Granulomatous Pneumocystis carinii
Pneumonia in Three Patients with the Acquired Immune Deficiency Syndrome

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Pneumocystis carinii pneumonia is a frequent manifestation of the acquired immune deficiency syndrome (AIDS). It usually presents radiologically as diffuse bilateral infiltrates and histologically as a foamy, eosinophilic intra-alveolar exudate containing the organisms' cysts. We recently studied two rare cases of P carinii pneumonia presenting as pulmonary nodules on chest x-ray films in two patients with AIDS. The corresponding histologies were a combination of the usual intra-alveolar pattern, with an alveolar and interstitial granulomatous appearance. Pneumocystis carinii was present in both areas and was the only organism found in the tissues examined. A third case presented with the more common radiographic appearance but also had a granulomatous histology. We conclude that P carinii pneumonia should be considered in the differential diagnosis of pulmonary nodules in immunocompromised patients and that pathologists should be aware of the possibility of a granulomatous reaction to this organism. (Chest 1988; 94:580-83)

Pneumocystis carinii is a pathogen common to the respiratory tracts of immunosuppressed patients, which has recently become more prevalent with its frequent occurrence in the setting of the acquired immune deficiency syndrome (AIDS). Its typical radiographic presentation is that of diffuse bilateral, "fluffy" infiltrates on chest x-ray film. Histologically, this usually corresponds to a foamy, acellular eosinophilic intra-alveolar exudate in which the cysts of the organism are readily demonstrated with silver stains. The radiographic presentation of P carinii pneumonia as a single nodule has only rarely been reported, with some of the reports not having provided adequate descriptions of the lesion histologic appearances. Atypical and occasionally granulomatous histologic appearances of this infection have also been described, usually in the setting of iatrogenic immunosuppression for malignancies or transplants. Although P carinii pneumonia is extremely common in AIDS, we found only one report concerning two patients with AIDS who presented with nodular pulmonary densities. A detailed histologic description was not provided in these cases. A granulomatous reaction to the organism has not, to our knowledge, been reported in the setting of AIDS.

We report here three patients with AIDS, two of whom presented with nodular densities (solitary or multiple) on chest x-ray film, the third presenting with bilateral fluffy infiltrates. Transbronchial biopsies of two and open lung biopsy of one revealed a mixed granulomatous (atypical) and nongranulomatous (typical) reaction to P carinii. This underscores the importance of recognizing the different radiographic and histologic appearances that the organism can produce.

Case Reports

Case 1

A 37-year-old white woman, a former IV drug abuser was admitted to the Mount Sinai Hospital for recurrent dyspnea on exertion, persistent fever, and anorexia. She had presented five months earlier at another institution with exertional dyspnea, and a chest x-ray film at the time revealed a left suprahilar nodule. The ELISA and Western blot tests for human immunodeficiency virus (HIV) antibodies were positive, and all cultures were negative. Her symptoms continued over the next two months, and a repeated chest x-ray film was unchanged. A transcutaneous needle biopsy of the nodule showed nonspecific fibrosis. Special stains for organisms were negative. A 5-TU tuberculin test was nonreactive. Several weeks later she was admitted to Mount Sinai Hospital. Her past medical history was remarkable for an upper GI bleed secondary to peptic ulcer disease several months earlier, a herpes zoster infection one year earlier, and a cigarette smoking history of one pack per day. Physical examination revealed a temperature of 38.3°C, oral thrush, and clear lungs on auscultation. Her admission blood gas analysis values were pH, 7.44; PaCO₂, 38.7 mm Hg; and PaO₂, 92 mm Hg on room air. A chest x-ray film again revealed a nodule, and a chest CT scan confirmed a 2 x 3-cm left suprahilar parenchymal mass and a smaller, ill-defined left lingular mass (Fig 1). An indium scan revealed no pulmonary uptake of the isotope. Pulmonary function tests disclosed a forced vital capacity of 4.77 L (111 percent predicted), and the carbon monoxide diffusing capacity was 20.27 ml/mm Hg (89 percent predicted). Transbronchial and transcuta-
neous biopsies were again nondiagnostic, and a left anterior thoracotomy was performed, revealing a large yellow, granular-appearing mass in the left upper lobe anterior segment, which was biopsied, and two smaller lingular masses, which were excised with a rim of surrounding lung tissue. The nodules were circumscribed and exhibited a yellow color with soft, necrotic areas with surrounding hemorrhagic, somewhat gray pulmonary parenchyma. Routine hematoxylin-eosin-stained sections revealed necrotic, calcifying granulomas with rare multinucleated giant cells and a predominantly histiocytic and minimal lymphocytic response (Fig 2). In areas the necrotic and calcifying tissue merged with the foamy acellular eosinophilic exudate typical of P carinii pneumonia. In the surrounding lung tissue, this exudate was found in a peculiar perivascular distribution, and occasionally filling pulmonary interstitium, flanked on one side by hyperplastic type II alveolar pneumocytes and on the other by capillary endothelium; occasional alveolar spaces also contained the exudate (Fig 3). Grocott methenamine silver stains revealed numerous cysts of P carinii both within the foamy exudate and within the areas of necrosis and calcification. The organisms in the calcified areas exhibited lighter silver staining than those in other areas, possibly implying their presence for a longer time than those staining darker. Stains for acid-fast bacilli were negative. The patient received a three-week course of trimethoprim-sulfamethoxazole with subsequent resolution of symptoms.

CASE 2

A 28-year-old woman with no known risk factors for AIDS was admitted to the Mount Sinai Hospital with a 9-kg weight loss, fever, shortness of breath, nonproductive cough, and oral thrush. Chest x-ray film showed slightly increased interstitial markings and a stellate nodular density in the right upper lobe (Fig 4). She underwent fiberoptic bronchoscopy; and transbronchial biopsies were obtained under fluoroscopic guidance. Routine histologic sections were prepared and stained with hematoxylin-eosin, Grocott methenamine silver, Ziehl Nielsen acid-fast, and Giemsa stains. An intra-alveolar and interstitial infiltrate of pale staining histiocytic-appearing cells and lymphocytes was seen. No multinucleated giant cells were present. There was also focal intra-alveolar foamy acellular eosinophilic exudate. Cysts of P carinii were readily found both within the area of exudate as well as in the granulomatous areas. No other organisms were identified. The patient was treated with IV trimethoprim-sulfamethoxazole for three weeks and had clinical and radiologic improvement. Culture of transbronchially obtained material eventually grew Mycobacterium avium-intracellulare. HIV antibody tests were not performed.

CASE 3

A 32-year-old Hispanic male IV drug abuser presented to the Bronx Veterans Administration Medical Center with a two-week...
The patient was treated with trimethoprim-sulfamethoxazole and had repeated bouts of pneumonia, the diagnosis of granulomatous pneumocystosis eventually being made on open lung biopsy. The granulomas in that case consisted of noncaseating clusters of epithelioid cells, most of which were present in the alveolar spaces, with a few present in the interstitium. A few lymphocytes were also seen, and only an occasional multinucleated giant cell was found. Pneumocystis carinii was seen diffusely throughout the granulomas.

Since this initial description, other reports have noted necrotizing granulomas, one of which showed fibrosis to the degree usually seen in later-stage sarcoid granulomas. Both patients in these reports carried a diagnosis of malignant lymphoma, and at least one of them had been undergoing chemotherapy.

The entire subject of typical and atypical appearances of P carinii pneumonia was reviewed by Weber et al in 1975, with the addition of other occasionally occurring atypical features such as interstitial fibrosis, a dense interstitial infiltrate, severe infiltration of alveolar macrophages, and calcification. These authors found atypical histologic features present in 69 percent of the 36 cases they studied. Nearly all of these patients had either a primary immunodeficiency or had been immunosuppressed secondary to chemotherapy for malignancy or transplantation.

We believe that our cases are the first descriptions of this histologic variant in the setting of the AIDS. In two of the three cases, the only organism implicated by all available studies was P carinii. Although cultures of one of the cases eventually grew Mycobacterium avium-intracellulare, we believe that the granulomas we observed in this case were in large part due to the presence of Pneumocystis, since the organism was

**Figure 5.** Transbronchial biopsy specimen (case 3) showing a better formed granuloma composed of histiocytic cells and a few lymphocytes. (Hematoxylin-eosin ×200.)

**Figure 6.** Area identical to that in Figure 5 showing numerous cysts of Pneumocystis carinii within the granuloma (arrow). (Grocott methenamine silver ×200.)
seen directly within the granulomas, and no acid-fast bacilli were found. The possibility of coexistent infection in this case remains.

These cases are especially interesting in light of the fact that well-formed granulomas are generally not seen in AIDS patients, even in the presence of mycobacterial infection. Although this is generally ascribed to these patients' defective T-cell function, one of us has observed granuloma formation in a study of nude rats injected with BCG; thus, proper T-cell function may not be absolutely essential for the granulomatous response. Unfortunately, studies of T-cell function such as T-helper/suppressor ratios were not available in our cases.

Finally, P carinii may rarely be found in other organs, usually lymph nodes or spleen, with widespread dissemination also possible. Again, this nearly always occurs in the setting of an immunosuppressed patient, with recent reports documenting both extrapulmonary mass lesions containing Pneumocystis and disseminated P carinii in AIDS patients.

In some of these cases the tissue response to the organism has been granulomatous, although most have revealed an acellular exudate similar to that typically seen in the lung.

We believe that with the current incidence of AIDS and the frequent occurrence of P carinii pneumonia as one of its components, it is essential to keep in mind all of the possible radiographic and pathologic manifestations of this organism, no matter how rare its atypical presentations may be.

ADDENDUM

Since this article was submitted, we have seen an additional case of granulomatous Pneumocystis carinii pneumonia in a patient with Hodgkin's disease and therapy-associated acute myelogenous leukemia. There was no evidence of AIDS in this patient.

ACKNOWLEDGMENT: The authors wish to thank Mr. Norman Katz for his photographic assistance.

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