**CASE REPORT**

Sarcoidosis and HIV infection: a case report and a review of the literature

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Sarcoidosis occurring in patients with AIDS is rare. This infrequent association has been attributed to the impairment of the immune system that may interfere with the granuloma formation in HIV infected patients. However, the introduction of highly active antiretroviral therapy (HAART) has brought about a substantial and sustained increase in CD4+ T lymphocyte cells, and has consequently led to the development of the so called “immune restoration disease”.

The case of an HIV infected man who developed sarcoidosis after the initiation of HAART is described. Skin nodule images and histological specimens are reported. The association between sarcoidosis and HIV infection is also reviewed.

In recent years, our understanding of the basic mechanisms of HIV immunology and the biology of specific opportunistic pathogens and malignancies, together with the introduction of highly active antiretroviral therapy (HAART), have led to a significant decrease in the incidence of opportunistic infections and HIV related mortality.1

After HAART initiation, individuals infected with HIV may experience “paradoxical reactions” or the so called “clinical flares” that have been defined as the transient worsening or appearance of new signs, symptoms, or radiographic manifestations of underlying opportunistic infections, because of the early restoration of “dysregulated” pathogen specific immune response of the host, rather than the result of antiretroviral treatment failure or a relapse of previous opportunistic infections.2 3

The association of HIV infection and sarcoidosis has rarely been reported, as it is thought that the relative lack of CD4+ T lymphocytes in HIV disease might inhibit the development of sarcoidosis, where these cells play a central part in granuloma formation.3 4 Since HAART has become the standard of care in HIV infected patients, the incidence and outcome of concomitant sarcoidosis and HIV infection has not yet been defined.

We report a case of an HIV positive patient receiving HAART who developed a cutaneous and pulmonary sarcoidosis probably related to the immune restoration syndrome. Prolonged corticosteroid therapy was necessary to control the disease.

**CASE REPORT**

A 44 year old ex-drug addicted white man was diagnosed with HIV in December 1988. In September 2000 he presented with persistent low grade fever (37.8°C) and weight loss. Laboratory studies revealed a CD4+ T cell count of 130 cells/µl and a peripheral white blood cell count of 6560 cells/µl; total lymphocyte count, 2070 cells/µl (CD4+ T lymphocyte count, 2070 cells/µl, 31%) and a CD4+ T cell count of 510 cells/µl, CD8+ T lymphocytes of 1053 cells/µl with a CD4/CD8 ratio of 0.4; HIV-1 RNA level was 3500 copies/ml. Other laboratory findings were unremarkable with the exception of a mild increase in the sedimentation rate (35 mm/hour; normal value <28) and an increase of the serum angiotensin converting enzyme (SACE) level (200 UI/ml; normal value, <52 UI/ml). The tuberculin skin test was negative. Cultures performed on blood, sputum, and urine were negative for bacteria, mycobacteria, fungi, as well as all serological investigations of Mycoplasma pneumoniae, Chlamydia psittaci, Chlamydia pneumoniae, Coxiella burnetii, Legionella spp, and respiratory viruses.

Both chest radiography and lung computed tomography demonstrated diffuse reticulonodular infiltrates and mediastinal and hilar lymphadenopathy. A bronchoscopy was performed and microbiological cultures of bronchoalveolar lavage (BAL) did not yield any pathogens. Morphological and immunophenotypic profile of BAL showed a mild increase in the total cells recovered (300 000/ml: macrophage, 90%; lymphocytes, 9%) and lymphocyte subsets revealing a CD4+ cell count of 52%, and a CD8+ cell count of 43%, with CD4/CD8 ratio of 1.2. Transbronchial biopsy was considered immunovirological response in four months (CD4+ = 290/µl; HIV-1 RNA <40 copies/ml). Twenty months later the patient complained of asthenia, non-productive cough, dyspnoea on exertion, and multiple subcutaneous nodules in the forearms (fig 1). No symptoms referable to eyes, peripheral nerves, kidneys, liver, or heart were reported. Laboratory evaluation revealed a peripheral white blood cell count of 6560 cells/µl (total lymphocyte count, 2070 cells/µl, 31%) and a CD4+ T cell count of 510 cells/µl, CD8+ T lymphocytes of 1053 cells/µl with a CD4/CD8 ratio of 0.4; HIV-1 RNA level was 3500 copies/ml. Other laboratory findings were unremarkable with the exception of a mild increase in the erythrocyte sedimentation rate (35 mm/hour; normal value <28) and an increase of the serum angiotensin converting enzyme (SACE) level (200 UI/ml; normal value, <52 UI/ml). The tuberculin skin test was negative. Cultures performed on blood, sputum, and urine were negative for bacteria, mycobacteria, fungi, as well as all serological investigations of Mycoplasma pneumoniae, Chlamydia psittaci, Chlamydia pneumoniae, Coxiella burnetii, Legionella spp, and respiratory viruses.

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 Abbreviations: BAL, bronchoalveolar lavage; HAART, highly active antiretroviral therapy; SACE, serum angiotensin converting enzyme

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**Figure 1** Subcutaneous nodules in forearm.
but not obtained because the patient refused. A biopsy specimen of one subcutaneous nodule was therefore obtained. Histological examination revealed epithelioid cell granulomas with polynucleated giant cells suggesting a sarcoid granuloma (fig 2). Instead, special stains and microbiological cultures for bacteria, acid-fast bacilli, parasitic organisms, and fungi remained negative. Sarcoidosis with skin and pulmonary involvement was subsequently diagnosed and treatment with prednisolone at a daily dosage of 50 mg was initiated and gradually tapered. Over the next 2–3 weeks, all skin nodules and pulmonary symptoms resolved and SACE level returned to normal. The CD4+ cell count was 720/µl, and HIV-1 RNA viral load was 1200 copies/ml. However a month later, the patient abruptly discontinued steroid therapy and within a few days developed new skin nodules that required the reintroduction of steroid therapy. Steroid treatment was continued for two months and then gradually tapered without relapse of the disease.

DISCUSSION

A review of the English language medical literature identified 20 established cases of sarcoidosis occurring in patients with HIV infection: 14,6–16 and six,17–22 cases, respectively, before and after the introduction of HAART. In 13 of the former 14 patients, sarcoidosis preceded the diagnosis of HIV infection and the CD4+ T cell counts were mostly >200 cells/µl. Instead, in the one patient who presented with HIV infection before sarcoidosis, the CD4+ T cell count was more than 600 cells/µl. These observations suggest an occurrence of two independent conditions in the same patient rather than a causal relationship between the two diseases. However, since the start of HAART, a different scenario has been observed: sarcoidosis occurs when both a complete HIV viral load suppression and a sustained restoration of the immune system have been achieved (table 1). This occurred both for patients who presented with sarcoidosis for the first time and for the three patients in which a recurrence of sarcoidosis was diagnosed.

Since 1998, when the first five cases of focal granulomatous lymphadenitis due to Mycobacterium avium complex occurring after the initiation of HAART were described, an increasing number of reports have focused their attention on the effect of boosting the immunological function induced by HAART.23 Other clinical presentations of this unusual “infectious-inflammatory reaction” occurring in AIDS patients after HAART initiation included vitritis in the setting of cytomegalovirus retinitis, paradoxical reactions associated with HIV related tuberculosis, hepatic necrosis due to the reactivation of chronic hepatitis C, and lymph node inflammation related to a latent cryptococcal infection.24–27 These cases are collectively known as “immune restoration diseases” and support the idea...
that an improvement in the immune response during the initial phase of HAART may alter the clinical, radiographic, and histopathological appearance of an opportunistic infection in an otherwise immunodeficient host.

Sarcoidosis is an immune mediated systemic disease: all available evidence suggests that active sarcoidosis results from an exaggerated cellular immune response to a variety of antigens or self antigens, in which the process of T lymphocyte triggering, proliferation, and activation is sustained by the CD4+ type 1 (T helper 1) subclass of lymphocytes, that is probably the major effector cell in the cell mediated immunity of this disease. T helper 1 cells are characterised by their ability to produce many cytokines such as interferon-γ, interleukin-2, and tumour necrosis factor, that all together enhance immune activation. The result is an exaggerated T helper 1 lymphocyte response, a release of T helper 1 cytokines after extensive recruitment of lymphocytes in the affected organs, and thus the attraction and activation of mononuclear phagocytes that induce the granuloma formation.

Therefore, it could be assumed that, similar to what has been reported in the tuberculosis immune response, the development of sarcoidosis usually occurs when a significant increase in CD4+ T cell count induced by HAART has been acquired. In our patient, HIV-1 RNA was not completely suppressed despite the good immunological response. It is possible that a stable immune restoration rather than an undetectable viral load may play a major part in the dynamics of sarcoidosis development. An increase in CD8 cells, rather than memory T cells which seem to be implicated in the sarcoid-granuloma formation immune reconstitution granulomatous processes, remains controversial. In the case of sarcoidosis, everything seems easier: steroids are the treatment of choice for sarcoidosis in HIV negative patients, and steroids, at least for some authors, should generally take precedence over antimicrobial therapy in the immune reconstitution syndrome in HIV positive patients.

In our case, the decision to initiate corticosteroid therapy was based upon the worsening condition of the patient. The therapy was beneficial, well tolerated, and no long term complications were observed. Finally, since sarcoidosis tends to improve spontaneously, systemic corticosteroid therapy should therefore be reserved for symptomatic cases of active sarcoidosis.

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Submitted 16 March 2003
Accepted 24 May 2003

REFERENCES

Images in Medicine

Technetium-99m labelled red blood cell blood pool imaging versus contrast venography in a patient with extensive blue rubber bleb naevi

A 16 year old boy with non-familial, multiple subcutaneous blue rubber bleb nevi (BRBN) since birth presented to us at the age of 13. The BRBN had increased in size over the years. He also had other minor dysmorphic anomalies and was mentally and physically mildly subnormal. Although some of his features were similar to those seen in Noonan's syndrome, he lacked major elements of this condition and the presence of BRBN was extremely unusual. Bean's syndrome (BRBN and gastrointestinal bleeding or iron deficiency anaemia) was considered but he had no gastrointestinal involvement. The absence of enchondromata argued against Maffucci's syndrome (BRBN and enchondromata) in this boy. His chromosomes were normal. After thorough investigation the overall picture remained that of an uncertain or a non-specific syndrome. Because of the widespread blebs he underwent a number of imaging examinations including contrast venography of the arms, technetium-99m ($^{99m}$Tc) red blood cell blood pool scanning, and magnetic resonance imaging (MRI) of the brain. Venography revealed multiple haemangiomata and was restricted to limited views of the hand (fig 1) and arm. $^{99m}$Tc red blood cell blood pool imaging of the entire body demonstrated several subcutaneous lesions as well as in other soft tissues and feet (fig 2A, B, C). MRI confirmed sparing of the brain.

This case demonstrates the ability of the $^{99m}$Tc red blood cell blood pool scan to detect widely scattered lesions. The whole body was surveyed during a single examination without any increase in the radiation burden to the patient as only one dose is required. Furthermore, this procedure is non-invasive and relatively simple to perform. On the other hand, contrast venography was limited to views of the upper limb, as once the presence of haemangiomata was confirmed the study was stopped in order to reduce the radiation exposure and amount of contrast given, particularly because of the patient's young age.

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Figure 1 Contrast venography of the arm showing multiple haemangiomata.

Figure 2 Radionuclide blood pool images demonstrating multiple lesions in (A) head, (B) arms, and (C) legs and feet.
Technetium-99m labelled red blood cell blood pool imaging versus contrast venography in a patient with extensive blue rubber bleb naevi

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Postgrad Med J 2003 79: 538
doi: 10.1136/pmj.79.935.538

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