

Diffuse pulmonary infiltrates in an immunocompromised patient

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Immunocompromised patients with diffuse pulmonary infiltrates present enormous challenges because the differential diagnosis includes a broad array of infectious and noninfectious causes (Table I). Prompt and accurate diagnosis is critical because these pulmonary complications can result in considerable morbidity and mortality.¹ We present the following case to illustrate an unusual manifestation of a relatively common opportunistic organism and to demonstrate the utility and safety of newer methods of lung biopsy in children.

CASE REPORT

A 6-year-old boy with a history of trisomy 21 and acute lymphoid leukemia was admitted for fever and upper respiratory tract symptoms. At the time of admission, the patient was receiving maintenance chemotherapy with methotrexate, dexamethasone, and mercaptopurine. To prevent *Pneumocystis jirovecii*-induced pneumonia (PJP), he was also receiving prophylactic doses of dapsone because he was allergic to trimethoprim-sulfamethoxazole. A chest radiograph on admission showed diffuse pulmonary infiltrates. He initially required oxygen, 2 to 3 L/min through a nasal cannula, and was given a 1-week course of intravenous ceftazidime and clarithromycin.

Despite antibiotic therapy, the patient's oxygen requirement increased to 8 L/min by face mask, and he continued to have fevers. Bronchoalveolar lavage (BAL) through a flexible fiberoptic bronchoscopy revealed no organisms and negative cultures. Blood and urine cultures were negative as well. The patient was continued on intravenous antibiotics and appeared to improve clinically, with a decreased oxygen requirement to 1/4 L/min by the third week of hospitalization. However, his chest radiograph

Abbreviations used

BAL: Bronchoalveolar lavage

PJP: *Pneumocystis jirovecii*-induced pneumonia

TABLE I. Cause of pulmonary infiltrates in the immunocompromised host

Bacterial infections (<i>Pseudomonas</i> and <i>Staphylococcus</i> species)
Fungal infections (<i>Aspergillus</i> , <i>Mucormycosis</i> , and <i>Candida</i> species)
Viruses (cytomegalovirus, varicella, herpes, Respiratory syncytial virus, parainfluenza, influenza)
<i>Pneumocystis jirovecii</i> -induced pneumonia
Mycobacteria
Pulmonary edema
Drug toxicity
Radiation therapy
Progression of underlying disease
Graft-versus-host disease
Bronchiolitis obliterans
Alveolar proteinosis
Posttransplantation lymphoproliferative disease
Transfusion-related acute lung injury
Idiopathic pulmonary syndrome

remained abnormal, and he did not tolerate being off oxygen therapy. High-resolution computed tomographic scanning of the chest showed bilateral diffuse reticulonodular opacities, which were greatest in the lower lobes (Fig 1).

The patient underwent lung biopsy by means of video-assisted thoracoscopic surgery. The biopsy specimen showed PJP by means of silver staining within an unusual pattern of granulomatous pneumonitis and organizing pneumonia (Fig 2). The patient tolerated the procedure well, and a chest tube, placed at the time of surgery, was removed after 2 days. He was given a 14-day course of intravenous pentamidine, which resulted in resolution of his symptoms and oxygen requirement and clearing of his chest radiograph. He was discharged on monthly inhaled pentamidine treatments and has not had any subsequent recurrences of pneumonia.

DISCUSSION

The presence of pulmonary infiltrates in an immunocompromised patient is a serious finding that warrants an aggressive

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FIG 1. High-resolution computed tomography of the chest in this patient revealed diffuse reticulonodular opacities and patchy ground-glass opacities.

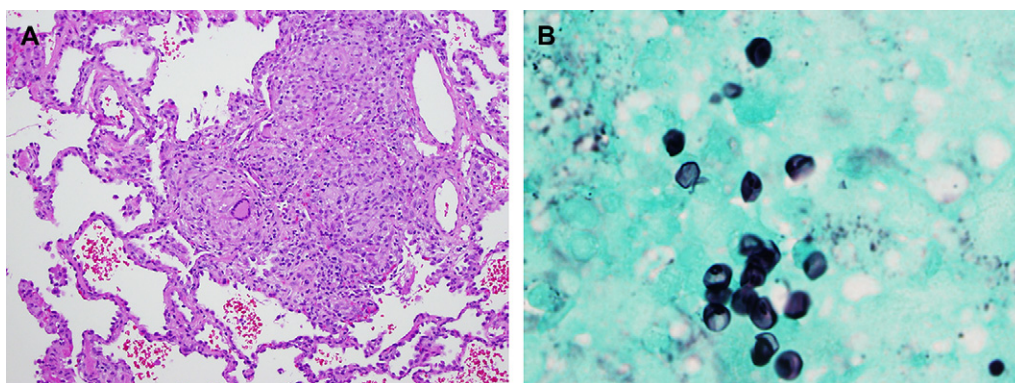


FIG 2. **A**, Lung biopsy in this patient showed patchy areas of individual and confluent epithelioid granulomas. Most were small and nonnecrotizing, with scattered associated lymphocytes, multinucleate giant cells, and focal organizing pneumonia pattern (hematoxylin and eosin stain, $\times 10$ magnification). **B**, Silver staining showed only a few *Pneumocystis* species organisms within the granulomas distributed individually and in small clusters, the largest of which is demonstrated here (methenamine silver nitrate stain, $\times 1000$ magnification).

approach to diagnosis and treatment. Although the incidence of PJP among this population has decreased dramatically since the use of prophylactic antibiotics, this case illustrates that breakthrough cases do occur.² Clinical history, physical examination, and diagnostic imaging studies in patients with PJP are very non-specific. History can include fever, nonproductive cough, weight loss, and chills. Physical examination can reveal fever, tachypnea, tachycardia, cyanosis, and subcostal/intercostal retractions. Auscultation is often characterized by the absence of crackles until the late or recovery stage. Chest radiography often shows varying degrees of diffuse interstitial and alveolar infiltrates. The classic high-resolution computed tomographic appearance is patchy areas of ground-glass attenuation with a background of interlobular septal thickening.

Although expectorated sputum has a very low sensitivity, sputum induced with hypertonic saline has a somewhat higher diagnostic yield.³ BAL is usually the procedure of choice and carries a diagnostic yield approaching 80% in some series. However, a negative BAL result does not rule out PJP, as this case illustrates. In patients with a nondiagnostic BAL result and persistent infiltrates, lung biopsy should be considered. With the development of video-assisted thoracoscopic surgery for children, lung biopsy can now be performed with comparable results to conventional open lung biopsy but with less morbidity in terms of duration of surgery, chest tube placement, and hospital stay.⁴ Examples of lung biopsy procedures using video-assisted thoracoscopic surgery in infants and children are shown in the online video clips (available in the [Online Repository at www.jacionline.org](http://www.jacionline.org)).

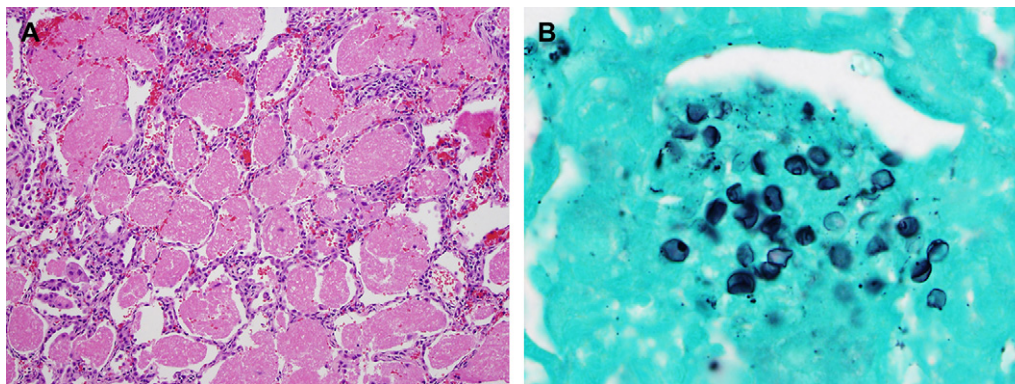


FIG 3. **A**, This lung biopsy specimen from a patient undergoing lung transplantation demonstrates the “classic” pattern of PJP, including abundant “frothy” alveolar proteinaceous material (hematoxylin and eosin stain, $\times 100$ magnification). The finely vacuolated appearance of the alveolar material is produced by negative contrast of the organism within the exudates. **B**, Diagnosis is confirmed by silver staining, which highlights abundant cup-shaped organisms, some of which show characteristic dot-like capsular thickening (methenamine silver nitrate stain, $\times 1000$ magnification).

Classic pathologic findings of PJP consist of foamy intra-alveolar eosinophilic exudates with trophozoites and cysts of the organism, as shown in Fig 3.¹ In contrast, our patient demonstrated a more unusual granulomatous pattern. The presence of organisms in interstitial granulomas rather than in the alveolar air spaces probably explains why the BAL result was negative.

Granulomatous PJP has been previously described, although it is a rare phenomenon. In these cases, biopsy specimens show palisades of epithelioid cells forming granulomas with organisms found within the granulomas rather than the alveolar space.⁵ BAL results are often negative for PJP organisms, and patients have required open lung biopsy to confirm the diagnosis. The relative insensitivity of BAL might be due to a decreased load of organisms or absence of organisms in the alveolar space.⁵

The mechanism for granuloma formation is not well understood but might be an inflammatory reaction after immune reconstitution in patients receiving immunosuppressive therapies.⁶ The theory of immune reconstitution inflammatory syndrome is best described in the patients with acquired immunodeficiency syndromes, such as HIV. Patients experience increased CD4⁺ lymphocyte function and a decrease in HIV plasma viral load after initiating antiretroviral therapy. This has been associated with multiple opportunistic infections and intense inflammatory response and granuloma formation. Although rarely described in the patient without HIV, a similar immune reconstitution inflammatory response can occur after hematologic recovery in patients with leukemia.⁶ An additional explanation for the development of granulomas might be related to genetic diversity among strains of *P jirovecii*, which alters the histologic response of the host to PJP.⁵

Despite adequate chemoprophylaxis, PJP does occur, but the mechanism is not well described. Sulfa and sulfone resistance are

characterized in bacterial pathogens due to genetic mutations at the dihydropteroate synthase active site. It is postulated that similar mutations in the *P jirovecii* organism might contribute to resistance.⁷

In this case of PJP, the patient had the appropriate diagnostic studies for his presentation. Although his symptoms appeared to improve clinically, he remained hypoxemic, prompting a decision to pursue further studies that included computed tomography and video-assisted thoracoscopic surgery. The patient tolerated the procedure well, and a diagnostic biopsy altered the therapeutic regimen with subsequent clinical improvement. Thus this case confirms the utility of lung biopsy in immunocompromised patients with diffuse pulmonary infiltrates when less invasive procedures are nondiagnostic. With the development of video-assisted thoracoscopic surgery in infants and children, lung biopsy can be performed with acceptable risk in most patients.

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