Pulmonary Infection in a Patient After Stem Cell Transplantation

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A 69-year-old male with a past medical history of hypertension, diabetes mellitus, and acute myelogenous leukemia (AML) who underwent allogeneic hematopoietic stem cell transplantation (HSCT) presented with recurrent fever and cough.

The patient had undergone allogeneic HSCT from a matched unrelated donor 17 months previously, conditioned by fludarabine, melphalan, and alemtuzumab. His posttransplant course was complicated by graft versus host disease and multiple central venous catheter infections with coagulase-negative *Staphylococcus* spp., vancomycin-resistant *Enterococcus*, *Lactobacillus*, and alpha-hemolytic *Streptococcus*. During his initial course, he also developed a nodular pneumonia, and the subsequent workup included a bronchoscopy that was nondiagnostic. The pneumonia resolved with empiric posaconazole treatment. Sixteen months after the transplant, the patient developed fatigue, low-grade fevers, and cough. Chest x-ray (CXR) showed a new, left lower lobe infiltrate. A sputum culture then grew fluoroquinolone-susceptible *Pseudomonas*, and the Oncology Service subsequently discharged the patient home on moxifloxacin alone. Three weeks later, he presented again with recurrent cough and fever and was readmitted. A CXR showed a new, right lower lobe infiltrate.

The patient had a remote history of symptomatic bradycardia for which he had undergone pacemaker placement. He was a former cigarette smoker (40 pack-years), but he denied any intravenous drug use. He was a retired automobile mechanic and lived at home with his wife and a dog. He had traveled recently to Las Vegas for a short trip to visit casinos.

His medications on admission included acyclovir, fluconazole, and dapsone prophylaxis. He previously had an adverse reaction to imipenem, which caused a rash, and to voriconazole, which caused visual hallucinations.

On physical examination, he was alert and oriented. His temperature was 100.5 °F, heart rate 86 beats per minute, blood pressure 134/94 mmHg, respiratory rate 20 breaths per minute, and oxygen saturation 90% on ambient air. He had mild bilateral crackles at the lung bases and a well-healed, non-tender, non-erythematous surgical scar at the site of the pacemaker pocket on the anterior chest wall. The remainder of his physical examination was unremarkable.

Laboratory values were significant for pancytopenia, with WBC count of 3500/μl, (76% neutrophils, 8% lymphocytes, and 12% monocytes), hemoglobin 11.6 g/dL (normal range, 13.5–17.5 g/dL), and platelet count of 122,000/μL (normal range, 150,000–450,000/μL). Other laboratory

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studies, including the basic metabolic panel, liver function tests, lactate dehydrogenase (LDH), total protein, and albumin were normal. Two sets of blood cultures, peripheral blood for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) polymerase chain reaction (PCR), serum *Aspergillus* antigen, *Legionella* urinary antigen test (UAT), pneumococcal-UAT, and *Histoplasma*-UAT were all negative. A nasal swab tested positive for parainfluenza on direct fluorescent antibody (DFA). A sputum culture grew normal flora. A high-resolution computed tomography (CT) scan of the lungs showed bilateral interstitial and nodular infiltrates (Fig. 26.1). Because the patient had fever on presentation, did not have signs of congestive heart failure, was not exposed to radiation, did not receive drugs known to cause lung injury, and did not receive any blood transfusion, we suspected that his symptoms were most likely due to an infection. When the parainfluenza virus (PIV) DFA test came back positive, it was therefore decided to treat him with empiric antibiotics to cover the common bacterial pathogens that cause pneumonia, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The differential diagnosis for diffuse interstitial infiltrates in immunocompromised patients is presented in Table 26.1.

The patient was treated with intravenous (IV) vancomycin, IV aztreonam, and inhaled ribavirin for 5 days; however, he became progressively more hypoxic over the next 10 days. Serial CXR demonstrated the development of an interstitial pattern with diffuse infiltrates. An aminoglycoside was added to cover the possibility of antibiotic-resistant *Pseudomonas* pneumonia because he showed no significant improvement. Subsequently, he had a bronchoscopy without transbronchial biopsy to rule out other etiologies. A bronchoalveolar lavage (BAL) specimen was sent for Gram stain and bacterial culture, acid-fast bacillus (AFB) smear and culture, fungal and viral cultures, and *Pneumocystis jirovecii* DFA testing, which were all negative. We nevertheless began empiric therapy for *P. jirovecii* pneumonia (PJP) with clindamycin and primaquine and also restarted inhaled ribavirin. Over the next several days, the patient's dyspnea progressed, ultimately necessitating intubation. After extensive discussion, he

Table 26.1 Differential diagnosis of diffuse pulmonary infiltrates in the immunocompromised patient [5]

Infectious causes
Bacteria – *Mycoplasma pneumoniae* – *Legionella* spp. – *Nocardia* spp. – *Staphylococcus aureus* – *Pseudomonas aeruginosa*
Viruses – Cytomegalovirus (CMV) – Influenza – Respiratory viruses, especially respiratory syncytial virus (RSV), parainfluenza viruses, adenovirus, and human metapneumovirus
Fungi – *Pneumocystis jirovecii* – *Aspergillus* spp. – Mucormycosis agents – Histoplasmosis (*Histoplasma capsulatum*) – Blastomycosis (*Blastomyces dermatitidis*)
Mycobacteria – *Mycobacterium tuberculosis* – Nontuberculous mycobacteria, including *M. avium* Complex, *M. kansasii*, and *M. abscessus*
Noninfectious causes
Congestive heart failure
Acute respiratory distress syndrome
Malignancy (leukemic infiltrates, lymphoma, metastatic disease)
Pulmonary hemorrhage
Drug-induced lung injury
Engraftment syndrome
Transfusion-related lung injury
Radiation toxicity

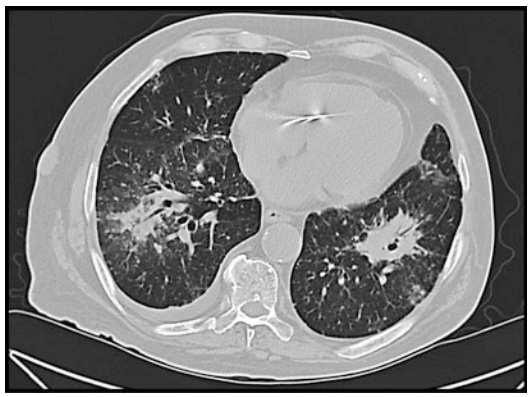

Fig. 26.1 CT scan of the lungs showing diffuse bilateral micronodular and interstitial infiltrates

underwent video-assisted thoracoscopy with lung biopsy. Histopathology findings were consistent with viral infection, and DFA testing was positive for *P. jirovecii.* Because the patient had deteriorated while on clindamycin and primaquine, this therapy was changed to trimethoprim/sulfamethoxazole (TMP-SMX).

Subsequently, he was successfully extubated, weaned to room air, and transferred to a rehabilitation facility. At a 6-month follow-up visit, he was doing well, confirming the efficacy of his PJP therapy and resolution of PIV pneumonia. One month later, unfortunately, he was readmitted to our hospital with sepsis. An extensive workup failed to reveal an etiology. He developed multisystem organ failure and he expired. An autopsy was not performed.

26.1 Parainfluenza Pneumonia in Immunocompromised Hosts

Parainfluenza viruses (PIV) are enveloped RNA viruses of the family Paramyxoviridae [1]. PIV are common respiratory pathogens known primarily to cause infection in children. However, immunity is incomplete and reinfection can occur [2]. PIV infection in immunocompromised patients, particularly in the setting of hematologic malignancy, solid organ transplantation, or HSCT [3], is increasingly recognized and can be associated with a wide spectrum of disease, ranging from mild upper respiratory symptoms to pneumonitis and severe respiratory failure. The mortality rate of PIV lower respiratory disease has varied among studies, reaching more than 50% in some reports [2, 3].

When PIV infection is suspected, the diagnosis is made primarily by detection of PIV antigen by direct or indirect fluorescence antibody testing from a nasopharyngeal wash, swab, or BAL, a test with limited sensitivity but high specificity. Viral culture is also used, but it may take several days to return positive. PIV PCR is highly sensitive and specific, but it may not be readily available or may take more time than antibody assays [4]. Recently multiplex PCR testing has become available for multiple respiratory pathogens including parainfluenza viruses. The University of Chicago lab currently performs the PCR amplification method with analysis by automated nested multiplex PCR by a commercially available assay. The test is performed in house everyday with a 6- to 8-h turnover, and it detects the important respiratory viruses (influenza A; influenza A subtypes H1, H3, and H1-2009; influenza B; respiratory syncytial virus; parainfluenza viruses types 1–4; adenovirus; human metapneumovirus; coronavirus HKU1, NL63, and 229E; and enterovirus/rhinovirus) and three bacterial pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Bordetella pertussis*).

CT scan of the lungs is usually the preferred imaging modality for identifying pulmonary abnormalities [5, 6]. Radiographic findings in PIV infection are variable; they can be focal or diffuse, interstitial, and alveolar-interstitial infiltrates [2, 7]. Some studies suggest that having multiple small, non-cavitating pulmonary nodules might be indicative of a viral etiology of pneumonia, such as PIV [6].

Currently, no antiviral is approved for treatment of PIV. Small studies and cases reports have shown mixed results regarding the clinical benefit of aerosolized or systemic ribavirin, with or without IV gamma globulin. The majority of studies to date have failed to demonstrate improved outcomes in treated patients in terms of progression to pneumonia, need for mechanical ventilation, duration of illness, or mortality [3, 8]. Many of the patients in these studies had other respiratory co-pathogens, which was associated with higher mortality. Organisms identified included mixed viral infection (e.g., CMV, adenovirus, or respiratory syncytial virus), superimposed bacterial or fungal infection (particularly aspergillosis), and mycobacterial infection [3, 8]. Dual infection with *P. jirovecii* and a respiratory virus has also been reported [9]. Recently, DAS181, a sialidase fusion protein that cleaves Neu5Ac alpha (2,3) and (2,6)-Gal linkages of sialic acid from respiratory endothelial cell surfaces, has been used in 16 HSCT recipients with PIV infection (14 with pneumonia), with complete clinical response in

9 patients and partial in 4. There was no control group in the study. The drug is administered either by oral inhalation using a dry powder inhaler or by nebulizer for intubated patients. It targets a host protein to which PIV binds rather than a viral structure [10].

26.2 *Pneumocystis jirovecii* Pneumonia (PJP) in Non-HIV-Infected Patients

PJP is caused by the fungus *P. jirovecii*, previously known as *P. carinii*. However, *P. carinii* is now understood to be a separate species that infects rodents, whereas *P. jirovecii* infects humans, hence the name change. Most *P. jirovecii* infections are diagnosed in persons infected with the human immunodeficiency virus (HIV) who have an absolute CD4+ T lymphocyte count below 200 cells/mm^3.

Non-HIV-infected immunocompromised patients are at increased risk for invasive fungal infection including *P. jirovecii* [11]. Consequently, prophylaxis has been recommended with TMP-SMX. However, TMP-SMX use has been limited by adverse reactions such as skin rash, nausea, vomiting, nephrotoxicity, and bone marrow suppression. Dapsone is considered an acceptable alternative despite a higher rate of breakthrough infection [12].

Non-HIV-infected patients who have PJP demonstrate a more acute clinical course, often with delays in treatment initiation and higher mortality compared to patients with HIV infection [13]. TMP-SMX remains the treatment of choice, based primarily on studies in HIV-infected patients [14].

P. jirovecii cannot be cultured, and the diagnosis requires identification of the organism by staining of fluid from an induced sputum, BAL, or lung biopsy specimen by microscopy. DFA staining has become the most commonly used method. In some studies among immunocompromised patients without HIV there was a lower organism burden and a poorer diagnostic yield of conventional staining of a specimen from induced sputum or BAL [15]. Although the *P. jirovecii* real-time PCR has a higher sensitivity and specificity than DFA and can be particularly useful in this population [16], the test may not be able to differentiate colonization from true infection. Therefore, tissue sampling for diagnosis may be necessary to confirm PJP in non-HIV-infected patients [17].

Key Points/Pearls

- The differential diagnosis of pulmonary infiltrates in the immunocompromised host is broad, and a detailed history and workup are essential to establish a specific etiology.
- Tissue sampling is frequently needed to establish a definitive diagnosis of PJP in non-HIV-infected immunocompromised patients.
- Multiple simultaneous infectious and noninfectious pathologic processes are common in immunocompromised patients.
- PJP should be considered in the differential diagnosis of patients with HIV, as well as immunocompromised patients without HIV who are presenting with pneumonia.
- The mainstay of therapy for PIV infection remains supportive, given the lack of evidence supporting the use of ribavirin or IV gamma globulin, although DAS181, a sialidase fusion protein that cleaves Neu5Ac alpha (2,3) and (2,6)-Gal linkages of sialic acid from respiratory endothelial cell surfaces, has been used in 16 HSCT recipients with PIV infection, with good response in 13 patients.
- Multiplex PCR testing has become available for multiple respiratory pathogens including influenza A; influenza A subtypes H1, H3, and H1-2009; influenza B; respiratory syncytial virus; parainfluenza viruses types 1–4; adenovirus; human metapneumovirus; coronavirus HKU1, NL63, and 229E; enterovirus/rhinovirus; *Mycoplasma pneumoniae*; *Chlamydophila pneumoniae*; and *Bordetella pertussis.*
- In AIDS patients with PJP, the addition of steroids is recommended if the A-a gradient is >35 or $PaO_2 < 70$; the use of steroids in other immunocompromised patients with PJP who meet these criteria is also recommended.
- The most effective drug to treat PJP is high-dose trimethoprim/sulfamethoxazole;

alternatives are clindamycin plus primaquine (test for G6PD deficiency) or pentamidine (much more toxic).
- The prognosis of PJP in non-HIV-infected immunocompromised patients is worse, most likely due to a delay in diagnosis and a more acute presentation.

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