Invasive Metaplastic Carcinoma

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Synonyms

Carcinoma with pseudosarcomatous metaplasia; Carcinosarcoma; Matrix-producing carcinoma; Sarcomatoid carcinoma; Spindle cell metaplastic tumor

Definition

Metaplastic carcinomas represent a morphologically heterogeneous group of invasive breast cancers in which a variable proportion of the tumor shows squamous and/or mesenchymal differentiation featuring, for instance, spindle, chondroid, osseous, or rhabdoid cells (Lakhani et al. 2012).

Clinical Features

- **Incidence**: Metaplastic carcinomas represent an uncommon histologic type of breast cancer accounting for 0.2–5% of all breast carcinomas (Lakhani et al. 2012).
- **Age**: Although the range of age at presentation is similar to that of invasive carcinomas of no special type (IC-NST), two studies have reported an older mean age at presentation in metaplastic carcinomas compared to that of patients affected by IC-NSTs (Lai et al. 2013; Pezzi et al. 2007).
- **Sex**: Most of the cases have been described in female patients; however there are reports of metaplastic carcinomas diagnosed in male patients.
- **Site**: The location in the breast in which metaplastic carcinomas arise is not dissimilar to that of any IC-NSTs.
- **Treatment**: The treatment is based on a surgical approach with sentinel node biopsy. It should be noted that mastectomy is more common than breast-conserving surgery in these patients, most likely because of the large tumor size at presentation. In addition, axillary involvement is less frequent than in IC-NSTs. Nevertheless, axillary sentinel lymph node biopsy is a recommended good practice. Surgery is followed by adjuvant chemotherapy-based regimens and radiotherapy, depending on clinicopathological parameters.

When considering a therapeutic approach with neoadjuvant chemotherapy, it should be kept in mind that these carcinomas usually show a poor response to chemotherapy

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compared to conventional types of triple-negative breast cancer (TNBC) (Jung et al. 2010). A recent study has demonstrated that patients affected by a metaplastic breast carcinoma and treated with chemotherapy in the neoadjuvant setting were more likely to have a clinically progressive disease during neoadjuvant therapy compared to other types of TNBC and also showed a poorer disease-free survival (Tanabe et al. 2017). There seems to be a difference in response to chemotherapy across distinct transcriptomic subtypes (see section "Molecular Features"): those cases classified as mesenchymal, basal-like2, and luminal androgen receptor show a lesser degree of response to neoadjuvant chemotherapy compared to basal-like1 cases (Lehmann et al. 2016).

- **Outcome**: Unlike conventional forms of TNBC, metaplastic carcinomas have been reported to be resistant to chemotherapy and to have a worse outcome (Jung et al. 2010). Although metaplastic carcinomas are mostly high grade and display an aggressive behavior, it should be acknowledged that there are two low-grade forms of metaplastic carcinoma, i.e., fibromatosis-like metaplastic carcinoma and low-grade adenosquamous carcinoma (Marchiò et al. 2016). Fibromatosis-like metaplastic carcinoma still has a long-term metastatic potential, although less than high-grade metaplastic carcinomas, and must be surgically treated as carcinomas (Gobbi et al. 2003; Sneige et al. 2001). ▶ Low Grade Adenosquamous Carcinoma tends to recur locally; nevertheless its metastatic potential is minimal, and therefore chemotherapy should be avoided (Marchiò et al. 2016).

Macroscopy

The gross appearance of these tumors is not distinctive: similarly to other types of breast cancer, they can show either well-circumscribed or indistinct, irregular borders (Collins and Schnitt 2013). It should be noted however that they can occasionally present as a cystic lesion, and this is particularly the case for squamous cell carcinomas; in addition, when heterologous elements are abundant and predominant, the macroscopic appearance may be more distinctive. For instance, on cut surface, squamous or chondroid areas may appear as pearly white to gray glistening areas.

Finally, at the time of diagnosis, they tend to be larger than IC-NSTs, with a reported mean size of 3.9 cm (Collins and Schnitt 2013).

Microscopy

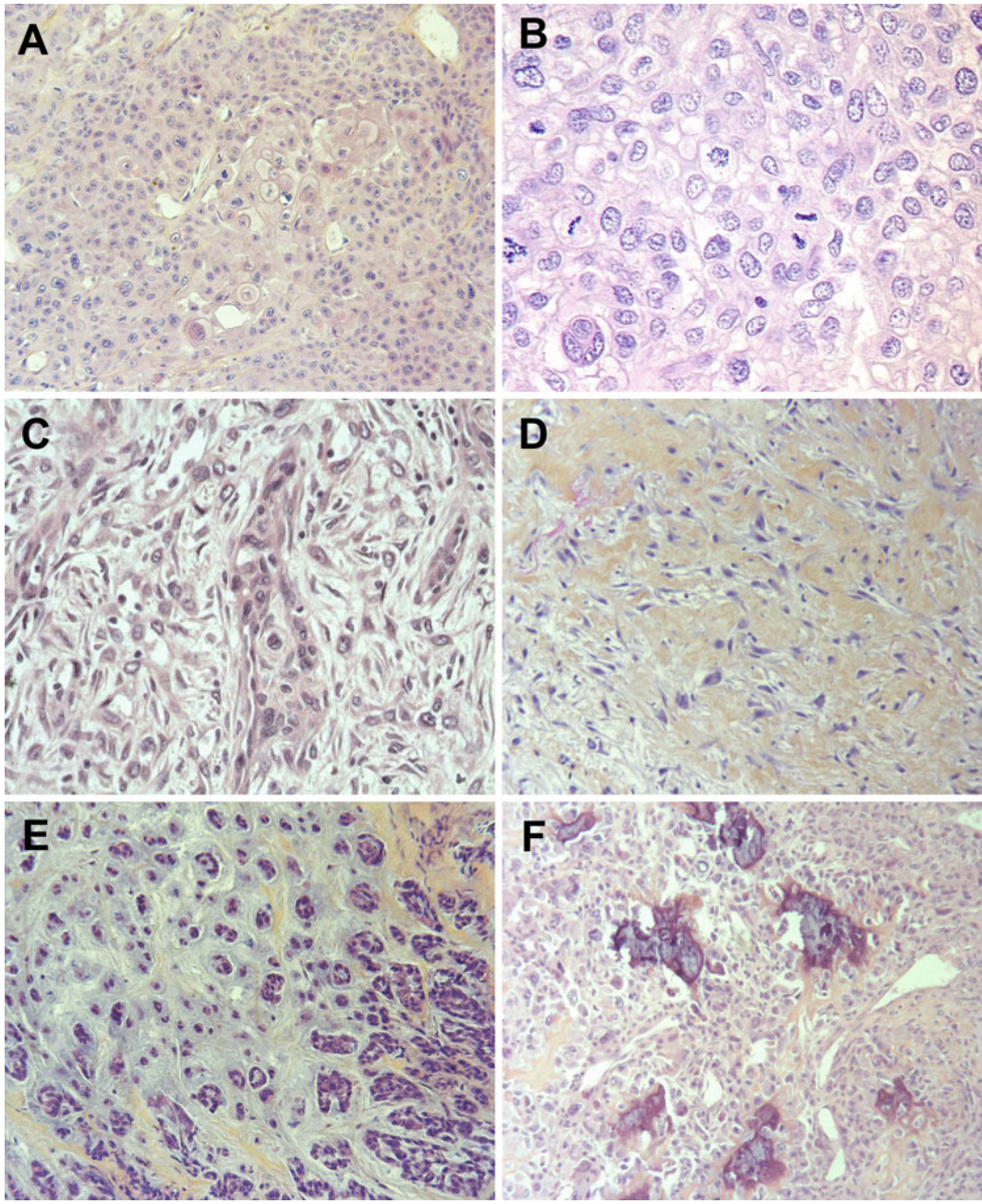
Histologically these tumors are most often of high grade, with conspicuous nuclear pleomorphism and mitotic activity; however they constitute a heterogeneous group of lesions encompassing several entities (Fig. 1). The 2012 WHO classification has adopted a descriptive classification including:

- Squamous cell carcinoma
- Metaplastic carcinoma with mesenchymal differentiation
- Spindle cell carcinoma
- Fibromatosis-like metaplastic carcinoma
- Low-grade adenosquamous carcinoma

When diagnosing a metaplastic breast cancer, one should clearly describe the distinct morphological components present as this may have clinical implications.

Squamous Cell Carcinoma

Metaplastic squamous cell carcinomas can be pure or admixed with an IC-NST (Lakhani et al. 2012; Collins and Schnitt 2013). Pure squamous cell carcinomas of the breast are rare. It is important to keep in mind that some degree of squamous differentiation can be observed in invasive carcinomas of no special type and is more commonly seen in carcinomas with medullary features (Lakhani et al. 2012; Collins and Schnitt 2013). It is good practice to rule out the possibility of a metastasis from other organs such as the skin and, when dealing with male patients or whenever a



Invasive Metaplastic Carcinoma, Fig. 1 Representative micrographs of the heterogeneity of metaplastic carcinomas. (**a**) squamous cell carcinoma. (**b**) A higher magnification of a metaplastic carcinoma with epidermoid features showing high mitotic count. (**c**) Spindle cell carcinoma. (**d**) Fibromatosis-like metaplastic carcinoma. (**e, f**) Two examples of a metaplastic carcinoma with mesenchymal differentiation, one featuring chondroid differentiation (**e**) and the other showing bone tissue formation (**f**)

patient has a history of lung cancer or is heavy smoker, the lung (see below for section "Differential Diagnosis").

Squamous cell carcinomas of the breast typically present as a cystic lesion where the cavity is lined by a squamous epithelium with

variable nuclear atypia, and there is evidence of neoplastic infiltration in the adjacent stroma that usually displays a marked inflammatory infiltrate (Lakhani et al. 2012).

The squamous differentiation of the neoplastic cells can show well to poorly differentiated features (Fig. 1a and b, H&E), and a spindle cell morphology can also be appreciated, typically at the infiltrative border of the tumor (Lakhani et al. 2012).

An acantholytic variant of squamous cell carcinoma has also been described, featuring irregular spaces lined by squamous cells. These spaces can be misinterpreted as vascular spaces and lead to a wrong diagnosis of angiosarcoma (Lakhani et al. 2012; Collins and Schnitt 2013).

Metaplastic Carcinoma with Mesenchymal Differentiation

These lesions are defined by the presence of a varying degree of heterologous differentiation of mesenchymal origin (Collins and Schnitt 2013) and can also be called "matrix-producing carcinomas." The most frequent heterologous differentiation encountered in metaplastic carcinomas of the breast is either osseous or cartilaginous (Fig. 1e and f, H&E) (Collins and Schnitt 2013).

As a general rule, the heterologous components may appear either benign or malignant, in the latter case resembling/mimicking a sarcomatous component. Based on this, whenever the mesenchymal component is predominant a differential diagnosis with (i) a malignant phyllodes tumor with heterologous differentiation or (ii) a sarcoma (primary or metastatic) has to be taken into account (Collins and Schnitt 2013; Rakha et al. 2016).

In these cases, an extensive sampling of the lesion is often required to look for unequivocal epithelial elements or foci of ductal carcinoma in situ (Collins and Schnitt 2013; Rakha et al. 2016). As discussed in the differential diagnosis paragraph, this is the typical scenario in which a panel of cytokeratins is employed to demonstrate even a focal expression. It has to be stressed that not all metaplastic carcinomas express cytokeratins and that focal cytokeratin expression can also be observed in phyllodes tumors, thus making the differential diagnosis particularly challenging and, in some cases, not possible (Collins and Schnitt 2013).

Spindle Cell Carcinoma

Metaplastic carcinomas can present as a proliferation of atypical spindle cells (Lakhani et al. 2012), thus posing important differential diagnosis issues with other spindle cell lesions of the breast. The neoplastic spindle cells show a wide morphological spectrum and may have a fascicular, storiform, or haphazard growth pattern (Fig. 1c, H&E) with infiltrative borders (Lakhani et al. 2012). The nuclear atypia varies from moderate to high grade. An inflammatory infiltrate of lymphocytes and dendritic cells is often found (Lakhani et al. 2012).

The presence of a carcinomatous component in the mixed tumors makes the diagnosis relatively straightforward. On the other side, the diagnosis of high-grade spindle cell carcinoma with no morphological evidence of epithelial differentiation is challenging (Rakha et al. 2016). This represents another scenario in which extensive sampling and thorough immunohistochemical investigation with a panel of markers including more than one cytokeratin are useful (Collins and Schnitt 2013; Rakha et al. 2016). As discussed above for metaplastic carcinomas with mesenchymal differentiation, foci of ductal carcinoma in situ or small cohesive epithelial foci should be sought. A pure spindle cell malignancy with no evidence of these features or even focal cytokeratin expression should prompt to consider, in the differential diagnosis, malignant phyllodes tumor, sarcomas, and metastatic sarcomatoid tumors (Collins and Schnitt 2013; Rakha et al. 2016).

A low-grade form of spindle cell carcinoma has also been described and is labeled as "Fibromatosis-like Metaplastic Carcinoma" and is discussed here below.

Fibromatosis-like Metaplastic Carcinoma

This tumor type, described by Gobbi et al. (1999), represents a low-grade variant of metaplastic carcinoma with spindle-like features. The authors originally described this lesion by using the term "tumor" to avoid the word "carcinoma" because

neither the phenotype nor the behavior seemed to be that of a carcinoma (Gobbi et al. 1999); however this entity was labeled as "carcinoma" in the 2012 WHO classification.

The microscopic growth pattern is typically infiltrative, with finger-like projections extending into adjacent mammary structures and fat tissue; however lesions with ill-defined border or nodular appearance have also been described (Gobbi et al. 1999). It is characterized by a dominant proliferation of spindle cells displaying pale eosinophilic cytoplasm and slender nuclei with mild cytologic atypia (Fig. 1d H&E, and Fig. 2a and b, H&E) (Gobbi et al. 1999). The stroma shows varying degree of collagenization. Focal plump fusiform and polygonal tumor cells, with more rounded nuclei, arranged in "epithelioid" clumps can be observed. Spindle cells are often arranged in wavy interlacing fascicles (Lakhani et al. 2012). In addition, foci of glandular or squamous elements associated with the spindle cells can be encountered posing issues in differential diagnosis with low-grade adenosquamous carcinomas (see below); in fibromatosis-like carcinomas, foci of glandular or squamous elements should represent less than 5% of the overall tumor cell component. Ductal carcinoma in situ can be associated (Gobbi et al. 1999).

Cytokeratin expression is typically found; however it is important to note that it can be focal and occasionally restricted to the plump spindle and more epithelioid cells. Expression of p63 is invariably observed in these lesions.

Low-Grade Adenosquamous Carcinoma

This is a rare histologic type of metaplastic carcinoma showing a distinctive combination of glandular and squamous differentiation. It is characterized by well-developed gland/tubule formation intimately admixed with solid nests of squamous cells in a spindle cell background. Despite the presence of metaplastic elements, these tumors display a low-grade histological pattern. In agreement with their low-grade morphological features, the majority of low-grade adenosquamous carcinomas exhibit an excellent prognosis, with a low incidence of lymph node metastasis (Collins and Schnitt 2013). A proportion of cases, however, can behave in a locally aggressive manner.

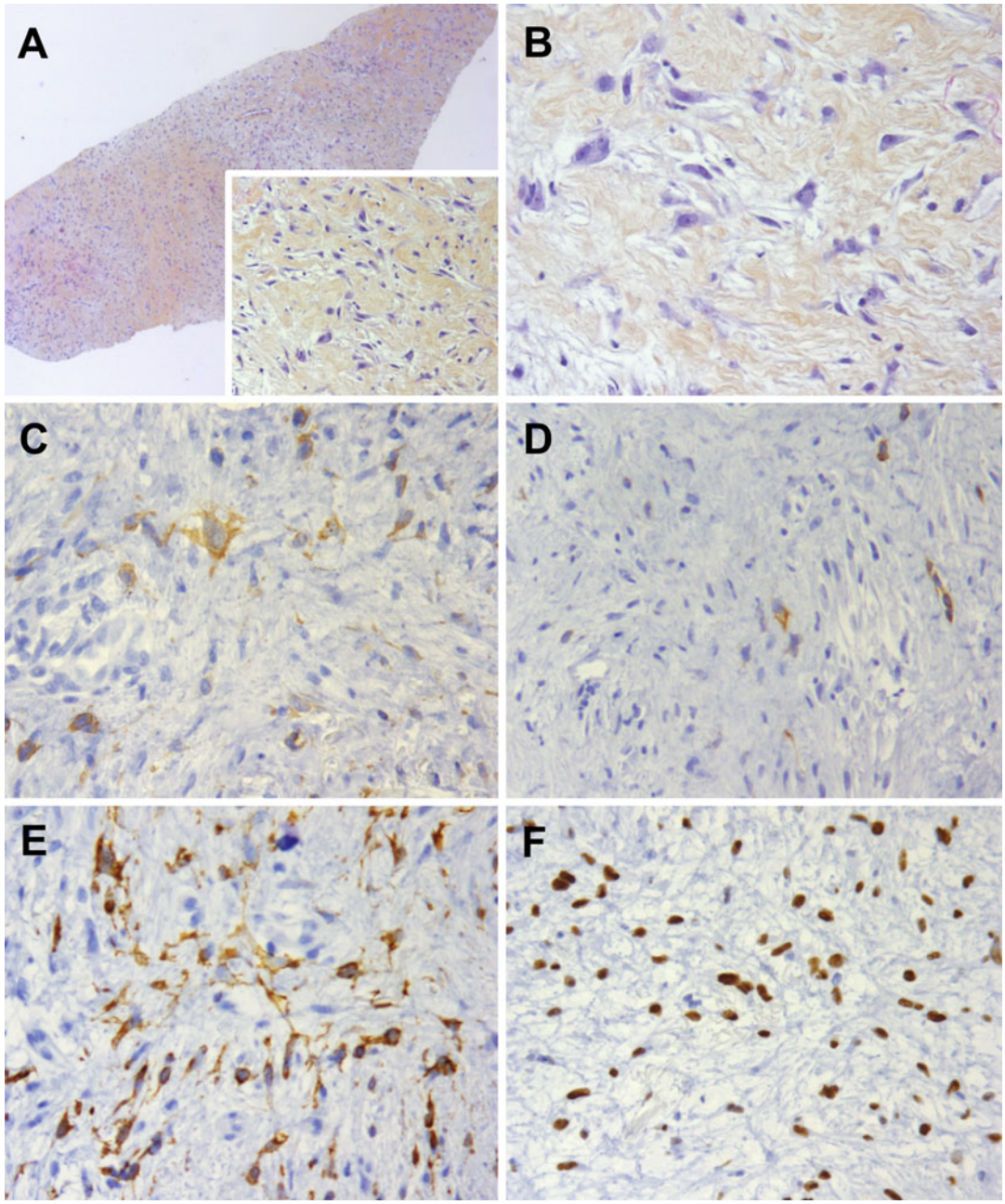
A more detailed description of this entity can be found in the chapter entitled "▶ Invasive Adenosquamous Carcinoma" (▶ Low Grade Adenosquamous Carcinoma).

Immunophenotype

The large majority (>90%) of these tumors are of triple-negative phenotype, i.e., they lack expression of estrogen receptor (ER), progesterone receptor (PR), and HER2. The search for an epithelial phenotype is of key importance for the differential diagnosis. Any positivity for an epithelial marker would support a diagnosis of metaplastic carcinoma. A large panel of epithelial markers has to be assessed, taking into account pancytokeratins (such as AE1/AE3, KL1), EMA, and E-cadherin. Luminal cytokeratins (CKs) such as CK8/18 can be expressed but in a low proportion of cases (Collins and Schnitt 2013; Rakha et al. 2017). Of note, expression of high molecular weight (basal) CKs, including CK5/6, CK5, CK14, and CK17, is frequently observed (Collins and Schnitt 2013; Rakha et al. 2017) (Fig. 2 (c) pancytokeratin; (d) CK5/6; (e) CK14; (f) p63). Indeed, it has been shown that 90.8% of MBCs show a basal-like immunophenotype (Reis-Filho et al. 2006).

Expression of markers usually expressed in normal myoepithelial cells, such as p63 and smooth muscle actin, is also frequently encountered and orients the diagnosis toward a metaplastic carcinoma (Collins and Schnitt 2013; Rakha et al. 2017). The expression of such markers should not be misinterpreted as synonymous of a myoepithelial carcinoma. Luminal cells, in a way akin to all breast carcinomas, including triple-negative breast cancers, represent the cells of origin of metaplastic carcinomas.

A recent study has comprehensively analyzed a wide panel of immunohistochemical markers across a large series of metaplastic carcinomas reported in the literature (Rakha et al. 2017), and results are summarized in Table 1.



Invasive Metaplastic Carcinoma, Fig. 2 A core biopsy sample showing a spindle cell proliferation in the mammary gland featuring fusiform cells displaying pale eosinophilic cytoplasm and slender nuclei with bland cytologic atypia. The neoplastic cells show mild pancytokeratin expression, focal CK5/6 expression, and more pervasive and intense CK14 expression. The lesion shows diffuse p63 expression. The neoplastic cells are negative for hormone receptors and HER2

Invasive Metaplastic Carcinoma, Table 1 Expression of CKs and epithelial differentiation markers in the main subgroups of metaplastic carcinomas. Data are extracted from a series of published cohorts of metaplastic carcinomas. This table has been modified and adapted from Table 2 reported in Rakha et al. (2017). Number of positive cases/total number of cases (percentages). *LGASC* low-grade adenosquamous carcinoma

		Squamous carcinoma	Metaplastic carcinoma with mesenchymal differentiation	Spindle cell carcinoma	Fibromatosis-like carcinoma	LGASC
Cytokeratins	**AE1/AE3**	11/13 (85)	36/36 (100)	99/117 (85)	30/30 (100)	13/14 (93)
	CK8/18	17/18 (94)	7/13 (94)	14/54 (26)	1/2 (50)	18/21 (86)
	CK7	//	4/4 (100)	0/2 (0)	0/25 (0)	21/22 (95)
	CK19	//	5/7 (71)	0/2 (0)	//	2/2 (100)
	MNF116	//	7/10(70)	38/40 (95)	//	2/2 (100)
	34βE12	//	10/15 (67)	7/9 (78)	28/28 (100)	23/23 (100)
	CK5/6	59/63 (94)	41/56 (73)	25/34 (74)	6/6 (100)	25/27 (93)
	CK14	17/19 (89)	38/52 (73)	35/43 (81)	//	2/3 (67)
	CK17	//	5/9 (56)	6/7 (86)	//	//
Myoepithelial markers	**p63**	46/53 (87)	58/84 (69)	73/100 (73)	7/7 (100)	32/88 (84)
	SMA	3/6 (50)	14/30 (47)	77/92 (84)	22/30 (73)	5/23 (22)
	SMM	//	2/16 (12)	1/10 (10)	0/24 (0)	0/19 (0)
	CD10	//	9/18 (50)	14/15 (93)	//	0/17 (0)
	Calponin	//	24/30 (80)	1/7 (14)	//	0/7 (0)
	S100	//	59/63 (94)	32/86 (37)	1/5 (20)	//
Epithelial differentiation	**EGFR**	95/114 (83)	47/76 (62)	35/49 (71)	//	//
	EMA	0/3 (0)	14/15 (93)	32/101 (32)	//	//
	E-CAD	18/20 (90)	0/19 (0)	0/10 (0)	0/3 (0)	//

Molecular Features

In a way akin to TNBC, metaplastic carcinomas are characterized by high levels of genetic instability showing a similar constellation of gene copy number alterations (Hennessy et al. 2009). Amplification of the epidermal growth factor receptor (*EGFR*) gene with associated overexpression has been reported in a subset of metaplastic carcinomas and seems to be prevalent in tumors with squamous and/or spindle cell morphology (Geyer et al. 2010). At the transcriptomic level, metaplastic carcinomas preferentially pertain to the basal-like or claudin-low molecular subtypes; those displaying spindle cell morphology are the ones more likely to be classified as claudin-low (Hennessy et al. 2009: Lien et al. 2004; Weigelt et al. 2009). When using the six molecular subtype classification of TNBC proposed by Lehmann and colleagues (Lehmann

et al. 2011), it has been observed that MBCs are preferentially of mesenchymal-like and mesenchymal stem-like subtype (Weigelt et al. 2015). On the other side, if the integrative clustering approach is employed, metaplastic carcinomas preferentially belong to IntClust 4, IntClust 1, IntClust 8, and IntClust 9 (Weigelt et al. 2015).

Interestingly, it has also been shown that different histologic components of metaplastic carcinomas are associated with specific molecular features (Weigelt et al. 2015). As an example, samples exclusively or predominantly composed of areas of spindle cells or showing chondroid morphology are of claudin-low intrinsic molecular subtype and of mesenchymal-like subtype, respectively, whereas those samples exclusively or predominantly composed of squamous cells show a higher degree of heterogeneity. A characterization of the landscape of somatic genetic alterations in metaplastic breast carcinomas has been recently provided (Ng et al. 2017). Although metaplastic carcinomas and common forms of TNBC harbor a similar mutational frequency in the *TP53* gene, they seem to be genetically distinct. Indeed, metaplastic carcinomas show more frequent mutations in *PIK3CA*, *PIK3R1*, *PTEN*, and Wnt pathway genes, to the extent that 57% and 51% of cases harbor somatic mutations in genes of the PI3K/AKT/mTOR pathway and of the Wnt pathway, respectively (Ng et al. 2017). These data are of clinical interest as they provide a molecular basis for the recent preclinical and clinical observations that Wnt and PI3K/AKT/mTOR pathway inhibition may be beneficial for a subset of patients with metaplastic carcinoma (Ng et al. 2017).

Differential Diagnosis

Due to the rarity and the histological diversity of metaplastic carcinoma of the breast, its diagnosis in routine diagnostic practice can be sometimes challenging (Rakha et al. 2017).

As a general rule, if an invasive lesion of the breast shows mesenchymal or squamous differentiation and is associated with conventional mammary invasive or in situ carcinoma, the diagnosis of a metaplastic carcinoma is usually straightforward. If these features are absent, evidence for epithelial differentiation of the neoplastic cells should be provided by using immunohistochemistry (Fig. 2) (Rakha et al. 2017). A wide spectrum of benign, locally aggressive, and highly aggressive lesions has to be taken in account for the differential diagnosis (Rakha et al. 2017). For instance, in order to render a diagnosis of primary squamous cell carcinomas of the breast, a squamous cell carcinoma of other sites, and in particular of the skin and of the lung, should be ruled out (Lakhani et al. 2012).

Clinical history and radiological findings would be crucial in this scenario. However, if there is no evidence of an in situ carcinoma, the differential diagnosis may be not possible. There is no specific marker that is preferentially expressed in lung versus breast squamous cell carcinoma: in this scenario ER and PR cannot be of help, and markers such as p40, p63, or basal CKs are usually expressed by both entities. GATA3 expression is not consistently found in metaplastic carcinomas (Wendroth et al. 2015; Hattori et al. 2015) and, although rarely, can be found in lung squamous cell carcinomas (Hattori et al. 2015). Other markers of breast origin include mammaglobin and gross cystic disease fluid protein-15 (GCDFP-15), an apocrine differentiation marker. Mammaglobin is reported not to be expressed by metaplastic carcinomas (Reyes et al. 2012); GCDFP15 expression is detected in a minority of metaplastic carcinomas and can be occasionally encountered in squamous cell carcinomas of the lung (Provenzano et al. 2016).

Another example is given by low-grade fibromatosis-like metaplastic carcinomas, which have to be distinguished from desmoid-type fibromatosis or other benign spindle cell lesions of the breast (Marchiò et al. 2016). Furthermore, low-grade adenosquamous carcinomas may closely resemble tubular carcinomas or syringomatous tumors of the nipple (▶ Low Grade Adenosquamous Carcinoma).

It is crucial to keep in mind that no marker is expressed consistently in all metaplastic carcinomas. As a consequence, it is good practice to use a panel of markers (see Fig. 2) (Rakha et al. 2017).

Most metaplastic carcinomas express at least one of the epithelial differentiation markers. The frequency of staining may be related to the degree of differentiation of the tumors with fibromatosis-like spindle cell carcinoma and low-grade adenosquamous carcinoma showing very high rates of expression of several markers and in a larger proportion of tumor cells (>10%) (Table 1, see Fig. 2) (Rakha et al. 2017).

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