Pulmonary Complications of Bone Marrow Transplantation

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Rodolfo M. Pascual, MD

INTRODUCTION

Bone marrow transplantation (BMT) is a rapidly evolving technology that offers the possibility of cure to many patients diagnosed with diseases that formerly had a very poor prognosis. When cells are collected from the peripheral blood rather than the marrow, the terms hematopoietic cell transplant and stem cell transplant are used. Although BMT is most often used to treat hematologic malignancies and diseases with a poor prognosis (eg, acute leukemia, chronic myelogenous leukemia, and aplastic anemia), it also has been used as salvage treatment after intensive chemotherapy for lymphoma, breast cancer, and a variety of other tumors. Patients with malignancy who undergo transplantation with a graft of their own cells (autologous) or a donor’s cells (allogeneic) receive pretreatment conditioning that subjects all organs, particularly the lungs, to a heavy dose of cytotoxic chemotherapeutic agents and sometimes radiation therapy. In addition, most patients approach transplantation immunocompromised to some degree because of underlying disease and prior chemotherapy. Allogeneic transplantation requires post-transplant immunosuppressive regimens to prevent graft rejection and hence predisposes these patients to infectious disease caused by typical and atypical bacteria, molds, yeasts, Pneumocystis carinii (PCP), and viruses.

Graft-versus-host disease (GVHD) causes substantial morbidity and mortality following BMT. GVHD frequently occurs in patients who undergo allogeneic transplantation even when the donor is a well-matched sibling and prophylactic immunosuppressive therapy is initiated. Acute GVHD presents as a rash, usually maculopapular, that can progress to a blistering form similar to toxic epidermal necrolysis. Acute GVHD typically involves the liver and gastrointestinal tract and sometimes leads to life-threatening complications. Therapy for acute GVHD includes steroids and other immunosuppressive agents, particularly those that suppress T-lymphocyte function. Although this complication usually is not associated with direct lung toxicity, it often leads to chronic GVHD, which is an important risk factor in several posttransplant pulmonary complications, including cytomegalovirus (CMV) pneumonitis, idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans organizing pneumonia (BOOP), and chronic airflow obstruction, often due to bronchiolitis obliterans. Pulmonary complications affect 40% to 60% of allogeneic BMT recipients and present considerable diagnostic and therapeutic challenges.

LATE NONINFECTIOUS PULMONARY COMPLICATIONS

CASE PATIENT
Initial Presentation and History

A 50-year-old man diagnosed with acute myelogenous leukemia undergoes allogeneic BMT with bone marrow donated by his HLA-matched sister. The transplantation is completed following a standard conditioning regimen consisting of high-dose cyclophosphamide, total body irradiation, and busulfan. Pretreatment with antithymocyte globulin and cyclosporine was used as prophylaxis for GVHD.

Bone marrow biopsy results demonstrate successful engraftment. At the same time, the patient develops a maculopapular rash on the neck, hands, and feet as well as mild diarrhea. A skin biopsy sample is consistent with acute GVHD. High-dose steroids are administered, and the rash and diarrhea resolve; the patient remains on maintenance prednisone. He has been taking trimethoprim-sulfamethoxazole (TMP-SMZ) since engraftment occurred. He does well for 4 months but then presents with a nonproductive cough, dyspnea with exertion, and low-grade fever (100°F).

Physical Examination

The patient appears to become short of breath with movement. The temperature is 100.3°F, pulse is 100 bpm, respiratory rate is 22 breaths/min, blood pressure is 122/88 mm Hg, and pulse oximetry shows an oxygen saturation of 91% on room air. Scattered crackles are
detected at the lung bases, and the heart and abdomen are normal. There is hyperpigmented, thickened skin over the neck and hands. A chest radiograph shows bilateral patchy infiltrates and ground glass opacities.

• What diagnoses should be considered?

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of pulmonary complications following BMT can be broadly categorized into infectious (Table 1) and noninfectious (Table 2) etiologies as well as by whether the complication occurs early or later (principally after engraftment) in the post-transplantation period. This patient has nonspecific clinical and radiographic findings (bilateral patchy infiltrates). However, because infectious pneumonia occurs in 20% to 25% of BMT recipients,2,3 infectious etiologies should be excluded before noninfectious etiologies are considered. In addition, many of the noninfectious entities are treated with immunosuppressive agents and corticosteroids; using these agents while infection is present would further impair the patient’s immunologic response and potentially exacerbate the infection.

This patient developed dyspnea, fever, and cough more than 100 days after engraftment, making community-acquired pneumonia a strong consideration. Potential pathogens include pneumococci, *Haemophilus* species, and *Legionella* species. Persistent deficiencies in immunity may predispose post-BMT patients to infection with *Pseudomonas* and other aerobic gram-negative bacilli. Immunosuppression is a direct consequence of both GVHD and the drugs used to treat it. Recurrent infections occur in nearly all patients who develop GVHD.

Viral pathogens are an important consideration once engraftment has occurred. CMV pneumonia is common and is associated with a poor outcome.4 The other viral and mycobacterial infections listed in Table 1 must also be considered. A seasonal pattern is typical for some viruses, such as respiratory syncytial virus (RSV). IPS and BOOP would be the most likely noninfectious etiologies.

• What diagnostic tests should be ordered?

Because the risk of an opportunistic infection following BMT is high and adequate cultures generally cannot be obtained noninvasively, bronchoscopy and culture of a bronchoalveolar lavage (BAL) or biopsy specimen are often the initial diagnostic studies. The diagnostic yield of a single BAL and culture is less than 50%.5 A second culture of a BAL specimen can be done after 1 to 2 weeks to increase diagnostic yield in lieu of the alternative—open lung biopsy. Surgical biopsy offers the advantage of assisting with the diagnosis of noninfectious causes, and this

### Table 1. Infectious Pulmonary Complications of Bone Marrow Transplantation

<table>
<thead>
<tr>
<th>Complication</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>Clinical findings include fever and focal/lobar consolidation</td>
</tr>
<tr>
<td>Invasive fungal infection</td>
<td>Nodular and/or persistent infiltrates are seen; prolonged neutropenia is major risk factor; usually aspergillus species</td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em> infection</td>
<td>Unusual if prophylaxis used; TMP-SMZ is most efficacious</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Reactivation, brain uniformly affected, associated with GVHD</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Rare if acyclovir is used for prophylaxis</td>
</tr>
<tr>
<td><strong>Postengraftment</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>Pathogens are typical community-acquired organisms but also <em>Staphylococcus aureus</em>, <em>Legionella</em>, <em>Pseudomonas</em>, and other gram-negative bacilli</td>
</tr>
<tr>
<td>Cyto megalovirus</td>
<td>Later complication; seronegative recipient with seropositive donor confers highest risk</td>
</tr>
<tr>
<td>Herpes viruses</td>
<td>Human herpes viruses 6 and 7 are implicated; acyclovir is used in seropositive recipients; varicella zoster virus is uncommon</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>Ranges from laryngitis (croup-like) to bronchiolitis and pneumonia (often fatal)</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Peak incidence is January–March; ribavirin is used, especially in children</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Affects airway and causes pneumonia; gastrointestinal symptoms are prominent</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Pathogens are <em>Mycobacterium tuberculosis</em>, especially in endemic areas, and <em>Mycobacterium haemophilum</em></td>
</tr>
</tbody>
</table>

GVHD = graft-versus-host disease; TMP-SMZ = trimethoprim-sulfamethoxazole.
procedure should be considered when there is significant respiratory failure.

**CASE: HOSPITAL ADMISSION AND LABORATORY EVALUATION**

Laboratory test results demonstrate mild anemia, a normal leukocyte count and platelet count, and a normal creatinine level. The serum alkaline phosphatase and total bilirubin level are mildly elevated. Arterial blood gas analysis shows a pH of 7.48, PaCO₂ of 33 mm Hg, and PaO₂ of 64 mm Hg on room air. The most recent bone marrow examination does not show evidence of leukemia. A computed tomography (CT) scan of the chest demonstrates scattered ground glass opacity and areas of consolidation. Pulmonary function tests show a moderate restrictive defect accompanied by a moderate reduction in diffusion capacity. There is no bronchial obstruction. Cultures of BAL specimens for fungal, viral, and bacterial organisms are negative. PCP is excluded with special stains, and a CMV blood antigenemia assay is negative. A specimen obtained via a video-assisted thoracoscopy and biopsy procedure is examined by special stains for virus, fungi, PCP, and bacteria; all stains are negative. Histopathology shows a chronic mononuclear and interstitial pneumonitis with evidence of diffuse alveolar damage, supporting the diagnosis of IPS. Methylprednisolone is started, but the patient develops progressive respiratory failure and dies 10 days later.

- **What is IPS?**

**IDIOPATHIC PNEUMONIA SYNDROME**

This case illustrates many of the challenges presented by post-BMT noninfectious pulmonary complications. Fever and other findings consistent with infectious pneumonia are common during the early posttransplant period. Because infection is common and clinical and radiographic findings are often nonspecific, the general approach to management of post-BMT patients is to begin therapy for bacterial infection and sometimes viral and fungal pathogens while undertaking a careful search for a pathogen. Late pneumonias, or those that occur after discharge from the hospital, affect more than 25% of patients who undergo BMT. They are more common in allogeneic than in autologous transplantation and are especially prevalent when unrelated or mismatched related donors are employed. Presumed bacterial and culture-proven bacterial pneumonias comprise more than half of late pneumonias. Fungal pneumonias, mostly caused by aspergillus species, are important late infections and are associated with an especially poor prognosis.

IPS is probably a heterogeneous group of disorders that affects 10% to 15% of all patients after allogeneic BMT. A National Institutes of Health working group proposed a case definition of IPS as “widespread alveolar injury without evidence of active lower respiratory tract infection after transplantation.” Alveolar injury is usually characterized by multifocal infiltrates seen on chest radiograph or CT scan with an increase in the alveolararterial oxygen gradient or new restrictive findings on pulmonary function testing. Often, a presumptive diagnosis is made based on these findings if no pathogen is identified by an invasive culture (eg, BAL). IPS is believed to result from a combination of insults to the lungs, including toxicity from chemotherapy and radiation, cell-mediated immunologic injury, and injury from unidentified infection. Risk factors for IPS include use of a more aggressive or “myeloablative” conditioning regimen and use of higher amounts of total body radiation. Increasing age and acute GVHD have been identified as risk factors in multiple series. IPS also seems to

<table>
<thead>
<tr>
<th>Complication</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Pulmonary edema</td>
<td>Usually early, multifactorial</td>
</tr>
<tr>
<td>Idiopathic pneumonia syndrome</td>
<td>Occurs after engraftment; associated with GVHD</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>Early complication that is more common with autologous graft</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>Late complication; GVHD and viral infections increase risk</td>
</tr>
<tr>
<td>Bronchiolitis obliterans organizing pneumonia</td>
<td>Associated with cytomegalovirus and GVHD; responds to steroids</td>
</tr>
<tr>
<td>Secondary cancers</td>
<td>Lymphoma, especially associated with Epstein-Barr virus</td>
</tr>
<tr>
<td>Relapse of primary cancer with lung involvement</td>
<td>Probably caused by chemoradiation-induced vascular injury</td>
</tr>
<tr>
<td>Pulmonary alveolar proteinosis</td>
<td>Rare</td>
</tr>
</tbody>
</table>

GVHD = graft-versus-host disease.

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4 Hospital Physician Board Review Manual
be more common in patients who undergo BMT due to malignancy than in those with nonmalignant disease.6 Mortality associated with IPS is greater than 50%, and is greatly increased once mechanical ventilation is required.8 Corticosteroids are usually administered, but they have not been shown to alter the outcome of IPS.

- What are the effects of BMT on pulmonary function tests?

PULMONARY FUNCTION TESTING

Airflow obstruction or a reduced forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio is common following BMT,9 and it may affect more than 25% of patients.10 Airflow obstruction may be asymptomatic or may present with a rapidly progressive course leading to death, as in severe bronchiolitis obliterans. It is associated with GVHD and increased mortality.11 Post-BMT airflow obstruction is more likely to result in morbidity when lung function is abnormal prior to transplant; therefore, baseline pulmonary function tests are often obtained prior to transplantation. Restrictive lung disease, defined by a pattern of reduced lung volume, is also common in this population.10 Attributable factors include lung injury from chemotherapy or radiation, IPS, and scarring from repeated infections. Finally, the carbon monoxide diffusion capacity (DLCO) is frequently abnormal in these patients, and it may be reduced in up to 50% of patients after transplantation. Although all posttransplant pulmonary complications can reduce diffusion capacity, some that deserve special mention include pulmonary alveolar proteinosis, diffuse alveolar hemorrhage, and pulmonary veno-occlusive disease.

EARLY NONINFECTIOUS PULMONARY COMPLICATIONS

CASE PATIENT Initial Presentation and History

A 38-year-old woman with metastatic breast cancer seeks medical attention because of hip pain. A plain radiograph demonstrated a lytic lesion in the femoral neck, and a bone scan was suggestive of multiple metastatic lesions. The patient opts to be enrolled in a protocol comparing the efficacy of high-dose chemotherapy followed by autologous BMT to conventional chemotherapy. She is randomized to the high-dose arm with BMT. She undergoes marrow harvesting and her cells are washed and then cryopreserved. She then receives high-dose cyclophosphamide, carboplatin, and thiotepa. She develops pancytopenia and several days later undergoes autologous BMT. On day 4 post-transplant, she develops a fever to 101°F with chills, cough, and dyspnea.

Physical Examination

The patient does not have chest pain and the cough is nonproductive. She complains of a sore throat, loose stools, and some dysphagia; her bone pain has improved since admission. The respiratory rate is 24 breath/min, blood pressure is 136/69 mm Hg, pulse is 125 bpm, and the oxygen saturation is 93% while the patient is breathing from a mask (FiO2 50%). The skin is warm and free of rash except for a few petechiae. There is moderate mucositis in the oropharynx. On auscultation of the chest, the lungs are clear, but there are diminished breath sounds at the bases. There are some intercostal retractions, and the breaths are rapid and shallow. The abdomen is soft with mild diffuse tenderness. The remainder of the physical examination is normal.

- What diagnoses should be considered?

DIFFERENTIAL DIAGNOSIS

This patient has an early pulmonary complication. Many of the early pulmonary complications that occur in autologous and allogeneic BMT are the same (Tables 1 and 2). High-dose conditioning chemotherapy with its attendant risk of lung injury and profound immunosuppression is used in both types of grafts. Most patients who receive an autograft have an advanced cancer and hence have variable degrees of immunosuppression prior to transplantation. Significant radiation exposure of lung tissue can occur. Respiratory infections in the first 2 posttransplant weeks usually are caused by bacteria or fungi and are especially prominent while there is neutropenia. This patient would be expected to have neutropenia this early in the course. Bacterial pneumonias often are due to pneumococci, streptococci, staphylococci, and gram-negative bacilli. Aspergillus is the most common fungal pathogen, while Candida species and endemic fungi occur less frequently.3,5

Several common noninfectious causes of respiratory failure should be considered in this patient. Pulmonary edema following BMT is common and likely multifactorial in origin. It may be part of a systemic capillary leak syndrome, or it may result from the use of high doses of potentially cardiotoxic agents such as cyclophosphamide during pretransplant conditioning. Anthracyclines such as adriamycin are particularly cardiotoxic. In
addition, many patients have cardiac dysfunction from prior chemotherapy. An echocardiogram may exclude significant myocardial dysfunction. Pulmonary edema may be prevented by careful attention to volume status and the judicious use of fluids and diuretics. A spectrum of lung injury due to chemotherapy may be present, with severe injury presenting as the acute respiratory distress syndrome (ARDS). ARDS, especially in its early stages, can be indistinguishable from pulmonary edema; the pathologic correlate would be diffuse alveolar damage on biopsy. An aspiration pneumonitis should be considered because patients often have mucositis and impaired swallowing function following BMT. This entity may be difficult to distinguish from ARDS or cardiogenic pulmonary edema. Finally, diffuse alveolar hemorrhage (DAH) is seen with autologous transplantation, usually during the first 2 weeks post-transplant. Respiratory failure may ensue rapidly, and mortality is high, especially if mechanical ventilation is required.

CASE: LABORATORY EVALUATION AND HOSPITAL COURSE

A complete blood count reveals a platelet count of 18,000/mm³, white blood cell (WBC) count of 700/mm³, and a hematocrit of 27% (was 33% on the prior day). A chest radiograph shows patchy airspace opacities without pleural effusion. A transthoracic echocardiogram shows normal left ventricular systolic and diastolic function and normal valvular flow profiles. Blood and urine cultures are negative after 48 hours. Because of the presence of fever, cough, and infiltrates, the patient is begun on broad-spectrum antibiotics. Bronchoscopy with BAL shows a progressively bloodier return; very few leukocytes and no organisms are seen on Gram stain and special stains for fungi. The patient is promptly begun on methylprednisolone 500 mg/day for DAH, with clinical improvement seen by day 3 of treatment. Prednisone is then utilized and tapered over 14 days, and there is continued radiographic improvement. She is eventually discharged from the hospital.

- How is the diagnosis of DAH made?
- What treatment is used for DAH?

DIFFUSE ALVEOLAR HEMORRHAGE

Interestingly, hemoptysis occurs in a minority of patients with DAH, and bronchoscopy is often required for diagnosis. The classic finding is a progressively bloodier return on BAL in the absence of an infectious etiology (bacterial and fungal infections can precipitate hemorrhage). BAL typically involves the serial installation and removal of aliquots of saline using a wedged scope. Aliquots instilled later in the procedure contain a higher proportion of fluid from alveoli, while aliquots instilled earlier represent washings from more proximal conducting airways. A progressively bloodier return indicates hemorrhage at the level of the alveolar spaces. BAL provides very good specimens for culture, which can be used to diagnose a fungal or bacterial pneumonia. Although not ruled out in this patient, infection was less likely because cultures from multiple sites were negative. DAH can occur in the setting of congestive heart failure and pulmonary edema. Edema due to cardiac dysfunction was excluded by the echocardiogram.

Although the DLCO is frequently reduced following BMT, it may actually increase in the presence of hemorrhage because the alveolar blood acts as a sink for carbon monoxide. Early congestive heart failure without pulmonary edema can have a similar effect. Measurement of DLCO has been used to follow recurrent pulmonary hemorrhage and might be useful in the less severely affected outpatient. In sicker patients who are likely to have anemia (as in this patient), measurement of DLCO is less useful.

The treatment for DAH is high-dose corticosteroids, usually beginning with 500 to 1000 mg/day of methylprednisolone or the equivalent given for several days, followed by a prednisone taper. Because early steroids are felt to confer the greatest benefit and because of the high incidence of infection in this population, early bronchoscopy and lavage are often performed.
GVHD. Toxoplasmosis usually manifests in the brain, can occur after engraftment and is often associated with whenever BAL or biopsy is performed. Toxoplasmosis is greatly reduced when appropriate prophylaxis is started upon transplantation serologic status should be done when a viral respiratory pathogen is suspected. Knowledge of the patient’s serologic studies can be helpful in estimating the risk of CMV, although seropositive status does not exclude CMV from the differential diagnosis.

Physical Examination

The patient appears ill, with diaphoresis and apparent respiratory distress. His temperature is 100.8°F, pulse is 120 bpm, respiratory rate is 26 breaths/min, and blood pressure is 165/92 mm Hg. Pulse oximetry reveals a 93% oxygen saturation on 50% inspired oxygen. There is some dry blood in the posterior pharynx but no lesions. The heart sounds are normal. There are diffuse expiratory wheezes and scattered crackles on chest auscultation. The patient also has a diffuse pink maculopapular rash on his trunk and extremities.

• What infectious causes should be considered in the differential diagnosis?

POTENTIAL PATHOGENS

The patient underwent allogeneic transplantation, which is associated with a higher risk for infectious complications compared to autologous transplantation. Bacterial, viral, fungal, and PCP infection must be considered. Bacterial infections are more prominent prior to engraftment, and fungal infections such as aspergillosis are more common in the early neutropenic phase after transplantation. Disease recurrence resulting in neutropenia is a consideration because the patient required more aggressive immunosuppression after he developed GVHD. Viral pathogens are a major cause of morbidity and mortality in the postengraftment period.

PCP and Toxoplasma

The incidence of illness due to PCP infection is dramatically reduced when appropriate prophylaxis is taken. TMP-SMZ is the first-line agent, but because it may cause bone marrow suppression, alternative agents are often used (eg, dapsone and aerosolized pentamidine). Randomized controlled trials comparing these agents in BMT patients have not been performed, but some data suggest that TMP-SMZ is superior. PCP cannot be ruled out on clinical grounds, and usually a respiratory specimen is examined for evidence of PCP whenever BAL or biopsy is performed. Toxoplasmosis can occur after engraftment and is often associated with GVHD. Toxoplasmosis usually manifests in the brain, and the heart and lungs may also be affected; however, it is not a common cause of respiratory failure. Atypical mycobacteria and Mycobacterium tuberculosis can cause pneumonia in transplant patients but are uncommon causes of respiratory failure in the United States.

Cytomegalovirus

CMV pneumonitis does not occur until after engraftment, with a typical timeframe of approximately 6 weeks after transplantation (although it may occur after 1 year or as early as 2 weeks posttransplant). Risk factors for CMV infection include the presence of GVHD and long-term steroid use. The risk of CMV is greatest when a seronegative recipient is transplanted with marrow from a seropositive donor; however, CMV pneumonitis can occur in any recipient. A careful examination of the patient’s pretransplantation serologic status should be done when a viral respiratory pathogen is suspected. Knowledge of the patient’s serologic studies can be helpful in estimating the risk of CMV, although seropositive status does not exclude CMV from the differential diagnosis.

Because the chest radiograph findings can be subtle, especially with less severe disease, the clinical index of suspicion for CMV pneumonitis should remain high in any patient with cough and dyspnea in the postengraftment period, even if the radiograph is unimpressive. CT scan offers superior sensitivity compared with plain chest radiograph and usually shows prominent interstitial markings, fine nodules, and ground glass opacities. Studies have shown that universal prophylaxis with ganciclovir started upon transplantation reduces the incidence of CMV; however, ganciclovir therapy is associated with prolonged neutropenia. A CMV antigenemia assay of blood is widely employed at transplant centers, and if significant levels of antigen are detected, prophylaxis is usually initiated to prevent disseminated disease and pneumonitis. In some centers, this test is performed weekly to identify CMV disease early. Isolation of CMV from other sites may indicate shedding and increases the chance that CMV is a pathogen. BAL or biopsy is usually needed to make a definitive diagnosis. A specific diagnosis is often sought because ganciclovir, the first-line agent, frequently causes bone marrow suppression. A diagnosis can be made with a culture, but this process is slow. Fortunately, the shell-vial assay allows a diagnosis to be made within 24 hours and is widely available at transplant centers.

Other Viruses

The incidence of herpes simplex virus (HSV) pneumonia is greatly reduced by prophylaxis with acyclovir or an equivalent agent, and these agents are often given in seropositive individuals. Parainfluenza, depending on
the strain, can cause laryngotracheobronchitis (croup) and/or bronchiolitis with pneumonia. Because infection of the upper respiratory tract usually occurs first, a complete virus culture should be performed on a nasopharyngeal sample. Respiratory failure caused by para-influenza is almost always fatal; ribavirin can be administered, but data supporting its efficacy are lacking. Similarly, influenza viruses are more likely to cause severe disease in allogeneic transplant recipients posten- graftment and often cause death once respiratory failure occurs. RSV is often fatal and should also be considered in transplant patients who demonstrate diffuse infiltrates on radiograph. Rapid tests and cultures of respiratory tract secretions can be used to identify RSV, and this diagnosis should be sought especially during the peak season (mid-late winter). Some data suggest that ribavirin can be effective if given early. Adenovirus infection affects up to 5% of patients after BMT and may cause fatal pneumonia; it may affect any part of the respiratory tract. In contrast to the other viruses, adenovirus can affect the bladder (cystitis) and gastrointestinal tract (enteritis) and can be identified by culture. Successful treatment using α-interferon, ribavirin, and IgG to adenovirus has been reported, although clinical trial data are lacking.

• What noninfectious causes should be considered in this patient?

NONINFECTIOUS CAUSES

Several noninfectious causes of respiratory failure must be mentioned here. Pulmonary edema secondary to congestive heart failure or renal failure should be considered because chemotherapy given during the conditioning phase may cause myocardial or renal injury. DAH remains a consideration even though it is less common in allogeneic BMT and usually occurs earlier in the course. Diffuse alveolar damage (DAD) may manifest as respiratory failure with diffuse infiltrates and hypoxia and in its severe form as ARDS. DAD is a stereotypical response to lung injury and can be caused by infections, radiation, or chemotherapy. DAD/ARDS may be a manifestation of a primary lung infection or may be caused by sepsis from another cause. BOOP should be considered because it is associated with GVHD and CMV pneumonitis; however, BOOP is less likely in this case because it usually responds to steroids and the patient has been taking prednisone. It can occur during the tapering of steroid therapy, however. Finally, IPS is a possibility, although it usually occurs later after transplantation and is a diagnosis of exclusion that is considered once infections have been ruled out.

CASE: LABORATORY EVALUATION AND HOSPITAL COURSE

The peripheral blood count shows a WBC count of 4400/mm³, hemoglobin of 9.8 g/dL, and platelet count of 20,000/mm³. The serum creatinine level is 1.9 mg/dL and unchanged since the patient’s recent discharge. Liver function tests are mildly abnormal, with aspartate aminotransferase and alanine aminotransferase levels elevated 2 or 3 times control and an alkaline phosphatase level elevated 2 times control. Urinalysis results are unremarkable. A chest radiograph (Figure 1A) demonstrates a diffuse increase in interstitial markings when compared to the baseline radiograph (Figure 1B). A cardiac echocardiogram shows normal to hyperdynamic left ventricular function and is unchanged compared with an echocardiogram obtained at the recent admission. A bronchoscopy with BAL and protected specimen brushing are done. There is a moderate amount of bleeding during the procedure with accompanying oxygen desaturation. Approximately 24 hours after the procedure, the patient’s respiratory distress worsens with hypoxemic respiratory failure; the patient is placed on mechanical ventilation. Blood and urine cultures are negative, while the BAL sample is positive for CMV. A CMV blood antigenemia assay is also positive.

• What therapy is used to treat CMV pneumonitis?

CMV is the most important viral pathogen in the posttransplant period. Morbidity and mortality associated with CMV infection have been substantially reduced by combination therapy with intravenous immunoglobulin (IVIG) and ganciclovir. Interestingly, the fact that IVIG has been shown to be effective therapy for CMV infection suggests that the pathogenesis of CMV may be related to other factors in addition to the cytotoxic effects of the virus.

• What risks are associated with bronchoscopy procedures in BMT patients?

Common minor complications of bronchoscopy include transient bleeding and oxygen desaturation. Many bronchoscopy procedures are performed during the early phase after transplantation, and nearly all of these patients have thrombocytopenia. Respiratory failure necessitating mechanical ventilation and death are rare. BAL and bronchial brushings are commonly done; BAL appears to be safer and less likely to result in bleeding than brushing. The diagnostic yield from bronchoscopy is surprisingly poor, partly because many patients who undergo the procedure are being treated with antibiotics at the time of the procedure. Nevertheless, bronchoscopy
is a useful tool in this setting, although the increased hazards require careful patient selection and preprocedure preparation. Suggestions for reducing bleeding complications are shown in Table 3.

**CASE: TREATMENT AND RESOLUTION**

The patient is begun on intravenous ganciclovir and IVIG. After several days, the patient improves and is extubated. All other cultures are negative and the patient is eventually discharged on low-dose oxygen.

**EARLY INFECTIOUS PULMONARY COMPLICATIONS**

**CASE PATIENT**

**Initial Presentation and History**

A previously healthy 63-year-old man presents to his physician complaining of fatigue, vague abdominal discomfort, and an enlarging abdominal mass. The physical examination is remarkable for a weight loss of 20% during a 3-month period, cervical lymphadenopathy, and a firm, immovable abdominal mass that is nontender and nonpulsatile. CT reveals diffuse bulky lymphadenopathy in the abdomen with some mediastinal involvement. A subsequent biopsy shows features consistent with diffuse large B-cell lymphoma (a type of non-Hodgkin’s lymphoma). The bone marrow biopsy shows no marrow infiltration, and the cerebrospinal fluid examination is normal. The patient undergoes radiation localized to the bulky abdominal disease and receives several cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone. Complete remission lasts for a few months, but surveillance CT scanning shows recurrent abdominal disease. He is referred for salvage therapy.

The patient opts to receive high-dose chemotherapy followed by autologous stem-cell transplantation. The patient receives ifosfamide, carboplatin, and etoposide followed by infusion of peripheral blood stem cells. These cells had been collected by leukopheresis prior to the consolidation phase. Neutropenia ensues and the patient does well for 10 days but then develops fever and cough with scant hemoptysis. He also notes vague chest discomfort that is worse with movement, cough, and inspiration. He is started on broad-spectrum antibacterial therapy. Blood and sputum cultures are negative for bacteria.

**Physical Examination**

The patient appears tired but is not in acute distress. His temperature has been greater than 102°F for 5 consecutive days. Blood pressure is 136/62 mm Hg, pulse is 90 bpm, and respirations are 18 breaths/min. Pulse oximetry shows a saturation of 92% on ambient air. The oropharynx shows mild mucositis. The heart examination is normal. There are some crackles at the left lung base but the lungs are mostly clear. The abdomen is nontender with a soft, nontender abdominal mass that is somewhat smaller than it had been on admission.

• **What is the differential diagnosis?**

**DIFFERENTIAL DIAGNOSIS**

This patient recently underwent transplantation, and engraftment has not yet occurred. Both infectious and noninfectious pulmonary complications causing...
respiratory failure may occur in an autologous hematopoietic cell recipient. As with allogeneic recipients, mortality is high if respiratory failure that requires mechanical ventilation occurs. Pulmonary edema is a potential early noninfectious cause; it can be cardiogenic in origin or due to DAD from chemotherapy or sepsis from a nonpulmonary source. DAH usually occurs early in the posttransplantation course, while BOOP and IPS usually occur later. As mentioned earlier, IPS is typically associated with allogeneic transplantation (especially if GVHD is present), but can occur in the setting of autologous hematopoietic cell transplantation.

A viral etiology is unlikely because engraftment has not yet occurred. HSV pneumonia notably may occur during the early phase but has become much less common since antibody screening and routine prophylaxis with acyclovir have become commonplace. When HSV is found, there is usually evident mucocutaneous disease. The most likely pathogens in this patient are bacteria and fungi, and the focal nature of the lung examination is consistent with this. However, it should be remembered that the physical examination and noninvasive laboratory findings are usually nonspecific after BMT. Bacterial infections often are due to gram-negative bacteria, staphylococci, and streptococci species. Since this patient has been hospitalized for some time, resistant hospital-acquired organisms like methicillin-resistant *S. aureus* and resistant gram-negative bacteria become more likely. Even resistant streptococcus pneumoniae may be considered. Other bacterial pathogens that have been reported include *Legionella*, which can occur during hospital outbreaks, and *Nocardia*, which typically presents as one or more lung nodules that may cavitate.

Aspergillus is the most common fungal pathogen reported in case series, and it usually occurs during the first 3 months after transplantation. Other notable fungi include *Candida* species, mucor (*zygomycosis*), *Histoplasma* species, and *Coccidioides immitis*. Mucor is a particularly aggressive mold that can cause rapidly fatal rhinocerebral disease and/or pneumonia with or without cavitations. Mucor also is much less susceptible to antifungals than is aspergillus; tissue resection is often required to achieve control. The most important risk factor for invasive fungal disease is prolonged neutropenia. Treatment with steroids and broad-spectrum antibiotics and the loss of mucosal integrity manifesting as mucositis have also been suggested to be risk factors for invasive fungal disease. The antemortem identification of fungal pathogens is difficult as they are ubiquitous in nature and are frequent laboratory contaminants.

### Table 3. Suggested Preparations for Coagulopathy Prior to Bronchoscopy

<table>
<thead>
<tr>
<th>Situation</th>
<th>Suggested Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td></td>
</tr>
<tr>
<td>&lt; 10,000/mm³</td>
<td>Bronchoscopy contraindicated</td>
</tr>
<tr>
<td>not responsive to transfusion</td>
<td></td>
</tr>
<tr>
<td>&lt; 10,000/mm³ responsive to transfusion</td>
<td>Transfuse prior to bronchoscopy</td>
</tr>
<tr>
<td></td>
<td>Avoid transbronchial lung biopsy</td>
</tr>
<tr>
<td></td>
<td>Avoid endobronchial brush biopsy</td>
</tr>
<tr>
<td>10,000–50,000/mm³</td>
<td>Proceed with BAL</td>
</tr>
<tr>
<td></td>
<td>Avoid transbronchial lung biopsy</td>
</tr>
<tr>
<td></td>
<td>Avoid endobronchial brush biopsy</td>
</tr>
<tr>
<td></td>
<td>Consider transoral route</td>
</tr>
<tr>
<td>&gt; 50,000/mm³</td>
<td>Proceed with BAL</td>
</tr>
<tr>
<td></td>
<td>Proceed with endobronchial brush biopsy</td>
</tr>
<tr>
<td></td>
<td>Exercise caution with transbronchial lung biopsy</td>
</tr>
<tr>
<td>Normal (&gt; 140,000/mm³)</td>
<td>Proceed with BAL, endobronchial, or transbronchial lung biopsy</td>
</tr>
<tr>
<td>Mild coagulopathy (ie, INR &lt; 2.0)</td>
<td>Proceed with BAL</td>
</tr>
<tr>
<td></td>
<td>Avoid transbronchial lung biopsy</td>
</tr>
<tr>
<td></td>
<td>Avoid endobronchial brush biopsy</td>
</tr>
<tr>
<td></td>
<td>Consider transoral route</td>
</tr>
<tr>
<td>Severe coagulopathy (ie, INR ≥ 2.0)</td>
<td>Correct to near normal prior to procedure</td>
</tr>
<tr>
<td></td>
<td>Avoid transbronchial lung biopsy</td>
</tr>
<tr>
<td></td>
<td>Avoid endobronchial brush biopsy</td>
</tr>
<tr>
<td></td>
<td>Consider transoral route</td>
</tr>
</tbody>
</table>

Note: These are only suggested parameters; estimation of risks and benefits should be individualized for each patient.

*BAL = bronchoalveolar lavage; INR = international normalized ratio.*

CT scanning is particularly helpful when fungal infection is suspected as there are nodules and masses in more than two thirds of cases of invasive fungal disease. In contrast to the innumerable tiny nodules usually seen with viral or mycobacterial disease, the nodules of invasive fungal disease are usually less numerous (< 10) and larger. The nodules typically have a peripheral distribution, are round, and may be surrounded by a rim of ground glass opacity (the halo sign). The halo sign is felt to indicate vasogenic edema due to vascular invasion and is highly suggestive of invasive fungal disease. Cavitary disease (air-crescent sign) due to aspergillus infection, while common in the immunocompetent host, is rare in the post-BMT patient.
The gold standard diagnostic test for invasive aspergillosis is a tissue biopsy with the finding of hyphae invading lung tissue, particularly blood vessels. This test requires a large tissue biopsy or resection specimen. Because of the hazards associated with lung biopsy in this population, the finding of mold in one or more culture specimens taken from a patient with compatible clinical and radiographic findings is often considered presumptive evidence of invasive fungal infection and sufficient reason to continue treatment. BAL is usually the first test performed when an invasive culture is obtained, and it is relatively safe.

**CASE: LABORATORY EVALUATION AND HOSPITAL COURSE**

Because of persistent fever, a CT scan of the chest is performed (Figure 2). A hazy rim of ground glass opacity surrounding a discrete nodule is noted. Broad-spectrum antibiotics are continued and the antifungal drug voriconazole is started. Bronchoscopy is planned and preprocedure plans include platelet count support with transfusions. BAL reveals a progressively bloodier return. A Gram-stain specimen and acid-fast smears are negative, and no fungal elements are seen. After 5 days of growth, a mold is observed and is eventually identified as *Aspergillus terreus*. On antifungal therapy, the nodules remain stable in size. Engraftment does not occur and profound neutropenia and thrombocytopenia persist for several weeks before the patient dies from an intracranial hemorrhage.

- **What aspergillus species cause pulmonary disease in BMT patients?**
- **What treatment is available?**

**ASPERGILLUS INFECTION**

The most common species of aspergillus that invades tissue is *A. fumigatus*. *A. flavus*, *A. niger*, and *A. terreus* are other important pathogens. These mold spores are ubiquitous in nature and are frequently inhaled; the low frequency of infection reflects the efficacy of intact immune defenses in normal hosts. Normally, resident alveolar macrophages kill these spores, but with repeated bouts of chemotherapy the number and function of macrophages are depleted. Neutrophils recruited to alveoli can damage spores as well, thus explaining why neutropenia is such a powerful risk factor. When hyphae invade tissue they typically cause vessel thrombosis and tissue infarction. The usual presentation of fungal infection in immunocompromised hosts is febrile neutropenia that may not respond to amphotericin, which is typically given if fever persists on antibacterial therapy.

For many years amphotericin was the only reliable agent for treating aspergillus infection. However, it is associated with predictable and dose-related renal toxicity, thus limiting its efficacy in many cases. Voriconazole is a new antifungal azole compound with a better side effect profile. It has good activity against all important aspergillus species and is now used widely. Some reports suggest that it may be superior to the previous standard amphotericin.22

Finally, this case illustrates the point that DAH is a diagnosis of exclusion. A progressively bloodier return was noted on BAL, but this finding is not specific as it can be found with pulmonary edema, DAD, and infection, particularly with organisms that invade vessels (eg, molds). This is important because steroids are used for...
DAH and would further impair host defenses to molds and bacteria.

REFERENCES