



# Respiratory Tract Diseases That May Be Mistaken for Infection

# 21

Robert M. Kotloff, Burton F. Dickey,  
and Nicholas Vander Els

## Introduction

The prevention, diagnosis, and treatment of pneumonia are critical to outcomes among transplantation patients. The diagnosis of pneumonia is usually considered when a new radiographic infiltrate is identified. Rarely, pneumonia may present initially without infiltrates in an immunocompromised host. However, even in severely immunosuppressed patients, infectious microbes cause inflammation through innate immune mechanisms that lead to tissue edema which is evident radiographically. The occurrence of pneumonia that is not apparent when a CT scan is included in the assessment is sufficiently rare that it will not be further considered here. Instead, we begin with an abnormal imaging study of the lungs, which is typically obtained during the workup of a symptom or sign such as cough, fever, or chills. The differential diagnosis of a lung infiltrate in a transplantation patient includes several common non-infectious causes. Failure to accurately diagnose non-infectious causes of lung infiltrates can lead to unnecessary treatment with antibiotics, and more importantly to failure to address the underlying pathophysiologic process. This chapter is focused on clinical presentations of pulmonary disorders that mimic infectious pneumonia.

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R. M. Kotloff  
Department of Pulmonary Medicine, Respiratory Institute,  
Cleveland Clinic, Cleveland, OH, USA  
e-mail: [kotlofr@ccf.org](mailto:kotlofr@ccf.org)

B. F. Dickey  
Department of Pulmonary Medicine, University of Texas MD  
Anderson Cancer Center, Houston, TX, USA  
e-mail: [bdickey@mdanderson.org](mailto:bdickey@mdanderson.org)

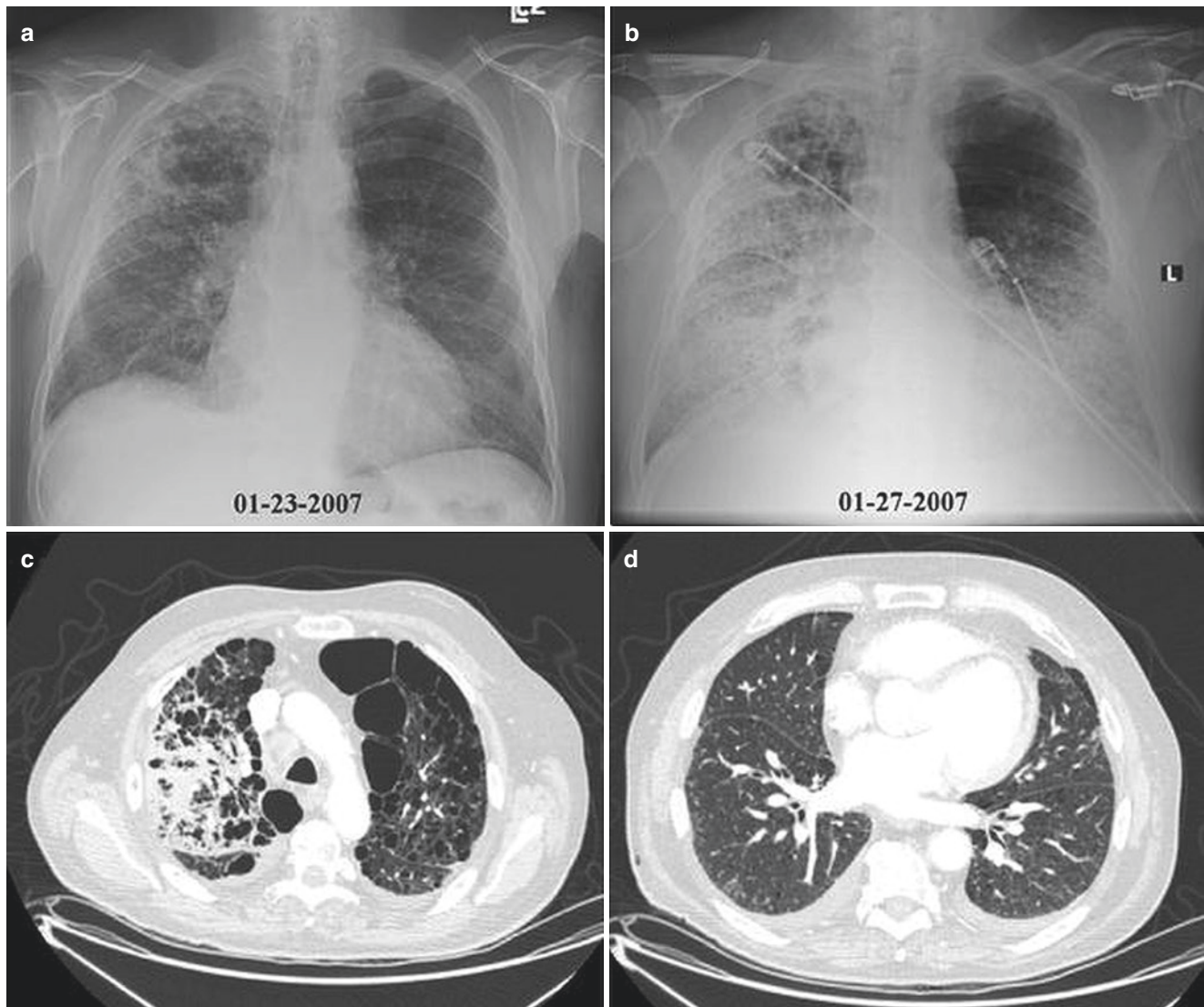
N. Vander Els (✉)  
Pulmonary Service, Memorial Sloan-Kettering Cancer Center,  
New York, NY, USA  
e-mail: [vanderen@mskcc.org](mailto:vanderen@mskcc.org)

## Hematopoietic Stem Cell Transplantation (HSCT)

Despite advances in treatment regimens and supportive care, pulmonary complications still occur in up to 60% of HSCT recipients [1]. These complications are mostly due to toxicities from conditioning regimens, delayed bone marrow recovery, prolonged immunosuppressive therapy, and graft-versus-host disease (GVHD). As the incidence of infectious pulmonary complications has diminished, largely due to effective prophylactic therapy, non-infectious pulmonary complications have emerged as a major cause of morbidity and mortality [2]. Pulmonary complications have been divided into those that occur “early” (during the first 100 days after transplantation) and those that occur “late,” but this is not a rigid division. In particular, some “late” complications such as cryptogenic organizing pneumonia and constrictive bronchiolitis occur with substantial frequency during the first 100 days.

## Pulmonary Edema

Cardiogenic (hydrostatic) pulmonary edema occurs with regularity in transplant patients due to the large volumes of fluid administered with chemotherapy and antibiotics, chemotherapy-induced cardiotoxicity, and co-morbidities (e.g., renal insufficiency) [3]. The classic presentation of cardiogenic pulmonary edema, consisting of acute, bilateral, symmetrical, perihilar infiltrates with interstitial thickening, an enlarged heart, and pleural effusions in a patient with pre-existing heart disease and associated findings of peripheral edema and bibasilar rales, is easy to recognize. However, cardiogenic pulmonary edema may also be the cause of asymmetrical infiltrates in a patient with underlying lung disease, such as bullous emphysema, that precludes alveolar filling in localized regions (see Fig. 21.1). An enlarged heart may not be present on the radiograph if cardiac dysfunction is not longstanding, so that the heart has not had time to



**Fig. 21.1** Atypical presentation of congestive heart failure. A 68-year-old male was receiving radiation therapy to a squamous cell carcinoma of the upper lobe of the right lung. He had received 19 of 37 planned fractions, when he was admitted because of increasing dyspnea and cough, presumed to be pneumonia. **(a)** The PA radiograph in the left upper corner shows the right upper lobe with associated radiation pneumonitis. **(b)** The AP radiograph in the right upper corner taken 4 days later shows lung infiltrates that spare the left upper lobe. **(c)** However, the CT angiogram on the lower panel performed on the day of admission 01-24-2007 shows that the left upper chest is mostly occupied by

emphysematous bullae, accounting for the sparing of the left upper lung field when pulmonary edema developed. **(d)** The remainder of the lung fields contain ground-glass opacities suggestive of *congestive heart failure*. The diagnosis of congestive heart failure was supported by the patient's history of prior episodes of pulmonary edema, bilateral ankle edema, a depressed left ventricular ejection fraction of 30–35%, moderate mitral regurgitation, elevated BNP of 1043, transudative pleural effusion, and improvement with diuresis [8]. (Reprinted from Kaplan et al. [8], with permission of Springer)

remodel (e.g., acute volume overload or diastolic dysfunction secondary to acute ischemia). In these cases, additional studies can be very helpful in establishing the diagnosis [4–6]. CT of the chest may show the diffuse nature of alveolar infiltrates and pleural effusions that are less apparent on plain films, and may additionally reveal interstitial edema and cardiac chamber enlargement. Review of serial radiographs may show infiltrates that wax and wane in association with variations in patient weight, peripheral edema, or

fluid administration. Echocardiography is very supportive when it reveals systolic dysfunction, but it is important to recognize that diastolic dysfunction is an equally prevalent cause of heart failure [7], potentially exacerbated by rhythm disturbances such as atrial fibrillation, valvular dysfunction, or transient ventricular wall stiffening due to ischemia. Brain natriuretic peptide (BNP) levels are quite specific and sensitive but are less elevated in diastolic than in systolic dysfunction [7].

Non-cardiogenic pulmonary edema due to increased permeability of the alveolocapillary membrane (acute lung injury and adult respiratory distress syndrome (ARDS)) can occur as a result of a wide variety of causes in transplant patients. Sepsis is the most common cause of permeability edema of the lungs in general [6, 9, 10] and can cause radiographic infiltrates in transplant patients. In addition, transplant patients are susceptible to lung injury from causes unique to this population, such as from chemotherapy or the effects of acute GVHD. Transplant patients are also frequently exposed to treatments associated with lung injury in the general hospital population, such as transfusion. Transfusion-related acute lung injury (TRALI) is the leading cause of mortality from transfusions [11] and has been associated with all plasma-containing blood products, including immunoglobulins. The incidence of TRALI is not known, but has been estimated at 0.02% per unit transfused and 0.16% per patient transfused [12]. Patients with TRALI commonly present with dyspnea, cough, fever, acute hypoxemia hypotension, and bilateral pulmonary infiltrates within 1–6 h after the transfusion. Transient leukopenia, due to pulmonary sequestration of the circulating pool of leukocytes, may be observed. The mainstay of treatment for TRALI is to discontinue the transfusion, followed by supportive care. Although there has never been a randomized controlled trial of glucocorticoid therapy, they have no effect on the 5–8% mortality. With supportive treatment, infiltrates usually resolve, within 96 h, and survivors have no long-term sequelae [13].

### Engraftment Syndrome (ES)

ES is characterized by a constellation of symptoms and signs including fever, erythrodermatous skin rash, diarrhea, and non-cardiogenic pulmonary edema with bilateral pulmonary infiltrates, which generally occur within 5 days of neutrophil engraftment following HSCT. In more severe cases, systemic involvement, i.e., renal failure, hepatic failure, encephalopathy, or seizures, may be observed. Seen most often following autologous HSCT, ES has also been described in those individuals who have undergone allogeneic HSCT with a non-myeloablative preparative therapy. Although the pathophysiology of ES is not well understood, it is thought to result from a combination of endothelial injury due to preconditioning chemotherapy and the production and release of cytokines and products of neutrophil degranulation and oxidative metabolism, leading to capillary leak, with either local injury in the lung or systemic tissue injury [14]. Bronchoalveolar lavage (BAL) may show a neutrophilic alveolitis. Surgical lung biopsies, when obtained, often reveal diffuse alveolar damage. Treatment entails observation and supportive care (i.e., antibiotics, intravenous fluids) in mild cases. High-dose corticosteroid therapy is very effective, often resulting in rapid

clinical improvement in those with progressive or symptomatic ES. Respiratory failure requiring mechanical ventilation has been observed, however, in up to one-third of patients [15].

### Idiopathic Pneumonia Syndrome (IPS)

In 1993, a panel convened by the NIH proposed a broad working definition of IPS as widespread non-lobar radiographic infiltrates in the absence of congestive heart failure or evidence of lower respiratory tract infection [16]. IPS occurs in 10% of HSCT recipients, usually 14–90 days following transplantation. Mortality rates range from 50% to 70% [17]. Possible etiologies of IPS include direct toxic effects of the chemoradiation conditioning regimen, occult infection, and/or the release of inflammatory cytokines secondary to some as yet unknown inciting stimuli. The association of IPS with the presence of acute GVHD after allogeneic HSCT suggests that alloreactive T cells may be at least one of these stimuli [17, 18].

The clinical presentation is non-specific, with symptoms of dyspnea, cough, and fever associated with diffuse infiltrates on chest radiograph. The diagnosis of IPS largely relies on the exclusion of infection on lower respiratory samples obtained from a diagnostic procedure, e.g., BAL or lung biopsy. Common pathologic findings of non-specific interstitial pneumonitis (NSIP) and/or diffuse alveolar damage (DAD) may be seen. Although no randomized controlled trials of treatment for IPS are available, current standards include high-dose intravenous corticosteroids and supportive care, such as supplemental oxygen and broad-spectrum antibiotics. Recent preclinical and clinical data suggest a potential role for tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in the pathogenesis of IPS [19–21], and a randomized trial using etanercept, a TNF receptor fusion protein, is being conducted by the Blood and Marrow Transplant Clinical Trials Network.

This same Network has included diffuse alveolar hemorrhage (DAH) within the definition of IPS, and we know of no reason to separate the two. Post-transplantation DAH was initially described in autologous HSCT recipients as widespread lung injury manifested by diffuse radiographic infiltrates that occurred in the absence of identifiable infection. DAH is now known to occur in both allogeneic and autologous transplant recipients and is seen in approximately 5% of all HSCT [22]. The etiology is unclear, but is not clearly related to any specific coagulopathy or to thrombocytopenia [23]. Pre-transplant high-dose chemotherapy, thoracic and/or total body irradiation, and undocumented infections are putative factors which may cause the initial injury, priming the lung for subsequent development of DAH. It can coincide with stem cell engraftment, but late onset (after the first 30 days) has been observed and is associated with a worse prognosis. Hemoptysis occurs in less than 20% of patients.

Bronchoscopic diagnostic criteria include progressively bloodier returns on BAL or the presence of 20% or more hemosiderin-laden macrophages on cytologic inspection of BAL fluid. However, these bronchoscopic criteria may be seen in association with diffuse lung injury from a wide variety of causes, including infections, congestive heart failure, and malignancy. There are no prospective randomized trials addressing the treatment of DAH. Earlier retrospective studies demonstrated reduced need for mechanical ventilation and mortality in a cohort of patients receiving high-dose corticosteroids, but more recent observational studies found no survival benefit [24, 25].

### Drug-Induced Lung Injury (DILI)

DILI may present with dyspnea, fever, and pulmonary infiltrates, clinically indistinguishable from a pneumonia [26]. DILI may present at the time of transplantation as a consequence of chemotherapy administered for treatment of an underlying cancer or after transplantation as a consequence of chemotherapy administered as part of the conditioning regimen, or given as prophylaxis of GVHD. Agents of concern are listed in Table 21.1. Symptoms vary with the severity of injury; fever can be absent, and patients may have only dyspnea on exertion or be asymptomatic. In such patients, diffuse infiltrates seen on radiographs or abnormalities on pulmonary function testing may be the only signs of lung injury. There is no pathognomonic finding unique for DILI, and the diagnosis is one of exclusion [27]. Given the severe immune compromise of HSCT patients, bronchoscopy to exclude infection is indicated for most patients with new diffuse infiltrates.

Lung injury may occur either from a drug's cytotoxic mechanism or from its presence as an antigen. The histologic and radiographic patterns produced vary and include Usual Interstitial Pneumonitis (UIP)/fibrosis, hypersensitivity pneumonitis, and acute lung injury (ALI)/ARDS. Bleomycin produces lung injury both by cytotoxic action and as an antigen. It is used primarily to treat Hodgkin's disease and forms a moiety

with ferrous ions that induces oxidative injury to tumor cells [28]. Human lungs and skin lack an enzyme, bleomycin hydrolase, which limits injury to other tissues. A UIP/fibrosis pathology is produced, with peripheral and basal infiltrates [29]. (See Fig. 21.2.) Exposure to supplemental oxygen can exacerbate this form of toxicity, by potentiating oxidative injury. As an antibiotic, bleomycin can cause hypersensitivity pneumonitis, with high fevers and acute infiltrates. This presentation tends to be responsive to steroid therapy [28–30]. Methotrexate also produces hypersensitivity pneumonitis. It is used both for the treatment of lymphoma and for prophylaxis against GVHD after HSCT. In contrast to bleomycin, the hypersensitivity from methotrexate can be accompanied by peripheral eosinophilia and thoracic adenopathy [31, 32]. Granulomas are seen on biopsy, and the toxicity is responsive to steroid therapy [31]. The substituted nucleoside fludarabine may also produce granulomatous disease, as well as eosinophilic pneumonia [33, 34]. Etoposide is rarely toxic but can produce a severe hypersensitivity reaction with symptoms of angioedema or ARDS [35, 36]. Etoposide use is common in HSCT, as a component of the ICE



**Fig. 21.2** Severe bleomycin toxicity, UIP presentation. Note peripheral and basal pattern of infiltration, as well as spontaneous pneumothorax seen anteriorly

**Table 21.1** Chemotherapeutic agents characterized by class, indication, and pulmonary toxicity

Agent	Class	Indication	Pulmonary toxicity
Anti-thymocyte globulin	Monoclonal antibody	Induction agent	ALI/ARDS
Bleomycin	Antibiotic	Lymphoma	IP/H/OP
Busulfan	Alkylating agent	Induction agent	IP/pleural effusion
Carmustine/BCNU	Nitrosourea	Induction agent	IP/fibrosis
Cyclophosphamide	Alkylating agent	Induction/lymphoma	IP/pleuritis
Cytarabine	Substituted nucleoside	AML	Capillary leak
Etoposide	Anti-podophyllotoxin	Induction agent/lymphoma	ALI/ARDS
Fludarabine	Substituted nucleoside	CLL/induction	EP/H
Melphalan	Alkylating agent	Induction agent	IP
Methotrexate	Antimetabolite	Induction/GVHD	H/pleuritis/adenopathy
Sirolimus	mTOR inhibitor	GVHD	IP

*Abbreviations:* ALI acute lung injury, EP eosinophilic pneumonia, H hypersensitivity, IP interstitial pneumonitis, OP organizing pneumonia

(ifosfamide, cisplatin, and etoposide) regimen, as a “salvage” regimen for lymphoma, and also as an induction agent [37, 38]. Cytarabine, commonly used to treat acute myeloid leukemia (AML), may cause non-cardiogenic pulmonary edema. This is usually responsive to steroid therapy and is resolved prior to transplant [39]. Dasatinib is a tyrosine kinase inhibitor useful in the treatment of CML. In addition to producing pleural effusions, ground-glass opacities can be seen as well as alveolar septal thickening [40].

HSCT patients receive high-dose chemotherapy as an induction regimen to eliminate marrow cells and prevent rejection of the graft. Following transplantation, immunosuppressive agents to prevent GVHD are prescribed for patients who received allogeneic grafts. Anti-thymocyte globulin is an antibody derived from rabbit or equine serum that can produce interstitial infiltrates and progress to ARDS [41, 42]. The mechanism of lung injury is not clear. As ATG is an anti-leukocyte antibody, the pathogenesis may be similar to that of transfusion-related lung injury (TRALI), or it may stem from its presence as a foreign protein [41, 42]. BCNU may produce DILI within 6 weeks of administration or as late as 20 years after administration to treat pediatric cancers [43, 44]. It presents with diffuse infiltrates and dyspnea, generally without fever, and is irregularly responsive to steroid therapy. The alkylating agents busulfan, melphalan, and cyclophosphamide can all produce a UIP/fibrosing pattern of injury [27]. Busulfan was the first cytotoxic agent described to produce lung injury more than 50 years ago [45]. In one series, the incidence of toxicity was 46% [46]. Today, it is only used as an induction agent for HSCT. Melphalan is well-tolerated at standard doses but given at the high doses used for induction can produce a DIP-like presentation [47]. Cyclophosphamide, used to treat lymphoma and for induction, can produce an early-onset pneumonitis, within 1–6 months of administration, which may be responsive to cessation of the drug or steroid therapy [48]. It can also produce fibrosis and pleural thickening that can chronically progress despite cessation. Rituximab, which is a B-cell-depleting monoclonal antibody, is used to treat lymphomas and rheumatologic ailments. It can be used for induction as well. Symptoms may appear as early as 30 days or as late as 5 months. It rarely causes interstitial lung disease, with only 121 cases reported to date; however, 15% of the cases were fatal [49]. Sirolimus, temsirolimus, and everolimus are mTOR inhibitors used for prevention of GVHD and for treatment of renal and other cancers [50, 51]. The mTOR inhibitors can all cause pneumonitis and are discussed in the subsequent section on solid organ transplantation.

### Radiation-Induced Lung Injury

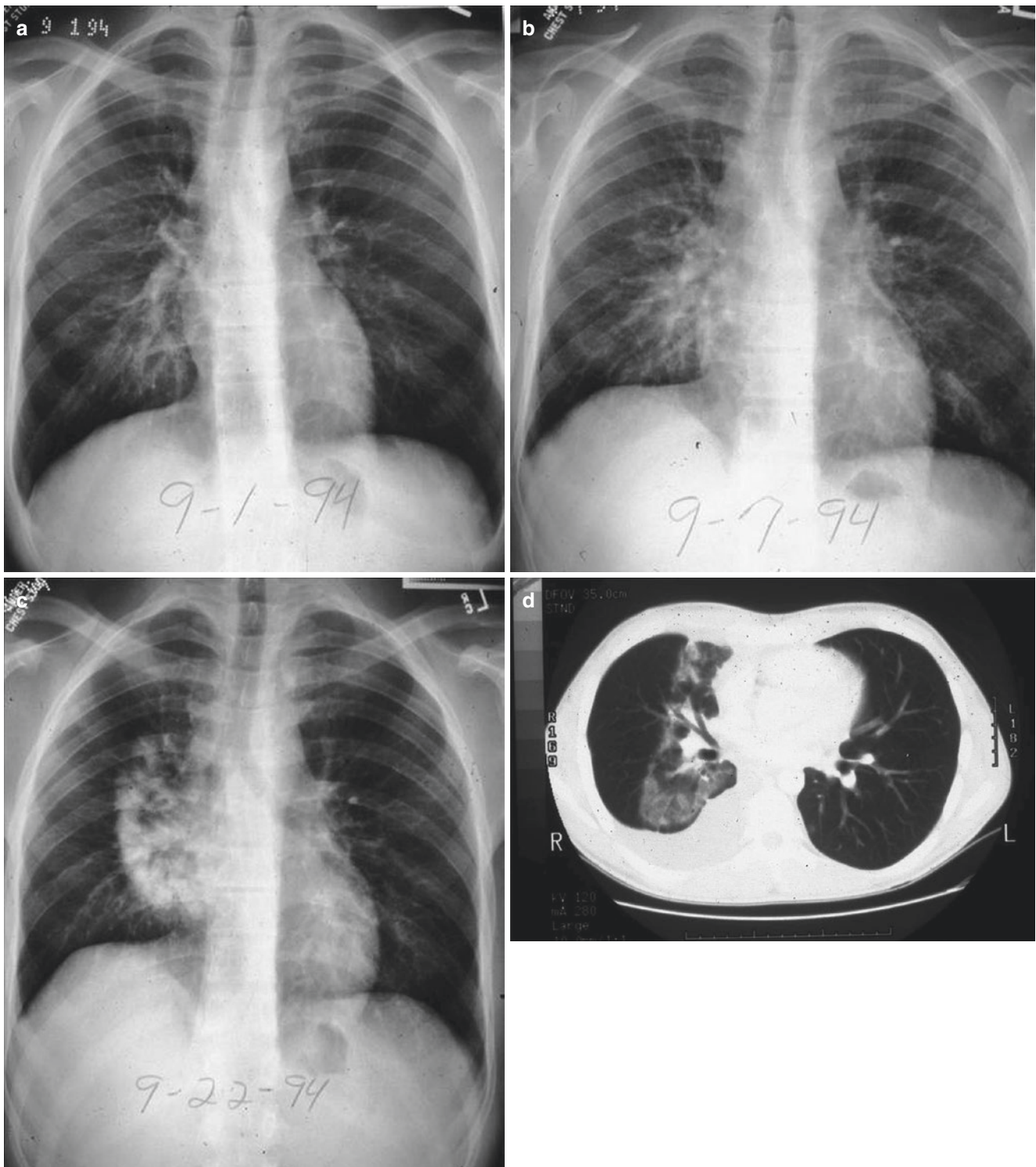
As with DILI, lung injury can be a consequence of radiation administered for control of a tumor prior to transplan-

tation or for radiation administered as part of an induction regimen for HSCT. The symptoms and radiographic findings are a consequence of both radiation injury per se to pulmonary parenchyma and the host immunologic response to the injury. Bilateral lymphocytic alveolitis is seen after radiation is administered to only one lung [52, 53]. Roberts et al. performed bilateral BAL on 17 patients receiving radiation therapy for breast cancer, and bilateral lymphocytic alveolitis was seen even in the 15 asymptomatic patients [52]. This type presentation can be appreciated as part of the natural course of radiation-induced lung injury in the young patient shown in Fig. 21.3. Three months earlier, he had received a hilar “boost” of radiation therapy prior to an HSCT for Hodgkin’s disease. Low-grade fevers and increased interstitial markings (Fig. 21.3a, b) evolved over weeks into the dramatic infiltrate seen in Fig. 21.3c. By the time of the final radiograph, fevers had resolved and no steroids were prescribed. In general, radiation lung injury may be treated as a self-limited process, with steroid therapy reserved for patients who are febrile or hypoxic.

Total body irradiation (TBI) administered for induction is associated with acute pulmonary toxicity. Among 101 patients undergoing HSCT with TBI at Duke, one-third developed severe pulmonary toxicity, though the only independent factor correlated with the development of pulmonary toxicity was the number of chemotherapy regimens prior to transplant [54]. Gopal et al. found a similar rate of severe pulmonary toxicity among patients receiving 12 cGy of TBI in 4 once-daily fractions (6 of 24 patients, 25%) [55]. There was a lower incidence of severe toxicity among patients treated with 10.2 cGy in 6 twice-daily fractions (7 of 57, 12%); however, the difference was not significant ( $P=0.19$ ). TBI has also been associated with alveolar hemorrhage in patients undergoing autologous transplantation [23].

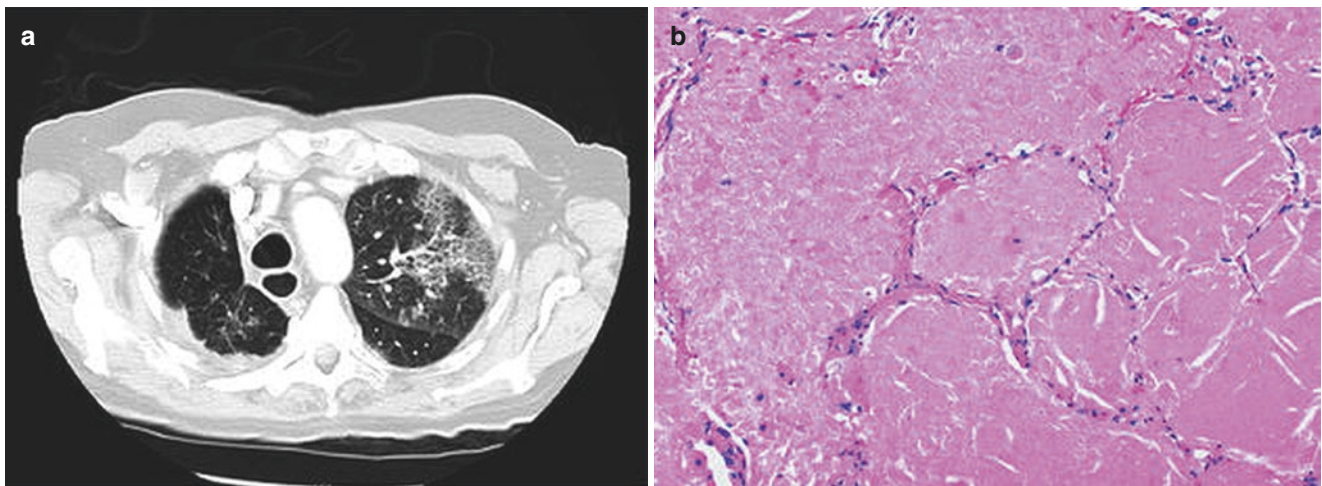
### Pulmonary Alveolar Proteinosis (PAP)

PAP is a rare complication that may occur within the first 100 days after HSCT [56, 57]. Patients typically present with slowly progressive dyspnea and a non-productive cough. Bilateral diffuse alveolar densities and diffuse ground-glass attenuation with superimposed interlobular septal thickening and intralobular lines in a “crazy-paving” pattern on chest CT are non-specific, but supportive radiographic findings (see Fig. 21.4a). Bronchoscopic examination demonstrates copious, milky BAL effluent, which on cytologic examination contains foamy macrophages engorged with periodic acid-Schiff-positive intracellular inclusions and granular, acellular eosinophilic proteinaceous material (see Fig. 21.4b). Concentrically laminated phospholipid lamellar bodies may be seen on electron microscopy, which is occasionally necessary to confirm the diagnosis. Spontaneous reversal of PAP



**Fig. 21.3** Natural progression of radiation pneumonitis, 3 months after treatment. A young man underwent autologous HSCT for Hodgkin's disease in June of 1994 after receiving a right hilar "boost" to an enlarged lymph node. (a) A PA chest radiograph from 09-01-1994 showed increased interstitial markings on the right. (b) A PA chest radiograph on 09-07-1994 during a febrile episode attributed to an

infected catheter showed an increase in the interstitial infiltrates. (c) The pulmonary service was consulted to evaluate this PA chest radiograph on 09-22-1994; however, the patient was asymptomatic. (d) A chest CT confirmed the linear border of the infiltrate and revealed an unsuspected small effusion. No treatment was prescribed



**Fig. 21.4** Pulmonary alveolar proteinosis (PAP) in a patient with chronic myeloid leukemia. (a) CT chest demonstrates a “crazy-paving” pattern, with a network of smoothly thickened reticular (i.e., septal) lines superimposed on ground-glass opacities. (b) Histopathologic find-

ings in PAP include the filling of alveolar spaces with eosinophilic proteinaceous material, which may stain periodic acid-Schiff-positive [8]. (From Kaplan et al. [8], with permission of Springer)

has been described after the resolution of neutropenia or an associated infection. In patients with severe dyspnea and/or significant hypoxemia, whole lung lavage or GM-CSF administered either subcutaneously or via nebulization have been effective in patients with PAP not associated with HSCT [58, 59]. Steroids are not recommended, since they may increase mortality.

### Cryptogenic Organizing Pneumonitis (COP)

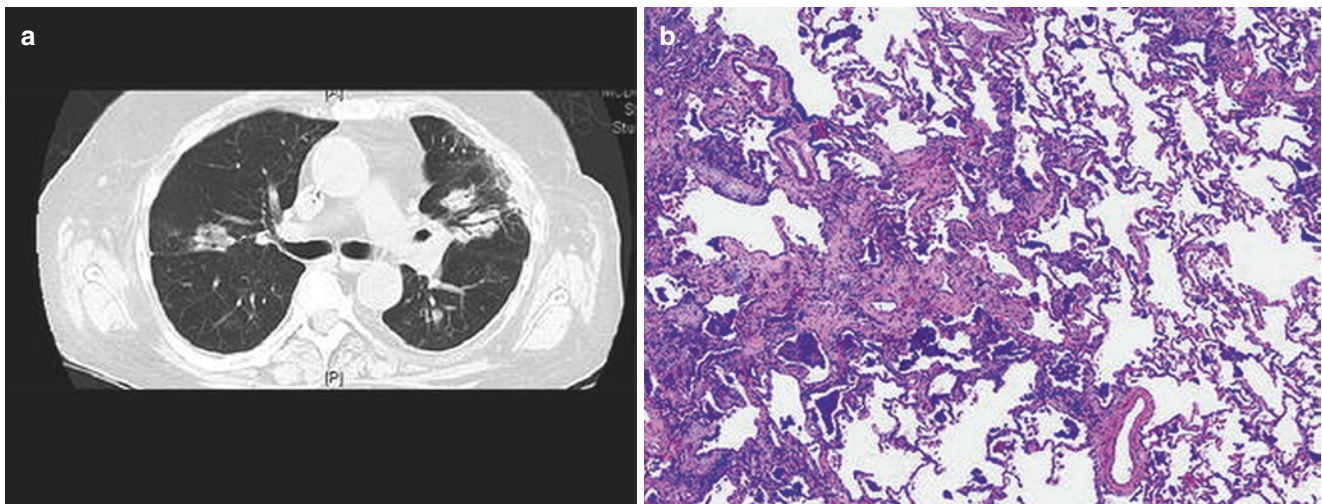
COP [formerly, Bronchiolitis Obliterans with Organizing Pneumonia (BOOP)] occurs mostly in allogeneic HSCT recipients with GVHD or following CMV pneumonitis [60], with an onset between 1 and 13 months after transplantation. It is less common than post-transplantation constrictive bronchiolitis (PTCB) and should not be confused with it since PTCB is not associated with radiographic infiltrates. Cough and fever are the most common symptoms of COP on presentation; dyspnea, if present, is mild, and, in some cases, patients are asymptomatic [61]. COP usually presents with patchy bilateral alveolar opacities which can be migratory on chest radiograph. The opacities have a lower lobe predominance and are peripheral in location. They may appear as ground-glass opacities or consolidation with air bronchograms on high-resolution CT scans (see Fig. 21.5a). Occasionally, COP can present radiographically as a solitary nodule or mass mimicking a neoplasm or chronic non-resolving pneumonia. In 1 retrospective study of 43 cancer patients, 81% of patients with solid organ tumors had nodular

or mass-like radiographic abnormalities, and 19% presented with diffuse infiltrates [62]. In the same study, diffuse infiltrates were seen in the majority of patients with hematologic malignancies, including HSCT, and mimicked infection and drug-induced toxicity.

Pathologically, COP is characterized by the presence of granulation tissue within the lumen of the distal air spaces with or without bronchoalveolar involvement (see Fig. 21.5b). This pathologic picture can be seen with multiple other accompanying diagnoses, such as congestive heart failure, infections, and drug-induced toxicity; hence, in the HSCT recipient, other diagnoses should be excluded before a diagnosis of COP is made. COP is highly responsive to corticosteroids. The minimal effective dose and duration of therapy are unknown; however, a prolonged steroid course with a slow taper is usually necessary due to high relapse rates. Macrolides have been used with success in some cases and might be considered in those individuals who are intolerant to steroid therapy or in whom relapse occurs [63]. Although the specific mechanism of action is not known, macrolides are thought to exert their beneficial effects through anti-inflammatory rather than anti-microbial activities.

### Post-transplantation Lymphoproliferative Disorder (PTLD)

PTLD occurs in approximately 1% of HSCT patients, usually within the first 4–12 months after transplantation [1, 64]. The clinical constellation may include fever, lymphadenopathy,



**Fig. 21.5** Organizing pneumonia in a patient with a history of chronically waxing and waning pulmonary infiltrates. **(a)** Patchy airspace consolidation with air bronchograms, often in a subpleural location, is a characteristic radiographic presentation for organizing pneumonia. **(b)**

On histopathologic examination, granulation tissue can be seen within the lumen of the distal air spaces, swirling into alveoli, associated with chronic inflammation in the surrounding alveoli [8]. (From Kaplan et al. [8], with permission of Springer)

pharyngitis, hepatosplenomegaly, and neurologic symptoms. There appears to be a greater incidence of fulminant, disseminated PTLD in HSCT recipients as compared to solid organ transplant recipients, possibly accounting for the increased mortality associated with PTLD in this population [65]. The lung is involved only 20% of the time, usually as a component of disseminated disease, most commonly with ill-defined nodular infiltrates. It can also present as well-defined nodules, surrounded by a rim of ground-glass density (halo sign), mimicking the features of invasive aspergillosis. Hilar and mediastinal adenopathy and pleural effusions may also be seen. The pathogenesis of PTLD and its treatment are addressed below under Solid Organ Transplantation.

## Solid Organ Transplantation

A number of non-infectious pulmonary complications affecting solid organ transplant recipients present with clinical and radiographic features that may mimic infection. These are described in the following sections; complications limited to specific organ recipient populations are noted in the subheadings.

### Primary Graft Dysfunction (Lung Transplantation)

Primary graft dysfunction (PGD) represents a form of acute lung injury associated with the development of non-cardiogenic pulmonary edema within the first 72 h following lung transplantation [66]. It is presumed to result from

ischemia-reperfusion injury to the allograft(s), but inflammatory events triggered by brain death in the donor prior to implantation, as well as surgical trauma and lymphatic disruption, may be contributing factors. In most cases, the process is mild and transient, with fleeting pulmonary infiltrates on chest x-ray. In approximately 10% of cases, however, the presentation and course are similar to the acute respiratory distress syndrome (ARDS) with severe hypoxemia, widespread airspace opacities on chest x-ray, and the need for mechanical ventilator support. In common with ARDS, lung biopsies performed in patients with PGD demonstrate a prevailing pattern of diffuse alveolar damage.

A multitude of factors have been identified as associated with an increased risk of developing PGD, though the causal nature and mechanisms underlying these associations have not been established. Donor-related risk factors include female gender, African-American race, older age, and low donor PaO<sub>2</sub>/FiO<sub>2</sub> ratio [67–69]. An elevated level of interleukin-8 in bronchoalveolar lavage fluid recovered from the donor has been associated with the development of severe PGD, supporting the notion that inflammatory events preceding organ harvest may play a role. Recipient risk factors include an underlying diagnosis of idiopathic pulmonary arterial hypertension as well as the presence of elevated pulmonary artery pressures independent of diagnosis. An association between graft ischemic time and PGD has not been consistently demonstrated. A possible explanation for the conflicting data is that ischemic time may become a factor only when it exceeds a certain threshold, suggested by one study as occurring beyond 6 h [70].

PGD should be considered when pulmonary infiltrates appear in the allograft(s) (sparing the native lung in cases



of single lung transplantation) within the initial 3 days after lung transplantation. The diagnosis is one of exclusion. Other entities to be considered include volume overload, hyperacute rejection, aspiration pneumonitis, and pulmonary venous outflow obstruction. Pneumonia, transmitted from the donor via the allograft or acquired *de novo* post-transplantation, is an additional consideration. Evaluation should include assessment of hemodynamics (especially pulmonary capillary wedge pressure if a right heart catheter is in place), bronchoscopy to assess for purulent secretions and to obtain cultures, transesophageal echocardiography to visualize the pulmonary veins, and immunological testing for the presence of donor-specific anti-HLA antibodies.

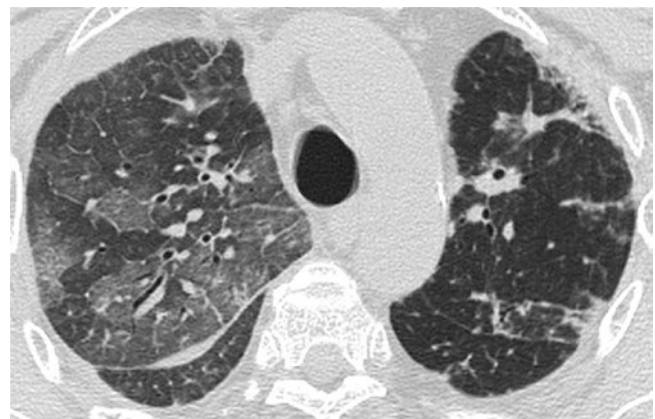
As with ARDS due to other causes, treatment of severe PGD is supportive. Mechanical ventilation, employing a “low stretch” protocol, is the mainstay of care. Adjunct measures considered when oxygenation is tenuous include use of inhaled nitric oxide or prostacyclin and extracorporeal life support. Results of emergent retransplantation in this setting have been poor [71]. Severe PGD is associated with a mortality rate in the range of 30–40% and represents a leading cause of perioperative death among lung transplant recipients. Recovery among survivors is often protracted, but achievement of normal graft function is possible. Survivors do appear to be at increased risk of developing bronchiolitis obliterans syndrome [72].

### Allograft Rejection (Lung Transplantation)

Hyperacute rejection is a rare cause of widespread pulmonary infiltrates in the immediate postoperative period following lung transplantation [73]. This form of rejection is mediated by preformed donor-specific anti-HLA antibodies present in the recipient at the time of transplantation. These antibodies target the pulmonary microvasculature, leading to complement- and neutrophil-mediated damage and widespread deposition of platelet/fibrin thrombi. Hyperacute rejection becomes clinically manifest within minutes to hours of establishing perfusion to the freshly implanted allograft. Intraoperatively, the allograft often appears dusky, mottled, and grossly edematous. Profound hypoxemia, hemodynamic instability, and dense opacification of the allograft(s) on chest x-ray are accompanying features. Four of five patients with this complication reported in the literature died; the one survivor was treated with a combination of plasmapheresis, anti-thymocyte globulin, and cyclophosphamide [74, 75]. Routine screening of all lung transplant candidates for preformed anti-HLA antibodies and either avoidance of donors with the targeted antigens or prospective cross-matching prior to transplantation have proven to be highly effective in minimizing the risk of hyperacute rejection.

Acute cellular rejection is a common alloimmune phenomenon, occurring in up to 75% of lung transplant recipients during the first post-transplant year but diminishing markedly in frequency beyond this time point [76]. It may be clinically and radiographically silent in up to 40% of cases, detected only by surveillance transbronchial lung biopsies. When clinically overt, symptoms include malaise, low-grade fever, dyspnea, and cough. Radiographic features are varied and include consolidation, ground-glass opacities, interstitial opacities, and pleural effusions (Fig. 21.6). A decline in oxygenation and/or spirometry values is often seen. Notably, similar clinical, radiographic, and physiologic features accompany bouts of infection; reliance on these features to make a diagnosis of acute rejection runs the risk of misdiagnosis and needless augmentation of immunosuppression. Rather, transbronchial lung biopsies should be obtained in all suspected cases, unless contraindicated by severe hypoxemia or marginal lung function. The reported sensitivity of transbronchial biopsies in the diagnosis of acute cellular rejection is 61–94% and the specificity exceeds 90% [77]. Diagnosis requires demonstration of perivascular lymphocytic infiltrates that in more severe cases spill over into the adjacent interstitium and alveolar spaces. Lymphocytic bronchiolitis may accompany the parenchymal involvement or may be an independent feature. Standard treatment for acute cellular rejection consists of a 3-day pulse of intravenous methylprednisolone, typically at a dose of 15 mg/kg. In most cases, this leads to clinical and radiographic improvement within several days. Anti-thymocyte globulin is employed in refractory cases.

Antibody-mediated rejection is a more recently recognized but still ill-defined form of acute rejection in lung transplant recipients [78]. In contrast to hyperacute rejection, in which donor-specific anti-HLA alloantibodies are present in the recipient at the time of transplantation, this process is mediated by antibodies that develop *de novo* after transplantation,



**Fig. 21.6** Chest CT demonstrating ground-glass opacities and interlobular septal thickening in the right lung allograft of a single lung transplant recipient. Transbronchial biopsies demonstrated acute cellular rejection

and it is therefore delayed in onset. The clinical presentation can be indistinguishable from acute cellular rejection or infection, with dyspnea, hypoxemia, and diffuse radiographic opacities. Hemoptysis, reflecting the presence of capillaritis, is an important clue but occurs in only 25% of cases [79]. Proposed diagnostic criteria for acute antibody-mediated rejection are (1) presence of circulating donor-specific anti-HLA antibodies, (2) histopathological evidence of capillaritis, and (3) detection of endothelial cell C4d deposition. Treatment with high-dose corticosteroids is effective in less than half of patients; the addition of plasmapheresis is beneficial in the majority of steroid-refractory cases [79]. Intravenous immunoglobulin and anti-CD20 monoclonal antibodies have also been used as adjunctive therapy.

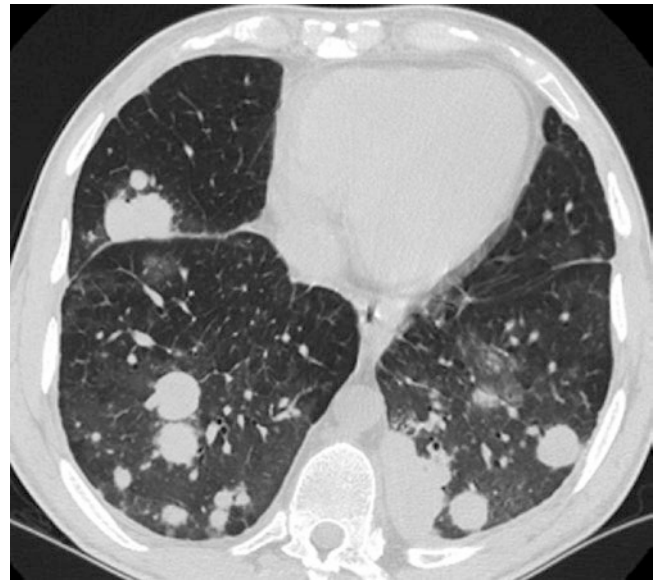
### Post-transplantation Lymphoproliferative Disorder (PTLD)

PTLD encompasses a spectrum of abnormal proliferative responses involving B cells in the majority of cases and ranging from benign hyperplasia to frank lymphomas. Epstein-Barr virus is responsible for driving B-cell proliferation in approximately 90% of cases. Proliferation occurs in an unregulated fashion due to absence of the normal cytotoxic T-cell response in the immunosuppressed patient. The proliferating B cells are of recipient origin in most cases. In contrast to B-cell-derived PTLT, the less commonly encountered T-cell neoplasms are predominantly EBV-negative.

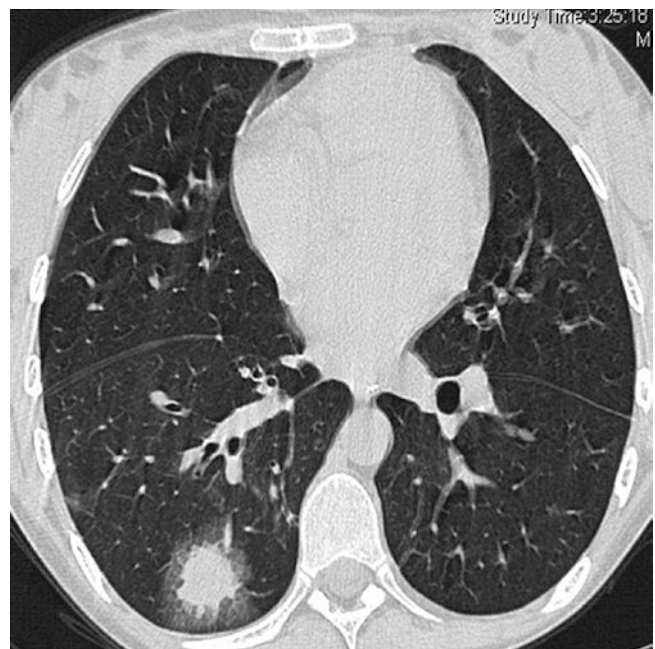
The prevalence of PTLT varies considerably among the different solid organ transplant populations. The prevalence is lowest in kidney recipients (1%); intermediate in liver (2–5%), heart (2–5%), and lung (2–8%) transplant recipients; and highest in bowel transplant recipients (up to 30%) [80, 81]. Across all organ types, EBV-naïve recipients who receive organs from EBV-positive donors are at greatest risk for developing PTLT [82]. The net state of immunosuppression and, in particular, the use of anti-lymphocyte antibodies, has also been implicated as a risk factor. A recent study of lung transplant recipients documented a decline in the incidence of PTLT at one large center in recent years; the authors speculate that this may relate to the shift from anti-lymphocyte antibodies to the less immunosuppressive interleukin-2 antagonists for induction [83].

The risk of PTLT is greatest in the first post-transplantation year. The development of this complication may be heralded by constitutional symptoms of fever, malaise, sweats, and weight loss. The particular pattern of organ involvement varies among the different solid organ transplant populations and includes lung, intestine, central nervous system, liver, kidney, and lymph nodes. Intrathoracic involvement occurs in the majority of cases of PTLT in lung and heart-lung transplant recipients. It occurs less commonly in other recipient popula-

tions, with reported frequencies of 16–32% in heart transplant recipients, 4.2–24% in liver recipients, and 4.4–15% in kidney recipients [81, 84]. Lung involvement typically manifests as one or multiple nodules or masses (Fig. 21.7). Occasionally, these opacities may have a surrounding halo, mimicking the radiographic appearance of invasive aspergillosis (Fig. 21.8). Airspace consolidation is a less common radiographic



**Fig. 21.7** Multiple lung nodules and masses due to PTLT in a bilateral lung transplant recipient



**Fig. 21.8** Halo sign (lung nodule with surrounding rim of ground glass) associated with PTLT. This finding is more commonly associated with invasive aspergillosis and invasive lung disease due to other opportunistic mold infections

manifestation, but one that similarly creates diagnostic confusion with infection. Intrathoracic lymphadenopathy may accompany parenchymal abnormalities or may occur in isolation. Pleural effusions are uncommon.

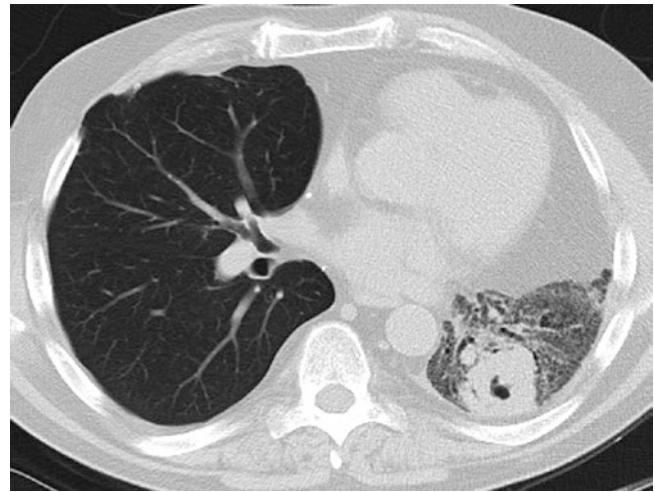
Definitive diagnosis of PTLD requires tissue biopsy; fine needle aspiration rarely yields sufficient material to establish a diagnosis with confidence. Pathological analysis should include flow cytometry to determine clonality, in situ hybridization or immunohistochemical staining to assess for the presence of EBV, and determination of CD-20 expression to assist in planning treatment. Determination of EBV viral load by quantitative polymerase chain reaction assays has been touted as an ancillary diagnostic tool. However, this technique is limited by a lack of consensus on the appropriate specimen source (serum, whole blood, or peripheral mononuclear cells) and by varying threshold value definitions of a positive result. As a consequence of this, performance characteristics of EBV viral load testing in the diagnosis of PTLD vary considerably in the published literature [85, 86].

The initial treatment of PTLD involves reduction in the magnitude of immunosuppression to allow partial reconstitution of host T cellular immunity against EBV. Regression of tumor ensues in up to three-quarters of patients, typically within 2–4 weeks [87]. While often successful, reduction in immunosuppression carries the attendant risk of precipitating acute or chronic allograft rejection, documented in 39% of patients in one series [87]. Factors predictive of failure to respond to reduced immunosuppression include elevated serum lactate dehydrogenase level, severe organ dysfunction (need for hemodialysis, mechanical ventilation, vasopressors (bilirubin >4 mg/dL), and multiple visceral sites of involvement [87].

For patients with CD-20-positive PTLD who fail to respond to reduced immunosuppression alone or have more aggressive tumors, administration of anti-CD20 monoclonal antibodies (rituximab) has emerged as the treatment of choice. This agent is generally well-tolerated and has been associated with remission rates of up to 60% and improved survival [88, 89]. Standard chemotherapy is reserved for patients with CD-20-negative PTLD, for rituximab failures, and for aggressive, life-threatening disease. While effective, chemotherapy is often poorly tolerated and associated with a significant risk of lethal infectious complications [89]. Antiviral therapy is not effective in the treatment of established PTLD, but prophylactic use of antiviral agents for other purposes has been associated with a reduced risk of subsequent development of PTLD.

### Lung Cancer (Heart and Lung Transplantation)

The reported incidence of lung cancer is 1.6–4.1% in heart transplant recipients and 2–4% in lung transplant recipients



**Fig. 21.9** Cavitary squamous cell carcinoma in the fibrotic native lung of a single lung transplant recipient

[90]. These rates are considerably higher than that reported in other solid organ recipient populations and in the general population. It is not clear, however, that these rates truly represent increased risk or simply reflect expected occurrence rates in populations with similar risk factors. Among lung transplant patients, the vast majority of reported cases involve the native lung of single lung transplant recipients with underlying chronic obstructive pulmonary disease or pulmonary fibrosis (Fig. 21.9), the majority of whom were former smokers. In one study that specifically examined the incidence by transplant type, lung cancer developed in 6.9% of single lung transplant recipients compared to none of the bilateral lung recipients [91]. Risk factors other than transplant type that were identified in this study were increasing age and >60 pack-year history of cigarette smoking. Rarely, lung cancer of donor origin has been transmitted to recipients via the allograft. Lung cancer in the transplant recipient often progresses at a rapid pace, potentially leading to initial confusion with an infectious process. Overall prognosis is poor but should not preclude attempts at curative resection in the minority of cases in which early stage disease is encountered.

### Sirolimus (mTOR Inhibitor) Pneumonitis

Sirolimus, also known as rapamycin, is used with varying frequency in different solid organ transplant populations as a component of the maintenance immunosuppressive regimen. Since its introduction into clinical practice, there have been numerous reports of interstitial pneumonitis developing in association with sirolimus [92–94]. The incidence of this complication remains poorly defined. Initial reports suggested that interstitial pneumonitis was largely a



**Fig. 21.10** Areas of dense consolidation due to sirolimus pneumonitis in the right lung allograft of a single lung transplant recipient

complication of excessive sirolimus blood concentrations, but more recent reports have documented cases in the setting of therapeutic drug levels. Approximately 50% of cases develop within the first 6 months after initiation of the drug. Onset is usually insidious, but acute and fulminant presentations have been described [95]. Common presenting symptoms include dyspnea, non-productive cough, and fever; hemoptysis is occasionally present. Radiographic abnormalities include bilateral interstitial infiltrates, alveolar consolidation, ground-glass opacities, and nodules (Fig. 21.10). Bronchoalveolar lavage reveals evidence of a lymphocytic alveolitis and, less commonly, of alveolar hemorrhage. Histological findings are diverse and include bronchiolitis obliterans with organizing pneumonia, interstitial lymphocytic infiltrates, alveolar hemorrhage, and non-necrotizing granulomas. Discontinuation of the drug typically leads to prompt clinical improvement while radiographic abnormalities may take several months to fully resolve. In more severe cases, high doses of corticosteroids have been administered, but the true efficacy of these agents remains uncertain.

## Conclusion

Multiple common disorders in transplantation patients are associated with radiographic lung infiltrates that can be confused with infectious pneumonia. While pneumonia is a serious complication in transplantation patients, leading to an appropriately high index of suspicion, accurate diagnosis of both infectious and non-infectious etiologies of lung infiltrates is essential to optimal treatment. The identification of

non-infectious etiologies of lung infiltrates can usually be made on the basis of clinical findings and imaging studies, but invasive studies are sometimes necessary.

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