

Subacute hypersensitivity pneumonitis in an HIV infected patient receiving antiretroviral therapy

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Abstract

Abnormal pulmonary immune response to various antigens can lead to hypersensitivity pneumonitis. This disease has not previously been reported in HIV infected patients. This case report describes an HIV infected woman who developed subacute hypersensitivity pneumonitis in response to bird exposure. The disease manifested itself only after the patient experienced an improvement in her CD4 positive T lymphocyte count secondary to antiretroviral therapy. This case emphasises the need to consider non-HIV associated diseases in patients with HIV and suggests that diseases in which host immune response plays an essential role in pathogenesis may become more prevalent in HIV infected patients receiving effective antiretroviral therapy.

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Keywords: hypersensitivity pneumonitis; HIV; antiretroviral therapy

Hypersensitivity pneumonitis results from immunologically mediated lung damage provoked by antigen exposure. Common antigens include bird and animal proteins, chemicals, drugs, and fungi.¹ Although the pathogenesis of hypersensitivity pneumonitis is incompletely understood, lymphocytes appear to play an important part. Bronchoalveolar lavage (BAL) fluid from patients with hypersensitivity pneumonitis contains increased numbers of lymphocytes, with relatively larger increases in

CD8 positive T lymphocytes than in CD4 positive lymphocytes.^{2,3} Because the absolute numbers of CD4 and CD8 lymphocytes decrease along with the CD4 cell response to antigens in patients with advanced HIV infection, hypersensitivity pneumonitis should be an infrequent disease in this population. In fact, the literature contains no cases of HIV infected patients with hypersensitivity pneumonitis. However, many patients who receive highly active antiretroviral therapy (HAART) are experiencing improvement in their immune status,⁴ raising the possibility that diseases such as hypersensitivity pneumonitis, where host immune response plays an essential role in disease pathogenesis, may become more common. We report the case of a woman with AIDS who developed hypersensitivity pneumonitis after a significant improvement in her immune function due to HAART.

Case report

A 32 year old woman with AIDS and a nadir CD4 lymphocyte count of 86 cells/ μ l presented with three months of gradually increasing dyspnoea and non-productive cough. She denied fevers or chest pain, but had lost seven pounds in weight. She was a non-smoker and had a previous history of injection drug use, with none for the past three years. The patient was taking daily trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia (PCP) prophylaxis. Her antiretroviral regimen consisted of abacavir (Ziagen; GlaxoWellcome, North Carolina, USA), nevirapine (Viramune; Roxane, Columbus, Ohio, USA), saquinavir (Invirase; Roche, Nutley, New Jersey, USA), and nelfinavir (Viracept; Agouron, LaJolla, California, USA). At the time of initiation of this regimen, the patient's CD4 count was 147 cells/ μ l and her viral load was 43 800 copies/ml (fig 1). One month later her CD4 count had risen to 220 cells/ μ l, her viral load had become undetectable (less than 500 copies/ml), and her CD8 cell count was 728 cells/ μ l. At this time she began experiencing mild shortness of breath. She did not present for evaluation until two months later when her CD4 count was 273 cells/ μ l. Of note, the patient had owned lovebirds (*Agapornis* species) for two years and had acquired a button quail (*Turnix* species) and diamond dove (*Geopelia* species) four months prior to presentation.

Physical examination was unremarkable and her chest radiograph was normal. Oxygen saturation was 98% at rest, but decreased to 94% on exertion. Pulmonary function tests were remarkable for a transfer factor of 65%

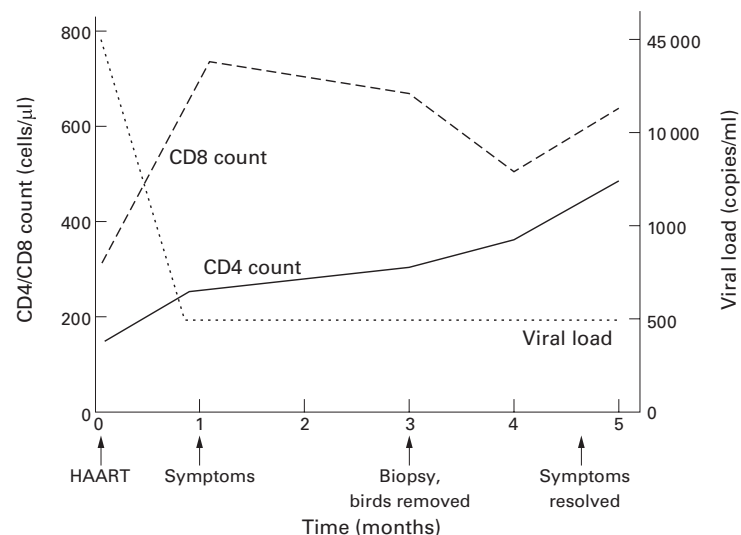


Figure 1 Time course of CD4 count, CD8 count, and viral load in relationship to clinical course.

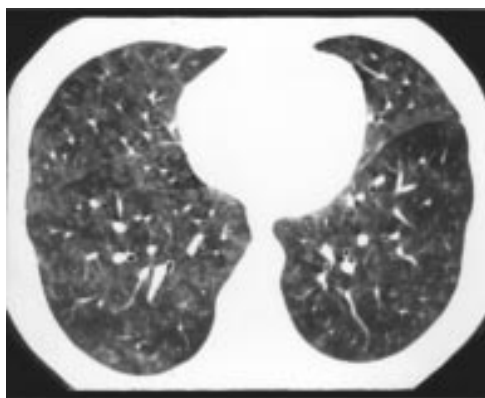


Figure 2 HRCT scan of the chest showing ill defined areas of ground glass opacities and multiple centrilobular nodules that become confluent in some areas.

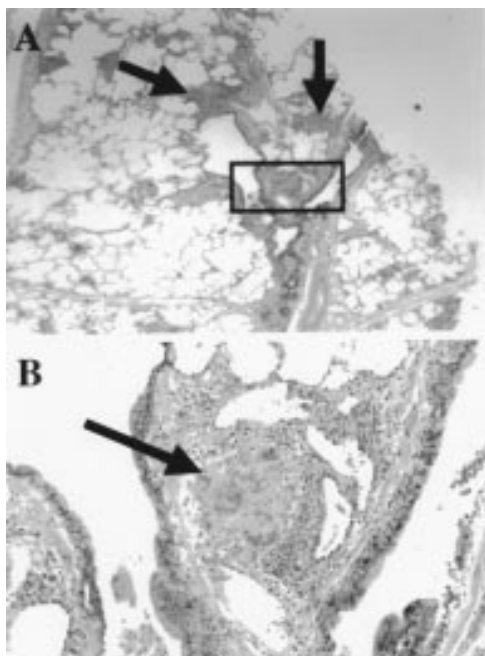


Figure 3 (A) Low power photomicrograph of a representative section of lung parenchyma obtained from an open lung biopsy specimen showing interstitial inflammation (arrows) extending out from a terminal bronchiole. (B) High power photomicrograph of the boxed region in A showing a non-necrotising granuloma with giant cells (arrows) adjacent to a bronchiole with a cellular lymphocytic bronchiolitis.

predicted, corrected for haemoglobin. Because of a suspicion for PCP, the patient underwent sputum induction and bronchoalveolar lavage (BAL), both of which were negative for *Pneumocystis*. Her symptoms progressed and her oxygen saturation declined to 92% at rest so further evaluation was performed. A high resolution computed tomographic (HRCT) chest scan showed patchy areas of ground glass opacities with evidence of air trapping and small nodules (fig 2). Repeat BAL with transbronchial biopsy specimens was negative for *Pneumocystis* and other pathogens. The BAL fluid showed lymphocytosis with a CD4/CD8 ratio of 0.7, similar to the ratio in her peripheral blood. Serum precipitins to pigeon antigens were negative.

Thoracoscopic lung biopsy sections were taken, and histological examination revealed a

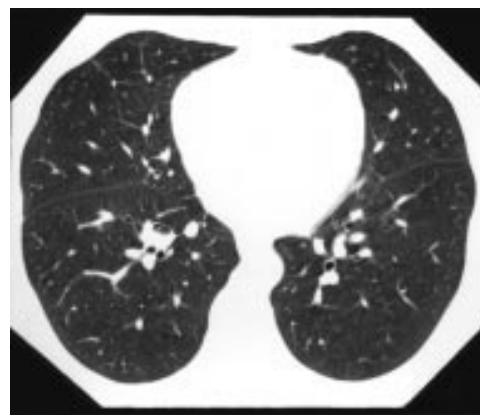


Figure 4 Repeat HRCT scan obtained six months after the end of the patient's exposure to birds. This image shows almost complete resolution of the ground glass opacities and nodules.

marked chronic interstitial inflammatory cell infiltrate with a cellular bronchiolitis of the medium and small airways (fig 3). Multiple small non-necrotising granulomas with giant cells were evenly distributed throughout the lung parenchyma. No organisms were seen on acid fast or fungal stains and no growth was observed in microbiological cultures. There was no evidence of injected silicates, established fibrosis, or honeycombing. Because the granulomas did not follow a bronchovascular pattern of distribution, the findings were felt to be more consistent with hypersensitivity pneumonitis than with sarcoidosis.

In this patient possible causes of hypersensitivity pneumonitis included her birds or antiretroviral medications. Because the patient had an excellent response to these medications, she was reluctant to discontinue them. It was therefore decided to remove her birds from the house. The patient did not receive steroids and the doses of her antiviral medications were not changed. Within several weeks her symptoms resolved completely. A repeat HRCT scan showed improvement of the ground glass opacities and nodules (fig 4). Repeat measurement of the transfer factor showed an improvement to 74% predicted.

Discussion

This patient's clinical history and pathology were consistent with subacute hypersensitivity pneumonitis which typically presents with the gradual onset of dyspnoea, cough, and weight loss.¹ The chest radiograph may be normal or may have reticulonodular and ground glass infiltrates. The HRCT scan usually contains small nodules with areas of ground glass opacities.³ Air trapping may also be present. The patient's HRCT scan was highly suggestive of hypersensitivity pneumonitis, and the pathology was characteristic with findings of interstitial inflammation, bronchiolitis, and non-necrotising granulomas.⁶ The distribution and appearance of the granulomas were sufficient to distinguish the disease from sarcoidosis and mycobacterial or fungal disease.

BAL fluid lymphocyte subsets can be helpful in diagnosing hypersensitivity pneumonitis in

the non-immunocompromised patient, but the interpretation of BAL lymphocyte subsets in the HIV infected patient is less straightforward. Studies have shown a BAL fluid lymphocytosis in HIV/AIDS patients with a CD4/CD8 ratio that generally reflects the ratio in the peripheral blood.^{7,8} These findings would be indistinguishable from those expected in hypersensitivity pneumonitis and would therefore not be useful in an HIV infected patient undergoing evaluation for hypersensitivity pneumonitis.³

This patient's sequence of development of hypersensitivity pneumonitis is intriguing. Her symptoms began shortly after she experienced a substantial increase in her CD4 lymphocyte count. The CD8 lymphocyte count has also been shown to increase when patients respond to HAART.⁹ Although difficult to prove conclusively, it is likely that the improvement in her immune function played some part in the development of hypersensitivity pneumonitis. This presentation is similar to cases of immune stimulation after initiation of HAART in the setting of infection with tuberculosis, *Mycobacterium avium* complex, and hepatitis C virus.¹⁰⁻¹⁴ In the present case the patient's immune system overreacted to an antigen instead of an infectious organism.

A recent report documented two cases of a sarcoid-like pulmonary illness that also occurred after immune reconstitution.¹⁵ These cases differed somewhat from the case presented here. One patient was asymptomatic and had chest radiograph abnormalities incidentally noted more than a year after the initiation of HAART. Treatment was not changed and the patient never became ill. The second patient developed respiratory symptoms shortly after beginning HAART. Treatment with interleukin-2 was discontinued, but antiretroviral agents were not changed. The patient's symptoms and pulmonary function gradually normalised. The pulmonary pathology in both these patients was consistent with sarcoidosis, not hypersensitivity pneumonitis as in our patient. Whether these various presentations are related solely to immune reconstitution or result from other factors cannot be fully determined; however, it is likely that the return of immune function played

some part in the development of the hypersensitivity in our patient.

The advent of effective treatment for HIV infection has changed many aspects of the disease. Patients are surviving longer, but are also developing new and unusual complications.⁴ Given the dramatic immune response seen in patients treated with HAART, future observations of HIV infected patients with responses to HAART may show an increase in the prevalence of hypersensitivity pneumonitis and other immune mediated diseases.

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