11 Pulmonary Disease in the Immunocompromised Host

G. Simonetti, L. Bonomo, P. Rossi, G.L. Sergiacomi, L. Migliorato and A. Moscone

Introduction

Immunodeficiency develops when one or more natural defence mechanisms of the human body are compromised [1–3]; the immunocompromised host is at a greater risk to acquire infections. Pulmonary complications are a common cause of morbidity and mortality in the immunocompromised host. In these patients, the lung is the organ most frequently involved by pathologic manifestations (70%), most of which are infectious (70–90%) and burdened with a high mortality [4].

The immunodeficiency condition may be congenital, often hereditary, more frequently acquired. Most common causes of acquired immunosuppression are, at the present, AIDS, hematologic malignancies, steroid and cytotoxic therapy performed for neoplasms, collagenosis, organ and bone marrow transplantation [5–9]. The congenital immunodeficiencies may involve any part of the immune system and manifest themselves with recurrent infections, generally during the first months of life when the maternal antibodies decline [10,11]. Other common causes of pulmonary abnormalities in these patients include signs of underlying disease, drug-induced lung disease, neoplasms, pulmonary edema and hemorrhage [10,12,13].

The elements predisposing to infection, often appearing together, may be local or involving an entire system. The most important are: granulocytopenia, humoral and cellular abnormalities. Granulocytopenia is the most serious condition among the immunodeficiencies [4]. In studies performed on patients with acute leukemia and neutropenia, the incidence of infection has been related to the severity and duration of neutropenia and linked to the increase in the neutrophil count [1,4]. Patients with a neutrophil count below 1000/mmc are considered at risk, but many studies reported severe infections leading to death when the neutrophil count reading was less than 500 per mmc.

The humoral immunity alterations involve principally immunoglobulin synthesis; the affected subjects are more susceptible to infection caused by capsulated bacteria, due to a deficiency of the opsonic antibody. Therefore, a reduction of all phagocytic cells (macrophages, monocytes, granulocytes) is documented. Multiple myeloma and chronic lymphatic leukemia are the typical diseases due to humoral immunity alterations [2,4,6–9].

Cellular immunity alterations are present in diseases like Hodgkin's lymphoma, acute lymphatic leukemia and AIDS. In addition, cellular immunity may be compromised by organ or allogenic bone-marrow transplantation, by immunosuppressive therapy, radiotherapy, drugs like corticosteroids, azathiopirine and cyclosporine; all of these produce different effects that alter the immune cellular response. The immune cellular response can be evaluated with the study of the T and B lymphocytes, the T4/T8 ratio, the cytokin levels (interferon gamma, IL-2 etc.), the proliferation responses to

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mitogens and T lymphocytes (ConA, phytohemagglutinin) and the complement C3 fraction level. The diagnosis of AIDS is based on molecular biology techniques, through viral RNA (Western blot) or immunoflorescence. Severe systemic infections develop in patients with T4 lymphocytes level less than 200 per mmc. Local predisposing factors are: damage of natural anatomic barriers (introduction of venous or urethral catheters), endoscopic procedures, surgical interventions, damage produced by chemotherapy or radiotherapy on mucous membranes and epithelial cells and obstructive events of anatomic natural ways.

Pulmonary infections are the most frequent in immunocompromised patients and can be primary of the lungs or secondary to bacteremia. The most common pathogens are bacteria (35–50%) and in particular the gram-negative *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli* but also *Staphylococcus aureus* and *Streptococcus viridans* pneumonia can be found. In addition to bacteria, other agents can be responsible for pulmonary infections: fungus filamentosus (*Aspergillus*, *Mucor*), or capsulated (*Candida*), protozoa (*Toxoplasma gondii*, *Pneumocystis carinii*) and viruses [2,3]. In a patient with neutropenia, the clinical finding of a pulmonary infection is not always clear, although elevated temperature is often present [4,6,14,15]. Early chest radiographs are generally negative, since neutropenia slows down the formation of infection points [2]. In the immunocompromised patient, especially if neutropenic, treatment for bacterial infection should be started immediately, although is very often empiric: several drugs are used at the same time, generally a cephalosporin coupled with an aminoglycoside.

Pulmonary infections by fungus filamentosus may present peculiar clinical characteristics. When a cavity is formed, pneumothorax can develop and moreover, expecially in the perihilar foci, massive hemoptysis, usually fatal, can be experienced, due to vascular erosion. The definitive diagnosis of fungus infection can be made only by histology with evidence of the mycete, since the culture alone is not significant. More invasive procedures like bronchoscopy with bronchoalveolar lavage (BAL) or biopsy cannot be performed because of the precarious general conditions of the patient and the presence of thrombocytopenia [6,15,16].

Clinically, viral infections in neutropenic patients are not different from those with interstitial pneumonia caused by other agents. Non-specific symptoms may be present: dyspnea, dry cough, fever and arterial hypoxia, leading to acute respiratory insufficiency. However, it should be noted that the presence of fever is not always indicative of infection and that its absence does not always rule it out [10,11].

The major problem in these patients is the need to establish a prompt diagnosis since the different pathologic conditions often show a rapid evolution. In these cases, non-invasive diagnostic procedures such as sputum culture are not resolvent: neutropenic patients usually do not produce expectoration and, at the same time, one or more organisms or saprophytes potentially pathogenic in the immunocompromised patient may be present. Respiratory function tests and gallium scintigraphy have low specificity; although depicting diffuse involvement, they fail to detect the pathogenic agent [13]. It must be remembered that, in different studies, in one-third to half of cases open biopsy does not provide a diagnosis of the agent's nature [2,5]. Diagnostic imaging studies may aid in providing a prompt diagnosis and are continuously evoked in these cases [10–13]. Radiology is fundamental in many situations: (a) in demonstrating the presence of lung pathologic findings: (b) in suggesting a definite pathologic diagnosis or, at least, a series of possibilities or lastly, in providing a non-infective alternative to an infective hypothesis; (c) in detecting eventual complications; d) in giving indications for which invasive procedure to employ and where to perform biopsy and brochoalveolar lavage and e) in monitoring the therapeutic response. Chest radiography remains the first imaging modality performed in immunodepressed patients with suspected lung abnormalities; however, it may be normal in up to 10% of patients with symptomatic disease, and it seldom allows a confident specific diagnosis. Computed tomography (CT) and, in particular, high resolution CT (HRCT) are superior to the standard radiogram and helpful in the assessment of these patients [2,10,12,13,17]. In particular, HRCT may be effective: (a) in showing the early presence of parenchymal abnormalities in patients with negative or non-specific radiographic findings; (b) in demonstrating the site, distribution, and extent of parenchymal abnormalities; (c) in providing more specific findings for an etiologic diagnosis and (d) it may also be helpful as a guide in selecting the optimal site for lung biopsy.

However, the use of HRCT is not always necessary since its findings are often useful and decisive only in certain diseases. For example, it does not add significant diagnostic findings, compared to chest radiograph and conventional CT, in bacterial infections which represent the most common infective processes (35–50%) in the immunocompromised patient. On the contrary, HRCT provides fundamental diagnostic signs in other infective and non-infective processes (*Pneumocystis carinii* and

Cytomegalovirus infections, invasive aspergillosis, Kaposi sarcoma, etc.) [10–13].

Infections

An appropriate clinical context is mandatory for a correct interpretation of the radiologic findings. Patients with AIDS are susceptible to develop community-acquired infections, but the most common life-threatening complication is *Pneumocystis carinii* pneumonia (PCP) [11,13,18]. Patients with severe granulocytopenia, especially those with leukemia who are receiving immunosuppressive therapy, are particularly prone in developing invasive aspergillosis. Instead, patients undergoing organ transplantation are at increased risk of Cytomegalovirus pneumonia [11,13].

Bacterial Infections

Solitary or multiple lobar or focal opacities of consolidation are indicative of bacterial pulmonary infection. Gram-negative bacteria such as *Klebsiella, Enterobacter, Pseudomonas, Escherichia coli, Serratia* and *Proteus* are the most frequently involved. Among Gram-positive bacteria, *Staphylococcus* is the most commonly found [2,19–21].

The aspecificity of the radiologic pattern does not allow the identification of a specific pathogen even if some minor signs such as the enlargement of the involved lobe are more frequently observed in some types of infection such as *Klebsiella* or *Pneumococcus* [5,11,13]. (Figure 11.1). Bacterial pneumonia can show solitary or multiple cavitations in the form of microabscesses. Pleural effusion, if present, is typically moderate and empyema is extremely rare [13]. Focal density, in addition, may be caused by tuberculosis, mycosis or *Pneumocystis carinii* [2,11,13,22]. In the differential diagnosis, possible non-infective causes such as pulmonary infarcts or thoracic localization of the underlying disease (lymphoma, leukemia) should also be considered [2].

Fungal Infections

Fungal pneumonia characteristically develops in patients with hematologic malignancies who have a severe neutropenia due to the cytotoxic therapy. Fungal infections are relatively uncommon in AIDS, being seen in less than 5% of patients [13]. There are many fungi responsible for acute lung disease, and they include the commensals such as *Aspergillus, Candida, Mucor*, and true pathogenetic fungi such as *Cryptococcus, Rhodococcus, Histoplama capsulatum*. The most frequent pathogens will be discussed [2,3,23–26].

Aspergillus

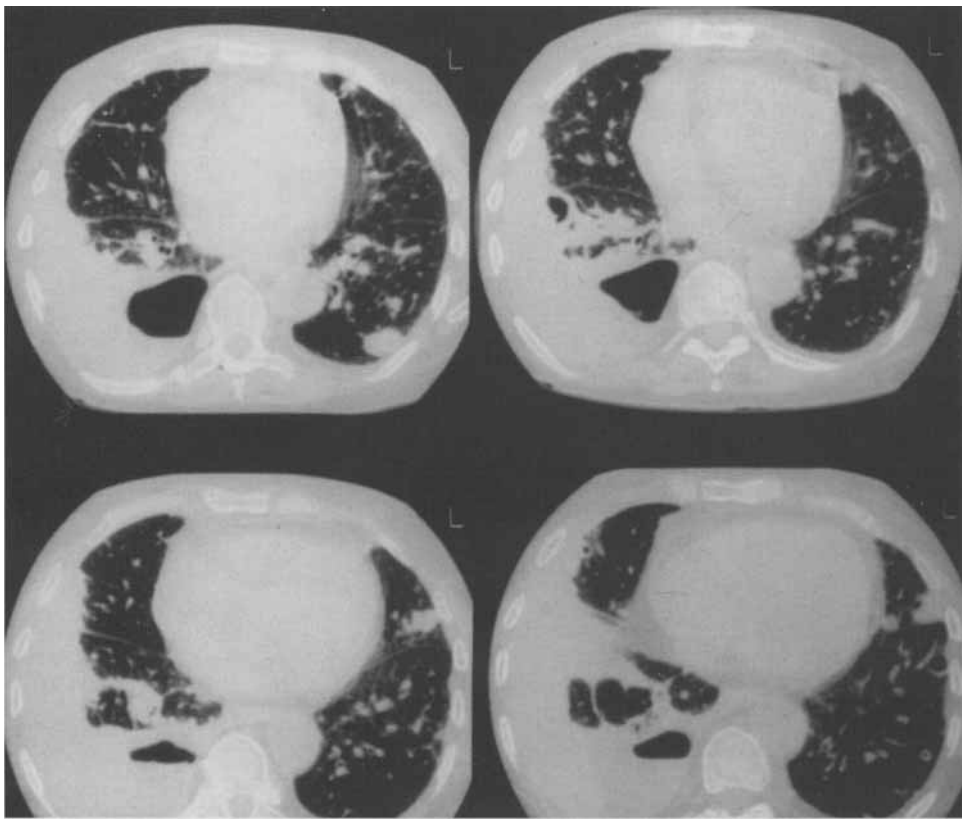
Aspergillus pneumonia is definitely the most common fungal infection in immunocompromised patients. It is a necrotizing pneumonia characterized, pathologically, by vascular invasion and thrombosis leading to hemorrhagic infarction. Early diagnosis is important so that prompt antifungal therapy can be administered [11,27]. The radiographic pattern is represented by multiple areas of consolidation, grossly triangular with the base toward the pleural surface (Figure 11.2a). These lesions on CT show the characteristic appearance of nodules with a surrounding halo of ground-glass attenuation (CT halo sign) (Figure 11.2b). This sign may be found also in candidiasis, Cytomegalovirus and Herpes simplex virus pneumonia [2,4,6,12,13, 28–32]. The halo of ground-glass is caused by hemorrhagic necrosis and it can be documented in patients with a very severe neutropenia. Hruban has demonstrated that the lesion consists of a central part containing the microorganism and surrounded by a rim of hemorrhagic infarct [33]. The air-crescent sign and the subsequent cavitation are late signs and important indices of restoration of granulocyte function [13] (Figure 11.2c).

Candida Albicans

Pulmonary candidiasis is a relatively common complication in patients with leukemia and lymphoma. The findings on chest radiograph are non-specific, consisting of patchy, bilateral air space consolidation or, occasionally, a diffuse miliary pattern. Invasive biopsy usually is required for diagnosis. A nodular pattern with or without the halo sign may be observed on CT scan [2,11,13,24–26] (Figure 11.3).

Histoplasma Capsulatum

In the primary benign form, the chest radiograph shows peripheral calcified nodules or lymph nodes. At the onset, the clinical pattern may be characterized by minor respiratory symptoms, or fever and erythema nodosum. The pneumonic form is an acute disease, radiologically characterized by homo-



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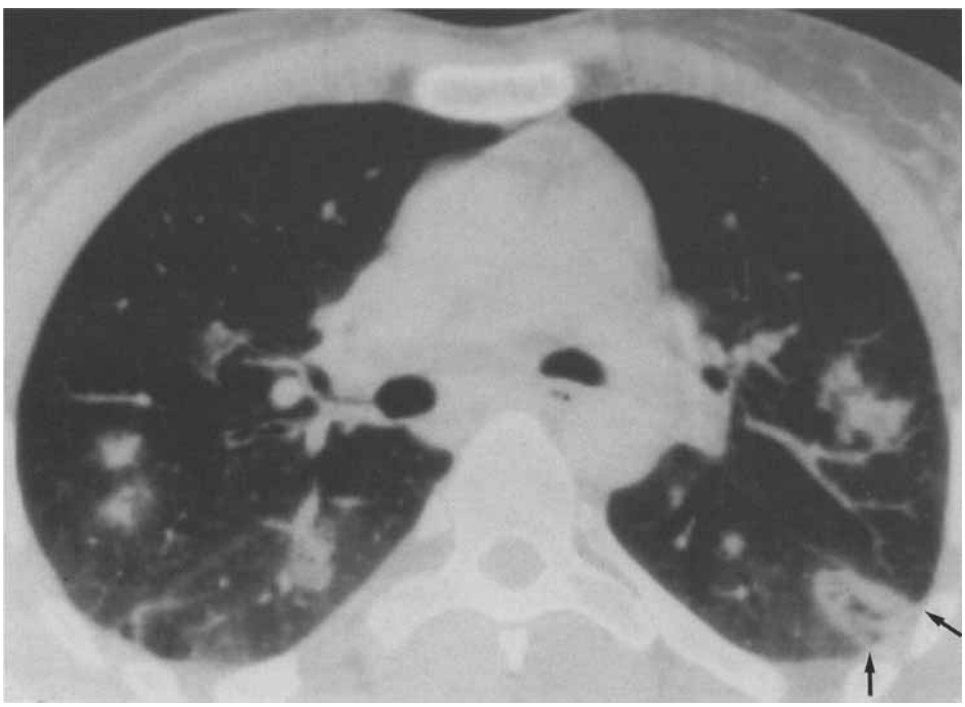

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Figure 11.1 a, b. *Staphylococcus* infection in HIV-positive patients, with lobar consolidation and pleural effusion in corrispondence of the right lung. Nodular opacities are present in the left lung (**a**). *Pneumococcus* infection in granulopenic patient with multiple ill-defined nodular lesions. One of these shows an initial excavation (arrows) (**b**).

geneously distributed parenchymal consolidations, mimicking a bacterial pneumonia, although the histoplasmosis lesions have the tendency to heal in one area and subsequently showing up in another one; frequently enlargement of hilar lymph nodes and excavation may develop [13].

Cryptococcus Neophormans

Cryptococcosis is prevalently seen in AIDS patients. The infection is generally systemic, with frequent cerebral involvement and neurologic symptoms. The radiological pattern is characterized by solitary or multiple nodular lesions, with or without excavation; other findings can be represented by lobar or segmentary consolidation and more rarely by diffuse parenchymal infiltration [2,24–26].

Septic Emboli

The development of septic emboli phenomena is a frequent condition in drug-addict HIV-positive patients, following repeated injections, and in subjects with a central venous catheter for cytotoxic therapy [34]. The radiologic aspect is characterized by the presence of multiple nodular opacities of various dimensions and excavation stages, localized mostly peripherally, often associated with pleural effusion and pneumothorax. Moreover the relationship of the nodules with vascular structures is characteristic. CT scan allows well defined margins to be seen and, most of all, by means of HRCT, it is possible to visualize initial signs of excavation (Figure 11.4a). Rarely, in the presence of large emboli, a radiological pattern of lung infarction is seen in triangular shape with the base on the pleural surface [11] (Figure 11.4b).

Viral Infections

Cytomegalovirus

Viral pneumonias rarely occur in immunocompromised patients. Usually, these viral infections are caused by Herpes viruses (zoster or simplex). Organ transplant recipients, however, constitute a subpopu-

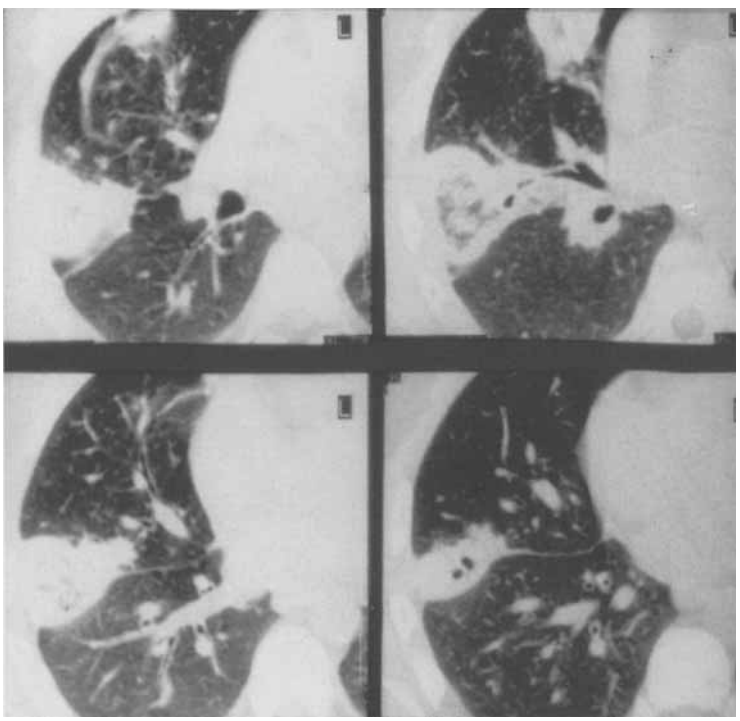

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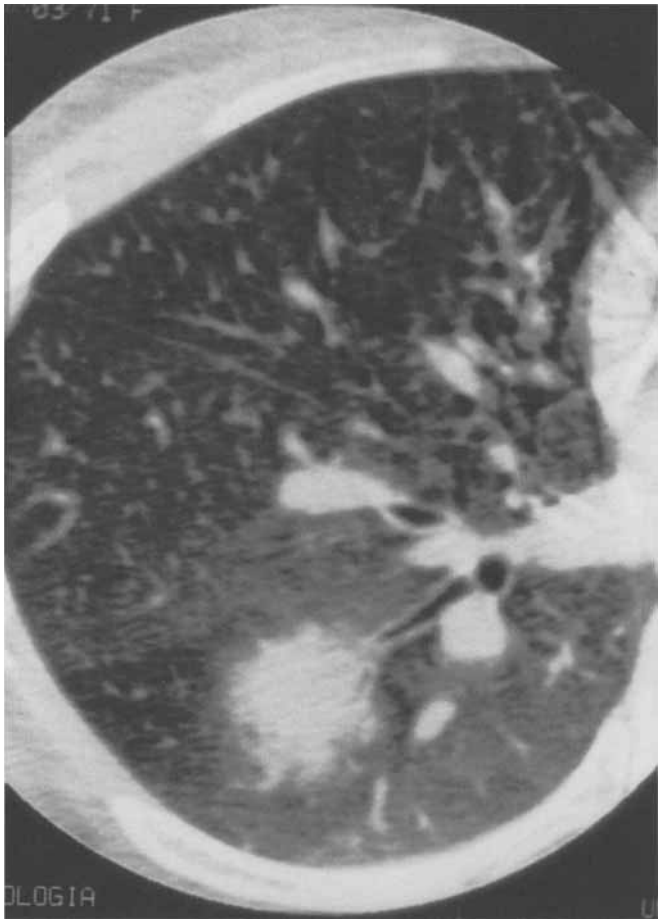
Figure 11.2 a, b, c. Invasive aspergillosis in leukemic patient, with triangular-shaped consolidation in the early stage of the disease. An initial central cavitation is well depicted by HRCT (**a**). A large fungine lesion, surrounded by a peripheral 'ground-glass' (halo sign) and distal air-bronchogram is detected by HRCT in the lower right lobe (**b**). Invasive aspergillosis in a leukemic patient, with restoration of granulocyte function, shows the 'air-crescent sign' due to the interposition of air between the infarcted lung tissue and the adjacent healthy parenchyma (**c**). (Figure 11.2b, c continued overleaf.)

b



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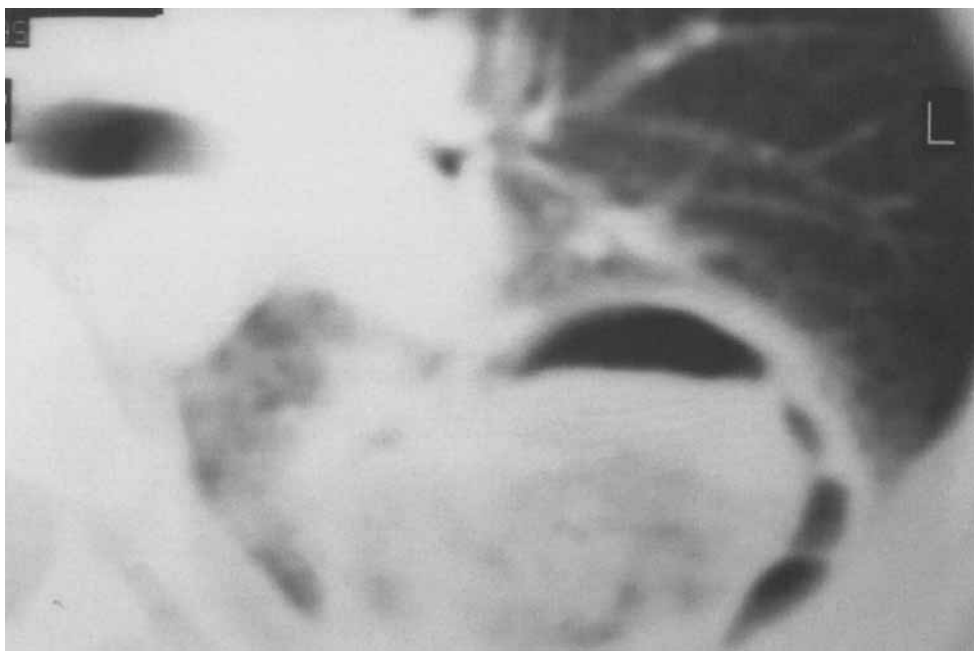


Figure 11.2b, c

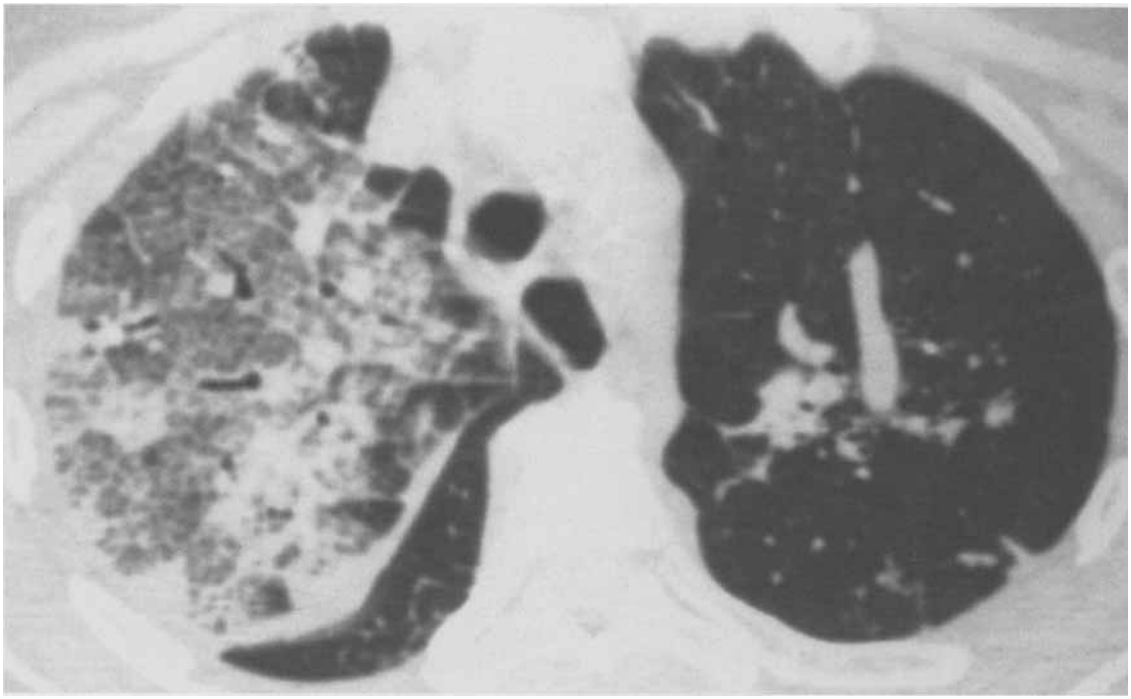


Figure 11.3. *Candida albicans* pneumonia in a patient suffering from NHL. HRCT shows patchy air space consolidations localized in the upper lobe of the right lung and small nodules in the left lung without 'halo sign'.

lation at high risk for viral pneumonia. By far, the most common agent of viral infections in these patients is cytomegalovirus (CMV). It typically occurs more than 2 months after bone marrow transplantation [10]. Among renal transplantation recipients, evidence of active infection exceeds 90% in some series. However, clinical disease, including pneumonia, is much less frequent.

CMV rarely appears to be a pulmonary pathogen in patients with AIDS [2,4,20,35–39]. On X-ray examination, CMV pulmonary infection is characterized by a linear or nodular symmetric, diffuse and bilateral pattern originating from the lower lobes and subsequently extending to the entire lung (Figure 11.5a,b).

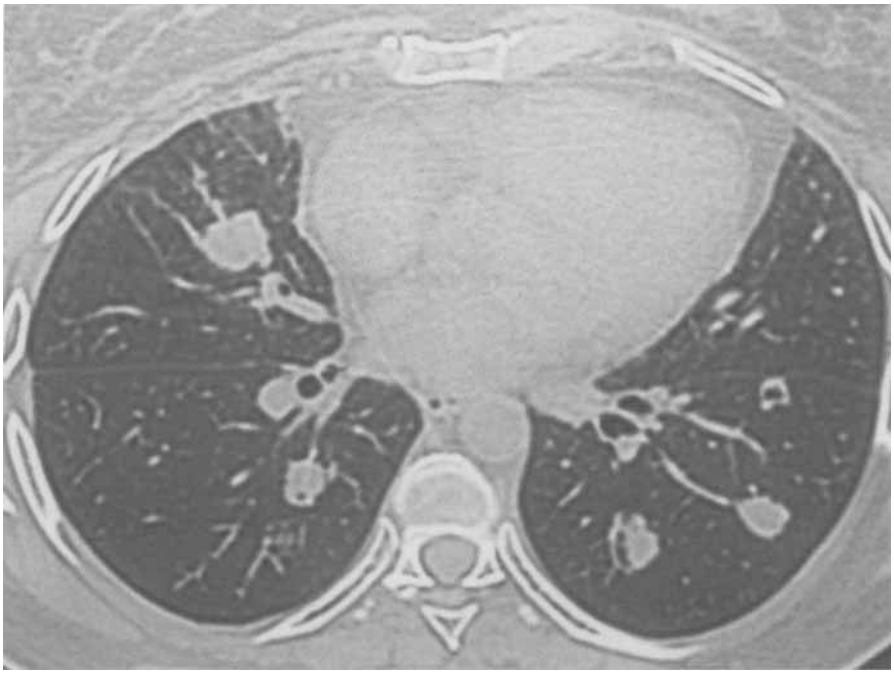
The most common findings on HRCT are multiple small nodules with associated areas of ground-glass attenuation. This correlates with the pathologic appearance of CMV pneumonia, which is characterized by the presence of hemorrhagic nodules [11,40]. To confirm the diagnosis, biopsy is often required for the identification of the typical intranuclear inclusions [2,15].

Herpes Virus

HRCT shows multiple and fairly well-defined peripheral nodules of various sizes, or areas of consolidation containing air-bronchogram (Figure 11.6). These findings are non-specific and may indicate the presence of a number of pathogens or neoplasms [11,41]. The diagnosis of Herpes simplex virus pneumonia can be suspected by the presence of associated cutaneous, oral and esophageal involvement [11].

Pneumocystis Carinii Infections

In HIV-positive patients, depressed cell-mediated immunity predisposes more frequently to mycobacterial, nocardial, legionella, fungal and viral infections and, in particular, to *Pneumocystis carinii* pneumonia. The latter is an opportunistic pathogen of the lung which has been considered for many years a protozoal agent, but recently a series of ribosomal RNA studies postulated a fungal origin [18]. *Pneumocystis carinii* (PC) is by far the most common cause of acute diffuse lung disease in AIDS patients and is responsible for about 40% of diffuse pneumonia in immunocompromised patients; in most patients (85%) PC presents itself with a CD4 'helper' lymphocyte count of less than 200/mmc. In hematologic patients, PC infection frequently occurs after the end of chemotherapy and the



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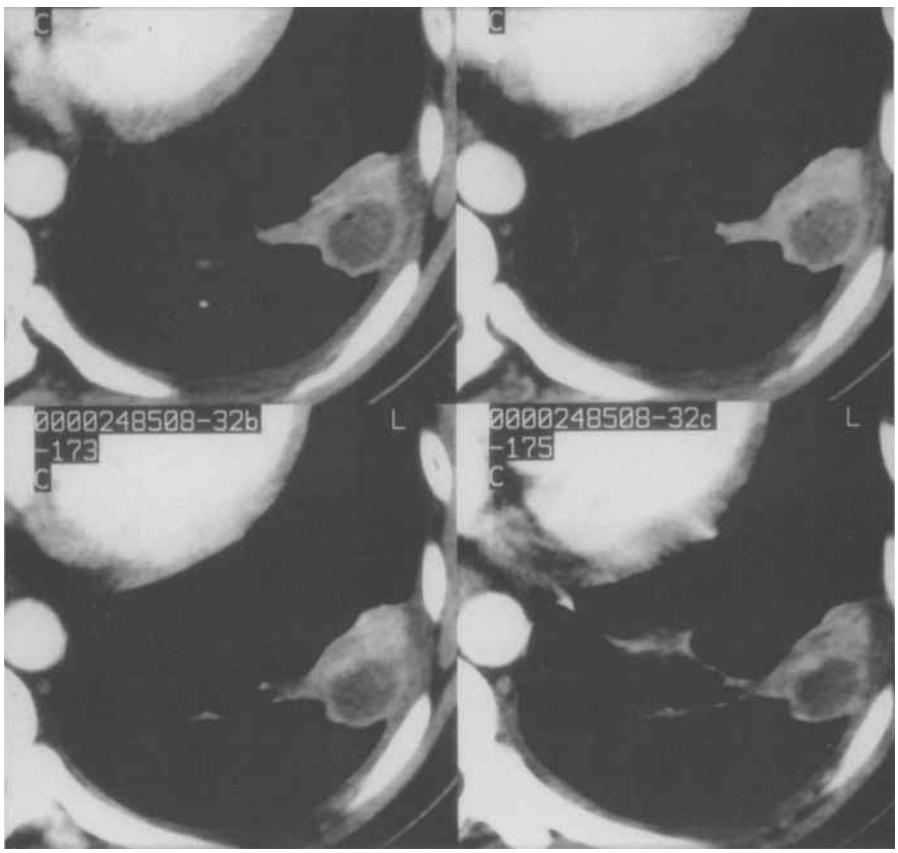

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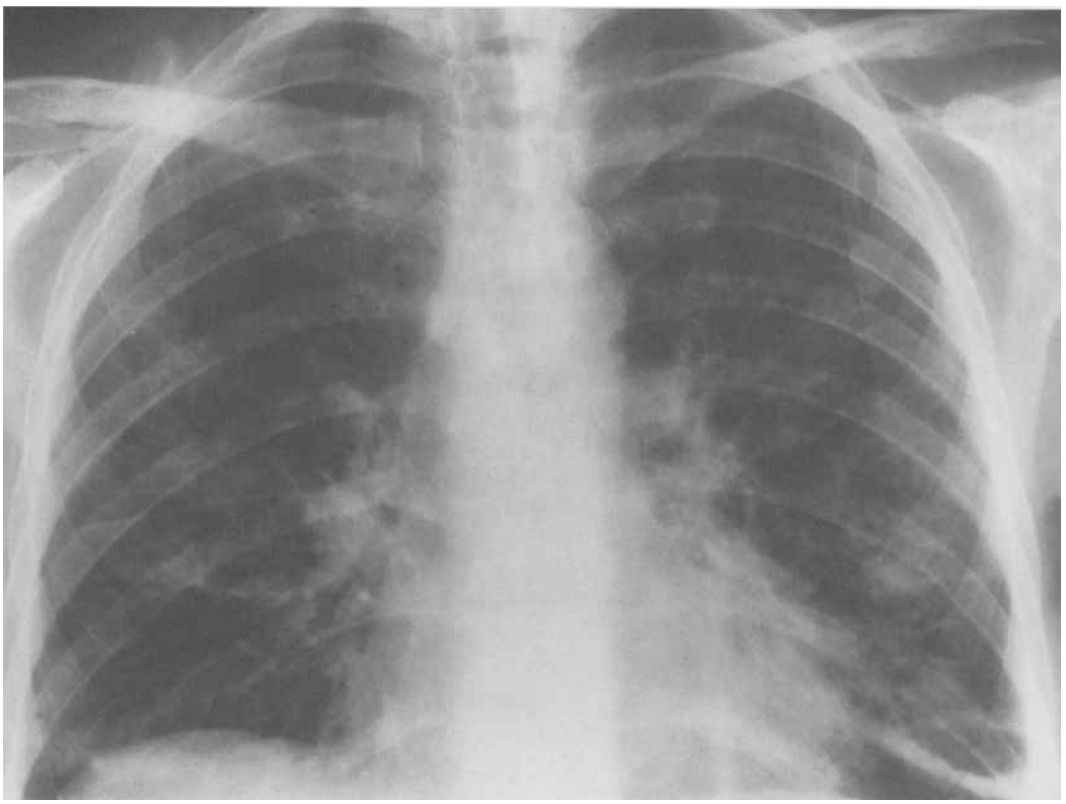
Figure 11.4 a, b. Septic emboli in HIV-positive patient in which HRCT scan shows multiple well-defined nodular lesions, partly excavated, in connection with vascular structures (**a**). CT scan after contrast medium administration, showing a large septic embolism with lung infarction and central necrosis (**b**).



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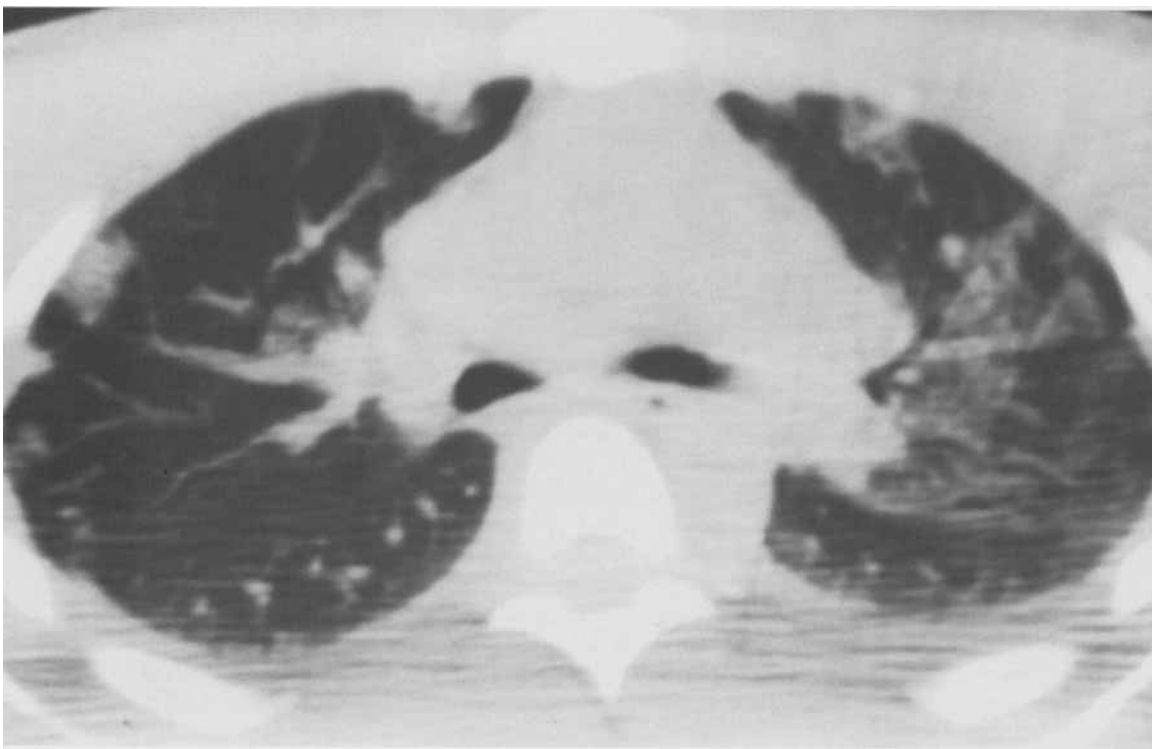

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Figure 11.5 a, b. CMV infection in liver transplant patient, with diffuse interstitial pattern, mostly localized in lower lung fields in chest X-ray PA view (**a**). CT scan confirms the interstitial involvement, showing multiple subpleural nodules (**b**).

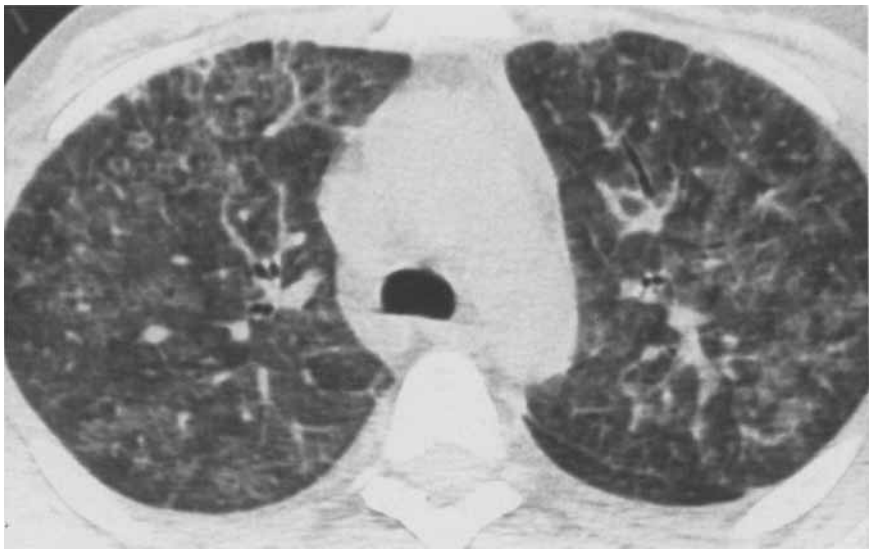


Figure 11.6. AIDS-positive with *Pneumocystis carinii* pneumonia. HRCT shows 'ground-glass' opacity with initial septal and peribronchial thickness due to active disease coupled with chronic manifestation.

resulting pneumonia (PCP) is progressive and fatal. Although prophylaxis has significantly reduced the incidence of PCP in patients with AIDS, it affects approximately 65% of HIV patients and accounts for nearly 25% of AIDS-related deaths. An early diagnosis is extremely important in such cases, considering the positive clinical response to pharmacological therapy observed when administered in the early stages of PCP, with success rates of 85%. The clinical response is less satisfactory when therapy is instituted in later stages of disease, while a lack of diagnosis or a delayed intervention leads to 100% mortality [2,10–13,18,42,43].

The most characteristic features at chest X-ray are reticular or nodular opacities, or ill-defined hazy consolidation; atypical findings include asymmetric infiltrates, miliary nodules, cavitary nodules, pleural effusion, adenopathy and pneumothoraces. However, in as many as 15% of proven cases, the chest radiograph remains normal [13]. The most characteristic finding of PCP is the presence, at HRCT scan, of areas of ground-glass attenuation (homogeneous increase of density without obscuration of underlying pulmonary vessels).

CT findings in patients with PCP reflect the stage of the disease. In the early stage, the predominant CT abnormalities are represented by areas of ground-glass opacity; a diffuse and bilateral or a 'mosaic' pattern with normal lung tissue between scattered, focal areas of parenchymal involvement. Usually the peripheral regions of the lung are spared. In the acute phase, areas of air space consolidation are commonly described. Moreover, initially scattered foci of ground-glass opacity or air space consolidation can be identified, corresponding to the presence of intra-alveolar exudates as well as some degree of thickening of the alveolar septa. With time, interstitial abnormalities representing thickening of interlobular septa and intralobar lines predominate in patients with PCP; it typically occurs in areas in which ground-glass was present during the acute phase of the disease (Figure 11.6). Rarely, PCP results in diffuse lung fibrosis [2,11–13].

Cystic changes are frequently observed by CT with an incidence of about 35%. Their pathogenesis has not yet been completely defined. Most authors interpret cystic abnormalities as manifestations of bronchiolitis which, by a 'check-valve mechanism', are responsible for the distention of the underlying lung tissue. This could explain the rapid dimensional variation frequently observed in these cysts. According to other investigators, these cysts could result from necrosis of the lung tissue due to macrophagic activity with release of elastasis or to a direct cytotoxic effect of the HIV virus [18]. Initially the cysts appear in areas of parenchymal consolidation, showing a totally random distribution; they must be differentiated from the changes occurring in the bullous lung disease secondary to intravenous-drug abuse which is characterized by peripheral cystic abnormalities. Furthermore, they present a very thin wall, and their distribution does not involve the central portions of the lung [2,13].

Successively the cysts in PCP, with coalescence, form irregular thick-walled lesions that sometimes appear septated. Subpleural cysts have the tendency

to communicate with the pleural space, accounting for the high incidence of pneumothoraces in these patients (4.8%) [18]. Lesions can regress, after therapy, and a complete disappearance or residual nodules or masses can be observed. In these cases, CT can be effective in suggesting the appropriate diagnosis and in differentiating these lesions from those caused by other cavitary diseases, in particular septic emboli and mycotic infections [12,13].

Mycobacterial Infection

Different forms of mycobacteria may cause pulmonary and pleural diseases, particularly frequent in immunocompromised HIV-positive patients, and the *Mycobacterium tuberculosis* is the etiologic agent in 90% of cases [10,13]. Tuberculosis (TBC) may be the onset of a latent disease. The clinical and radiological pattern is variable in relation to the immunodeficiency state: from exudative and cavitation forms, with extrapulmonary localizations, to hilar-mediastinal lymph nodes, to more severe forms of miliary dissemination.

The above-described patterns change in relationship to the level of CD4 lymphocytes subpopulation. The radiological abnormalities may be similar to the one seen in traditional TBC or may be polymorph, when superimposition of other pathogenic agents occurs and, thus, with many different diagnostic problems. The pulmonary parenchymal lesions are different: in primary TBC, the typical lesion is represented by air space consolidations, with variable diameters ranging between 1 and 7 cm and a homogeneous density with shaded margins.

The enlargement of hilar or paratracheal lymph nodes is a radiologic finding which differentiates primary from post-primary TBC. In primary TBC the lesions are more frequently localized in the apical segments and supero-posterior lung zones, probably due to higher PO_2 level in this areas, because of the elevated ventilo-perfusion ratio. The right lung is more involved than the left one. In the defined exudative forms, scattered or confluent acinar consolidation areas are present, located specifically in the superior segment of one inferior lobe. The opacities are generally homogeneous with ill-defined borders and excavation may be present; these cavities have a thin, smooth wall and at times, an air-fluid level can be observed [2,10,12,13]. Chest X-ray does not always allow the diagnosis of the presence of excavation; the presence of caseous matter in a tubercular lesion, indeed, masks the excavation, due to its high lipid contents (Figure 11.7a).

The above-mentioned pattern is generally found in patients with relatively mild immunodeficiency; in cases of severe immunocompromisation, the radiographic findings have the aspects of primary TBC, often reaching the form of miliary TBC and rarely showing excavation.

While CT is very sensitive in showing minute parenchymal lesions, HRCT is the method of choice to evaluate the miliary form and the bronchogenic lesions [13,44] (Figure 11.7b). HRCT is particularly sensitive in depicting nodular lesions of 7–10 mm size, even if ill-defined, and smaller centrolobular nodules (2–4 mm) due to the presence of caseous material surrounding the terminal bronchioli. Moreover, on HRCT, the endobronchial spread of TBC in the small airways may be evidence for the presence of branching centrolobular opacities described as mimicking 'tree in bud' [13]. HRCT is also able to distinguish bronchial wall and interlobular septa thickening and to visualize, early, the minimal miliary lesions in correspondence to intralobular interstitium and interlobular septa (Figure 11.7c).

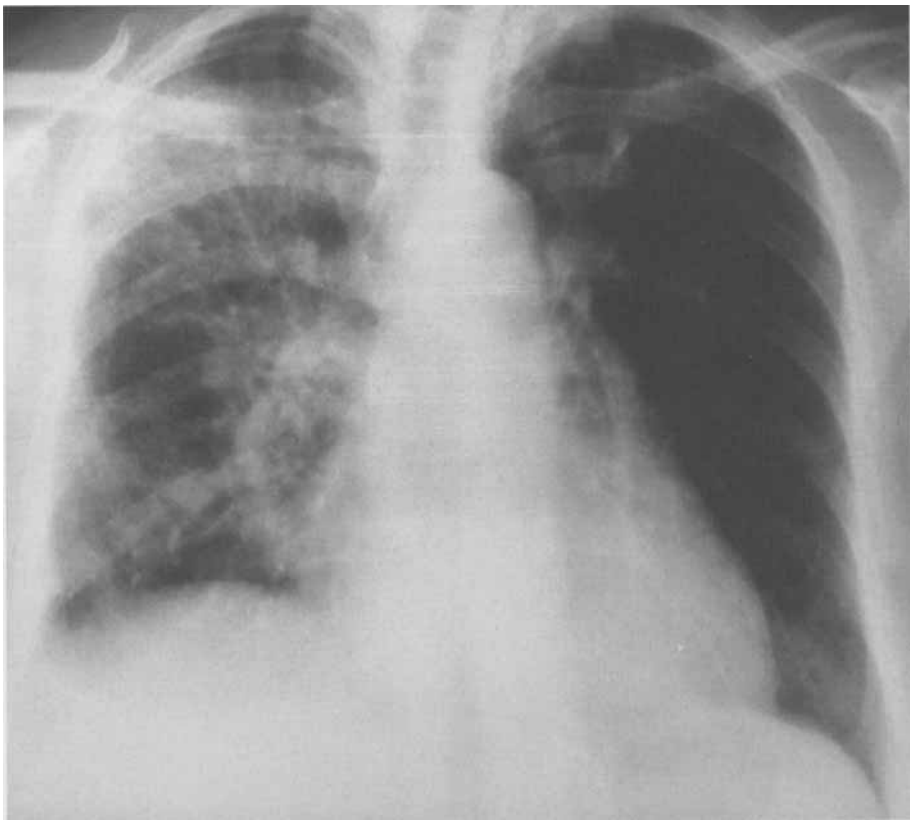
CT study with contrast media administration shows tubercular lymphadenopathies presenting a central area of low density, due to necrosis, and peripheral enhancement. This pattern, although not a pathognomonic sign can be seen also in mycoses, and is strongly suggestive of TBC infection.

The atypical mycobacteria diseases are most frequently caused by *M. avium* and *M. kansasi* and affect severely immunocompromised patients; the extra-thoracic diffusion is common. The radiological manifestations of atypical mycobacteria are extremely similar to those present in TBC infection, with frequent lymph nodal involvement; rare is the miliary form and pleural effusion. Also the clinical presentation is not easily distinguishable from that of TBC [11,13].

Non-infectious Diseases

Neoplasms

Lymphoma is observed with high frequency in patients with AIDS and in bone marrow and organ transplant recipients. Thoracic involvement is common in patients with lymphoma or leukemia. At presentation, radiographic lung abnormalities are present only in 12% of patients with Hodgkin's lymphoma and in 4% of patients with non-Hodgkin's lymphoma [11,45–49]. Patients with AIDS are pre-



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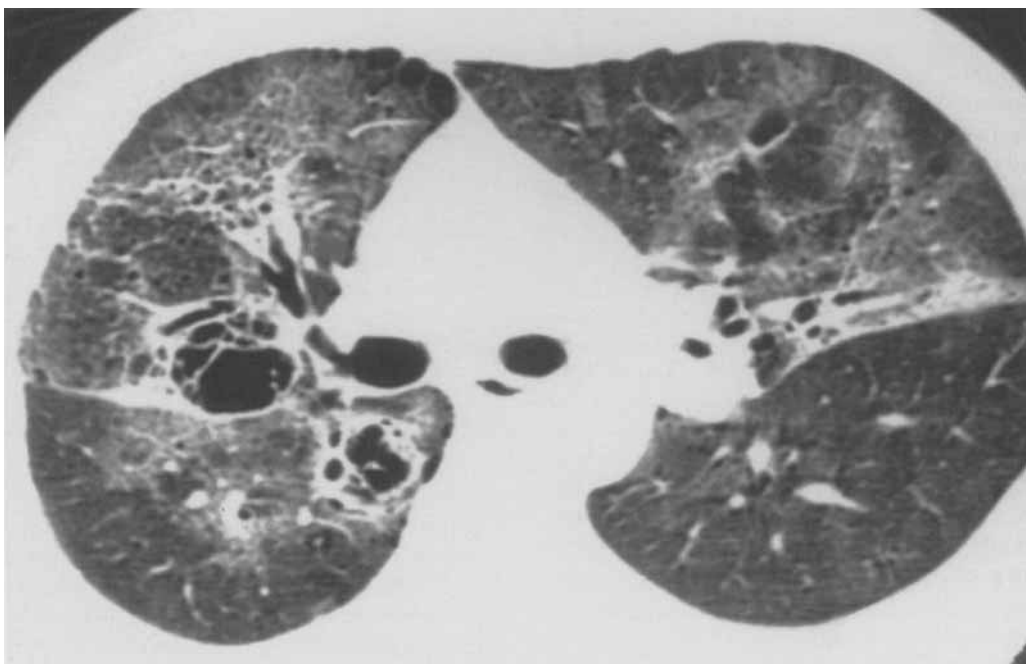

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Figure 11.7 a, b, c. Chest X-ray study in HIV-positive patient with severe pulmonary TBC, showing an extensive involvement of the right lung and the basal left lung (**a**). HRCT depicts multiple cavitary lesions in the right lung, associated with diffuse interstitial bilateral disease (**b**). Diffuse miliary lesions and centrolobular opacities are shown by HRCT, in a HIV-positive patient in the area of the left lower lobe (arrow) (**c**).

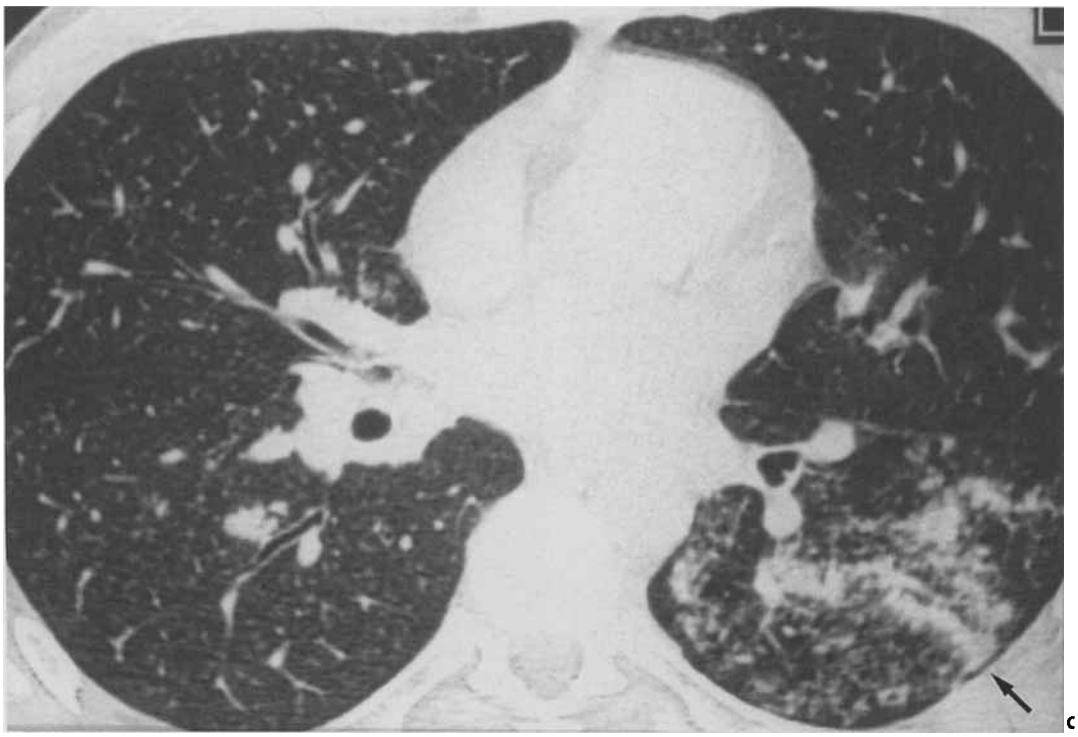


Figure 11.7 (continued)

disposed to develop neoplasms, in particular Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma. Almost 15% of AIDS patients have KS, with a male to female ratio of approximately 50:1. KS has been reported in 21% of homosexual or bisexual men, and in only 1% of men with hemophilia.

Almost all patients with pulmonary KS have evidence of skin involvement. Chest radiographs show diffuse and bilateral interstitial or nodular alterations, accompanied by pleural effusion (30% of patients). In this setting, CT may be valuable in detecting, eventually, the presence of opportunistic infections and allowing a presumptive diagnosis of KS. The presence of ill-defined nodules or areas of consolidation in a peribronchovascular distribution is indicative of KS at high resolution CT (Figure 11.8a,b). Gallium scans may be useful in the diagnosis, since they are almost always negative in patients with documented pulmonary KS, whereas thallium scans are positive [11,13].

Pulmonary Edema

Immunocompromised patients could develop pulmonary edema as the result of an underlying cardiac abnormality, impaired cardiac function due to drug toxicity, fluid overload, or a combination of these. Radiographic findings are well known, but it is important to recognize the appearance of pulmonary edema on CT. Interlobular septal thickening, dependant areas or ground-glass attenuation or air space consolidation and enlarged pulmonary vessels are the alterations observed on CT. Early edema can mimic an opportunistic infection for the presence of bilateral areas of ground-glass attenuation [11,13].

Drug Toxicity

Many drugs can cause cytotoxic effects upon the lung; however, it is not easy to associate pulmonary lesions with the administration of the drug, since the delay time between cause and effect may be highly variable, up to 1 year [13]. In addition, in immunocompromised patients the damage produced by the drug may be unnoticed for a long time due to superimposed pulmonary complications. An early diagnosis of such reactions is extremely important since the discontinuation of the drug can determine a regression of the pathologic process, thus preventing a further progression of the disease. In these cases, HRCT allows a prompt evidentiation of minimal parenchymal changes in comparison to

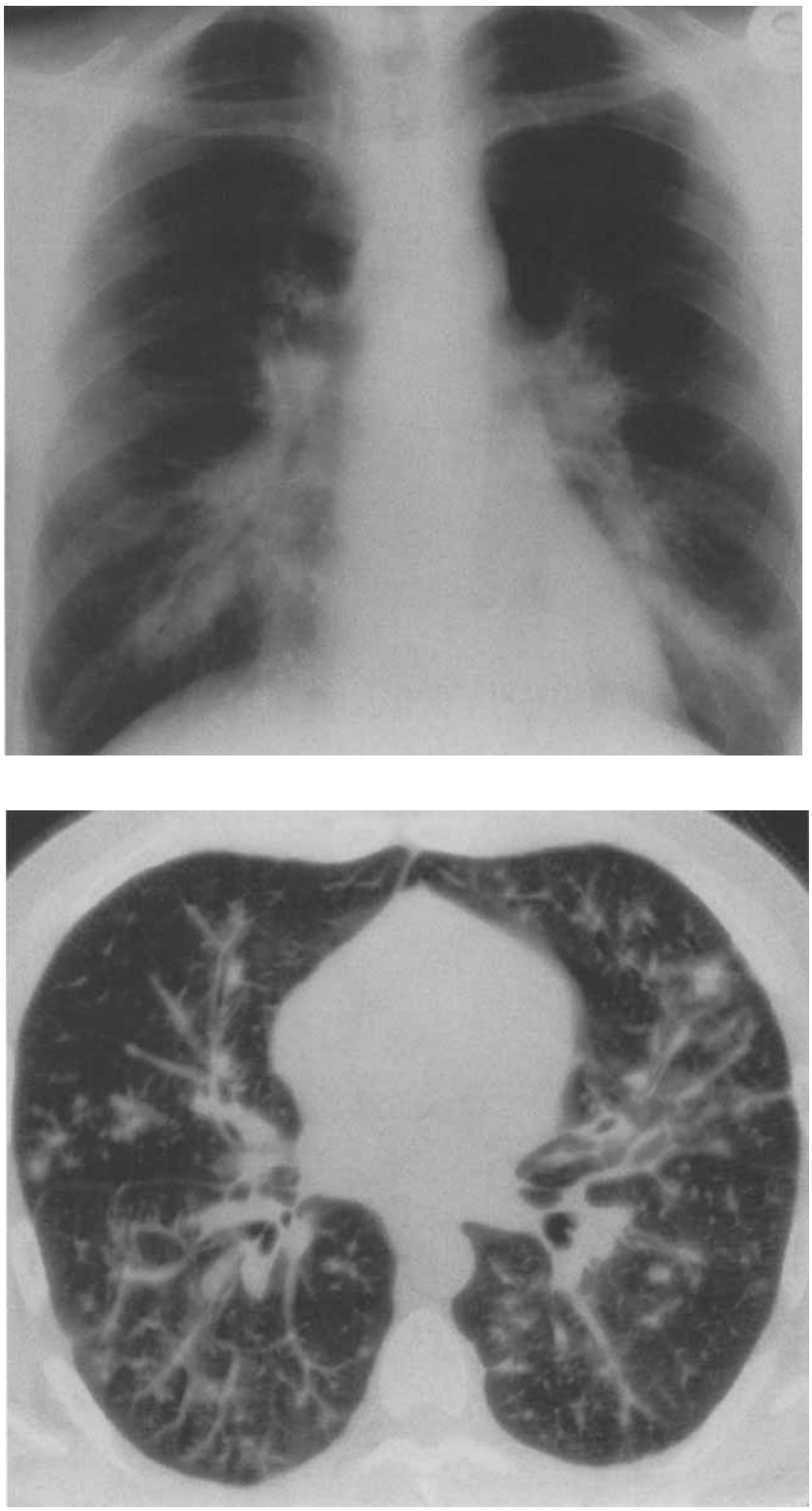


Figure 11.8 a, b. HIV-positive, drug addict, homosexual patient, with Kaposi's sarcoma, showing a bilateral interstitial pattern with thickening of bronchovascular bundles in the chest plain film (**a**). HRCT depicts very well the presence of ill-defined peripheral consolidations and nodular lesions, coupled with a diffuse interstitial involvement (**b**).

the conventional X-ray study [11,13]. Drugs most frequently producing lung cytotoxicity are those used in chemotherapy as bleomycin, methotrexate, cyclophosfamide, cytosine arabinoside, BCNU and nitrofurantoin.

Three different patterns can be seen at HRCT.

(a) Reticular or reticulonodular lesions with further parenchymal distortion, evolving in pulmonary fibrosis, with or without lung consolidation (Figure 11.9). This pattern may be correlated to bleomycin administration, where the lesions are located in the basal subpleural areas, bilaterally. This can be seen, also, in case of nitrofurantion administration, with a typical distribution of the lesions along the bronchovascular interstitium. Fibrotic pulmonary changes can be observed after busulfan, methotrexate and BCNU administration.
(b) 'Ground-glass' areas with spotted bilateral distribution, associated or not to parenchymal consolidations. This pattern can be caused by adult respiratory distress syndrome (ARDS) due to capillary damage as in the case of cytosine arabinoside use. A hypersensitivity pneumonia represents the acute reaction to drugs like busulfan, methotrexate, bleomycin, cyclophosfamide and BCNU.
(c) Parenchymal consolidations are diffusely present in the case of ARDS, which develops suddenly in a few days after chemotherapy with mytomycin C and cyclophosphamide.

Therefore, HRCT is the elective method of investigating these pathologies. However, in many cases the definitive diagnosis is achieved only after discontinuation of the therapy, considering the aspecificity of the radiological findings [11–13].

Lymphocytic-Interstitial Pneumonia (LIP)

LIP is a chronic pulmonary idiopathic complication associated with various immunologic disorders, such as collagen and chronic liver diseases and HIV immunodeficiency. In children less than 3 years old, the histologic confirmation of LIP is considered diagnostic for AIDS. The histologic pattern is characterized by interstitial infiltration by lymphocytes, histiocytes and plasma cells, extending even to the alveolar septa. Although etiologically unknown, it has been suggested that LIP could represent the lung reaction to the presence HIV virus [2,13].

Radiologic findings are non-specific and are characterized by subtle reticular infiltrates, 3–5 mm nodules or reticulo nodular aspects. In patients with

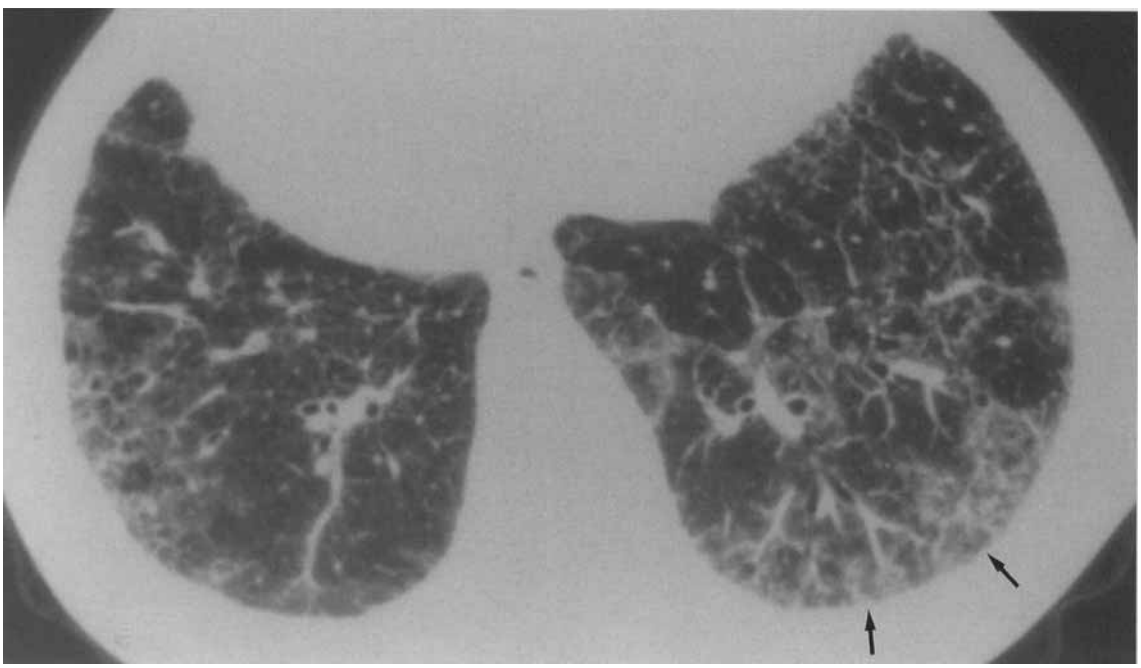
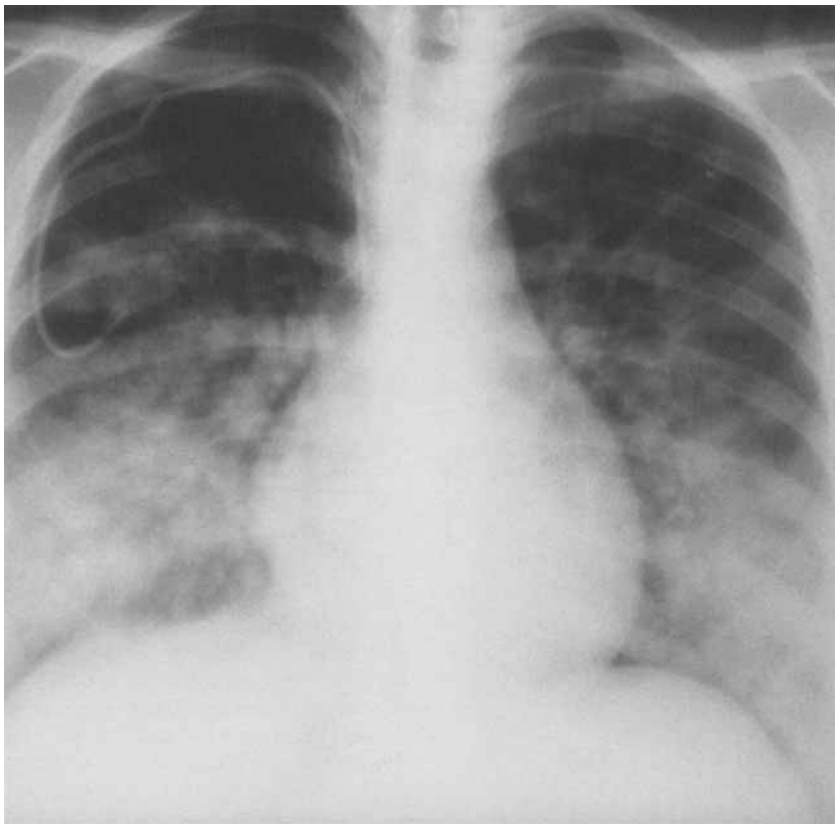
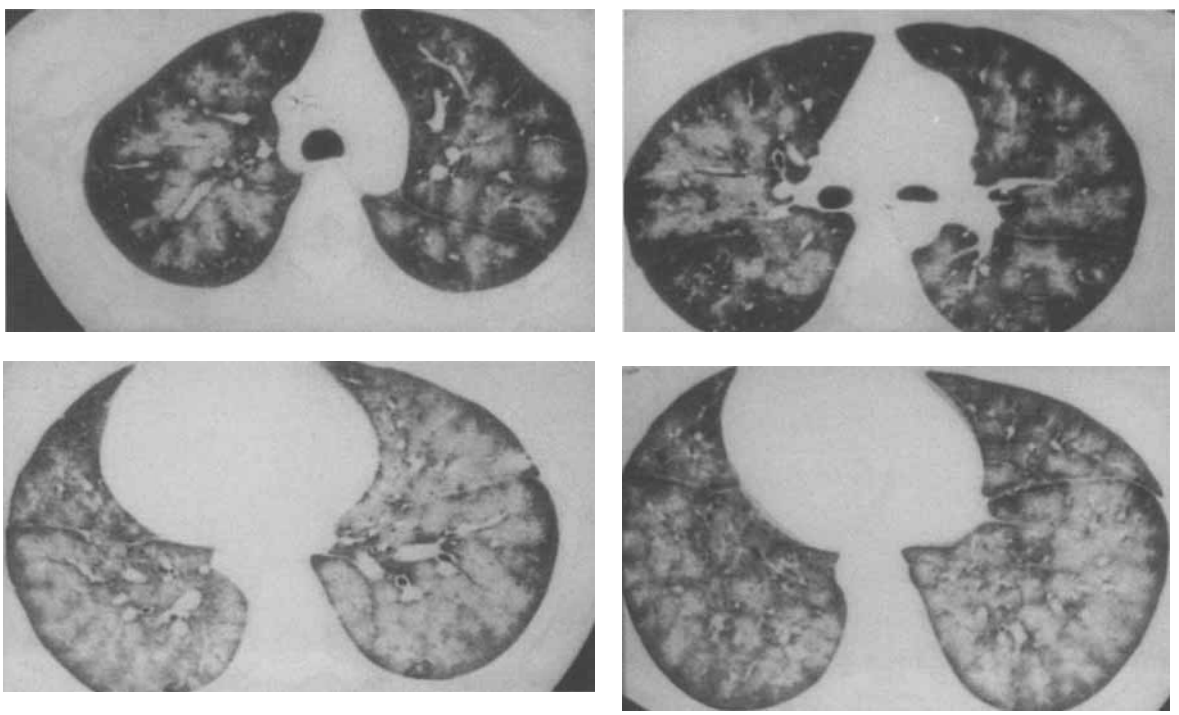


Figure 11.9. HRCT scan in a neoplastic patient treated with bleomycin, in prone position, showing a diffuse alteration of pleuro-parenchymal interfaces and fibrotic changes, mostly localized in the area of the lower posterior left lung (arrows).



a



b

Figure 11.10 a. Diffuse homogeneous consolidation in the lower lung zones, bilaterally in a patient submitted to bone marrow transplantation, with a c.v.c. in SVC. **b.** HRCT shows a severe interstitial-alveolar involvement, with consolidation of the alveolar spaces, due to mononucleate cell deposition and air space hemorrhages.

AIDS, LIP does not progress toward lymphoma, and it appears responsive to corticosteroid therapy; therefore LIP may be considered a benign process [2,50,51].

Non-specific Interstitial Pneumonia (NIP)

Non-specific interstitial pneumonia (NIP) affects HIV-positive patients and subjects undergoing bone-marrow transplantation. Histologically it presents interstitial infiltrates of mononucleate cells, with diffuse damage and alveolar hemorrhage. HRCT shows a pattern of interstitial changes or, less commonly, parenchymal consolidation (Figure 11.10a,b). This pathologic condition seems to be benign and frequently has a spontaneous resolution without specific therapy, nevertheless it may recur [2].

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