Pulmonary Hemorrhage*

An Uncommon Cause of Pulmonary Infiltrates in Patients With AIDS

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We describe two patients with AIDS who developed new diffuse pulmonary infiltrates during the course of their hospitalization. In both cases, the infiltrates were attributed to pulmonary hemorrhage complicating an existing condition rather than representing a new pulmonary process. Identification of pulmonary hemorrhage in these patients allowed for discontinuation of treatment with empiric medications and continued appropriate supportive care. (Chest 1994; 106:1591-94)

Key words: AIDS; alveolar hemorrhage; pulmonary infiltrates

The development of pulmonary infiltrates in individu- als infected with human immunodeficiency virus type 1 (HIV) remains a common clinical problem. 1 This pre- sented the clinician with an extensive differential diagno- sis 2-6 with the focus often on infectious etiologies.6

Pulmonary hemorrhage has been reported in association with a number of disorders.7 Although pulmonary hemor- rhage has been reported in immunocompromised hosts,8-13 this entity is not commonly considered in the diag- nosis of pulmonary infiltrates in patients with AIDS.2 We present a retrospective review of two cases of HIV-infected individuals who developed pulmonary infiltrates during the course of their hospitalization. In each case, findings consistent with pulmonary hemorrhage were observed.

CASE REPORTS

Case 1

A 35-year-old white bisexual man was determined to have positive HIV serologic test results 8 months prior to hospital ad- mission (PTA) when he was diagnosed as having Pneumocystis carinii pneumonia. Following complete recovery from P. carinii pneumonia, he received monthly aerosolized pentamidine prophylaxis. Additional complications of HIV-related disease included cutaneous Kaposi’s sarcoma, herpetic esophagitis, anemia, and leukopenia.

The patient was hospitalized with a 7-day history of fever, chills, nausea, vomiting, and acute renal failure. Empiric treat- ment with ceftriaxone and vancomycin was initiated for fevers. Renal biopsy specimens disclosed no evidence for vasculitis, mali- gnancy, or microbial pathogens, including bacterial, fungal, P. carinii, or acid-fast bacilli (AFB). Progression to anemic renal failure necessitated hemodialysis.

On the seventh hospital day, the patient developed melena, hematemia, hematuria, and a hemorrhagic pericardial effusion with tamponade. Development of small bilateral pulmonary infiltrates prompted the addition of empiric trimethoprim- sulfamethoxazole therapy. The radiographic abnormalities pro- gressed to extensive diffuse bilateral alveolar infiltrates (Fig 1), precipitating respiratory failure requiring intubation and me- chanical ventilation. Laboratory data at that time disclosed the following values: hematocrit, 25.3%; prothrombin time (PT), 13.1 s; partial thromboplastin time (PTT), 41 s; platelet count, 41,000/mm3; serum urea nitrogen, 56 mg/dL; and creatinine, 9.0

References

mg/dL. Radiographic progression of the infiltrates prompted the addition of empiric amphotericin B and methylprednisolone.

On the ninth hospital day, fiberoptic bronchoscopy with bilateral bronchoalveolar lavage (BAL) demonstrated return of persistently grossly bloody fluid. No endobronchial lesions were observed. Examination of the BAL specimen failed to demonstrate the presence of routine bacteria, *P. carinii*, fungal elements, or AFB by special stains and cultures. Cytologic examination demonstrated hemosiderin-laden macrophages (Fig. 2).

With no evidence for a new pulmonary infectious process, treatment with corticosteroids, amphotericin B, and trimethoprim-sulfamethoxazole was discontinued. The patient received blood products and supportive therapy. Although the platelet count remained low, serum creatinine concentration improved to a value of 5.2 mg/dL. The patient demonstrated clinical and radiographic improvement and was successfully extubated within 4 days of initial intubation.

**Figure 1.** Chest radiograph at the time of fiberoptic bronchoscopy demonstrating bilateral diffuse alveolar infiltrates.

**Figure 2.** High-power light photomicrograph (original magnification X600) of a cytology smear from a BAL specimen demonstrates hemosiderin-laden macrophages (arrow). The cell pellet was isolated from the BAL fluid by centrifugation. A portion of the cell pellet was applied onto a slide, fixed in 95% ethanol, and stained by Paponicolou method.

**Figure 3.** Chest radiograph at the time of fiberoptic bronchoscopy demonstrating diffuse bilateral infiltrates.

**Case 2**

This 44-year-old homosexual male nonsmoker, with a history of hepatitis B infection and recurrent thoracic herpes zoster, was determined to have positive HIV serology test results 36 months PTA. Fifteen months PTA he developed fever, nausea, vomiting, rectal pain, and abnormal results of liver function tests. A liver biopsy specimen disclosed granulomatous hepatitis, without evidence for AFB or fungal disease. However, symptoms and liver function test abnormalities resolved entirely within 3 weeks of receiving empiric isoniazid, rifampin, and ethambutol. Treatment with these drugs was discontinued 3 months PTA on return of abdominal pain, nausea, vomiting, weight loss, malaise, and night sweats. An extensive gastrointestinal evaluation was unrevealing and the patient was admitted to the hospital for progression of symptoms.

At the time of hospital admission, the patient also complained of dyspnea, and was found to have a new large right pleural effusion with right lower lobe consolidation and atelectasis, in addition to a smaller left pleural effusion. A diagnostic right thoracentesis yielded serosanguineous fluid compatible with an exudate (total protein, 4,000 mg/dL; lactate dehydrogenase [LDH], 441 IU/mL [serum, 451 IU/mL]; glucose, 84 mg/dL [serum glucose not available]; RBC, 3,575/mm³; WBC, 170/mm³ [20% polymorphonuclear leukocytes, 60% lymphocytes, 20% mesothelial cells]); special stains and cultures for routine bacterial, AFB, and fungal pathogens were negative. A pleural biopsy specimen demonstrated abundant invasive fungal elements involving the pleura, with morphologic features consistent with *Histoplasma capsulatum*, prompting initiation of intravenous amphotericin B therapy.

On the seventh hospital day, the patient developed hypotension, melena, hematemeses, and abdominal pain. The patient was successfully resuscitated with intravenous crystalloid, 4 U of packed RBCs, and 6 U of fresh frozen plasma, but he required intubation for progressive respiratory compromise. A chest radiograph demonstrated increased interstitial markings bilaterally, enlarged cardiac silhouette, and bilateral pleural effusions, findings that were interpreted as representing congestive heart failure.
Despite aggressive diuretic management, subsequent chest radiographs demonstrated progressive diffuse pulmonary air-space disease (Fig 3). Empiric therapy with vancomycin, metronidazole, ceftriaxone, gentamicin, and dihydroxypropoxymethylquanine (DHPG) were initiated. Laboratory determinations disclosed the following values: PT, 19.3 s; PTT, 51 s; and platelet count, 128,000/mm³; and arterial blood gas determination demonstrated a pH of 7.42, PCO₂ of 29, and PO₂ of 122 while breathing 40% FIO₂ via an endotrachial tube.

On the 14th hospital day, diagnostic fiberoptic bronchoscopy demonstrated return of persistently bloody fluid, bilaterally. There were no endobronchial abnormalities. Specimens for special stains and cultures of routine microbiology and P carinii were negative. Hemosiderin-laden macrophages were demonstrated on cytologic examination (Fig 4).

In the absence of identification of new pulmonary pathogens, amphotericin B therapy was continued, while other empiric antimicrobials were discontinued. The patient received a total of 11 U of packed RBCs, 6 U of fresh frozen plasma, vitamin K, and continued supportive care. Sequential radiographs demonstrated gradual resolution of the pulmonary infiltrates, and the patient was successfully extubated.

**DISCUSSION**

Pulmonary infiltrates in HIV-infected individuals represent a common clinical problem, and the differential diagnosis includes infection, pulmonary edema, immune-mediated processes, neoplasia, and drug or radiation-induced disease.5,6 Diagnostic bronchoscopy with BAL has been established as effective in diagnosing many of these processes.14 As empiric treatment can introduce potentially toxic or immunosuppressive agents or medications with a high adverse effect profile, early use of BAL can be helpful in confirming clinical suspicions and in guiding the selection or modification of treatment. In contrast, the inability to establish an etiology for new pulmonary infiltrates in patients with AIDS often results in the administration of empiric drugs for prolonged periods.

Pulmonary hemorrhage has been described in association with a number of disorders, including necrotizing pulmonary infection, vasculitis, antibody-mediated disorders, and pulmonary infarction.7 Often, correction of the underlying disorder results in resolution of the pulmonary hemorrhage. Pulmonary hemorrhage is not commonly considered in the diagnosis of new pulmonary infiltrates in HIV-infected individuals,2-6 where the emphasis generally remains on evaluating and empirically treating for new infectious etiologies.6

McKenzie and coworkers15 reviewed the causes of death in 75 HIV-infected individuals and describe only one case of pulmonary hemorrhage. Kahn and coworkers16 described 51 immunocompromised patients with severe pulmonary hemorrhage, of whom 3 patients had AIDS. Roland and coworkers17 identified AIDS as a risk factor for developing hemorrhage and speculated that the hemorrhage was attributed to pulmonary Kaposi’s sarcoma. Grebski and coworkers18 described alveolar hemorrhage in 2 of 38 patients with AIDS and pulmonary infiltrates, one patient with an unspecified interstitial pneumonia, and another with non-Hodgkin’s lymphoma. However, specific clinical details were not available in these reports.

We describe two HIV-infected patients who developed pulmonary infiltrates during the course of their hospitalization. In each case, BAL findings were consistent with pulmonary hemorrhage. Although the exact mechanism for pulmonary hemorrhage is not readily apparent, hemorrhage in these patients with AIDS appears to represent a complication of an underlying predisposition rather than an independent phenomenon or a new infectious process.

In both cases, a transient bleeding diathesis could account for the development of pulmonary hemorrhage. In case 1, pulmonary hemorrhage could be attributed to thrombocytopenia5 or to the platelet dysfunction of uremia. In case 2, pulmonary hemorrhage may have resulted from a transient coagulopathy secondary to disseminated intravascular coagulation, liver synthetic dysfunction, or antibiotics. Alternatively, the pulmonary hemorrhage may represent a complication of H capsulatum infection. However, in contrast to aspergillosis infection,16 hemorrhage due to H capsulatum infection is not usual.19,20 A pulmonary-renal syndrome could be postulated in either case, but this is unlikely in view of the clinical recovery in the absence of specific therapy. Kaposi’s sarcoma could account for pulmonary hemorrhage, especially in case 1, although the absence of characteristic endobronchial lesions makes this less likely. Although a specific infectious etiology could be postulated, no new infection was identified in either case. Importantly in both cases, the pulmonary infiltrates resolved despite discontinuing empirically initiated treatment with antimicrobial medications.

The diagnosis of pulmonary hemorrhage requires a high index of suspicion, as clinical clues such as hemoptysis are not usual. Consideration of this entity will prompt an awareness for the characteristic features of lavage fluid to support this diagnosis.12 This includes documentation of persistently bloody return following sequential instillation of saline solution aliquots, demonstration of bilateral return of hemorrhagic BAL fluid in the case of diffuse radiographic abnormalities, and the demonstration of hemosiderin staining of macrophages. These characteristics differentiate pulmonary hemorrhage from trauma induced by bronchoscopy.21

Some investigators have advocated performing semi-quantitative analysis of the amount of hemorrhage in BAL specimens by determination of a macrophage hemosiderin.
score.16 This scoring system reportedly correlates highly with the degree of hemorrhage observed on autopsy lung specimens. However, Grebski and colleagues15 recently reported a limited utility of the hemosiderin score. Although scoring of hemosiderin-laden macrophages supports the diagnosis of pulmonary hemorrhage, the score is not able to distinguish among different specific etiologies that predispose to pulmonary hemorrhage.

The purpose of this report is to add the entity of pulmonary hemorrhage to the differential diagnosis of new pulmonary infiltrates in the hospitalized HIV-infected patient. The importance of properly identifying pulmonary hemorrhage is to facilitate subsequent evaluation. Consequently, in the absence of evidence for a new infection or vasculitis, correct identification of pulmonary hemorrhage may support the decision to discontinue treatment with empiric medications, preclude alterations in medical management, and obviate further invasive investigation. The treatment of pulmonary hemorrhage in patients with AIDS may simply require continued supportive measures while known underlying conditions predisposing to hemorrhage are corrected.

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Thoracic Endometriosis*

Recurrence Following Hysterectomy With Bilateral Salpingo-oophorectomy and Successful Treatment With Talc Pleurodesis

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This is a report of an unusual patient who had four of the five manifestations of thoracic endometriosis, including right pneumothorax, left hemThorax, chest pain, and hemoptysis. This patient shows that recurrence of symptoms can occur while a patient is receiving hormonal replacement therapy even after hysterectomy and bilateral salpingo-oophorectomy; estrogen replacement should probably be delayed for several months to allow complete regression of the ectopic endometrial tissue. Alternatively, chemical pleurodesis can be effective in treating recurrent pneumothorax or hemoptysis while the patient is receiving hormonal replacement. Bilateral pleural involvement and hemoptysis suggest microembolization of endometrial tissue as the pathogenic mechanism for thoracic endometriosis. (Chest 1994; 106:1894-96)

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