):470–9.
162. Fanburg-Smith JC, Thompson LDR. Benign soft tissue tumors. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 46–50.
163. Fu YS, Perzin KH. Nonepithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx. A clinicopathologic study. VI. Fibrous tissue tumors (fibroma, fibromatosis, fibrosarcoma). Cancer. 1976;37(6):2912–28.
164. Mills SE, Stelow EB, Hunt JL. Fibroblastic and myofibroblastic tumors. Tumors of the upper respiratory tract and ear. AFIP atlas of tumor pathology. Washington, DC: ARP Press; 2013. p. 353–79.
165. Perzin KH, Fu YS. Non-epithelial tumors of the nasal cavity, paranasal sinuses and nasopharynx: a clinico-pathologic study XI. fibrous histiocytomas. Cancer. 1980;45(10):2616–26.
166. Fu YS, Perzin KH. Nonepithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathologic study. IV. Smooth muscle tumors (leiomyoma, leiomyosarcoma). Cancer. 1975;35(5):1300–8.
167. Huang HY, Antonescu CR. Sinonasal smooth muscle cell tumors: a clinicopathologic and immunohistochemical analysis of 12 cases with emphasis on the low-grade end of the spectrum. Arch Pathol Lab Med. 2003;127(3):297–304.
168. Beck JC, Devaney KO, Weatherly RA, Koopmann Jr CF, Lesperance MM. Pediatric myofibromatosis of the head and neck. Arch Otolaryngol Head Neck Surg. 1999;125(1):39–44.
169. Chung EB, Enzinger FM. Infantile myofibromatosis. Cancer. 1981;48(8):1807–18.
170. Foss RD, Ellis GL. Myofibromas and myofibromatosis of the oral region: a clinicopathologic analysis of 79 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;89(1):57–65.
171. Hasegawa SL, Mentzel T, Fletcher CD. Schwannomas of the sinonasal tract and nasopharynx. Mod Pathol. 1997;10(8):777–84.
172. Cardesa A, Ribalta T, Von SB, Palacin A, Mohr U. Experimental model of tumors associated with neurofibromatosis. Cancer. 1989;63(9):1737–49.
173. Hillstrom RP, Zarbo RJ, Jacobs JR. Nerve sheath tumors of the paranasal sinuses: electron microscopy and histopathologic diagnosis. Otolaryngol Head Neck Surg. 1990;102(3):257–63.
174. Wong BY, Hui Y, Lam KY, Wei WI. Neurothekeoma of the paranasal sinuses in a 3-year-old boy. Int J Pediatr Otorhinolaryngol. 2002;62(1):69–73.
175. Ho K. Primary meningioma of the nasal cavity and paranasal sinuses. Cancer. 1980;46:1442–7.
176. Thompson LD, Gyure KA. Extracranial sinonasal tract meningiomas: a clinicopathologic study of 30 cases with a review of the literature. Am J Surg Pathol. 2000;24(5):640–50.
177. Thompson LDR, Fanburg-Smith JC. Nasopharyngeal angiofibroma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 102–3.
178. Jacobsson M, Petruson B, Svendsen P, Berthelsen B. Juvenile nasopharyngeal angiofibroma. A report of eighteen cases. Acta Otolaryngol. 1988;105(1–2):132–9.
179. Neel III HB, Whicker JH, Devine KD, Weiland LH. Juvenile angiofibroma. Review of 120 cases. Am J Surg. 1973; 126(4):547–56.
180. Hwang HC, Mills SE, Patterson K, Gown AM. Expression of androgen receptors in nasopharyngeal angiofibroma: an immunohistochemical study of 24 cases. Mod Pathol. 1998;11:1122–6.
181. Topilko A, Zakrzewski A, Pichard E, Viron A. Ultrastructural cytochemistry of intranuclear dense granules in nasopharyngeal angiofibroma. Ultrastruct Pathol. 1984;6(2–3):221–8.
182. Siniluoto TM, Luotonen JP, Tikkakoski TA, Leinonen AS, Jokinen KE. Value of pre-operative embolization in surgery for nasopharyngeal angiofibroma. J Laryngol Otol. 1993;107(6):514–21.
183. Tse LL, Chan JK. Sinonasal haemangiopericytoma-like tumor: a sinonasal glomus tumor or a haemangiopericytoma? Histopathology. 2002;40(6):510–7.
184. Thompson LDR, Fanburg-Smith JC, Wenig BM. Borderline and low malignant potential tumors of soft tissues. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 43–5.
185. Compagno J, Hyams VJ. Hemangiopericytoma-like intranasal tumors. A clinicopathologic study of 23 cases. Am J Clin Pathol. 1976;66(4):672–83.
186. Compagno J. Hemangiopericytoma-like tumors of the nasal cavity: a comparison with hemangiopericytoma of soft tissues. Laryngoscope. 1978;88(3):460–9.
187. Beech TJ, Rokade A, Gittoes N, Johnson AP. A haemangiopericytoma of the ethmoid sinus causing oncogenic osteomalacia: a case report and review of the literature. Int J Oral Maxillofac Surg. 2007;36(10):956–8.
188. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. Am J Surg Pathol. 2004;28(1):1–30.
189. Thompson LDR, Miettinen M, Wenig BM. Sinonasal-type hemangiopericytoma: a clinicopathologic and immunophenotypic analysis of 104 cases showing perivascular myoid differentiation. Am J Surg Pathol. 2003;27(6):737–49.
190. Kowalski PJ, Paulino AF. Proliferation index as a prognostic marker in hemangiopericytoma of the head and neck. Head Neck. 2001;23(6):492–6.
191. Gnepp DR, Henley J, Weiss S, Heffner D. Desmoid fibromatosis of the sinonasal tract and nasopharynx. A clinicopathologic study of 25 cases. Cancer. 1996;78(12):2572–9.
192. Bhattacharya B, Dilworth HP, Iacobuzio-Donahue C, Ricci F, Weber K, Furlong MA, et al. Nuclear beta-catenin expression dis-

tinguishes deep fibromatosis from other benign and malignant fibroblastic and myofibroblastic lesions. Am J Surg Pathol. 2005;29(5):653–9.
193. Cates JM, Stricker TP. Surgical resection margins in desmoid-type fibromatosis: a critical reassessment. Am J Surg Pathol. 2014;38(12):1707–14.
194. Alobid I, Alos L, Blanch JL, Benitez P, Bernal-Sprekelsen M, Mullol J. Solitary fibrous tumor of the nasal cavity and paranasal sinuses. Acta Otolaryngol. 2003;123(1):71–4.
195. Mentzel T, Bainbridge TC, Katenkamp D. Solitary fibrous tumor: clinicopathological, immunohistochemical, and ultrastructural analysis of 12 cases arising in soft tissues, nasal cavity and nasopharynx, urinary bladder and prostate. Virchows Arch. 1997; 430(6):445–53.
196. Zukerberg LR, Rosenberg AE, Randolph G, Pilch BZ, Goodman ML. Solitary fibrous tumor of the nasal cavity and paranasal sinuses. Am J Surg Pathol. 1991;15(2):126–30.
197. Ganly I, Patel SG, Stambuk HE, Coleman M, Ghossein R, Carlson D, et al. Solitary fibrous tumors of the head and neck: a clinicopathologic and radiologic review. Arch Otolaryngol Head Neck Surg. 2006;132(5):517–25.
198. Morales-Cadena M, Zubiaur FM, Alvarez R, Madrigal J, Zarate-Osorno A. Solitary fibrous tumor of the nasal cavity and paranasal sinuses. Otolaryngol Head Neck Surg. 2006;135(6):980–2.
199. Witkin GB, Rosai J. Solitary fibrous tumor of the upper respiratory tract. A report of six cases. Am J Surg Pathol. 1991;15(9):842–8.
200. Zeitler DM, Kanowitz SJ, Har-El G. Malignant solitary fibrous tumor of the nasal cavity. Skull Base. 2007;17(4):239–46.
201. Batsakis JG, Rice DH, Solomon AR. The pathology of head and neck tumors: squamous and mucous-gland carcinomas of the nasal cavity, paranasal sinuses, and larynx, part 6. Head Neck Surg. 1980;2(6):497–508.
202. Pilch BZ, Bouquot J, Thompson LDR. Squamous cell carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 15–7.
203. Hunt JL, Barnes L, Lewis Jr JS, Mahfouz ME, Slootweg PJ, Thompson LD, et al. Molecular diagnostic alterations in squamous cell carcinoma of the head and neck and potential diagnostic applications. Eur Arch Otorhinolaryngol. 2014;271(2):211–23.
204. Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005.
205. Mills SE, Stelow EB, Hunt JL, editors. Tumors of the upper respiratory tract and ear. Series 4 ed. Washington, DC: ARP Press; 2013.
206. Barnes L, Tse LL, Hunt JL, Brandwein-Gensler M, Curtin HD, Boffetta P. Tumors of the nasal cavity and paranasal sinuses: introduction. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 12–4.
207. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. p. 21–78.
208. Kagan AR, Nussbaum H, Rao A, Chan P, Gilbert H, Hintz B, et al. The management of carcinoma of the nasal vestibule. Head Neck Surg. 1981;4(2):125–8.
209. Mendenhall WM, Stringer SP, Cassisi NJ, Mendenhall NP. Squamous cell carcinoma of the nasal vestibule. Head Neck. 1999;21(5):385–93.
210. Taxy JB. Squamous carcinoma of the nasal vestibule. An analysis of five cases and literature review. Am J Clin Pathol. 1997;107:698–703.
211. Tufano RP, Mokadam NA, Montone KT, Weinstein GS, Chalian AA, Wolf PF, et al. Malignant tumors of the nose and paranasal sinuses: hospital of the University of Pennsylvania experience 1990-1997. Am J Rhinol. 1999;13(2):117–23.
212. Gadeberg CC, Hjelm-Hansen M, Sögaard H, Elbrond O. Malignant tumors of the paranasal sinuses and nasal cavity. A series of 180 patients. Acta Radiol Oncol. 1984;23(2–3):181–7.
213. Traserra J, Avellaneda R, Cuchi M, Abelló P. Tumores rinosinusales. Otorrinolaringologia. Barcelona: Salvat; 1984. p. 123–33.
214. Robin PE, Powell DJ. Regional node involvement and distant metastases in carcinoma of the nasal cavity and paranasal sinuses. J Laryngol Otol. 1980;94(3):301–9.
215. Klein-Szanto AJ, Boysen M, Reith A. Keratin and involucrin in preneoplastic and neoplastic lesions. Distribution in the nasal mucosa of nickel workers. Arch Pathol Lab Med. 1987;111(11):1057–61.
216. Sunderman Jr FW, Morgan LG, Andersen A, Ashley D, Forouhar FA. Histopathology of sinonasal and lung cancers in nickel refinery workers. Ann Clin Lab Sci. 1989;19:44–50.
217. Torjussen W, Solberg LA, Hogetvit AC. Histopathologic changes of the nasal mucosa in nickel workers. A pilot study. Cancer. 1979;44:963–74.
218. Torjussen W, Haug FM, Andersen I. Concentration and distribution of heavy metals in nasal mucosa of nickel-exposed workers and of controls, studied with atomic absorption spectrophotometric analysis and with Timm's sulphide silver method. Acta Otolaryngol. 1978;86(5–6):449–63.
219. Rousch GC. Epidemiology of cancer of the nose and paranasal sinuses: current concepts. Head Neck Surg. 1979;2:3–11.
220. Larsson LG, Martensson G. Maxillary antral cancers. JAMA. 1972;219(3):342–5.
221. Beatty CW, Pearson BW, Kern EB. Carcinoma of the nasal septum: experience with 85 cases. Otolaryngol Head Neck Surg. 1982;90(1):90–4.
222. Goren AD, Harley N, Eisenbud L, Levin S, Cohen N. Clinical and radiobiologic features of Thorotrast-induced carcinoma of the maxillary sinus. A case report. Oral Surg Oral Med Oral Pathol. 1980;49(3):237–42.
223. Cardesa A, Pour P, Haas H, Althoff J, Mohr U. Histogenesis of tumors from the nasal cavities induced by diethylnitrosamine. Cancer. 1976;37(1):346–55.
224. Luce D, Gerin M, Leclerc A, Morcet JF, Brugere J, Goldberg M. Sinonasal cancer and occupational exposure to formaldehyde and other substances. Int J Cancer. 1993;53(2):224–31.
225. Hanna GS, Ali MH. Verrucous carcinoma of the nasal septum. J Laryngol Otol. 1987;101(2):184–7.
226. Piscioli F, Aldovini D, Bondi A, Eusebi V. Squamous cell carcinoma with sarcoma-like stroma of the nose and paranasal sinuses: report of two cases. Histopathology. 1984;8(4):633–9.
227. Zarbo RJ, Crissman JD, Venkat H, Weiss MA. Spindle-cell carcinoma of the upper aerodigestive tract mucosa. An immunohistologic and ultrastructural study of 18 biphasic tumors and comparison with seven monophasic spindle-cell tumors. Am J Surg Pathol. 1986;10(11):741–53.
228. Wieneke JA, Thompson LD, Wenig BM. Basaloid squamous cell carcinoma of the sinonasal tract. Cancer. 1999;85(4):841–54.
229. Banks ER, Frierson HF, Mills SE, George E, Zarbo RJ, Swanson PE. Basaloid squamous cell carcinoma of the head and neck. A clinicopathologic and immunohistochemical study of 40 cases. Am J Surg Pathol. 1992;16(10):939–46.
230. Alos L, Castillo M, Nadal A, Caballero M, Mallofre C, Palacin A, et al. Adenosquamous carcinoma of the head and neck: criteria for diagnosis in a study of 12 cases. Histopathology. 2004;44(6):570–9.
231. Gerughty RM, Hennigar GR, Brown FM. Adenosquamous carcinoma of the nasal, oral and laryngeal cavities. Cancer. 1984;22:1140–55.
232. Lin CY, Chen HH, Chen HH, Fang SY, Tsai ST. Ethmoid sinus cancer: results of treatment with surgery and combined therapy. Acta Otolaryngol. 2004;124(10):1220–5.

233. Kermer C, Poeschl PW, Wutzl A, Schopper C, Klug C, Poeschl E. Surgical treatment of squamous cell carcinoma of the maxilla and nasal sinuses. J Oral Maxillofac Surg. 2008;66(12):2449–53.
234. Bosch A, Vallecillo L, Frias Z. Cancer of the nasal cavity. Cancer. 1976;37(3):1458–63.
235. Ringertz N. Pathology of malignant tumors arising in the nasal and paranasal cavities and maxilla. Acta Otolaryngol. 1938;27:1–405.
236. Alos L, Moyano S, Nadal A, Alobid I, Blanch JL, Ayala E, et al. Human papillomaviruses are identified in a subgroup of sinonasal squamous cell carcinomas with favorable outcome. Cancer. 2009;115(12):2701–9.
237. El-Mofty SK, Lu DW. Prevalence of high-risk human papillomavirus DNA in non-keratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity. Am J Surg Pathol. 2005;29(10):1367–72.
238. Larque AB, Hakim S, Ordi J, Nadal A, Diaz A, Del Pino M, et al. High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas. Mod Pathol. 2014;27:343–51.
239. Hafkamp HC, Speel EJ, Haesevoets A, Bot FJ, Dinjens WN, Ramaekers FC, et al. A subset of head and neck squamous cell carcinomas exhibits integration of HPV 16/18 DNA and overexpression of p16INK4A and p53 in the absence of mutations in p53 exons 5–8. Int J Cancer. 2003;107(3):394–400.
240. Westra WH, Taube JM, Poeta ML, Begum S, Sidransky D, Koch WM. Inverse relationship between human papillomavirus-16 infection and disruptive p53 gene mutations in squamous cell carcinoma of the head and neck. Clin Cancer Res. 2008; 14(2):366–9.
241. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356(19):1944–56.
242. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000;92(9):709–20.
243. Bishop JA, Ogawa T, Stelow EB, Moskaluk CA, Koch WM, Pai SI, et al. Human papillomavirus-related carcinoma with adenoid cystic-like features: a peculiar variant of head and neck cancer restricted to the sinonasal tract. Am J Surg Pathol. 2013;37(6):836–44.
244. Bishop JA, Guo TW, Smith DF, Wang H, Ogawa T, Pai SI, et al. Human papillomavirus-related carcinomas of the sinonasal tract. Am J Surg Pathol. 2013;37(2):185–92.
245. Jo VY, Mills SE, Stoler MH, Stelow EB. Papillary squamous cell carcinoma of the head and neck: frequent association with human papillomavirus infection and invasive carcinoma. Am J Surg Pathol. 2009;33(11):1720–4.
246. Bishop JA, Montgomery EA, Westra WH. Use of p40 and p63 immunohistochemistry and human papillomavirus testing as ancillary tools for the recognition of head and neck sarcomatoid carcinoma and its distinction from benign and malignant mesenchymal processes. Am J Surg Pathol. 2014;38(2):257–64.
247. Maxwell JH, Kumar B, Feng FY, McHugh JB, Cordell KG, Eisbruch A, et al. HPV-positive/p16-positive/EBV-negative nasopharyngeal carcinoma in white North Americans. Head Neck. 2010;32(5):562–7.
248. Singhi AD, Stelow EB, Mills SE, Westra WH. Lymphoepithelial-like carcinoma of the oropharynx: a morphologic variant of HPV-related head and neck carcinoma. Am J Surg Pathol. 2010;34(6):800–5.
249. Bishop JA, Ma XJ, Wang H, Luo Y, Illei PB, Begum S, et al. Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA in situ hybridization method. Am J Surg Pathol. 2012;36(12):1874–82.
250. Lewis Jr JS, Chernock RD, Haynes W, El-Mofty SK. Low-grade papillary schneiderian carcinoma, a unique and deceptively bland malignant neoplasm: report of a case. Am J Surg Pathol. 2015;39(5):714–21.
251. Friedmann I, Osborn DA. Carcinoma of the surface epithelium (including ameloblastoma). Pathology of granulomas and neoplasms of the nose and paranasal sinuses. Edinburgh: Churchill Livingstone; 1982. p. 118–32.
252. Westra WH. The changing face of head and neck cancer in the 21st century: the impact of HPV on the epidemiology and pathology of oral cancer. Head Neck Pathol. 2009;3(1):78–81.
253. Kumar B, Cordell KG, Lee JS, Worden FP, Prince ME, Tran HH, et al. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. J Clin Oncol. 2008;26(19):3128–37.
254. Worden FP, Kumar B, Lee JS, Wolf GT, Cordell KG, Taylor JM, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. J Clin Oncol. 2008;26(19):3138–46.
255. Krupar R, Robold K, Gaag D, Spanier G, Kreutz M, Renner K, et al. Immunologic and metabolic characteristics of HPV-negative and HPV-positive head and neck squamous cell carcinomas are strikingly different. Virchows Arch. 2014;465(3):299–312.
256. Cerilli LA, Holst VA, Brandwein MS, Stoler MH, Mills SE. Sinonasal undifferentiated carcinoma: immunohistochemical profile and lack of EBV association. Am J Surg Pathol. 2001;25(2):156–63.
257. Frierson HF, Mills SE, Fechner RE, Taxy JB, Levine PA. Sinonasal undifferentiated carcinoma. An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. Am J Surg Pathol. 1986;10(11):771–9.
258. Helliwell TR, Yeoh LH, Stell PM. Anaplastic carcinoma of the nose and paranasal sinuses. Light microscopy, immunohistochemistry and clinical correlation. Cancer. 1986;58(9):2038–45.
259. Jeng YM, Sung MT, Fang CL, Huang HY, Mao TL, Cheng W, et al. Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma: two clinically, biologically, and histopathologically distinct entities. Am J Surg Pathol. 2002;26(3):371–6.
260. Gray ST, Herr MW, Sethi RK, Diercks G, Lee L, Curry W, et al. Treatment outcomes and prognostic factors, including human papillomavirus, for sinonasal undifferentiated carcinoma: a retrospective review. Head Neck. 2015;37(3):366–74.
261. Franchi A, Moroni M, Massi D, Paglierani M, Santucci M. Sinonasal undifferentiated carcinoma, nasopharyngeal-type undifferentiated carcinoma, and keratinizing and non-keratinizing squamous cell carcinoma express different cytokeratin patterns. Am J Surg Pathol. 2002;26(12):1597–604.
262. Wenig BM. Undifferentiated malignant neoplasms of the sinonasal tract. Arch Pathol Lab Med. 2009;133(5):699–712.
263. Gil Z, Orr-Urtreger A, Voskoboinik N, Trejo-Leider L, Spektor S, Shomrat R, et al. Cytogenetic analysis of sinonasal carcinomas. Otolaryngol Head Neck Surg. 2006;134(4):654–60.
264. Chernock RD, Perry A, Pfeifer JD, Holden JA, Lewis Jr JS. Receptor tyrosine kinases in sinonasal undifferentiated carcinomas – evaluation for EGFR, c-KIT, and HER2/neu expression. Head Neck. 2009;31(7):919–27.
265. Gelbard A, Hale KS, Takahashi Y, Davies M, Kupferman ME, El-Naggar AK, et al. Molecular profiling of sinonasal undifferentiated carcinoma. Head Neck. 2014;36(1):15–21.
266. Bishop JA, Westra WH. NUT midline carcinomas of the sinonasal tract. Am J Surg Pathol. 2012;36(8):1216–21.

267. Reiersen DA, Pahilan ME, Devaiah AK. Meta-analysis of treatment outcomes for sinonasal undifferentiated carcinoma. Otolaryngol Head Neck Surg. 2012;147(1):7–14.
268. Tanzler ED, Morris CG, Orlando CA, Werning JW, Mendenhall WM. Management of sinonasal undifferentiated carcinoma. Head Neck. 2008;30(5):595–9.
269. Mourad WF, Hauerstock D, Shourbaji RA, Hu KS, Culliney B, Li Z, et al. Trimodality management of sinonasal undifferentiated carcinoma and review of the literature. Am J Clin Oncol. 2013;36(6):584–8.
270. Stewart FM, Lazarus HM, Levine PA, Stewart KA, Tabbara IA, Spaulding CA. High-dose chemotherapy and autologous marrow transplantation for esthesioneuroblastoma and sinonasal undifferentiated carcinoma. Am J Clin Oncol. 1989; 12(3):217–21.
271. Tsang WYW, Chan JKC. Lymphoepithelial carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 18.
272. Bell D, Hanna EY, Weber RS, Demonte F, Triantafyllou A, Lewis Jr JS, et al. Neuroendocrine neoplasms of the sinonasal region. Head Neck. 2016;38 Suppl 1:E2259–66.
273. Babin E, Rouleau V, Vedrine PO, Toussaint B, de Raucourt D, Malard O, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. J Laryngol Otol. 2006;120(4):289–97.
274. Chaudry MR, Aktar S, Kim DS. Neuroendocrine carcinoma of the ethmoid sinus. Eur Arch Otorhinolaryngol. 1994;251:461–3.
275. Raychowdhuri RN. Oat cell carcinoma and paranasal sinuses. J Laryngol Otol. 1965;79:253–5.
276. Rejowski JE, Campanella RS, Block LJ. Small cell carcinoma of the nose and paranasal sinuses. Otolaryngol Head Neck Surg. 1982;90(4):516–7.
277. Weiss MD, deFries HO, Taxy JB, Braine H. Primary small cell carcinoma of the paranasal sinuses. Arch Otolaryngol. 1983;109(5):341–3.
278. Franchi A, Sardi I, Cetica V, Buccoliero A, Giordano F, Mussa F, et al. Pediatric sinonasal neuroendocrine carcinoma after treatment of retinoblastoma. Hum Pathol. 2009;40(5):750–5.
279. Mills SE, Gaffey MJ, Frierson HF. Tumors of the upper aerodigestive tract and ear. Washington, DC: Armed Forces Institute of Pathology; 2000.
280. Perez-Ordoñez B, Caruana SM, Huvos AG, Shah JP. Small cell neuroendocrine carcinoma of the of the nasal cavity and paranasal sinuses. Hum Pathol. 1998;29:826–32.
281. Kameya T, Shimosato Y, Adachi I, Abe K, Ebihara S, Ono I. Neuroendocrine carcinoma of the paranasal sinus: a morphological and endocrinological study. Cancer. 1980;45(2):330–9.
282. Lloreta-Trull J, Mackay B, Troncoso P, Ribalta-Farres T, Smith T, Khorana S. Neuroendocrine tumors of the nasal cavity: an ultrastructural and morphometric study of 24 cases. Ultrastruct Pathol. 1992;16(1–2):165–75.
283. Ordonez NG, Mackay B. Neuroendocrine tumors of the nasal cavity. Pathol Annu. 1993;28:77–111.
284. Silva EG, Butler JJ, Mackay B, Goepfert H. Neuroblastomas and neuroendocrine carcinomas of the nasal cavity: a proposed new classification. Cancer. 1982;50(11):2388–405.
285. Ferlito A, Strojan P, Lewis Jr JS, Perez-Ordoñez B, Rinaldo A. Large cell neuroendocrine carcinoma of the head and neck: a distinct clinicopathologic entity. Eur Arch Otorhinolaryngol. 2014;271(8):2093–5.
286. Kao HL, Chang WC, Li WY, Chia-Heng LA, Fen-Yau LA. Head and neck large cell neuroendocrine carcinoma should be separated from atypical carcinoid on the basis of different clinical features, overall survival, and pathogenesis. Am J Surg Pathol. 2012;36(2):185–92.
287. French CA. NUT midline carcinoma. Cancer Genet Cytogenet. 2010;203(1):16–20.
288. Stelow EB, Bellizzi AM, Taneja K, Mills SE, LeGallo RD, Kutok JL, et al. NUT rearrangement in undifferentiated carcinomas of the upper aerodigestive tract. Am J Surg Pathol. 2008;32(6): 828–34.
289. French CA. Demystified molecular pathology of NUT midline carcinomas. J Clin Pathol. 2010;63(6):492–6.
290. Haack H, Johnson LA, Fry CJ, Crosby K, Polakiewicz RD, Stelow EB, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol. 2009;33(7):984–91.
291. French CA. The importance of diagnosing NUT midline carcinoma. Head Neck Pathol. 2013;7(1):11–6.
292. Stelow EB, French CA. Carcinomas of the upper aerodigestive tract with rearrangement of the nuclear protein of the testis (NUT) gene (NUT midline carcinomas). Adv Anat Pathol. 2009;16(2): 92–6.
293. French CA, Kutok JL, Faquin WC, Toretsky JA, Antonescu CR, Griffin CA, et al. Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol. 2004;22(20):4135–9.
294. French CA, Ramirez CL, Kolmakova J, Hickman TT, Cameron MJ, Thyne ME, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene. 2008;27(15):2237–42.
295. Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB, Luer SC, et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res. 2012;18(20): 5773–9.
296. Agaimy A, Koch M, Lell M, Semrau S, Dudek W, Wachter DL, et al. SMARCB1(INI1)-deficient sinonasal basaloid carcinoma: a novel member of the expanding family of SMARCB1-deficient neoplasms. Am J Surg Pathol. 2014;38(9):1274–81.
297. Bishop JA, Antonescu CR, Westra WH. SMARCB1 (INI-1)-deficient carcinomas of the sinonasal tract. Am J Surg Pathol. 2014;38(9):1282–9.
298. Turner JH, Reh DD. Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. Head Neck. 2012;34(6):877–85.
299. Jarvi O. Heterotopic tumors with an intestinal mucous membrane structure in the nasal cavity. Acta Otolaryngol. 1945;33:471–85.
300. Sanchez-Casis G, Devine KD, Weiland LH. Nasal adenocarcinomas that closely simulate colonic carcinomas. Cancer. 1971; 28(3):714–20.
301. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. Clin Otolaryngol Allied Sci. 1979; 4(6):431–56.
302. Harbo G, Grau C, Bundgaard T, Overgaard M, Elbrond O, Sogaard H, et al. Cancer of the nasal cavity and paranasal sinuses. A clinico-pathological study of 277 patients. Acta Oncol. 1997;36(1):45–50.
303. Cardesa A, Alos L. Special tumors of the head and neck region: characterization of undifferentiated sinonasal tumors. Histopathology. 2002;41 Suppl 2:473–7.
304. Acheson ED, Cowdell RH, Jolles B. Nasal cancer in the Northamptonshire boot and shoe industry. Br Med J. 1970;1:385–93.
305. Acheson ED, Cowdell RH, Hadfield E, Macbeth RG. Nasal cancer in woodworkers in the furniture industry. Br Med J. 1968; 2:587–96.
306. Cecchi F, Buiatti E, Kriebel D, Nastasi L, Santucci M. Adenocarcinoma of the nose and paranasal sinuses in shoemakers and woodworkers in the province of Florence, Italy (1963-77). Br J Ind Med. 1980;37(3):222–5.

307. Hadfield EH, Macbeth RG. Adenocarcinoma of ethmoids in furniture workers. Ann Otol Rhinol Laryngol. 1971;80(5):699–703.
308. Imbus HR, Dyson WL. A review of nasal cancer in furniture manufacturing and woodworking in North Carolina, the United States, and other countries. J Occup Med. 1987;29(9):734–40.
309. Ironside P, Matthews J. Adenocarcinoma of the nose and paranasal sinuses in woodworkers in the state of Victoria, Australia. Cancer. 1975;36(3):1115–24.
310. Klintenberg C, Olofsson J, Hellquist H, Sokjer H. Adenocarcinoma of the ethmoid sinuses. A review of 28 cases with special reference to wood dust exposure. Cancer. 1984;54(3):482–8.
311. Kuijpens JH, Louwman MW, Peters R, Janssens GO, Burdorf AL, Coebergh JW. Trends in sinonasal cancer in The Netherlands: more squamous cell cancer, less adenocarcinoma. A population-based study 1973-2009. Eur J Cancer. 2012;48(15):2369–74.
312. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Am J Surg Pathol. 1986;10:192–202.
313. Schmid KO, Aubock L, Albegger K. Endocrine-amphicrine enteric carcinoma of the nasal mucosa. Virchows Arch. 1979; 383(3):329–43.
314. Wilhelmsson B, Hellquist H, Olofsson J, Klintenberg C. Nasal cuboidal metaplasia with dysplasia. Precursor to adenocarcinoma in wood-dust-exposed workers? Acta Otolaryngol. 1985; 99(5–6):641–8.
315. Batsakis JG, Holtz F, Sueper RH. Adenocarcinoma of the nasal and paranasal cavities. Arch Otolaryngol. 1963;77:625–33.
316. Mills SE, Fechner RE, Cantrell RW. Aggressive sinonasal lesion resembling normal intestinal mucosa. Am J Surg Pathol. 1982;6(8):803–9.
317. Franquemont DW, Fechner RE, Mills SE. Histologic classification of sinonasal intestinal-type adenocarcinoma. Am J Surg Pathol. 1991;15(4):368–75.
318. Franchi A, Gallo O, Santucci M. Clinical relevance of the histological classification of sinonasal intestinal-type adenocarcinomas. Hum Pathol. 1999;30(10):1140–5.
319. Kleinsasser O, Schroeder HG. Adenocarcinomas of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behavior in 79 cases. Arch Otorhinolaryngol. 1988;245(1):1–15.
320. Jain R, Gramigna V, Sanchez-Marull R, Perez-Ordoñez B. Composite intestinal-type adenocarcinoma and small cell carcinoma of sinonasal tract. J Clin Pathol. 2009;62(7):634–7.
321. Batsakis JG, Mackay B, Ordoñez NG. Enteric-type adenocarcinoma of the nasal cavity. An electron microscopic and immunocytochemical study. Cancer. 1984;54(5):855–60.
322. McKinney CD, Mills SE, Franquemont DW. Sinonasal intestinal-type adenocarcinoma: immunohistochemical profile and comparison with colonic adenocarcinoma. Mod Pathol. 1995;8(4):421–6.
323. Franchi A, Massi D, Palomba A, Biancalani M, Santucci M. CDX-2 cytokeratin 7 and cytokeratin 20 immunohistochemical expression in the differential diagnosis of primary adenocarcinomas of the sinonasal tract. Virchows Arch. 2004;445:63–7.
324. Abecasis J, Viana G, Pissarra C, Pereira T, Fonseca I, Soares J. Adenocarcinomas of the nasal cavity and paranasal sinuses: a clinicopathological and immunohistochemical study of 14 cases. Histopathology. 2004;45(3):254–9.
325. Frattini M, Perrone F, Suardi S, Balestra D, Caramuta S, Colombo F, et al. Phenotype-genotype correlation: challenge of intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Head Neck. 2006;28(10):909–15.
326. Bornholdt J, Hansen J, Steiniche T, Dictor M, Antonsen A, Wolff H, et al. K-ras mutations in sinonasal cancers in relation to wood dust exposure. BMC Cancer. 2008;8:53.
327. Lopez F, Garcia Inclan C, Perez-Escuredo J, Alvarez MC, Scola B, Suarez C, et al. KRAS and BRAF mutations in sinonasal cancer. Oral Oncol. 2012;48(8):692–7.
328. Franchi A, Fondi C, Paglierani M, Pepi M, Gallo O, Santucci M. Epidermal growth factor receptor expression and gene copy number in sinonasal intestinal type adenocarcinoma. Oral Oncol. 2009;45(9):835–8.
329. Licitra L, Suardi S, Bossi P, Locati LD, Mariani L, Quattrone P, et al. Prediction of TP53 status for primary cisplatin, fluorouracil, and leucovorin chemotherapy in ethmoid sinus intestinal-type adenocarcinoma. J Clin Oncol. 2004;22(24):4901–6.
330. Stelow EB, Jo VY, Mills SE, Carlson DL. A histologic and immunohistochemical study describing the diversity of tumors classified as sinonasal high-grade nonintestinal adenocarcinomas. Am J Surg Pathol. 2011;35(7):971–80.
331. Lund VJ, Chisholm EJ, Takes RP, Suarez C, Mendenhall WM, Rinaldo A, et al. Evidence for treatment strategies in sinonasal adenocarcinoma. Head Neck. 2012;34(8):1168–78.
332. Wenig BM, Hyams VJ, Heffner DK. Nasopharyngeal papillary adenocarcinoma. A clinicopathologic study of a low-grade carcinoma. Am J Surg Pathol. 1988;12(12):946–53.
333. Skalova A, Cardesa A, Leivo I, Pfaltz M, Ryska A, Simpson R, et al. Sinonasal tubulopapillary low-grade adenocarcinoma. Histopathological, immunohistochemical and ultrastructural features of poorly recognised entity. Virchows Arch. 2003;443(2): 152–8.
334. Kleinsasser O. Terminal tubulus adenocarcinoma of the nasal seromucous glands. Arch Otorhinolaryngol. 1985;241:183–93.
335. Neto AG, Pineda-Daboin K, Luna MA. Sinonasal tract seromucous adenocarcinomas: a report of 12 cases. Ann Diagn Pathol. 2003;7(3):154–9.
336. Jo VY, Mills SE, Cathro HP, Carlson DL, Stelow EB. Low-grade sinonasal adenocarcinomas: the association with and distinction from respiratory epithelial adenomatoid hamartomas and other glandular lesions. Am J Surg Pathol. 2009;33(3):401–8.
337. Storck K, Hadi UM, Simpson R, Ramer M, Brandwein-Gensler M. Sinonasal renal cell-like adenocarcinoma: a report on four patients. Head Neck Pathol. 2008;2(2):75–80.
338. Franchi A, Palomba A, Massi D, Biancalani M, Sardi I, Gallo O, et al. Low-grade salivary type tubulo-papillary adenocarcinoma of the sinonasal tract. Histopathology. 2006;48(7):881–4.
339. Seifert G. WHO histological typing of salivary gland tumors. Berlin: Springer; 1991.
340. Batsakis JG. Mucous gland tumors of the nose and paranasal sinuses. Ann Otol Rhinol Laryngol. 1970;79:557–62.
341. Perzin KH, Cantor JO, Johannessen JV. Acinic cell carcinoma arising in nasal cavity: report of a case with ultrastructural observations. Cancer. 1981;47(7):1818–22.
342. Delgado R, Klimstra D, Albores-Saavedra J. Low grade salivary duct carcinoma. A distinctive variant with a low grade histology and a predominant intraductal growth pattern. Cancer. 1996; 78(5):958–67.
343. Zur KB, Brandwein M, Wang B, Som P, Gordon R, Urken ML. Primary description of a new entity, renal cell-like carcinoma of the nasal cavity: van Meegeren in the house of Vermeer. Arch Otolaryngol Head Neck Surg. 2002;128(4):441–7.
344. Mills SE, Stelow EB, Hunt JL. Olfactory neuroblastoma. Tumors of the upper respiratory tract and ear. Washington, DC: ARP Press; 2013. p. 201–12.
345. Eveson JW. Salivary gland-type carcinomas. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 24–5.
346. Pitman KT, Prokopakis EP, Aydogan B, Segas J, Carrau RL, Snyderman CH, et al. The role of skull base surgery for the treatment of adenoid cystic carcinoma of the sinonasal tract. Head Neck. 1999;21(5):402–7.
347. Cardesa A, Bombi JA, Alos L. The classification of tumors of the minor salivary glands. Arq Patol Univ Coimbra Portugal. 1993;25:75–85.

348. Da-Quan M, Guang-Yan Y. Tumors of the minor salivary glands: a clinicopathologic study of 243 cases. Acta Otolaryngol. 1987;103(5–6):325–31.
349. Mesara BW, Batsakis JG. Glandular tumors of the upper respiratory tract. A clinicopathologic assessment. Arch Surg. 1966;92(6):872–8.
350. Tran L, Sidrys J, Horton D, Sadeghi A, Parker RG. Malignant salivary gland tumors of the paranasal sinuses and nasal cavity. The UCLA experience. Am J Clin Oncol. 1989;12(5):387–92.
351. Akiyama K, Karaki M, Hosikawa H, Mori N. A massive adenoid cystic carcinoma of nasal septum progressed into the skull base. Auris Nasus Larynx. 2013;40(2):239–42.
352. Lupinetti AD, Roberts DB, Williams MD, Kupferman ME, Rosenthal DI, Demonte F, et al. Sinonasal adenoid cystic carcinoma: the M. D. Anderson Cancer Center experience. Cancer. 2007;110(12):2726–31.
353. Toluie S, Thompson LD. Sinonasal tract adenoid cystic carcinoma ex-pleomorphic adenoma: a clinicopathologic and immunophenotypic study of 9 cases combined with a comprehensive review of the literature. Head Neck Pathol. 2012;6(4):409–21.
354. Nagao T, Gaffey TA, Serizawa H, Sugano I, Ishida Y, Yamazaki K, et al. Dedifferentiated adenoid cystic carcinoma: a clinicopathologic study of 6 cases. Mod Pathol. 2003;16(12):1265–72.
355. Ellis GL, Auclair PL. Adenoid cystic carcinoma. Tumors of salivary glands. Washington, DC: ARP Press; 2008. p. 225–46.
356. Park CY, Lee KE, Lim SJ, Kim HJ. Spontaneous regression of recurred adenoid cystic carcinoma in the nasal cavity. Head Neck Oncol. 2012;4:48.
357. Thorup C, Sebbesen L, Dano H, Leetmaa M, Andersen M, Buchwald C, et al. Carcinoma of the nasal cavity and paranasal sinuses in Denmark 1995-2004. Acta Oncol. 2010;49(3): 389–94.
358. Subramaniam V, Kumar P, Thahir M. Mucoepidermoid carcinoma of a nasal cavity – a rare tumor. Klin Onkol. 2010;23(5):354–7.
359. Wolfish EB, Nelson BL, Thompson LD. Sinonasal tract mucoepidermoid carcinoma: a clinicopathologic and immunophenotypic study of 19 cases combined with a comprehensive review of the literature. Head Neck Pathol. 2012;6(2):191–207.
360. Daryani D, Gopakumar R, Nagaraja A. High-grade mucoepidermoid carcinoma of maxillary sinus. J Oral Maxillofac Pathol. 2012;16(1):137–40.
361. Hanada T, Moriyama I, Fukami K. Acinic cell carcinoma originating in the nasal cavity. Arch Otorhinolaryngol. 1988;245(6): 344–7.
362. Ordoñez NG, Batsakis JG. Acinic cell carcinoma of the nasal cavity: electron-optic and immunohistochemical observations. J Laryngol Otol. 1986;100:345–9.
363. Sapci T, Yildirim G, Peker K, Karavus A, Akbulut UG. Acinic cell carcinoma originating in the nasal septum. Rhinology. 2000; 38(3):140–3.
364. Takimoto T, Kano M, Umeda R. Acinic cell carcinoma of the nasal cavity: a case report. Rhinology. 1989;27(3):191–6.
365. von Biberstein SE, Spiro JD, Mancoll W. Acinic cell carcinoma of the nasal cavity. Otolaryngol Head Neck Surg. 1999;120(5):759–62.
366. Fujii M, Kumanomidou H, Ohno Y, Kanzaki J. Acinic cell carcinoma of maxillary sinus. Auris Nasus Larynx. 1998;25(4):451–7.
367. Neto AG, Pineda-Daboin K, Spencer ML, Luna MA. Sinonasal acinic cell carcinoma: a clinicopathologic study of four cases. Head Neck. 2005;27(7):603–7.
368. Yoshihara T, Shino A, Shino M, Ishii T. Acinic cell tumor of the maxillary sinus: an unusual case initially diagnosed as parotid cancer. Rhinology. 1995;33(3):177–9.
369. Hellquist H, Skalova A. Acinic cell carcinoma. In: Hellquist H, Skalova A, editors. Histopathology of salivary glands. Berlin: Springer; 2014. p. 261–78.
370. Bishop JA, Yonescu R, Batista D, Eisele DW, Westra WH. Most nonparotid "acinic cell carcinomas" represent mammary analog secretory carcinomas. Am J Surg Pathol. 2013;37(7):1053–7.
371. Harada H, Kashiwagi SI, Fujiura H, Kusukawa J, Morimatsu M. Epithelial-myoepithelial carcinoma – report of a case arising in the nasal cavity. J Laryngol Otol. 1996;110(4):397–400.
372. Jin XL, Ding CN, Chu Q. Epithelial-myoepithelial carcinoma arising in the nasal cavity: a case report and review of literature. Pathology. 1999;31(2):148–51.
373. Lee HM, Kim AR, Lee SH. Epithelial-myoepithelial carcinoma of the nasal cavity. Eur Arch Otorhinolaryngol. 2000;257(7):376–8.
374. Patra SK, Panda NK, Saikia UN. Epithelial-myoepithelial carcinoma of the maxillary sinus: a rare case. Laryngoscope. 2012;122(7):1579–81.
375. Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. Am J Surg Pathol. 2007;31(1):44–57.
376. Sunami K, Yamane H, Konishi K, Iguchi H, Takayama M, Nakai Y, et al. Epithelial-myoepithelial carcinoma: an unusual tumor of the paranasal sinus. ORL J Otorhinolaryngol Relat Spec. 1999;61(2):113–6.
377. Yamanegi K, Uwa N, Hirokawa M, Ohyama H, Hata M, Yamada N, et al. Epithelial-myoepithelial carcinoma arising in the nasal cavity. Auris Nasus Larynx. 2008;35(3):408–13.
378. Cho KJ, El-Naggar AK, Mahanupab P, Luna MA, Batsakis JG. Carcinoma ex-pleomorphic adenoma of the nasal cavity: a report of two cases. J Laryngol Otol. 1995;109(7):677–9.
379. Petersson F, Chao SS, Ng SB. Anaplastic myoepithelial carcinoma of the sinonasal tract: an underrecognized salivary-type tumor among the sinonasal small round blue cell malignancies? Report of one case and a review of the literature. Head Neck Pathol. 2011;5(2):144–53.
380. Lloreta J, Serrano S, Corominas JM, Ferrer-Padro E. Polymorphous low-grade adenocarcinoma arising in the nasal cavities with an associated undifferentiated carcinoma. Ultrastruct Pathol. 1995;19(5):365–70.
381. Fonseca I, Soares J. Basal cell adenocarcinoma of minor salivary and seromucous glands of the head and neck region. Semin Diagn Pathol. 1996;13(2):128–37.
382. Hellquist H, Skalova A. Salivary duct carcinoma. In: Hellquist H, Skalova A, editors. Histopathology of the salivary glands. Berlin: Springer; 2014. p. 297–318.
383. Wenig BM, Dulguerov P, Kapadia SB, Prasad ML, Fanburg-Smith JC, Thompson LDR. Neuroectodermal tumors. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 65–75.
384. Cove H. Melanosis, melanocytic hyperplasia, and primary malignant melanoma of the nasal cavity. Cancer. 1994;44:1424–33.
385. Zak FG, Lawson W. The presence of melanocytes in the nasal cavity. Ann Otol Rhinol Laryngol. 1974;83(4):515–9.
386. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1998;83(8):1664–78.
387. Manolidis S, Donald PJ. Malignant mucosal melanoma of the head and neck: review of the literature and report of 14 patients. Cancer. 1997;80(8):1373–86.
388. Batsakis JG, Regezi JA, Solomon AR, Rice DH. The pathology of head and neck tumors: mucosal melanomas, part 13. Head Neck Surg. 1982;4(5):404–18.
389. Thompson LDR, Wieneke JA, Miettinen M. Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115

cases with a proposed staging system. Am J Surg Pathol. 2003;27(5):594–611.
390. Mendenhall WM, Amdur RJ, Hinerman RW, Werning JW, Villaret DB, Mendenhall NP. Head and neck mucosal melanoma. Am J Clin Oncol. 2005;28(6):626–30.
391. Moreno MA, Roberts DB, Kupferman ME, Demonte F, El-Naggar AK, Williams M, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M. D. Anderson Cancer Center. Cancer. 2010;116(9):2215–23.
392. Nandapalan V, Roland NJ, Helliwell TR, Williams EM, Hamilton JW, Jones AS. Mucosal melanoma of the head and neck. Clin Otolaryngol Allied Sci. 1998;23(2):107–16.
393. Lewis MG, Martin JA. Malignant melanoma of the nasal cavity in Ugandan Africans. Relationship of ectopic pigmentation. Cancer. 1967;20(10):1699–705.
394. Lopez F, Rodrigo JP, Cardesa A, Triantafyllou A, Devaney KO, Mendenhall WM, et al. Update on primary head and neck mucosal melanoma. Head Neck. 2016;38:147–55.
395. Holmstrom M, Lund VJ. Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde. Br J Ind Med. 1991;48(1):9–11.
396. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. Cancer. 2005;103(5):1000–7.
397. Satzger I, Schaefer T, Kuettler U, Broecker V, Voelker B, Ostertag H, et al. Analysis of c-KIT expression and KIT gene mutation in human mucosal melanomas. Br J Cancer. 2008; 99(12):2065–9.
398. Chraybi M, Abd Almasad I, Copie-Bergman C, Baia M, Andre J, Dumaz N, et al. Oncogene abnormalities in a series of primary melanomas of the sinonasal tract: NRAS mutations and cyclin D1 amplification are more frequent than KIT or BRAF mutations. Hum Pathol. 2013;44(9):1902–11.
399. Lourenco SV, Fernandes JD, Hsieh R, Coutinho-Camillo CM, Bologna S, Sangueza M, et al. Head and neck mucosal melanoma: a review. Am J Dermatopathol. 2014;36(7):578–87.
400. Suzuki N, Onda T, Yamamoto N, Katakura A, Mizoe JE, Shibahara T. Mutation of the p16/CDKN2 gene and loss of heterozygosity in malignant mucosal melanoma and adenoid cystic carcinoma of the head and neck. Int J Oncol. 2007;31(5):1061–7.
401. Turri-Zanoni M, Medicina D, Lombardi D, Ungari M, Balzarini P, Rossini C, et al. Sinonasal mucosal melanoma: molecular profile and therapeutic implications from a series of 32 cases. Head Neck. 2013;35(8):1066–77.
402. Gouldesbrough DR, Martin-Hirsch DP, Lannigan F. Intranasal malignant melanoma arising in an inverted papilloma. Histopathology. 1992;20(6):523–6.
403. Takeshita H, Miwa T, Furukawa M. Osteocartilaginous differentiation of mucosal melanoma in the sinonasal cavity. Ann Otol Rhinol Laryngol. 2002;111(12 Pt 1):1112–5.
404. Drier JK, Swanson PE, Cherwitz DL, Wick MR. S100 protein immunoreactivity in poorly differentiated carcinomas. Immunohistochemical comparison with malignant melanoma. Arch Pathol Lab Med. 1987;111(5):447–52.
405. Franquemont DW, Mills SE. Sinonasal malignant melanoma. A clinicopathologic and immunohistochemical study of 14 cases. Am J Clin Pathol. 1991;96(6):689–97.
406. Regauer S, Anderhuber W, Richtig E, Schachenreiter J, Ott A, Beham A. Primary mucosal melanomas of the nasal cavity and paranasal sinuses. A clinicopathological analysis of 14 cases. APMIS. 1998;106(3):403–10.
407. Prasad ML, Jungbluth AA, Iversen K, Huvos AG, Busam KJ. Expression of melanocytic differentiation markers in malignant melanomas of the oral and sinonasal mucosa. Am J Surg Pathol. 2001;25(6):782–7.
408. Mohamed A, Gonzalez RS, Lawson D, Wang J, Cohen C. SOX10 expression in malignant melanoma, carcinoma, and normal tissues. Appl Immunohistochem Mol Morphol. 2013;21(6):506–10.
409. Franchi A, Alos L, Gale N, Massi D, Paglierani M, Santucci M, et al. Expression of p16 in sinonasal malignant melanoma. Virchows Arch. 2006;449(6):667–72.
410. Fernandez PL, Cardesa A, Bombi JA, Palacin A, Traserra J. Malignant sinonasal epithelioid schwannoma. Virchows Arch. 1993;423:401–5.
411. Loree TR, Mullins AP, Spellman J, North JH, Hicks WL. Head and neck mucosal melanoma: a 32-year review. Ear Nose Throat J. 1999;78(5):372–5.
412. Freedman HM, DeSanto LW, Devine KD, Weiland LH. Malignant melanoma of the nasal cavity and paranasal sinuses. Arch Otolaryngol. 1973;97(4):322–5.
413. Harrison DFN. Malignant melanomata arising in the nasal mucous membrane. J Laryngol Otol. 1976;90:993–1005.
414. Trapp TK, Fu YS, Calcaterra TC. Melanoma of the nasal and paranasal sinus mucosa. Arch Otolaryngol Head Neck Surg. 1987;113(10):1086–9.
415. Berthelsen A, Andersen AP, Jensen TS, Hansen HS. Melanomas of the mucosa in the oral cavity and the upper respiratory passages. Cancer. 1984;54(5):907–12.
416. Kim DK, Kim DW, Kim SW, Kim DY, Lee CH, Rhee CS. Ki67 antigen as a predictive factor for prognosis of sinonasal mucosal melanoma. Clin Exp Otorhinolaryngol. 2008;1(4):206–10.
417. Ghamrawi KA, Glennie JM. The value of radiotherapy in the management of malignant melanoma of the nasal cavity. J Laryngol Otol. 1974;88(1):71–5.
418. Brandwein MS, Rothstein A, Lawson W, Bodian C, Urken ML. Sinonasal melanoma. A clinicopathologic study of 25 cases and literature meta-analysis. Arch Otolaryngol Head Neck Surg. 1997;123(3):290–6.
419. Bailey BJ, Barton S. Olfactory neuroblastoma. Management and prognosis. Arch Otolaryngol. 1975;101(1):1–5.
420. Mills SE, Frierson HF. Olfactory neuroblastoma. A clinicopathologic study of 21 cases. Am J Surg Pathol. 1985;9(5):317–27.
421. Taxy JB, Bharani NK, Mills SE, Frierson Jr HF, Gould VE. The spectrum of olfactory neural tumors. A light-microscopic immunohistochemical and ultrastructural analysis. Am J Surg Pathol. 1986;10(10):687–95.
422. Trojanowski JQ, Lee V, Pillsbury N, Lee S. Neuronal origin of human esthesioneuroblastoma demonstrated with anti-neurofilament monoclonal antibodies. N Engl J Med. 1982; 307(3):159–61.
423. Elkon D, Hightower SI, Lim ML, Cantrell RW, Constable WC. Esthesioneuroblastoma. Cancer. 1979;44(3):1087–94.
424. Nakashima T, Kimmelman CP, Snow JB. Structure of human fetal and adult olfactory neuroepithelium. Arch Otolaryngol. 1984; 110(10):641–6.
425. Ng HK, Poon WS, Poon CY, South JR. Intracranial olfactory neuroblastoma mimicking carcinoma: report of two cases. Histopathology. 1988;12(4):393–403.
426. Banerjee AK, Sharma BS, Vashista RK, Kak VK. Intracranial olfactory neuroblastoma: evidence for olfactory epithelial origin. J Clin Pathol. 1992;45(4):299–302.
427. Thompson LD. Olfactory neuroblastoma. Head Neck Pathol. 2009;3(3):252–9.
428. Guled M, Myllykangas S, Frierson Jr HF, Mills SE, Knuutila S, Stelow EB. Array comparative genomic hybridization analysis of olfactory neuroblastoma. Mod Pathol. 2008;21(6):770–8.
429. Argani P, Perez-Ordoñez B, Xiao H, Caruana SM, Huvos AG, Ladanyi M. Olfactory neuroblastoma is not related to the Ewing family of tumors: absence of EWS/FLI1 gene fusion and MIC2 expression. Am J Surg Pathol. 1998;22(4):391–8.

430. Curtis JL, Rubinstein LJ. Pigmented olfactory neuroblastoma: a new example of melanotic neuroepithelial neoplasm. Cancer. 1982;49(10):2136–43.
431. Miyagami M, Katayama Y, Kinukawa N, Sawada T. An ultrastructural and immunohistochemical study of olfactory neuroepithelioma with rhabdomyoblasts. Med Electron Microsc. 2002;35(3):160–6.
432. Slootweg PJ, Lubsen H. Rhabdomyoblasts in olfactory neuroblastoma. Histopathology. 1991;19(2):182–4.
433. Miller DC, Goodman ML, Pilch BZ, Shi SR, Dickersin GR, Halpern H, et al. Mixed olfactory neuroblastoma and carcinoma. A report of two cases. Cancer. 1984;54(9):2019–28.
434. Choi HS, Anderson PJ. Olfactory neuroblastoma: an immunoelectron microscopic study of S-100 protein-positive cells. J Neuropathol Exp Neurol. 1986;45(5):576–87.
435. Frierson HFJ, Ross GW, Mills SE, Frankfurter A. Olfactory neuroblastoma. Additional immunohistochemical characterization. Am J Surg Pathol. 1990;94:547–53.
436. Wick MR, Stanley SJ, Swanson PE. Immunohistochemical diagnosis of sinonasal melanoma, carcinoma, and neuroblastoma with monoclonal antibodies HMB-45 and anti-synaptophysin. Arch Pathol Lab Med. 1988;112(6):616–20.
437. Taxy JB, Hidvegi DF. Olfactory neuroblastoma: an ultrastructural study. Cancer. 1977;39(1):131–8.
438. Mackay B, Luna MA, Butler JJ. Adult neuroblastoma. Electron microscopic observations in nine cases. Cancer. 1976;37(3):1334–51.
439. Kahn LB. Esthesioneuroblastoma: a light and electron microscopic study. Hum Pathol. 1974;5(3):364–71.
440. Carney ME, O'Reilly RC, Sholevar B, Buiakova OI, Lowry LD, Keane WM, et al. Expression of the human Achaete-scute 1 gene in olfactory neuroblastoma (esthesioneuroblastoma). J Neurooncol. 1995;26(1):35–43.
441. Nakashima T, Kimmelman CP, Snow JB. Olfactory marker protein in the human olfactory pathway. Arch Otolaryngol. 1985;111(5):294–7.
442. Weidner N, Tjoe J. Immunohistochemical profile of monoclonal antibody O13 antibody that recognizes glycoprotein p30/32MIC2 and is useful in diagnosing Ewing's sarcoma and peripheral neuroepithelioma. Am J Surg Pathol. 1994;18:486–94.
443. Matayoshi R, Otaki JM. Immunohistochemical detection of olfactory-specific sensory transduction proteins in olfactory neuroblastoma. Neurosci Res. 2011;69(3):258–62.
444. Bishop JA, Thompson LD, Cardesa A, Barnes L, Lewis Jr JS, Triantafyllou A, et al. Rhabdomyoblastic differentiation in head and neck malignancies other than rhabdomyosarcoma. Head Neck Pathol. 2016 (in press).
445. Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. Neurosurgery. 1993;32(5):706–14.
446. Devaiah AK, Andreoli MT. Treatment of esthesioneuroblastoma: a 16-year meta-analysis of 361 patients. Laryngoscope. 2009;119(7):1412–6.
447. O'Connor Jr GT, Drake CR, Johns ME, Cail WS, Winn HR, Niskanen E. Treatment of advanced esthesioneuroblastoma with high-dose chemotherapy and autologous bone marrow transplantation. A case report. Cancer. 1985;55:347–9.
448. Eden BV, Debo RF, Larner JM, Kelly MD, Levine PA, Stewart FM, et al. Esthesioneuroblastoma. Long-term outcome and patterns of failure – the University of Virginia experience. Cancer. 1994;73(10):2556–62.
449. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer. 1976;37(3):1571–6.
450. Jethanamest D, Morris LG, Sikora AG, Kutler DI. Esthesioneuroblastoma: a population-based analysis of survival and prognostic factors. Arch Otolaryngol Head Neck Surg. 2007;133(3):276–80.
451. Rinaldo A, Ferlito A, Shaha AR, Wei WI, Lund VJ. Esthesioneuroblastoma and cervical lymph node metastases: clinical and therapeutic implications. Acta Otolaryngol. 2002;122(2):215–21.
452. Ushigome S, Machinami R, Sorensen PH. Ewing sarcoma/primitive neuroectodermal tumor (PNET). In: Fletcher CD, Uni KK, Mertens F, editors. Pathology and genetics of tumors of soft tissue and bone. Lyon: IARC Press; 2002. p. 298–300.
453. Thompson LDR. Ewing sarcoma. In: Thompson LDR, Wenig BM, Nelson BL, Müller S, editors. Diagnostic pathology head and neck. Amirsys Public Inc. Altona, Manitoba; 2011. p. 134–9.
454. Nikitakis NG, Salama AR, O'Malley Jr BW, Ord RA, Papadimitriou JC. Malignant peripheral primitive neuroectodermal tumor-peripheral neuroepithelioma of the head and neck: a clinicopathologic study of five cases and review of the literature. Head Neck. 2003;25(6):488–98.
455. Windfuhr JP. Primitive neuroectodermal tumor of the head and neck: incidence, diagnosis, and management. Ann Otol Rhinol Laryngol. 2004;113(7):533–43.
456. Cope JU, Tsokos M, Miller RW. Ewing sarcoma and sinonasal neuroectodermal tumors as second malignant tumors after retinoblastoma and other neoplasms. Med Pediatr Oncol. 2001; 36(2):290–4.
457. Klein EA, Anzil AP, Mezzacappa P, Borderon M, Ho V. Sinonasal primitive neuroectodermal tumor arising in a long-term survivor of heritable unilateral retinoblastoma. Cancer. 1992;70(2): 423–31.
458. Frierson Jr HF, Ross GW, Stewart FM, Newman SA, Kelly MD. Unusual sinonasal small-cell neoplasms following radiotherapy for bilateral retinoblastomas. Am J Surg Pathol. 1989; 13(11):947–54.
459. Llombart-Bosch A, Terrier-Lacombe MJ, Peydro-Olaya A, Contesso G. Peripheral neuroectodermal sarcoma of soft tissue (peripheral neuroepithelioma): a pathologic study of ten cases with differential diagnosis regarding other small, round-cell sarcomas. Hum Pathol. 1989;20(3):273–80.
460. Turc-Carel C, Aurias A, Mugneret F, Lizard S, Sidaner I, Volk C, et al. Chromosomes in Ewing's sarcoma. I. An evaluation of 85 cases of remarkable consistency of t(11;22)(q24;q12). Cancer Genet Cytogenet. 1988;32(2):229–38.
461. de Alava E, Gerald WL. Molecular biology of the Ewing's sarcoma/primitive neuroectodermal tumor family. J Clin Oncol. 2000;18(1):204–13.
462. Sorensen PH, Liu XF, Delattre O, Rowland JM, Biggs CA, Thomas G, et al. Reverse transcriptase PCR amplification of EWS/FLI-1 fusion transcripts as a diagnostic test for peripheral primitive neuroectodermal tumors of childhood. Diagn Mol Pathol. 1993;2(3):147–57.
463. Cordes B, Williams MD, Tirado Y, Bell D, Rosenthal DI, Al-Dhahri SF, et al. Molecular and phenotypic analysis of poorly differentiated sinonasal neoplasms: an integrated approach for early diagnosis and classification. Hum Pathol. 2009;40(3):283–92.
464. Kapadia SB, Barnes L, Deutsch M. Non-Hodgkin's lymphoma of the nose and paranasal sinuses: a study of 17 cases. Head Neck Surg. 1981;3(6):490–9.
465. Campo E, Cardesa A, Alos L, Palacin A, Cobarro J, Traserra J, et al. Non-Hodgkin's lymphomas of nasal cavity and paranasal sinuses. An immunohistochemical study. Am J Clin Pathol. 1991;96(2):184–90.
466. Abbondanzo SL, Wenig BM. Non-Hodgkin's lymphoma of the sinonasal tract. A clinicopathologic and immunophenotypic study of 120 cases. Cancer. 1995;75(6):1281–91.

467. Fellbaum C, Hansmann ML, Lennert K. Malignant lymphomas of the nasal cavity and paranasal sinuses. Virchows Arch. 1989; 414(5):399–405.
468. Ferry JA, Sklar J, Zukerberg LR, Harris NL. Nasal lymphoma. A clinicopathologic study with immunophenotypic and genotypic analysis. Am J Surg Pathol. 1991;15(3):268–79.
469. Frierson HFJ, Innes DJJ, Mills SE, Wick M. Immunophenotypic analysis of sinonasal non-Hodgkin's lymphomas. Hum Pathol. 1989;20:636–42.
470. Chan JK, Ng CS, Lau WH, Lo ST. Most nasal/nasopharyngeal lymphomas are peripheral T-cell neoplasms. Am J Surg Pathol. 1987;11(6):418–29.
471. Chan J. Natural killer cell neoplasms. Anat Pathol. 1998; 3:77–145.
472. Cheung MM, Chan JK, Lau WH, Foo W, Chan PT, Ng CS, et al. Primary non-Hodgkin's lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients. J Clin Oncol. 1998;16(1):70–7.
473. Gaal K, Sun NC, Hernandez AM, Arber DA. Sinonasal NK/T-cell lymphomas in the United States. Am J Surg Pathol. 2000;24(11):1511–7.
474. Piccaluga PP, Agostinelli C, Tripodo C, Gazzola A, Bacci F, Sabattini E, et al. Peripheral T-cell lymphoma classification: the matter of cellular derivation. Expert Rev Hematol. 2011;4(4):415–25.
475. Castro EB, Lewis JS, Strong EW. Plasmacytoma of paranasal sinuses and nasal cavity. Arch Otolaryngol. 1973;97(4):326–9.
476. Aguilera NS, Kapadia SB, Nalesnik MA, Swerdlow SH. Extramedullary plasmacytoma of the head and neck: use of paraffin sections to assess clonality with in situ hybridization, growth fraction, and the presence of Epstein-Barr virus. Mod Pathol. 1995;8(5):503–8.
477. Kapadia SB. Hematologic diseases: malignant lymphomas, leukemias, plasma cell dyscrasias, histiocytosis X, and reactive lymph node lesions. In: Barnes L, editor. Surgical pathology of the head and neck. New York: Marcel Dekker; 1985.
478. Robbins KT, Fuller LM, Vlasak M, Osborne B, Jing BS, Velasquez WS, et al. Primary lymphomas of the nasal cavity and paranasal sinuses. Cancer. 1985;56(4):814–9.
479. Coiffier B. Rituximab therapy in malignant lymphoma. Oncogene. 2007;26(25):3603–13.
480. Li S, Feng X, Li T, Zhang S, Zuo Z, Lin P, et al. Extranodal NK/T--cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. Am J Surg Pathol. 2013;37(1):14–23.
481. Chan ACL, Chan JKC, Cheung MMC, Kapadia SB. Hematolymphoid tumors. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 58–64.
482. Alexiou C, Kau RJ, Dietzfelbinger H, Kremer M, Spiess JC, Schratzenstaller B, et al. Extramedullary plasmacytoma: tumor occurrence and therapeutic concepts. Cancer. 1999;85(11): 2305–14.
483. Abemayor E, Canalis RF, Greenberg P, Wortham DG, Rowland JP, Sun NC. Plasma cell tumors of the head and neck. J Otolaryngol. 1988;17(7):376–81.
484. Navarrete ML, Quesada P, Pellicer M, Ruiz C. Extramedullary nasal plasmacytoma. J Laryngol Otol. 1991;105(1):41–3.
485. Fisher C. Adult fibrosarcoma. In: Fletcher CD, Uni KK, Mertens F, editors. Pathology and genetics of tumors of soft tissue and bone. Lyon: IARC Press; 2002. p. 100–1.
486. Broniatowski M, Haria C. Fibrosarcomas of the nose and paranasal sinuses. Ear Nose Throat J. 1981;60(7):302–6.
487. Plaza G, Ferrando J, Pinedo F. Sinonasal fibrosarcoma: a case report. Eur Arch Otorhinolaryngol. 2006;263(7):641–3.
488. Rockley TJ, Liu KC. Fibrosarcoma of the nose and paranasal sinuses. J Laryngol Otol. 1986;100(12):1417–20.
489. Smith MC, Soames JV. Fibrosarcoma of the ethmoid. J Laryngol Otol. 1989;103(7):686–9.
490. Thompson LDR, Fanburg-Smith JC. Malignant soft tissue tumors. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005.
491. Seraj AA. Ethmoid sinus fibrosarcoma arising as a frontal mucocele. Ear Nose Throat J. 1985;64(11):537–9.
492. Heffner DK, Gnepp DR. Sinonasal fibrosarcomas, malignant schwannomas, and "Triton" tumors. A clinicopathologic study of 67 cases. Cancer. 1992;70(5):1089–101.
493. Kuruvilla A, Wenig BM, Humphrey DM, Heffner DK. Leiomyosarcoma of the sinonasal tract. A clinicopathologic study of nine cases. Arch Otolaryngol Head Neck Surg. 1990;116(11): 1278–86.
494. Callender TA, Weber RS, Janjan N, Benjamin R, Zaher M, Wolf P, et al. Rhabdomyosarcoma of the nose and paranasal sinuses in adults and children. Otolaryngol Head Neck Surg. 1995; 112(2):252–7.
495. Herrmann BW, Sotelo-Avila C, Eisenbeis JF. Pediatric sinonasal rhabdomyosarcoma: three cases and a review of the literature. Am J Otolaryngol. 2003;24(3):174–80.
496. Miettinen M, Fetsch JF, Antonescu CR. Tumors with skeletal muscle differentiation. Tumors of the soft tissues. Washington, DC: ARP Press; 2014.
497. Barr FG. Gene fusions involving PAX and FOX family members in alveolar rhabdomyosarcoma. Oncogene. 2001;20(40): 5736–46.
498. Bridge JA, Liu J, Qualman SJ, Suijkerbuijk R, Wenger G, Zhang J, et al. Genomic gains and losses are similar in genetic and histologic subsets of rhabdomyosarcoma, whereas amplification predominates in embryonal with anaplasia and alveolar subtypes. Genes Chromosomes Cancer. 2002;33(3):310–21.
499. Kohsaka S, Shukla N, Ameur N, Ito T, Ng CK, Wang L, et al. A recurrent neomorphic mutation in MYOD1 defines a clinically aggressive subset of embryonal rhabdomyosarcoma associated with PI3K-AKT pathway mutations. Nat Genet. 2014;46(6): 595–600.
500. Hicks J, Flaitz C. Rhabdomyosarcoma of the head and neck in children. Oral Oncol. 2002;38(5):450–9.
501. Antonescu CR, Scheithauer BW, Woodruff JM. Malignant tumors of peripheral nerves. Tumors of the peripheral nervous system. Washington, DC: ARP Press; 2013. p. 381–474.
502. Mannan AA, Singh MK, Bahadur S, Hatimota P, Sharma MC. Solitary malignant schwannoma of the nasal cavity and paranasal sinuses: report of two rare cases. Ear Nose Throat J. 2003;82(8):634–6.
503. Hellquist HB, Lundgren J. Neurogenic sarcoma of the sinonasal tract. J Laryngol Otol. 1991;105(3):186–90.
504. Johnson PJ, Lydiatt DD, Hollins RR, Rydlund KW, Degenhardt JA. Malignant nerve sheath tumor of the nasal septum. Otolaryngol Head Neck Surg. 1996;115(1):132–4.
505. Muraki Y, Tateishi A, Tominaga K, Fukuda J, Haneji T, Iwata Y. Malignant peripheral nerve sheath tumor in the maxilla associated with von Recklinghausen's disease. Oral Dis. 1999;5(3):250–2.
506. Fletcher CD. Malignant peripheral nerve sheath tumors. Curr Top Pathol. 1995;89:333–54.
507. Loree TR, North Jr JH, Werness BA, Nangia R, Mullins AP, Hicks Jr WL. Malignant peripheral nerve sheath tumors of the head and neck: analysis of prognostic factors. Otolaryngol Head Neck Surg. 2000;122(5):667–72.
508. Kim ST, Kim CW, Han GC, Park C, Jang IH, Cha HE, et al. Malignant triton tumor of the nasal cavity. Head Neck. 2001;23(12):1075–8.

509. Lewis JT, Oliveira AM, Nascimento AG, Schembri-Wismayer D, Moore EA, Olsen KD, et al. Low-grade sinonasal sarcoma with neural and myogenic features: a clinicopathologic analysis of 28 cases. Am J Surg Pathol. 2012;36(4):517–25.
510. Huang SC, Ghossein RA, Bishop JA, Zhang L, Chen TC, Huang HY, et al. Novel PAX3-NCOA1 Fusions in Biphenotypic Sinonasal Sarcoma With Focal Rhabdomyoblastic Differentiation. Am J Surg Pathol. 2016;40:51–59.
511. Cardesa A, Luna MA. Germ cell tumors. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 76–9.
512. Frodel JL, Larrabee WF, Raisis J. The nasal dermoid. Otolaryngol Head Neck Surg. 1989;101(3):392–6.
513. Zerris VA, Annino D, Heilman CB. Nasofrontal dermoid sinus cyst: report of two cases. Neurosurgery. 2002;51(3):811–4.
514. Denoyelle F, Ducroz V, Roger G, Garabedian EN. Nasal dermoid sinus cysts in children. Laryngoscope. 1997;107(6):795–800.
515. Brarsman F. The median nasal sinus and dermoid cyst. Arch Otorhinolaryngol. 1980;226:107–13.
516. Torske KR, Benson GS, Warnock G. Dermoid cyst of the maxillary sinus. Ann Diagn Pathol. 2001;5(3):172–6.
517. Pivnick EK, Walter AW, Lawrence MD, Smith ME. Gorlin syndrome associated with midline nasal dermoid cyst. J Med Genet. 1996;33(8):704–6.
518. Wardinsky TD, Pagon RA, Kropp RJ, Hayden PW, Clarren SK. Nasal dermoid sinus cysts: association with intracranial extension and multiple malformations. Cleft Palate Craniofac J. 1991;28(1):87–95.
519. Abemayor E, Newman A, Bergstrom L, Dudley J, Magidson JG, Ljung BM. Teratomas of the head and neck in childhood. Laryngoscope. 1984;94(11 Pt 1):1489–92.
520. Tapper D, Lack EE. Teratomas in infancy and childhood. A 54-year experience at the Children's Hospital Medical Center. Ann Surg. 1983;198(3):398–410.
521. Guarisco JL, Butcher RB. Congenital cystic teratoma of the maxillary sinus. Otolaryngol Head Neck Surg. 1990;103(6):1035–8.
522. Mills RP, Hussain SS. Teratomas of the head and neck in infancy and childhood. Int J Pediatr Otorhinolaryngol. 1984;8(2): 177–80.
523. Morita T, Fujiki N, Sudo M, Miyata K, Kurata K. Neonatal mature teratoma of the sphenoidal sinus: a case report. Am J Otolaryngol. 2000;21(6):398–401.
524. Mwang'ombe NJ, Kirongo G, Byakika W. Fronto-ethmoidal teratoma: case report. East Afr Med J. 2002;79(2):106–7.
525. Shaheen KW, Cohen SR, Muraszko K, Newman MH. Massive teratoma of the sphenoid sinus in a premature infant. J Craniofac Surg. 1991;2(3):140–5.
526. Dehner LP, Mills A, Talerman A, Billman GF, Krous HF, Platz CE. Germ cell neoplasms of head and neck soft tissues: a pathologic spectrum of teratomatous and endodermal sinus tumors. Hum Pathol. 1990;21(3):309–18.
527. Kuhn JJ, Schoem SR, Warnock GR. Squamous cell carcinoma arising in a benign teratoma of the maxilla. Otolaryngol Head Neck Surg. 1996;114(3):447–52.
528. Petrovich Z, Wollman J, Acquarelli M, Barton R. Malignant teratoma of the nasal cavity. J Surg Oncol. 1977;9(1):21–8.
529. Dehner LP. Gonadal and extragonadal germ cell neoplasia of childhood. Hum Pathol. 1983;14(6):493–511.
530. Harms D, Janig U. Germ cell tumors of childhood. Report of 170 cases including 59 pure and partial yolk-sac tumors. Virchows Arch A Pathol Anat Histopathol. 1986;409(2):223–39.
531. Lack EE. Extragonadal germ cell tumors of the head and neck region: review of 16 cases. Hum Pathol. 1985;16(1):56–64.
532. Devaney KO, Ferlito A. Yolk sac tumors (endodermal sinus tumors) of the extracranial head and neck regions. Ann Otol Rhinol Laryngol. 1997;106(3):254–60.
533. Roth LM, Talerman A, Levy T, Sukmanov O, Czernobilsky B. Ovarian yolk sac tumors in older women arising from epithelial ovarian tumors or with no detectable epithelial component. Int J Gynecol Pathol. 2011;30(5):442–51.
534. Manivel C, Wick MR, Dehner LP. Transitional (cylindric) cell carcinoma with endodermal sinus tumor-like features of the nasopharynx and paranasal sinuses. Clinicopathologic and immunohistochemical study of two cases. Arch Pathol Lab Med. 1986;110(3):198–202.
535. Filho BC, McHugh JB, Carrau RL, Kassam AB. Yolk sac tumor in the nasal cavity. Am J Otolaryngol. 2008;29(4):250–4.
536. Gangopadhyay K, McArthur PD, Martin JM, Saleem M. Endodermal sinus tumor of the maxillary sinus: a case report. Ear Nose Throat J. 1999;78(5):376–2.
537. Mishra A, El-Naggar AK, Demonte F, Hanna EY. Endodermal sinus tumor of the paranasal sinuses. Head Neck. 2008; 30(4):539–43.
538. Westerveld GJ, Quak JJ, Bresters D, Zwaan CM, van der Valk P, Leemans CR. Endodermal sinus tumor of the maxillary sinus. Otolaryngol Head Neck Surg. 2001;124(6):691–2.
539. Heffner DK, Hyams VJ. Teratocarcinosarcoma (malignant teratoma?) of the nasal cavity and paranasal sinuses. A clinicopathologic study of 20 cases. Cancer. 1984;53(10):2140–54.
540. Fernandez PL, Cardesa A, Alos L, Pinto J, Traserra J. Sinonasal teratocarcinosarcoma: an unusual neoplasm. Path Res Pract. 1995;191:166–71.
541. Devgan BK, Devgan M, Gross CW. Teratocarcinoma of the ethmoid sinus: review of literature plus a new case report. Otolaryngology. 1978;86(5):689–95.
542. Luna MA. Critical commentary to "Sinonasal teratocarcinosarcoma". Path Res Pract. 1995;191:172.
543. Pai SA, Naresh KN, Masih K, Ramarao C, Borges AM. Teratocarcinosarcoma of the paranasal sinuses: a clinicopathologic and immunohistochemical study. Hum Pathol. 1998;29(7):718–22.
544. Shanmugaratnam K, Kunaratnam N, Chia KB, Chiang GS, Sinniah R. Teratoid carcinosarcoma of the paranasal sinuses. Pathology. 1983;15(4):413–9.
545. Carrizo F, Pineda-Daboin K, Neto AG, Luna MA. Pharyngeal teratocarcinosarcoma: review of the literature and report of two cases. Ann Diagn Pathol. 2006;10(6):339–42.
546. Smith SL, Hessel AC, Luna MA, Malpica A, Rosenthal DI, El-Naggar AK. Sinonasal teratocarcinosarcoma of the head and neck: a report of 10 patients treated at a single institution and comparison with reported series. Arch Otolaryngol Head Neck Surg. 2008;134(6):592–5.
547. Prasad KC, Pai RR, Padmanabhan K, Chawla S. Teratocarcinosarcoma of the nose, paranasal sinuses and nasopharynx. J Laryngol Otol. 2003;117(4):321–4.
548. Tchoyoson Lim CC, Thiagarajan A, Sim CS, Khoo ML, Shakespeare TP, Ng I. Craniospinal dissemination in teratocarcinosarcoma. J Neurosurg. 2008;109(2):321–4.
549. Nogales F, Talerman A, Kubik-Huch RA, Tavassoli FA. Germ cell tumors. In: Tavassoli FA, Devilee P, editors. Pathology and genetics of tumors of the breast and female genital organs. Lyon: IARC Press; 2003. p. 163–75.
550. Bell DM, Porras G, Tortoledo ME, Luna MA. Primary sinonasal choriocarcinoma. Ann Diagn Pathol. 2009;13(2):96–100.
551. Alici S, Bavbek SE, Eralp Y, Argon A, Basaran M, Aydiner A, et al. An atypical presentation of metastatic gestational choriocarcinoma with maxillary sinus and subcutaneous involvement; report of a case with literature review. J BUON. 2002; 7(4):373–6.
552. Salimi R. Metastatic choriocarcinoma of the nasal mucosa. J Surg Oncol. 1977;9(3):301–5.
553. Barnes L. Metastases to the head and neck: an overview. Head Neck Pathol. 2009;3(3):217–24.

554. Barnes L, Tse LL, Hunt JL. Secondary tumors. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005. p. 80.
555. Kent SE, Majumdar B. Metastatic tumors in the maxillary sinus. A report of two cases and a review of the literature. J Laryngol Otol. 1985;99(5):459–62.
556. Prescher A, Brors D. Metastases to the paranasal sinuses: case report and review of the literature. Laryngorhinootologie. 2001;80(10):583–94.
557. Bernstein JM, Montgomery WW, Balogh Jr K. Metastatic tumors to the maxilla, nose, and paranasal sinuses. Laryngoscope. 1966;76(4):621–50.
558. McClatchey KD, Lloyd RV, Schaldenbrand JD. Metastatic carcinoma to the sphenoid sinus. Case report and review of the literature. Arch Otorhinolaryngol. 1985;241(3):219–24.
559. Altman KW, Mirza N, Philippe L. Metastatic follicular thyroid carcinoma to the paranasal sinuses: a case report and review. J Laryngol Otol. 1997;111(7):647–51.
560. Freeman JL, Gershon A, Liavaag PG, Walfish PG. Papillary thyroid carcinoma metastasizing to the sphenoid-ethmoid sinuses and skull base. Thyroid. 1996;6(1):59–61.
561. Cama E, Agostino S, Ricci R, Scarano E. A rare case of metastases to the maxillary sinus from sigmoid colon adenocarcinoma. ORL J Otorhinolaryngol Relat Spec. 2002;64(5):364–7.
562. Chang CW, Wang TE, Chen LT, Chang WH, Leu YS, Fan YK, et al. Unusual presentation of metastatic hepatocellular carcinoma in the nasal septum: a case report and review of the literature. Med Oncol. 2008;25(3):264–8.
563. Conill C, Vargas M, Valduvieco I, Fernandez PL, Cardesa A, Capurro S. Metastasis to the nasal cavity from primary rectal adenocarcinoma. Clin Transl Oncol. 2009;11(2):117–9.
564. Huang HH, Chang PH, Fang TJ. Sinonasal metastatic hepatocellular carcinoma. Am J Otolaryngol. 2007;28(4):238–41.
565. Resto VA, Krane JF, Faquin WC, Lin DT. Immunohistochemical distinction of intestinal-type sinonasal adenocarcinoma from metastatic adenocarcinoma of intestinal origin. Ann Otol Rhinol Laryngol. 2006;115(1):59–64.
566. Tanaka K. A case of metastases to the paranasal sinus from rectal mucinous adenocarcinoma. Int J Clin Oncol. 2006;11(1):64–5.
567. Wenig BM. Sinonasal (Schneiderian) papilloma, section 1. In: Thompson LDR, Wenig BM, editors. Diagnostic pathology: head and neck. Amirsys. Canada, Amirsys; 2011. P. 55.