necrotic pulmonary nodules, a pulmonary manifestation of the disease were ruled out by histologic and clinical findings. In patients with pyoderma gangrenosum with the presence of radiologically visible multiple central necrotic pulmonary nodules, a pulmonary manifestation of the underlying disease should be considered.

**Discussion**

Since its first description by Brunsting et al in 1930, pyoderma gangrenosum has been reported in association with various systemic diseases with basic immunologic disorders, such as ulcerative colitis, Crohn's disease, polyarthritis, vasculitis, lymphoma, paraproteinemia, leukemia, or active chronic hepatitis.

The patient presented here showed immunologic abnormalities (ie, positive results of tests for antinuclear autoantibodies without the manifestation of other clinical complications except pulmonary nodules). Pulmonary manifestations in pyoderma gangrenosum are rare. With one exception, pulmonary disease in association with pyoderma gangrenosum occurred as a single unilateral opacity on a chest radiograph. Kasuga et al were the first authors to report a patient with multiple pulmonary nodules in association with pyoderma gangrenosum. In this particular case, the nodules were solid and were located in the peripheral portions of the lungs.

The finding of multiple pulmonary nodules with central necrosis in both lungs in association with pyoderma gangrenosum has not yet been described. Histologic examination of the pulmonary manifestations of pyoderma gangrenosum revealed aseptic inflammatory lesions similar to the findings presented here. As reported earlier, the pulmonary lesions rapidly decreased with steroid therapy.

In our patient, the histologic findings of the skin biopsy corresponded closely to the findings of the lung biopsy, CT-guided biopsies of lung lesions have a very high sensitivity and specificity. In a study by Belfiore et al, the cytologic diagnosis of CT-guided, fine-needle biopsy was confirmed in all 267 patients who underwent surgical or clinical follow-up. The ideal evaluation of these necrotic lung lesions would have been the acquisition of larger pieces of tissue (eg, by surgical lung biopsy). However, the patient refused this procedure and only gave consent for CT-guided, fine-needle biopsy.

With regard to the central necrotic pulmonary nodules detected on the CT scan, the most favorable radiologic diagnosis would have been Wegener's granulomatosis. However, Wegener's granulomatosis as well as septic emboli, sarcoidosis, tuberculosis, and metastatic malignant disease were ruled out by histologic and clinical findings.

**References**


**Recurrent Pulmonary Sarcoidosis in HIV-Infected Patients Receiving Highly Active Antiretroviral Therapy**

Roberta Lenner, MD; Zachary Bregman, MD; Alvin S. Teirstein, MD, FCCP; and Louis DePalo, MD, FCCP

HIV infection and sarcoidosis occur in the same age group, but there are only a few reports of the

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coexistence of the two disorders in the same individual. This infrequent occurrence has been attributed to the paucity of functioning CD4+ lymphocytes required for granuloma formation in patients with HIV infection. We report two patients with a history of remote sarcoidosis who later in life contracted HIV infection and developed recurrent, progressive pulmonary sarcoidosis while receiving highly active antiretroviral therapy (HAART). Progressive pulmonary sarcoidosis should be added to the differential diagnosis in patients receiving HAART for HIV infection who develop diffuse lung disease with recovery of CD4+ lymphocyte population.

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Key words: AIDS; HIV infection; immune reconstitution; pulmonary sarcoidosis

Abbreviations: HAART = highly active antiretroviral therapy; PCP = Pneumocystis carinii pneumonia

The HIV type 1 is estimated to infect > 1 million individuals in the United States. SARCOIDOSIS, a disease of unknown etiology, has an estimated prevalence of 10 to 80 per 100,000.2 The hallmark of HIV infection is the destruction of CD4+ T cells, which predisposes to the development of opportunistic infections. In contrast, sarcoidosis is characterized by a high CD4/CD8 ratio in affected tissues, which is thought to represent a dysfunctional immune response to an unidentified antigen or antigens leading to granuloma formation. HIV infection and sarcoidosis are relatively common in the same age group, yet the coexistence of the two disorders in the same individual is unusual. The granulomas of sarcoidosis are rich in CD4+ T lymphocytes. The relative lack of CD4+ T lymphocytes in HIV disease has been offered as the explanation for the rarity of coexistent sarcoidosis and HIV infection. Recently, the occurrence of a granulomatous pulmonary disorder in two HIV-infected patients receiving highly active antiretroviral therapy (HAART) has been described. We report two patients with a history of previous sarcoidosis that had remitted, who later in life contracted HIV infection and developed recurrent, progressive pulmonary sarcoidosis coincident with reconstitution of the CD4+ lymphocytes while receiving HAART.

Case Reports

Case 1

A 50-year-old African-American woman with AIDS was evaluated in September 1998 for shortness of breath, fatigue, fevers, and an abnormal chest radiograph. Sarcoidosis was diagnosed 15 years before. At that time, she presented with abnormal liver function test results. Liver biopsy showed noncaseating granulomas, and she had a positive result on Kveim-Siltzbach test. Her chest radiograph was normal. She received no therapy for sarcoidosis. In April 1996, she presented with Pneumocystis carinii pneumonia (PCP), at which time she was found to be HIV positive with a CD4 cell count of 178/μL. In May 1996, she started on HAART (zidovudine, 200 mg tid; lamivudine, 150 mg bid; and indinavir, 800 mg tid). By September 1997, she was well and her chest radiograph was normal. In June 1998, she experienced dyspnea, intermittent fevers, and increased pulmonary infiltrates on chest radiograph. Her CD4 cell count was 253/μL, and the HIV RNA level was < 40 copies/mL. She received empiric treatment for PCP with trimethoprim-sulfamethoxazole without improvement.

Oxygen saturation breathing room air was 93%. Physical examination was normal. Laboratory analysis revealed mild anemia and abnormal liver function tests (alkaline phosphatase, 473 U/L; γ-glutamyl transpeptidase, 590 U/L; aspartate transaminase, 47 IU/L; alanine transaminase 52 IU/L; and total bilirubin, 1.8 mg/dL). Her CD4 cell count was 250/μL with no detectable viral RNA. A chest radiograph was remarkable for diffuse infiltrates. Pulmonary function tests revealed a restrictive ventilatory pattern with decreased diffusing capacity (FVC, 1.73 L [50% of predicted]; FEV1, 1.09 L [46% of predicted]; FEV1/FVC, 63%; and diffusing capacity of the lung for carbon monoxide, 35% of predicted). Fiberoptic bronchoscopy with biopsy revealed massive accumulation of epitheloid, nonnecrotizing granulomas. Special stains and cultures of bronchial washing fluid and tissue specimen failed to detect mycobacteria, fungi, viral pathogens, PCP, or other opportunistic infections. The diagnosis of recurrent pulmonary sarcoidosis was made, and treatment with prednisone, 20 mg/d, and hydroxychloroquine, 200 mg bid, was initiated. On follow-up visit 2 weeks later, the patient reported marked improvement in her clinical symptoms. A repeat chest radiograph revealed improvement in the bilateral infiltrates with improved pulmonary function. With continued therapy, her pulmonary and functional abnormalities have continued to improve.

Case 2

A 64-year-old African-American man with HIV infection and a history of sarcoidosis presented with progressive dyspnea on exertion. As a young adult, a routine chest radiograph had revealed a right lower lobe infiltrate. The diagnosis of sarcoidosis was made by open lung biopsy. He had no symptoms and received no therapy. His chest radiograph reverted to normal. He recently received a diagnosis of HIV infection and is now receiving HAART (didanosine, 150 mg bid; stavudine, 30 mg bid; and nevirapine, 200 mg bid).

On presentation, his O2 saturation decreased from 96 to 87% with minimal exercise. Bilateral rales were heard. Laboratory studies revealed mild anemia. His CD4 cell count was 371/μL with no detectable viral RNA. Chest radiograph was remarkable for bilateral pulmonary infiltrates (Fig 1) confirmed by CT. Pulmonary function tests revealed restrictive ventilatory defect with reduced diffusing capacity (Table 1). Fiberoptic bronchoscopy with biopsy revealed epitheloid, nonnecrotizing granulomas. Special stains and cultures of bronchial washing fluid and tissue section specimens failed to detect mycobacteria, fungi, viral pathogens, PCP, or other opportunistic infections. With the diagnosis of recurrent pulmonary sarcoidosis established, treatment was initiated with prednisone, 30 mg/d. The patient reported marked improvement in his respiratory status. Chest radiograph later demonstrated significant resolution of the pulmonary abnormalities (Fig 2). The results of pulmonary function testing 4 months later were normal (Table 1).

Discussion

Helper CD4+ T cells are the main target of HIV infection. These cells play a central role in the formation of sarcoidosis granulomas. At the beginning of the HIV epidemic, the two diseases were thought to be mutually exclusive, based on the hypothesis that the decrease or absence of CD4+ cells might inhibit the development of sarcoidosis, or prevent flare of the disease. However, several patients with concomitant HIV infection and sarcoidosis have been reported. In these reports, HIV infection was diagnosed before, after, or at the
same time as sarcoidosis. The degree of immunosuppression by HIV infection was variable. Sarcoidosis in these patients resembled the disease affecting non-HIV infected individuals. The clinical spectrum ranged from asymptomatic presentation to multiple organ system involvement. Two patients with coexisting sarcoidosis and HIV infection who developed a positive reaction to Kveim-Siltzbach suspension were reported in 1992.7

Suppressive HIV therapy with HAART has been associated with prolonged inhibition of viral replication and increased CD4+ cell counts.11 These quantitative changes are also associated with qualitative improvement in the host immune responses, characterized by a dramatically reduced risk of opportunistic infections. However, the resultant immune reconstitution may cause exacerbation of other, lymphocyte-dependent diseases. Symptomatic hepatitis C virus12 as well as the paradoxical clinical progression of tuberculosis13 have been reported in HIV-infected patients receiving HAART therapy. A prominent inflammatory response consisting of focal lymphadenitis has been described in HIV-infected patients with previous subclinical Mycobacterium avium complex infection after successful treatment with indinavir.14 The development of “sarcoid-like” pulmonary granulomatous disease was reported in two HIV-infected patients receiving HAART.5 The CD4 cell count of these two patients were 219/μL and 318/μL, respectively, with RNA levels < 500 copies/mL. The presenting chest radiographs revealed diffuse bilateral infiltrates. Transbronchial biopsies revealed noncaseating granulomas in both cases. Examination of BAL fluid and tissue section specimens failed to detect infections or malignant processes. These patients had no history of sarcoidosis. Both patients responded to steroid therapy.

We report two patients with a history of remote sarcoidosis, who later in life contracted HIV infection and subsequently developed recurrent, progressive pulmonary sarcoidosis while receiving successful treatment with HAART. The initial diagnosis of sarcoidosis was established > 15 years prior to presentation in both cases. They were asymptomatic, had received no therapy for sarcoidosis, and their chest radiographs were considered normal at least 1 year prior to presentation. One of the patients suffered several episodes of opportunistic infections as a result of HIV infection; the other patient had limited immunosuppression. They both responded to HAART; the CD4 counts at the time of recurrent sarcoidosis were 250/μL and 371/μL, respectively, with no

Table 1—Pulmonary Function Tests at Diagnosis and After Treatment in Case 2*

<table>
<thead>
<tr>
<th>Pulmonary Function Parameters</th>
<th>At Diagnosis</th>
<th>Following Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>2.43</td>
<td>2.70</td>
</tr>
<tr>
<td>% of predicted</td>
<td>76</td>
<td>85</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.91</td>
<td>2.06</td>
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<tr>
<td>% of predicted</td>
<td>75</td>
<td>80</td>
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<tr>
<td>FEV1/FVC, %</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>DLCO, mL/min/mm Hg</td>
<td>11.4</td>
<td>19.05</td>
</tr>
<tr>
<td>% of predicted</td>
<td>45</td>
<td>75</td>
</tr>
</tbody>
</table>

*DLCO = diffusing capacity of the lung for carbon monoxide.
detectable viral load. Both patients presented with shortness of breath, hypoxia, restrictive pulmonary function patterns, and bilateral, diffuse infiltrates on chest radiographs. Transbronchial biopsies revealed noncaseating granulomas in both patients. Special stains and cultures of bronchial washing fluid and tissue section specimens failed to detect infectious or malignant processes. Both demonstrated dramatic improvement with steroid therapy. There is little doubt that these two cases represent recurrent, progressive pulmonary sarcoidosis.

Recurrence of sarcoidosis after immunologic reconstitution with HAART offers the opportunity of better understanding the pathogenesis of sarcoidosis. Most sarcoidosis patients have spontaneous resolution of their disease with no recurrent symptoms or radiographic abnormalities later in life. Careful analysis of the lym

References


Malignant Pleural Mesothelioma Produces Functional Granulocyte-Colony Stimulating Factor*

Ikuma Kasuga, MD; Shirou Ishizuka, MD; Kazushige Minemura, MD; Kenita Utsunami, MD; Hiroshi Serizawa, MD, and Kazuma Ohyashiki, MD

We report a patient with diffuse malignant pleural mesothelioma showing marked elevation of neutrophils. The level of serum granulocyte-colony stimulating factor (G-CSF) was elevated (138 pg/mL; normal range, < 20 pg/mL). The patient died 6 weeks after disease progression had been noted, and immunohistochemistry using a specific monoclonal antibody against recombinant G-CSF at autopsy demonstrated that the malignant mesothelioma cells actually produced G-CSF. Only three cases of malignant pleural mesothelioma, including the current patient, have been reported to produce G-CSF. We

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