Sarcoidosis in HIV-Infected Patients in the Era of Highly Active Antiretroviral Therapy

Guillaume Foulon,[1,2] Marie Wislez,[1] Jean-Marc Naccache,[5] François-Xavier Blanc,[6] Antoine Rabbat,[3] Dominique Israël-Biet,[4] Dominique Valeyre,[5] Charles Mayaud,[1] and Jacques Cadranel[1]

[1]Service de Pneumologie et Réanimation Respiratoire, Hôpital Tenon, [2]Service de Pneumologie, Hôpital Bichat, [3]Service de Pneumologie, Hôpital de l'Hôtel-Dieu, and [4]Service de Pneumologie, Hôpital Européen Georges Pompidou, Paris, [5]Service de Pneumologie, Hôpital Avicenne, Bobigny, and [6]Unité de Pneumologie, Service de Medicine Interne, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

To analyze the impact of highly active antiretroviral therapy (HAART) on the characteristics and outcome of sarcoidosis in patients infected with human immunodeficiency virus (HIV), we identified HIV-infected patients in whom sarcoidosis was diagnosed between 1996 and 2000 from the admission registers of the pneumology departments of 12 hospitals in the Paris region (France). Sarcoidosis was diagnosed in 11 HIV-infected patients, of whom 8 were receiving HAART. HIV infection was diagnosed before sarcoidosis in 9 cases. At diagnosis of sarcoidosis, the mean CD4 cell count (± SD) was 390 ± 213 cells/mm^3, and the mean plasma virus load was 4002 ± 10,183 copies/mL. Sarcoidosis occurred several months after HAART introduction, when the CD4 cell count had increased and the plasma HIV load had decreased. Clinical and radiological characteristics, laboratory values for bronchoalveolar lavage fluid samples, and outcome after a long follow-up were similar for the patients receiving HAART and for HIV-uninfected patients.

HAART reduces the incidence of opportunistic infections [1], morbidity, and death among HIV-infected patients [2]. However, the status of various HIV-related infections can deteriorate at the outset of HAART, as recently reviewed by Shelburne et al. [3]. This paradoxical deterioration has been related to immunologic reconstitution [4].

The onset of sarcoidosis in HIV-infected patients was documented before the HAART era [5–14]. We recently described 2 cases of pulmonary disorders mimicking sarcoidosis in HAART-treated patients, and we found evidence of a relationship with immune reconstitution [15]. Another 9 such cases have since been reported, all of which occurred or worsened during HAART [16–23]. Two other series [24, 25] reported 14 other cases of sarcoidosis diagnosed either before or after the HAART era, of which 7 occurred or worsened during receipt of HAART. The aims of this study were to identify cases of sarcoidosis in HIV-infected patients during the period 1996–2000 (the first 4 years of widespread use of HAART in France) and to describe the characteristics and long-term outcome of both HIV infection and sarcoidosis according to the treatment administered and changes in immunologic and/or virologic status.

PATIENTS AND METHODS

Study design. Twelve pneumology departments at university hospitals in the Paris region were contacted by e-mail and asked to identify, from their admission registers, cases of sarcoidosis diagnosed in HIV-infected patients between June 1996 and December 2000. To be included in the study, patients had to have normal findings of chest radiography before the onset of sarcoidosis. Only patients who had clinical and radiological findings consistent with sarcoidosis and at least 1 biopsy specimen showing noncaseating granulomas and were

Received 14 June 2003; accepted 23 September 2003; electronically published 14 January 2004.

Reprints or correspondence: Dr. J. Cadranel, Service de Pneumologie, Hôpital Tenon, 4 rue de la Chine, 75020 Paris, France (jacques.cadranel@tnn.ap-hop-paris.fr).

Clinical Infectious Diseases 2004; 38:418–25

1058-4838/2004/3803-0018$15.00

followed-up for >24 months were included in the study. Infectious causes of granulomatous diseases (especially tuberculosis and mycosis) had to be excluded by microbiological analyses and by the absence of any clinical or radiological improvement in patients receiving specific treatment. The characteristics of both HIV infection and sarcoidosis were investigated according to the treatment administered (HAART and/or steroids) and changes in plasma HIV virus load and the circulating CD4 cell count.

Published cases of sarcoidosis occurring in HIV-infected patients were identified by a Medline search of the literature published during 1980–2002, with use of the following keywords: "[sarcoidosis OR sarcoid-like granulomatous disorder] AND [HIV OR AIDS]." Only well-documented reports in English and French were analyzed.

Data collection. One physician (G.F.) used a standard form to record the characteristics of the patients from the medical files. The form gathered data on 4 groups of characteristics: (1) epidemiological characteristics (age, sex, race, and smoking history); (2) characteristics of HIV infection, including risk factor for infection, HIV disease status at hospitalization (prior diagnosis of seropositivity, according to the 1993 Centers for Disease Control and Prevention classification of HIV disease [26]), the circulating CD4 lymphocyte count, plasma HIV virus load (limit of detection, 50 or 500 copies/mL, depending on the date and treatment center), antiretroviral treatment received (1-, 2-, 3-, or 4-drug regimens), and antimicrobial chemoprophylaxis received; (3) characteristics of sarcoidosis, including pulmonary and extrapulmonary symptoms and physical signs at the time of hospital admission, the time between onset and hospital admission, serum angiotensin-converting–enzyme levels, tuberculin skin-test results, chest radiographic aspect (stages 0– 4, as recommended by DeRemee et al. [27]), findings of whole-body ^{67}Ga scanning, and pulmonary function test (PFT) results, including blood gas levels while breathing room air and the diffusion capacity for carbon monoxide; and (4) outcome data for both HIV infection and sarcoidosis (physical findings, PFT results, and chest radiologic findings) and immunologic and virologic status (circulating CD4 cell count and plasma HIV virus load), as evaluated every 3–6 months from the time of diagnosis to the cut-off date for analysis (September 2002).

Particular attention was paid to the results of fiber-optic bronchoscopy and analysis of bronchoalveolar lavage (BAL) fluid specimens; that is, total and differential BAL-fluid cell counts, identification of pathogens (mycobacteria, viruses, fungi, and parasites) by appropriate staining, and culture of BAL fluid smears. CD4 and CD8 lymphocyte counts in BAL and blood specimens obtained concomitantly were also recorded. Total and differential BAL-fluid cell counts in BAL fluid from 29 control subjects were used for comparison. They were extracted from a previously published study performed by some of us [28]. Control subjects were healthy volunteers enrolled to define normal values for BAL-fluid lymphocyte subsets in our laboratory. They were 18 men and 11 women with a mean age ($\pm$SD) of 45 $\pm$ 12 years; 9 were smokers, and 20 were nonsmokers. Mean age and proportion of smokers did not differ between case and control subjects.

Statistical analysis. All data are expressed as mean value ($\pm$SD). Because of the small population size, nonparametric tests were used. Statistical comparisons were performed using the Mann-Whitney *U* test for unpaired data and the Wilcoxon test for paired data. *P* values of $<.05$ were considered statistically significant.

RESULTS

All 12 participating hospitals responded to our request for data, and 7 did not report any cases of sarcoidosis in HIV-infected patients. Fourteen possible cases of sarcoidosis were reported by 5 of the 12 pneumology departments. Three cases were excluded after reviewing the medical charts: in 1 case because of isolation of *Mycobacterium tuberculosis* from culture, in 1 case because of clinical and radiological improvement after antituberculous treatment, and in 1 case because of the absence of histological proof of sarcoid granuloma. The remaining 11 cases were included in the present study; 2 of these have been described elsewhere [15, 29]. The incidence of newly diagnosed cases of sarcoidosis in patients hospitalized in the 12 participating hospitals ranged from 30.7–125.1 cases per year during the study period, which corresponds to an incidence of HIV-associated sarcoidosis of 3.20–7.24 cases per 1000 sarcoidosis-patient–years in the 5 pneumology departments in which the 11 cases were diagnosed.

Characteristics of HIV infection at the time of diagnosis of sarcoidosis. Epidemiological data and characteristics of HIV infection are summarized in table 1. HIV infection was diagnosed before sarcoidosis in 9 patients and concomitantly in 2 patients (patients 9 and 10). The interval between diagnosis of HIV infection and diagnosis of sarcoidosis was 92 $\pm$ 46 months.

Eight patients were receiving HAART at the time of diagnosis of sarcoidosis; the duration of HAART was 29 $\pm$ 16 months (range, 3–43 months). For 7 patients, HAART comprised 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 protease inhibitor; for 1 patient (patient 7), HAART comprised 2 NRTIs and 1 nonnucleoside reverse transcriptase inhibitor. The shortest interval between HAART initiation and diagnosis of sarcoidosis occurred for patient 4, who had received IL-2 immunotherapy 3 months previously. Patient 7 developed sarcoidosis 8 months after starting IFN-α therapy for chronic hepatitis C; at the time sarcoidosis was diagnosed, he had been receiving HAART for 36 months. The CD4 cell count at the

Table 1. Epidemiological data and characteristics of HIV infection at the time of diagnosis of sarcoidosis in 11 HIV-infected patients.

Patient	Age in years, sex	Race	Smoker	HIV infection risk factor	Prior AIDS class[a]	CD4 cell level			Virus load, copies/mL
						Count, cells/mm^3			
						Nadir	At diagnosis	Percentage	
1	30, F	White	No	Heterosexual	C1	4	683	28.4	<50
2[b]	44, M	White	No	Homosexual	C2	19	219	14	<500
3	46, M	White	No	Heterosexual	C2	89	225	13.2	75
4[b,c]	34, F	White	Yes	Heterosexual	B2	275	449	34	3500
5	48, M	White	Yes	Homosexual	B3	146	566	33	150
6	31, M	White	Yes	IDU	B1	34	166	10	<200
7	32, M	White	Yes	IDU	C2	139	263	28	<20
8	40, F	Black	No	Heterosexual	A2	NA	482	31	NA
9	32, M	Black	No	Heterosexual	A3	NA	168	12	ND
10	40, M	Black	No	Heterosexual	A2	NA	294	23	31,000
11	37, M	White	No	Homosexual	C1	11	771	20	<50

NOTE. IDU, injection drug user; NA, not applicable (patient was infected with HIV-2); ND, not determined.

[a] Defined in the 1993 CDC classification of HIV disease.

[b] Cases already reported [15].

[c] Case already reported [29].

time of diagnosis of sarcoidosis in HAART-treated patients was 418 ± 234 cells/mm^3 (range, 166–771 cells/mm^3), and the CD4 cell percentage was 22.6% ± 9.5% (range, 10%–34%); the plasma HIV virus load was 466 ± 315 copies/mL (range, <50–3500 copies/mL). All these patients had normal chest radiograph findings when HAART was started. As shown in figure 1, CD4 cell counts increased markedly and plasma virus loads fell before the onset of sarcoidosis in patients receiving HAART.

The 3 patients (patients 8, 9, and 10) who were not receiving antiretroviral treatment at the onset of sarcoidosis had asymptomatic HIV infection. Their blood CD4 cell count at the diagnosis of sarcoidosis was 315 ± 158 cells/mm^3 (range, 168–482 cells/mm^3), and their blood CD4 cell percentage was 22% ± 9.5% (12%–31%). The virus load was 31,000 copies/mL in 1 patient (patient 10), not available for 1 patient (patient 9), and not determinable in 1 patient who was infected with HIV-2 (patient 8).

Characteristics of sarcoidosis. The clinical and radiological characteristics of the patients with sarcoidosis are shown in table 2. All the patients had thoracic involvement, and 8

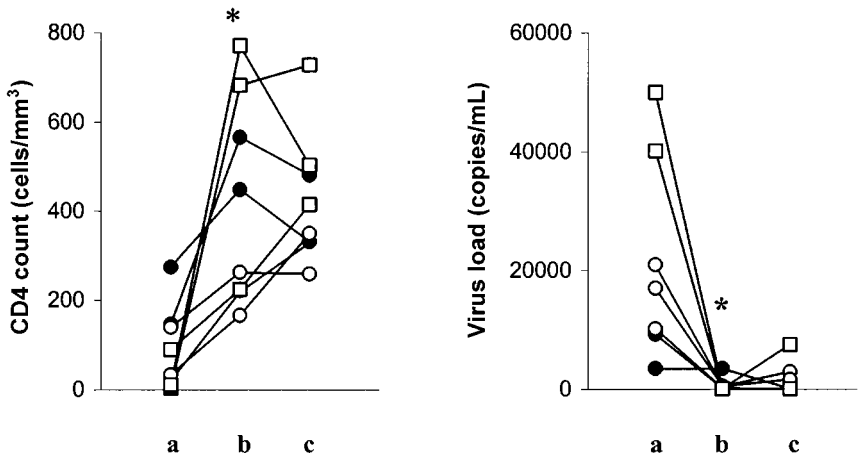

Figure 1. Time course of immunologic *(left)* and virologic *(right)* parameters for patients receiving HAART. *a,* Data obtained before initiation of HAART. *b,* Data at the diagnosis of sarcoidosis. *c,* Data at the end of follow-up. $P < .05$ for comparison of *a* and *b*. *Open squares* represent patients whose sarcoidosis was cured, *open circles* represent patients whose sarcoidosis was improved or stable, and *closed circles* represent patients receiving steroids for sarcoidosis aggravation.

Table 2. Characteristics of sarcoidosis in 11 HIV-infected patients.

Patient	Therapy at onset of sarcoidosis	Delay in initiation of HAART, months	Symptoms	Site(s) positive for sarcoidosis	Chest radiographic aspect, stage[a]	Extrathoracic involvement	Sarcoidosis treatment	Outcome of sarcoidosis
1	HAART	36	None	Mediastinal nodes	1	None	None	Cured
2[b]	HAART	11	None	Bronchus and lung	3	Salivary glands	None	Improved
3	HAART	40	Dyspnea	Bronchus	2	None	None	Cured
4[b,c]	HAART, IL-2	3	Cough, dyspnea	Bronchus and lung	3	Salivary glands, spleen	Oral steroids for dyspnea and deterioration of CXR and PFT findings	Improved, but relapsed during steroid therapy (5 mg/day)
5	HAART	34	Cough, dyspnea	Lung	3	None	Oral steroids for dyspnea and deterioration of PFT findings	Cured after withdrawal of steroid therapy
6	HAART	18	None	Lung	3	None	None	Stable
7	HAART, INF-α	43	Cough, dyspnea	Bronchus and skin	2	Skin, peripheral lymph node, liver	None	Improved
8	No HAART	NA	Cough, dyspnea	Bronchus and skin	2	Skin, eye, peripheral lymph node, muscle	Oral steroids for dyspnea, uveitis, and deterioration of PFT findings	Improved, but relapsed during steroid therapy (10 mg/day)
9	No HAART	NA	Dyspnea, weight loss	Bronchus	3	Peripheral lymph node, spleen, skin	Doxycycline for skin lesions	Improved
10	No HAART	NA	Cough, dyspnea, fever	Bronchus and mediastinal nodes	2	Fever, major asthenia, salivary glands, liver, spleen	Hydroxychloroquine for fever and major asthenia	Improved
11	HAART	43	Fever, sweats, weight loss	Mediastinal nodes	1	None	None	Cured

NOTE. CXR, chest radiograph; IL-2, IL-2 therapy; INF-α, INF-α therapy; NA, not applicable; ND, not determined; PFT, pulmonary function test.

[a] According to the recommendations of DeRemee et al. [27].

[b] Cases already reported [15].

[c] Case already reported [15, 29].

were symptomatic. Pulmonary function tests performed for all patients showed a restrictive pattern in 3 (for patients 3, 8, and 9, the total lung capacity was <80% of the predicted value) and an obstructive pattern in 1 (for patient 4, the forced expiratory volume in 1 s was <70% of the predicted value) (data not shown). The resting partial arterial pressure of oxygen was 78 ± 10 mm Hg (range, 63–97 mm Hg), and the ratio of the diffusion capacity for carbon monoxide to the alveolar gas volume was 67% ± 23% (range, 32%–10%). The angiotensin-converting–enzyme level was increased (to >1.5 times the upper limit of normal) in 5 of the 10 patients tested. Tuberculin skin-test reactions were negative for all 10 patients tested.

BAL was performed for every patient (table 3). Lymphocyte, neutrophil, and eosinophil counts in BAL fluid specimens, expressed as both the percentage of total BAL-fluid cell count and as absolute value, were significantly increased in case patients, compared with control subjects. Levels of T lymphocyte subsets were analyzed in BAL specimens from 9 patients, all but 2 of whom (patients 9 and 10) were receiving HAART at the onset of sarcoidosis. In patients receiving HAART, absolute CD4 and CD8 cell counts were both significantly higher than they were in control subjects. However, the increase in CD4 cells was greater, resulting in a significantly higher CD4:CD8 ratio in case patients than in control subjects. The CD4:CD8 cell ratio was also significantly higher in BAL fluid than in blood at the time of diagnosis of sarcoidosis (figure 2). In the 2 of the 3 patients who were not receiving HAART at the start of sarcoidosis, lymphocytic alveolitis was characterized by a predominance of CD8 cells in one patient (patient 9; CD4:CD8 ratio, 0.65) and of CD4 cells in another (patient 10; CD4:C8 ratio, 2) (data not shown); data were not available for the one other patient (patient 8).

Extrathoracic organ involvement was found, on the basis of clinical, biological, or morphological signs (including findings of ^{67}Ga scanning) in 6 patients (table 2), including the 3 patients who were not receiving HAART at the onset of sarcoidosis.

Treatment and outcome of HIV infection and sarcoidosis. All 11 patients were alive at the cut-off date for this analysis. HAART was never discontinued for the 8 patients who were receiving HAART at the time of diagnosis of sarcoidosis (table 2). HAART was started for 2 of the other 3 patients (patients 9 and 10), but patient 9 subsequently stopped taking it. HAART was not prescribed to the HIV-2–seropositive patient (patient 8) (table 2). Four patients received empirical antituberculous treatment for 2 months, and 3 did not improve (patients 2, 5, and 6). In the fourth patient (patient 9), the clinical manifestations of sarcoidosis initially improved as the immune deficiency worsened but were aggravated after initiation of HAART (and the concomitant increase in the CD4 cell count from 144 cells/mm^3, before HAART, to 351 cells/mm^3, 2 years later), despite renewal of antituberculous treatment.

Table 3. Bronchoalveolar lavage fluid cell counts and lymphocyte subsets in patients and control subjects.

Patient group, laboratory value	Mean value ± SD: Patients (n = 11)	Mean value ± SD: Control subjects (n = 29)	P
All patients			
BAL count, cells/μL	371 ± 215	218 ± 146	.03
Macrophages			
Percentage	57.2 ± 20.7	88 ± 6.5	<.0001
Count, cells/μL	219.7 ± 142.3	193.5 ± 137.8	NS
PMN neutrophils			
Percentage	3.8 ± 3.9	1.5 ± 1.6	.0495
Count, cells/μL	14.7 ± 15.3	3.7 ± 5.8	.0096
PMN eosinophils			
Percentage	1.6 ± 2.7	0.1 ± 0.3	.039
Count, cells/μL	3.5 ± 3.6	0.4 ± 1.3	.0138
Lymphocytes			
Percentage	37.1 ± 18.5	10.5 ± 6.3	<.0001
Count, cells/μL	132.3 ± 100.1	20.6 ± 15.5	<.0001
Patients receiving HAART[a]			
Lymphocytes			
Percentage	39.1 ± 19	10.5 ± 6.3	<.0001
Count, cells/μL	134 ± 105	20.6 ± 15.4	<.0001
CD4 lymphocytes			
Percentage	65.2 ± 17.5	54.6 ± 47.1	.0894
Count, cells/μL	95.7 ± 82.7	11.2 ± 9.4	.0009
CD8 lymphocytes			
Percentage	28.3 ± 15.8	38.3 ± 11.7	NS
Count, cells/μL	29.1 ± 17.8	8 ± 6.4	.0004
CD4:CD8 ratio	3.52 ± 2.55	1.59 ± 0.60	.066

NOTE. BAL, bronchoalveolar lavage fluid; PMN, polymorphonuclear.

[a] Data for the patients who were receiving HAART at the onset of sarcoidosis.

At the cut-off date, all the patients remained asymptomatic for HIV infection, and their immunologic and virologic status had not deteriorated (figure 1). Clinical and radiological cure of sarcoidosis was noted for 3 patients, all of whom were treated with HAART. In 5 patients (1 of whom [patient 9] was not receiving HAART at the onset of sarcoidosis), sarcoidosis improved or remained stable without steroid treatment. Systemic corticosteroid therapy was given to the remaining 3 patients (patients 4, 5, and 8) for dyspnea, deterioration of PFT results, and/or progression from radiological stage 2 to stage 3. No HIV-related or steroid-related complications were observed during the treatment. In 1 patient (patient 5), sarcoidosis was cured and steroid therapy was interrupted while HAART was being administered. In the other 2 case patients, steroid therapy could not be withdrawn after 12 and 16 months of treatment, respectively. One patient was of black race (patient 8), and 1 had received IL-2 (patient 4). There was no difference in the changes in immunologic and virologic parameters between pa-

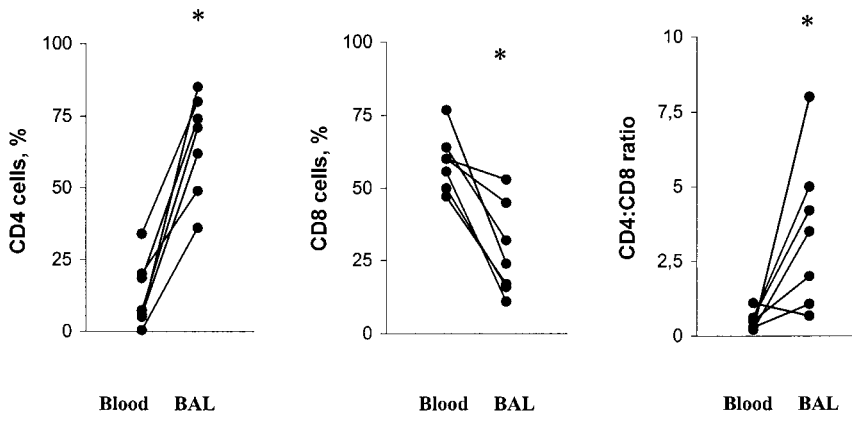

Figure 2. Comparison of levels of CD4 and CD8 lymphocytes in blood and bronchoalveolar lavage fluid (BAL) at the time of diagnosis of sarcoidosis in patients receiving HAART ($P < .05$).

tients in whom sarcoidosis was cured or improved and patients with sarcoidosis that remained stable or deteriorated.

DISCUSSION

The 11 patients described here met the usual criteria for sarcoidosis that were established for HIV-seronegative patients [30]. Their clinical histories were consistent with the diagnosis of sarcoidosis, with prominent pulmonary manifestations. The respiratory symptoms and radiological findings (mediastinal and hilar nodes and/or diffuse interstitial micronodular opacities with a predominantly perilymphatic distribution), as well as the extrathoracic involvement observed (of the salivary glands, eyes, skin, spleen, and liver) were those usually encountered in sarcoidosis. All of the patients had histological evidence of noncaseating granulomatosis disorders, as determined by intrathoracic biopsy. Other conditions usually associated with granulomatous disorders were ruled out; namely, environmental exposure, vasculitides, tumoral and infectious diseases, mycosis, and mycobacterial infection [30]. The pulmonary disorders did not improve, and sometimes worsened, in patients who received antituberculous treatment.

Our most important finding is that sarcoidosis occurred in patients receiving HAART in all but 3 cases. HIV infection is characterized by a profound alteration of the immune response components [31, 32] that are also involved in granuloma formation, namely the Th1-type CD4 cells that secrete IL-2 and INF-γ [33–35]. HAART can be associated with an "immune reconstitution inflammatory syndrome" [3]. Our findings suggest that sarcoidosis may be related to recovery of late memory and/or naive CD4 lymphocytes during HAART. Sarcoidosis generally occurred after marked increases in the CD4 cell count and a marked decreases in HIV load (figure 1). Granuloma formation was found in the lungs of all the patients. It was associated with CD4 cell recruitment from blood (figure 2) and mainly consisted of CD4 cells [15]. Recovery of Th1-type (memory) CD4 cell functions has been implicated in paradoxical aggravation of infectious granulomatous disorders (i.e., tuberculosis and other mycobacterial infections) [3, 36, 37]. However, the mean interval between HAART introduction and pulmonary onset in our patients with sarcoidosis was much longer (several months) than that reported for granulomatous disorders of infectious origin (a few weeks) [36,37]. This suggests the involvement of the naive CD4 cell pool, which has been shown to expand later than the memory cell pool in HIV-infected patients receiving HAART [4]. It is interesting to note that sarcoidosis developed more rapidly in the 2 patients also receiving Th1 cytokines (IL-2 and IFN), which are known to play a pivotal role in granuloma formation [33, 35].

In 3 patients, sarcoidosis occurred in the absence of HAART and was diagnosed at the same time as HIV infection. All 3 patients were of black race, which is a known risk factor for sarcoidosis [38], as is extrathoracic involvement [39], which was also observed in these patients. Findings for these patients were similar to those for cases that occurred before the HAART era [5–14], especially regarding the predominantly CD8-lymphocytic alveolitis in 1 case patient (patient 9) [6, 8, 9, 12], which has been related to HIV infection itself [40]. In this latter patient, the sarcoidosis first improved radiologically as the CD4 cell count fell, then worsened 2 years after initiation of HAART, as recently reported [17,22].

The course of sarcoidosis in our patients was similar to that observed in HIV-seronegative patients [30]. Most recovered or improved spontaneously, or remained stable, after lengthy follow-up, as did almost all those with a stage 1 or 2 radiological pattern [41]. In these patients, HAART was never withdrawn and immunologic parameters did not deteriorate (figure 1). Steroid treatment was needed in some patients and could not be interrupted for those with particular risk factors, namely a patient of black race with pulmonary and extrapulmonary sar-

coidosis [30] and a patient receiving IL-2 who developed an obstructive ventilatory disorder [41].

In conclusion, sarcoidosis can occur in HIV-infected patients with long-term immunologic reconstitution during HAART. Treatment with IL-2 or IFN-α 2a may be a risk factor for sarcoidosis. Clinical and radiological findings, BAL-fluid analysis findings, and outcome are similar to those observed for HIV-uninfected patients.

Acknowledgments

We thank Drs. Anne Bergeron, Marcel Bonay, Thierry Chinet, Louis-Jean Couderc, Bruno Crestani, Daniel Dusser, Bruno Housset, Marc Humbert, Hervé Mal, and Thierry Urban, for their participation, and Drs. Eric Oksenhendler, Laurence Weiss, Jean-Luc Meynard, and Vincent Jeantils, for providing information on the outcome of HIV infection in their patients.

References

1. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA **1999**; 282:2220–6.
2. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med **1998**; 338:853–60.
3. Shelburne SA III, Hamill RJ, Rodriguez-Barradas MC, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine (Baltimore) **2002**; 81:213–27.
4. Autran B, Carcelain G, Li TS, et al. Positive effects of combined antiretroviral therapy on $CD4^+$ T cell homeostasis and function in advanced HIV disease. Science **1997**; 277:112–6.
5. Gowda KS, Mayers I, Shafran SD. Concomitant sarcoidosis and HIV infection. CMAJ **1990**; 142:136–7.
6. Whitlock WL, Lowery WS, Dietrich RA. Bronchoalveolar lavage in sarcoidosis and HIV infection. Chest **1990**; 98:517.
7. Granieri J, Wisnieski JJ, Graham RC, Smith H, Gogate P, Aucott JN. Sarcoid myopathy in a patient with human immunodeficiency virus infection. South Med J **1995**; 88:591–5.
8. Lowery WS, Whitlock WL, Dietrich RA, Fine JM. Sarcoidosis complicated by HIV infection: three case reports and a review of the literature. Am Rev Respir Dis **1990**; 142:887–9.
9. Gormand F, Pacheco Y, Trepo C, Diperno D, Gilbert E, Perrin Fayolle M. Association sarcoïdose et SIDA. Presse Med **1989**; 18:361.
10. Coots LE, Lazarus AA. Sarcoidosis diagnosed in a patient with known HIV infection. Chest **1989**; 96:201–2.
11. Amin DN, Sperber K, Brown LK, Chusid ED, Teirstein AS. Positive Kveim test in patients with coexisting sarcoidosis and human immunodeficiency virus infection. Chest **1992**; 101:1454–6.
12. Newman TG, Minkowitz S, Hanna A, Sikand R, Fuleihan F. Coexistent sarcoidosis and HIV infection: a comparison of bronchoalveolar and peripheral blood lymphocytes. Chest **1992**; 102:1899–**1901**.
13. Kalter S, Lopez-Berestein G. Acquired immune deficiency syndrome in a patient with prior sarcoidosis: case report with monocyte function studies. Tex Med **1985**; 81:44–6.
14. Wurm K, Ewert G, Lohr G. Sarcoidosis complicated by HTLV-III infection: steroid therapy in combination with thymostimulin. Sarcoidosis **1987**; 4:68–70.
15. Naccache JM, Antoine M, Wislez M, et al. Sarcoid-like pulmonary disorder in human immunodeficiency virus–infected patients receiving antiretroviral therapy. Am J Respir Crit Care Med **1999**; 159:2009–13.
16. Mirmirani P, Maurer TA, Herndier B, McGrath M, Weinstein MD, Berger TG. Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome. J Am Acad Dermatol **1999**; 41:285–6.
17. Lenner R, Bregman Z, Teirstein AS, DePalo L. Recurrent pulmonary sarcoidosis in HIV-infected patients receiving highly active antiretroviral therapy. Chest **2001**; 119:978–81.
18. Blanche P, Gombert B, Rollot F, Salmon D, Sicard D. Sarcoidosis in a patient with acquired immunodeficiency syndrome treated with interleukin-2. Clin Infect Dis **2000**; 31:1493–4.
19. Gomez V, Smith PR, Burack J, Daley R, Rosa U. Sarcoidosis after antiretroviral therapy in a patient with acquired immunodeficiency syndrome. Clin Infect Dis **2000**; 31:1278–80.
20. Lee AK, Chronister CL. Sarcoidosis-related anterior uveitis in a patient with human immunodeficiency virus. J Am Optom Assoc **1999**; 70: 384–90.
21. Viani RM. Sarcoidosis and interstitial nephritis in a child with acquired immunodeficiency syndrome: implications of immune reconstitution syndrome with an indinavir-based regimen. Pediatr Infect Dis J **2002**; 21:435–8.
22. Hill KA, Till M, Laskin WB. Pathologic quiz case: pulmonary symptoms and lymphadenopathy in a human immunodeficiency virus–infected woman. Arch Pathol Lab Med **2003**; 127:111–2.
23. Wittram C, Fogg J, Farber H. Immune restoration syndrome manifested by pulmonary sarcoidosis. AJR Am J Roentgenol **2001**; 177:1427.
24. Haramati LB, Lee G, Singh A, Molina PL, White CS. Newly diagnosed pulmonary sarcoidosis in HIV-infected patients. Radiology **2001**; 218: 242–6.
25. Morris DG, Jasmer RM, Huang L, Gotway MB, Nishimura S, King TE Jr. Sarcoidosis following HIV infection: evidence for CD4(+) lymphocyte dependence. Chest **2003**; 124:929–35.
26. Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. JAMA **1993**; 269:729–30.
27. DeRemee RA. The roentgenographic staging of sarcoidosis: historic and contemporary perspectives. Chest **1983**; 83:128–33.
28. Akoun GM, Cadranel JL, Blanchette G, Milleron BJ, Mayaud CM. Bronchoalveolar lavage cell data in amiodarone-associated pneumonitis: evaluation in 22 patients. Chest **1991**; 99:1177–82.
29. Levy Y, Durier C, Krzysiek R, et al. Effects of interleukin-2 therapy combined with highly active antiretroviral therapy on immune restoration in HIV-1 infection: a randomized controlled trial. ANRS 079 Study Group. AIDS **2003**; 17:343–51.
30. Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med **1997**; 336: 1224–34.
31. Fauci AS. Multifactorial nature of human immunodeficiency virus disease: implications for therapy. Science **1993**; 262:1011–8.
32. Maggi E, Mazzetti M, Ravina A, et al. Ability of HIV to promote a TH1 to TH0 shift and to replicate preferentially in TH2 and TH0 cells. Science **1994**; 265:244–8.
33. Conron M, Du Bois RM. Immunological mechanisms in sarcoidosis. Clin Exp Allergy **2001**; 31:543–54.
34. Baumer I, Zissel G, Schlaak M, Muller-Quernheim J. Th1/Th2 cell distribution in pulmonary sarcoidosis. Am J Respir Cell Mol Biol **1997**; 16:171–7.
35. Hunninghake GW, Bedell GN, Zavala DC, Monick M, Brady M. Role of interleukin-2 release by lung T-cells in active pulmonary sarcoidosis. Am Rev Respir Dis **1983**; 128:634–8.
36. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med **1998**; 158:157–61.
37. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. Lancet **1998**; 351:252–5.

38. Rybicki BA, Maliarik MJ, Major M, Popovich J Jr, Iannuzzi MC. Epidemiology, demographics, and genetics of sarcoidosis. Semin Respir Infect **1998**; 13:166–73.
39. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Case Control Etiologic Study of Sarcoidosis (ACCESS) Research Group. Am J Respir Crit Care Med **2001**; 164:1885–9.
40. Mayaud CM, Cadranel J. HIV in the lung: guilty or not guilty? Thorax **1993**; 48:1191–5.
41. Viskum K, Vestbo J. Vital prognosis in intrathoracic sarcoidosis with special reference to pulmonary function and radiological stage. Eur Respir J **1993**; 6:349–53.