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.1,4 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 persistent low grade fever (37.8°C) and weight loss. Laboratory studies revealed a CD4+ T cell count of 130 cells/µl and a plasma HIV-1 RNA level of 150 000 copies/ml (by reverse transcription polymerase chain reaction; lower limit of detection, 40 copies/ml). Antiretroviral therapy with zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily) was initiated and he had a good immunovirological response in four months (CD4+ = 290/µl; HIV-1 RNA <40 copies/ml). Twenty months later the patient complained of asthma, 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 burnetti, 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.

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Figure 1 Subcutaneous nodules in forearm.

Abbreviations: BAL, bronchoalveolar lavage; HAART, highly active antiretroviral therapy; SACE, serum angiotensin converting enzyme
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 and six 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. 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. 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_h1) subclass of lymphocytes, that is probably the major effector cell in the cell mediated immunity of this disease. T_h1 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_h1 lymphocyte response, a release of T_h1 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 reactivation, 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.

It is well known that the sarcoid reaction is characterised by the sequestration, at sites of infection, of macrophages and activated T lymphocytes, which can represent up to 90% of total lymphocytes. In most patients cells bear the CD4+ phenotype, with a several-fold increase in the CD4/CD8 ratio, even if in rare cases CD8+ T lymphocytes represent the predominant cell type. The immunological features are not clearly exhibited in coexistent sarcoidosis/HIV infection. Before the introduction of HAART previous reports indicated a prevalence of lymphocytic alveolitis due to an increase in CD8 cells, with a very low CD4/CD8 ratio, which is a characteristic of HIV infection and not sarcoidosis, similar to that found in the peripheral blood in otherwise HIV positive patients.

Conversely, in the two cases reported by Nacache and coworkers, an intensive CD4+ lymphocytic alveolitis with a significant increase in BAL CD4/CD8 ratio was correlated to the local pulmonary immune inflammatory response induced by HAART. In our case, the BAL study did not reveal any marked sign of an immune response process even if the difference in the CD4/CD8 ratio between blood and BAL (0.4 vs 1.2) may suggest a positive correlation between the development of sarcoid-like pulmonary involvement and the improvement in HIV infection.

Furthermore, it is worth noting that in all reported clinical cases, sarcoidosis developed several months after the introduction of HAART; this is a longer delay compared with the onset of other typical immune reconstitution syndromes, such as the lymph node granuloma inflammation associated with Mycobacterium avium complex infection.

It is likely that naive or interleukin-2 receptor positive CD4+ T cells, rather than memory T cells which seem to be implicated in Mycobacterium avium complex exacerbation, may be involved in the sarcoid-granuloma formation immune response. In fact, recovery of naive or interleukin-2 receptor positive cells is delayed from three to six months after HAART introduction, whereas memory T cell recovery, appears with a delay of three weeks.

As finally, the need to initiate steroid therapy, as in other 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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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 (99mTc) 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. 99mTc 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 99mTc 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.

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