

CASE 5

Sarcoidosis in association with HAART
therapy in an HIV-infected patient

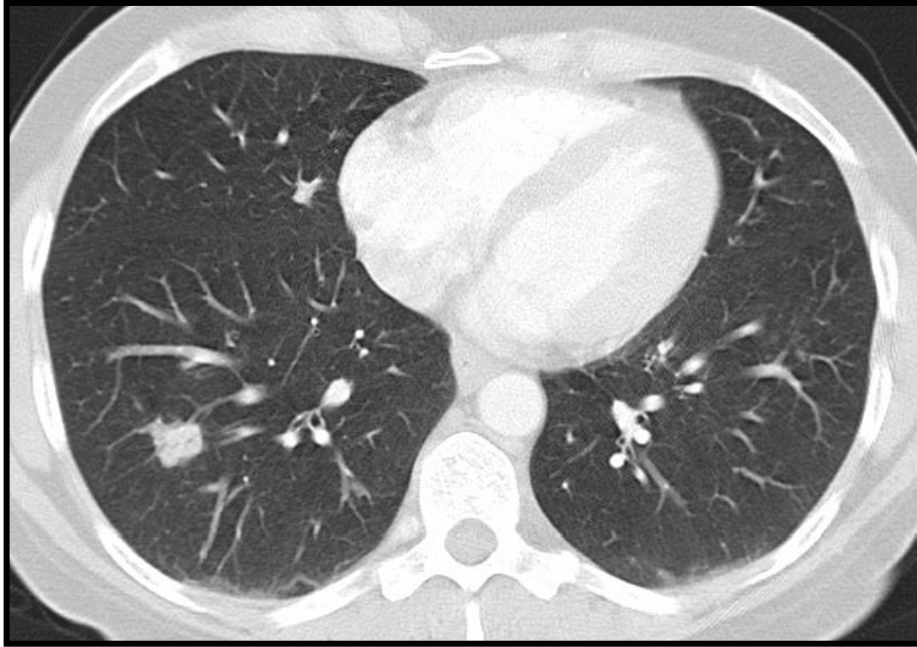
USCAP Pulmonary Panel 2007

Case 5

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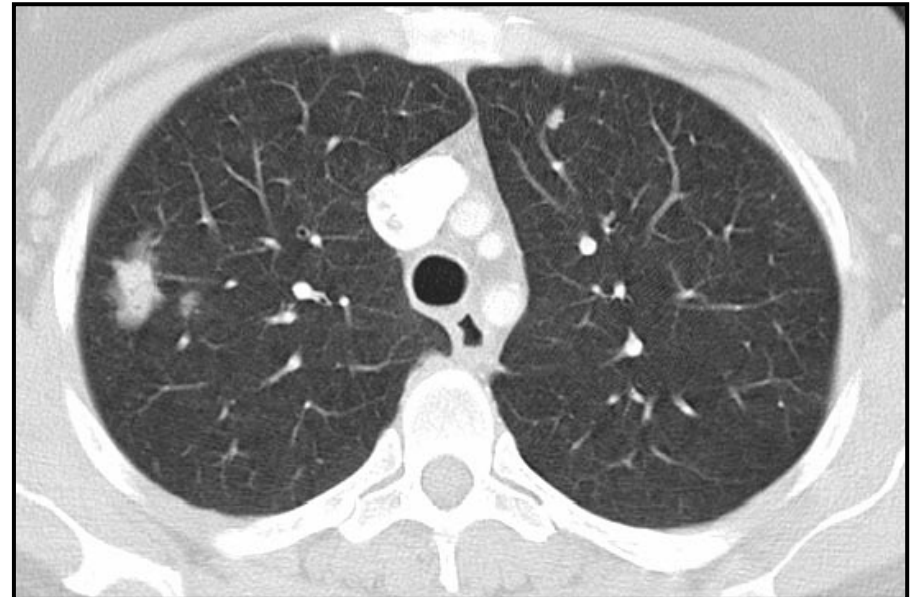
Case History

- 46 year old female presenting with increasing dyspnoea
- Had lost weight (2 stone) and was also lethargic.
- Past medical history includes HIV infection and alcohol abuse.
- Was undergoing highly active antiretroviral therapy (HAART) at the time of presentation with pulmonary symptoms, although weight had returned to normal levels.

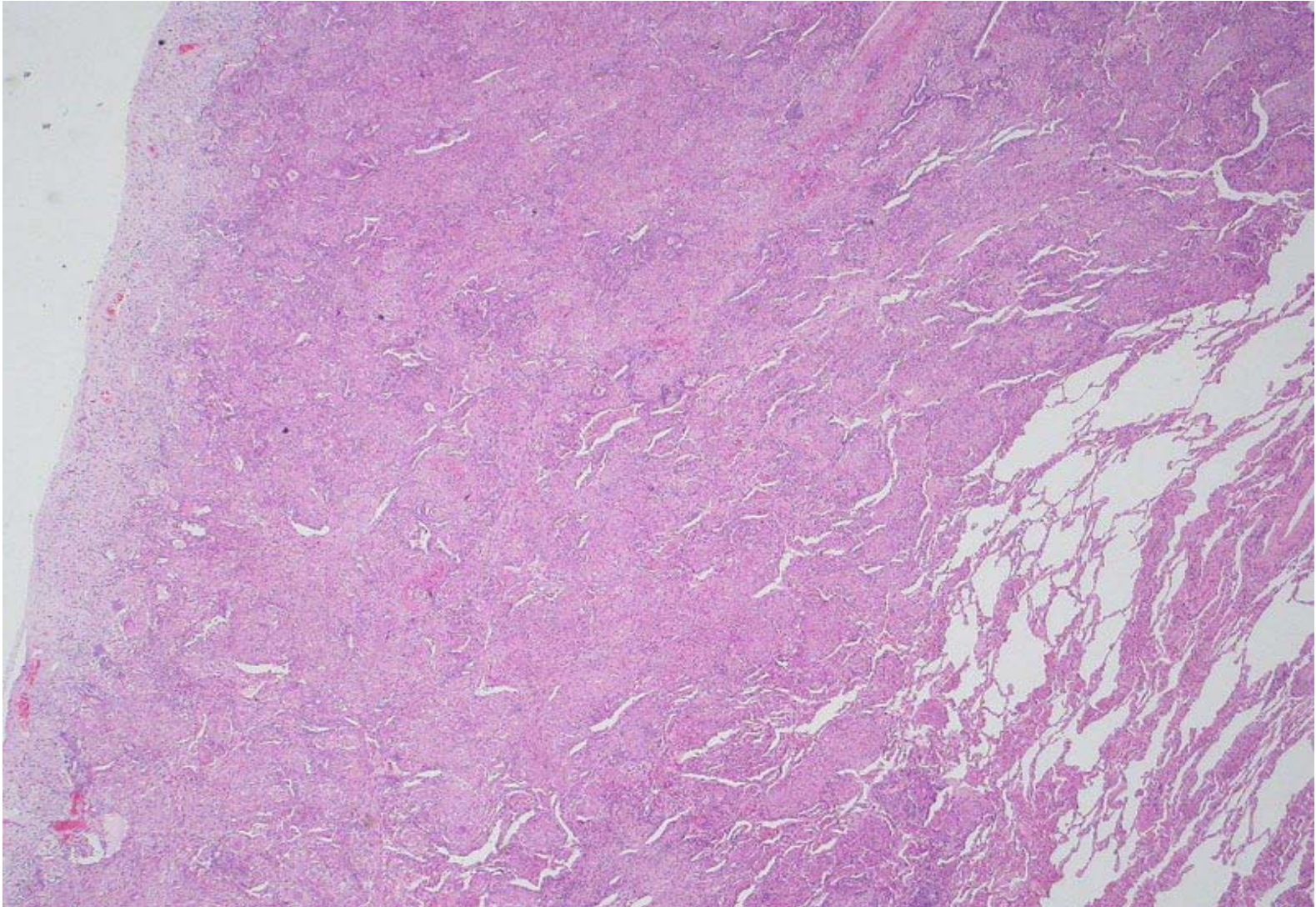


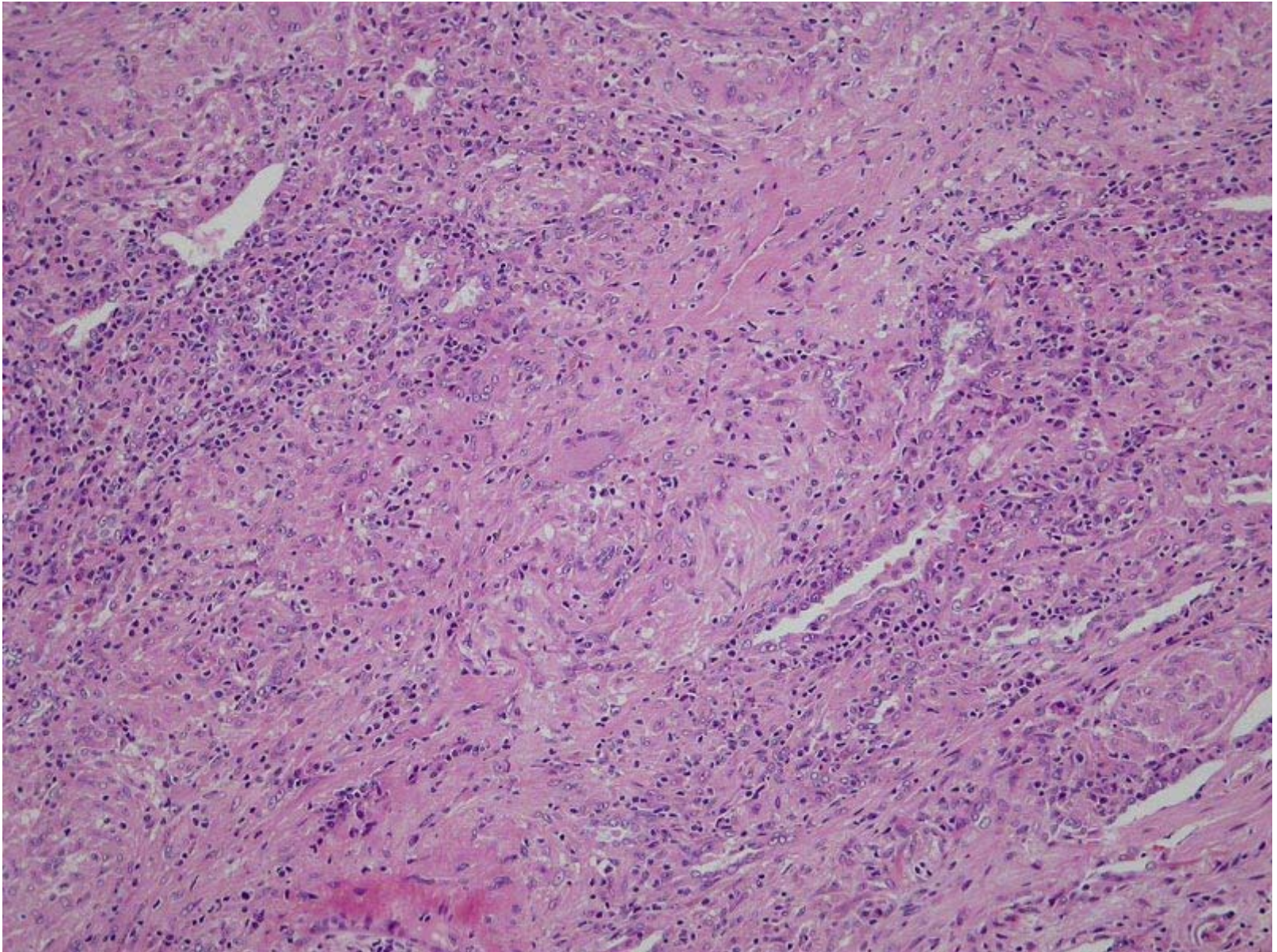
Neoplastic disease, in particular multicentric adenocarcinoma and lymphoproliferative disease...

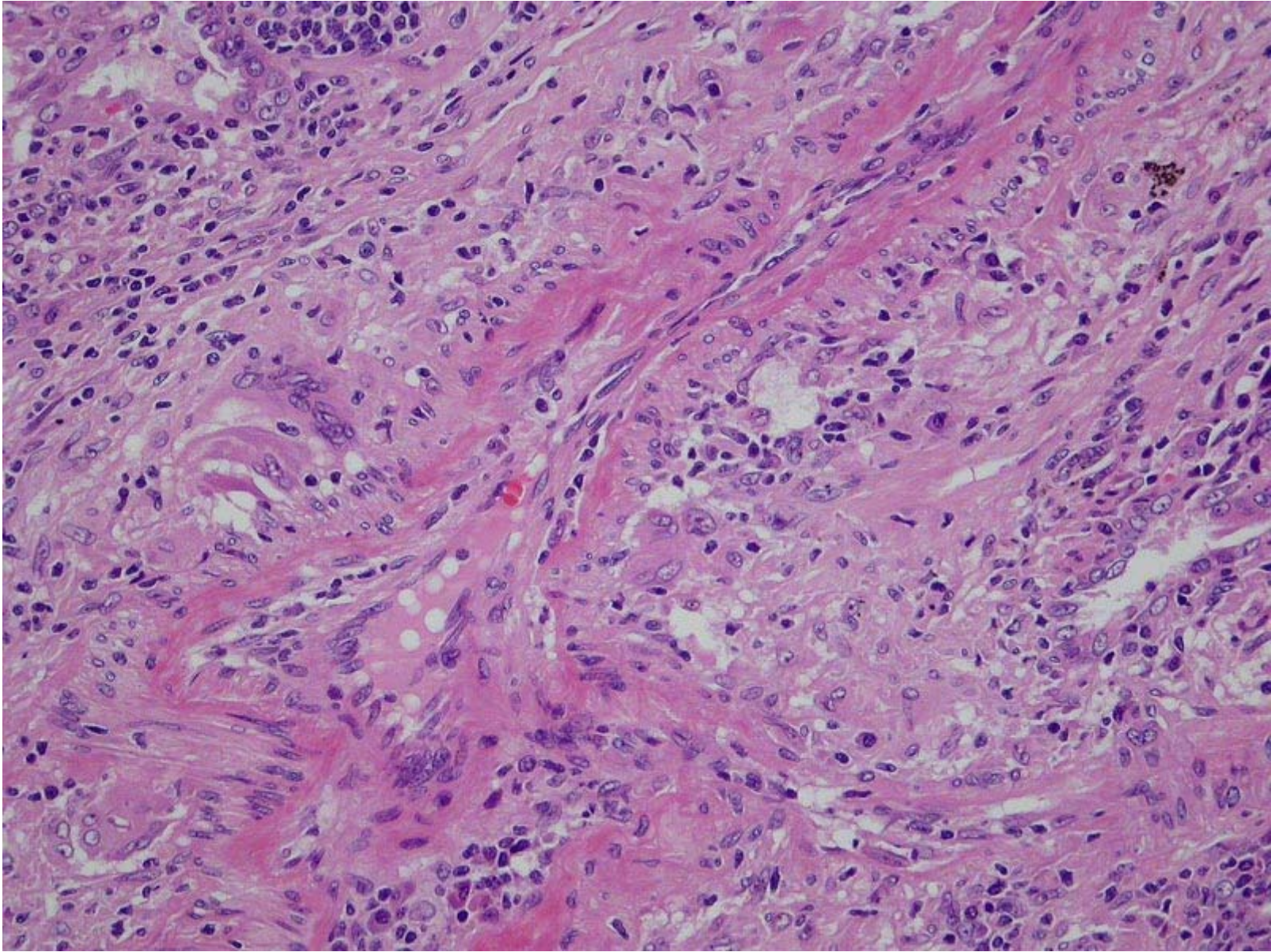
...No features to narrow the wide differential.



TBBx negative, BAL negative – proceeded to surgical lung biopsy. Two firm nodules sampled from the lung periphery.







Additional tests

- ZN and Grocott staining for organisms were negative.
- No evidence of an underlying vasculitis
- All microbiological tests negative.
- No evidence of background lymphoproliferative disease (reactive or neoplastic)

What is HAART?

- The aggressive use of antiretroviral drugs for HIV infection is now commonly referred to as **highly active antiretroviral therapy (HAART)**.
- Generally accepted as the use of 3 or more agents in combination (nucleoside reverse transcriptase inhibitors, protease inhibitors or non-nucleoside reverse transcriptase inhibitors) selected from among the growing list of approved agents active against HIV.

Impact of HAART on HIV patients

- In HIV-infected patients, HAART reduces:
 - incidence of opportunistic infections
 - morbidity
 - death
 - There is a marked decline in the progression to AIDS
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- Sanchez JM et al. Impact of highly active antiretroviral therapy on the morbidity and mortality in Spanish human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2003 Oct;22(10):863-7.
 - 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.
 - 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.

Impact of HAART on HIV patients

- However, a new spectrum of systemic complications largely attributed to HAART has arisen...
- Metabolic syndrome characterized by varying degrees of redistribution of body fat, insulin resistance, hyperlipidemia
- **Inflammatory syndrome attributed to the effects of immune reconstitution and directed primarily at occult pathogens (Immune reconstitution inflammatory syndrome or IRIS)**
- Wanke CA, Epidemiological and clinical aspects of the metabolic complications of HIV infection the fat redistribution syndrome, *AIDS* 13 1999;13: 1287-1293
- Shelburne SA III et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. *Medicine (Baltimore)* 2002; 81:21327.

IRIS

- **Approximately one-quarter of patients who start HAART experience an IRIS event.**
- **The majority are dermatological, in particular genital herpes and warts.**
- **The strongest independent predictors of IRIS were younger age at initiation of HAART (P=.003), baseline CD4 cell percentage of <10%**
- **Patients with advanced immunodeficiency at HAART initiation are at greatest risk of developing IRIS and should be appropriately screened and monitored.**
- Park WB et al. Immune reconstitution inflammatory syndrome in the first year after HAART: influence on long-term clinical outcome. *AIDS*. 2006 Nov 28;20:2390-2.

Sarcoidosis in HIV-infected patients in the era of HAART.

Foulon G et al. *Clin. Infect. Dis.* 2004;38:418-425

- Analysis of HIV-infected patients in whom sarcoidosis was diagnosed between 1996 and 2000 from 12 hospitals in the Paris region.
- Sarcoidosis was diagnosed in 11 HIV-infected patients, of whom 8 were receiving HAART. For 7 patients, HAART comprised 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 protease inhibitor; for 1 patient, HAART comprised 2 NRTIs and 1 nonnucleoside reverse transcriptase inhibitor.
- HIV infection was diagnosed before sarcoidosis in 9 cases.
- Sarcoidosis occurred several months after HAART introduction (duration of HAART was 29 ± 16 months (range, 3-43 months)) when the CD4 cell count had increased and the plasma HIV load had decreased. (**other data show more rapid presentation with sarcoid-like granulomas (3-11 months). Lasalle S et al. Sarcoid-like lesions associated with the immune restoration inflammatory syndrome in AIDS: absence of polymerase chain reaction detection of Mycobacterium tuberculosis in granulomas isolated by laser capture microdissection. *Virchows Archive* 2006;449:689-96)

Clinical characteristics of sarcoidosis in HIV-infected patients.

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- All the patients had thoracic involvement
- 8 were symptomatic.
- Extrathoracic organ involvement was found in 6 patients, including the 3 patients who were not receiving HAART at the onset of sarcoidosis (salivary glands, skin, liver, spleen, eyes).
- Pulmonary function tests performed 3 of 11 had a restrictive pattern in 3 and an obstructive pattern in 1 of 11.
- The angiotensin-converting enzyme level was increased (to >1.5 times the upper limit of normal) in 5 of 10 patients.
- Tuberculin skin-test reactions were negative in 10 patients tested.
- **Other studies have been negative for MTB DNA on PCR** (Lasalle S et al. Sarcoid-like lesions associated with the immune restoration inflammatory syndrome in AIDS: absence of polymerase chain reaction detection of *Mycobacterium tuberculosis* in granulomas isolated by laser capture microdissection. *Virchows Archive* 2006;449:689-96)
- **Granuloma formation was found in the lungs of all the patients. It was associated with CD4 cell recruitment from blood and mainly consisted of CD4 cells.**

Sarcoidosis in HIV-infected patients in the era of HAART.
Foulon G et al. *Clin. Infect. Dis.* 2004;38:418-425

- **BAL data**
- **Lymphocyte, neutrophil, and eosinophil counts in BAL fluid specimens, were significantly increased, compared with control subjects.**
- **In patients receiving HAART, absolute CD4 and CD8 cell counts were both significantly higher than they were in control subjects.**
- **The increase in CD4 cells was greater, resulting in a significantly higher CD4 : CD8 ratio in case patients than in control subjects.**

Treatment and outcome of HIV infection and sarcoidosis.

- Outcome is similar to that observed in HIV-seronegative patients Most recover or improve spontaneously, or remain stable.
- Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med 1997; 336:1224-34.
- In these patients, HAART is generally not withdrawn and immunologic parameters do not deteriorate.
- Steroid treatment is however needed in some patients (dyspnoea, deterioration of PFT results, and/or progression from radiological stage 2 to stage 3) and may need to be continued in those with particular risk factors (black race, extrapulmonary sarcoidosis, receiving IL-2 therapy).

- In one study:
- there were no HIV-related or steroid-related complications observed during the treatment.
- there was no difference in the changes in immunologic and virologic parameters between patients in whom sarcoidosis was cured or improved and patients with sarcoidosis that remained stable or deteriorated.

Sarcoidosis in HIV-infected patients without HAART therapy

- **Sarcoidosis was documented in HIV-infected patients before the HAART era, but this was rare.**
- **3 of 11 patients during HAART era without HAART therapy - all black race and all had extrathoracic involvement.**
- Sarcoidosis in HIV-infected patients in the era of HAART. Foulon G et al. *Clin. Infect. Dis.* 2004;38:418-425
- **Above findings are similar to those for cases that occurred before the HAART era**
- Gowda KS, Mayers I, Shafran SD. Concomitant sarcoidosis and HIV infection. *CMAJ* 1990; 142:136-7.
- Whitlock WL, Lowery WS, Dietrich RA. Bronchoalveolar lavage in sarcoidosis and HIV infection. *Chest* 1990; 98:517. 7.
- 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; 142:8879.
- Coots LE, Lazarus AA. Sarcoidosis diagnosed in a patient with known HIV infection. *Chest* 1989; 96:2012.
- 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; 101:14546.
- 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.
- Kalter S, Lopez-Berestein G. Acquired immune deficiency syndrome in a patient with prior sarcoidosis: case report with monocyte function studies.

Pathogenesis of sarcoidosis in HIV-infected patients

- **HIV infection is characterized by a profound alteration of immune response components that are also involved in granuloma formation, namely the Th1-type CD4 cells that secrete cytokines such as IL-2.**
- 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.
- Conron M, Du Bois RM. Immunological mechanisms in sarcoidosis. *Clin Exp Allergy* 2001; 31:543-54.
- 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.

- **Patients with a history of sarcoid either contract HIV infection and start HAART with return of symptomatic disease, or sarcoidosis worsens with receipt of HAART – recovery of late memory CD4 lymphocytes**
- Coexistent sarcoidosis and HIV infection: an immunological paradox? *J Infect.* 2006 Mar;52(3):195-201. Almeida FA et al.
- Lenner R, Bregman Z, Teirstein AS, DePalo L. Recurrent pulmonary sarcoidosis in HIV-infected patients receiving highly active antiretroviral therapy. *Chest* 2001; 119:97881
- Haramati LB, Lee G, Singh A, Molina PL, White CS. Newly diagnosed pulmonary sarcoidosis in HIV-infected patients. *Radiology* 2001; 218:24-26.
- 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

- **The mean interval between HAART introduction and pulmonary onset of sarcoidosis has been reported by one group as longer, than that reported for granulomatous disorders of infectious origin (a few weeks), although not found by others. 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.**

- Sarcoidosis has developed more rapidly in patients receiving Th1 cytokines (IL-2 and IFN), which are known to play a pivotal role in granuloma formation.

- **Development of sarcoidosis in HIV-infected patients may therefore be related to recovery of late memory and/or naive CD4 lymphocytes during HAART (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).**

Rheumatic complications of HIV infection in the era of HAART: emergence of a new syndrome of immune reconstitution and changing patterns of disease.

Calabrese LH et al. *Semin Arthritis Rheum.* 2005 Dec;35(3):166-74

- “Newly described syndrome of either the de novo appearance or the exacerbation of clinically occult autoimmunity following immune reconstitution from HAART”.
- 32 cases described - sarcoidosis and autoimmune thyroid disease are the most common. Arthritis and various forms of connective tissue disease comprise the remainder.
- Mean onset following HAART was at nearly 9 months
- Most resolved with little or no therapy.
- In addition, a longitudinal analysis of 395 HIV-infected patients from 1989 to 2000 designed to detect the appearance of rheumatic complications showed a dramatic decline in certain problems such as reactive arthritis, psoriatic arthritis, and various forms of connective tissue disease.
- Although beneficial, HAART has contributed to both an altered frequency and a different nature of rheumatic complications in the HIV-infected population.

HAART impact on HIV-associated pulmonary tuberculosis

- HIV patients receiving HAART with pulmonary TB, had a post-primary pattern more frequently than those not receiving this treatment (82% vs 44%). A primary pattern was significantly more frequent ($p < 0.001$), in patients with more severe immunosuppression.
- This observation is consistent with the partial restoration of cell-mediated immunity that can be induced by HAART

Radiological patterns in HIV-associated pulmonary tuberculosis: comparison between HAART-treated and non-HAART-treated patients. Busi Rizzi E et al. *Clin Radiol*. 2003;58:469-73.

Impact of HAART on malignancy in HIV-infected patients

- Pre-HAART, malignancies accounted < 10% of all deaths among HIV-infected patients.
- French review of 964 in the year 2000, showed 28% attributable to malignancies.
- AIDS-related malignancies were the underlying cause of 149 deaths (15%); among these malignancies were non-Hodgkin lymphoma (n = 105), Kaposi sarcoma and cervical carcinoma.
- **Non-AIDS-related malignancies were the underlying cause of 120 deaths included 103 solid tumors (50 respiratory tumours, 19 hepatocarcinomas, 9 digestive tumors, and 6 anal tumors)**
- Patients who died of solid tumors were more likely to be male, to smoke, to be older, and to have higher CD4 counts.
- **Malignant disease has been a major cause of death among HIV-infected patients in industrialized nations since the introduction of HAART.**
- **Whereas haemopathies and Kaposi sarcoma are associated with advanced immunosuppression, solid tumours can occur in patients with controlled HIV infection**

Bonnet F et al. Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. *Cancer*. 2004 Jul 15;101(2):317-24

Impact of HAART on lung cancer in HIV-infected patients

- Lung cancer now accounts for 11–40% of deaths from non-AIDS defining cancers, and 2–4% of all deaths in HIV+ patients
- The risk of developing lung cancer *seems* to be higher in HIV infected subjects than in the general population of the same age, partly because the former tend more frequently to be smokers.
- No clear relationship between the degree of immunosuppression and the risk of lung cancer.
- Mean age at diagnosis is 45 years, most symptomatic with advanced disease (75–90%).
- Adenocarcinoma is the most frequent histological type.
- The prognosis is worse in HIV infected patients than in the general lung cancer population.
- .
- Surgery remains the treatment of choice for localised disease.
- Other potential influences - ? Due to a decreased occurrence of opportunistic infections, ? chronicity of HIV infection, ? possible oncogenic role of HIV itself, ? aging of the HIV-infected population.
- Cadranel J et al. Lung cancer in HIV infected patients: facts, questions and challenges. *Thorax*. 2006 Nov;61(11):1000-8

Sarcoidosis in association with HAART therapy in HIV infected patients - Conclusions

1

- The decrease in AIDS related mortality has fallen sharply in industrialised countries since 1996 following the introduction of HAART

2

- This has led to a change in disease types seen in HIV-infected patients with:
- **(a) an increase in the proportion of deaths attributable to non-AIDS defining solid tumours, especially lung cancer.**
- **(b) increased incidence of sarcoidosis after ? long-term (months) immunologic reconstitution during HAART.**
- **(c) exacerbation of infections in the shorter term, plus changes in the manifestations of infections**
- **(d) changes in incidence and associated types of other autoimmune diseases**

3

- **Development of sarcoidosis is ? related to recovery of late memory and/or naive CD4 lymphocytes.**
- **Treatment with IL-2 or IFN- 2a may be a risk factor for sarcoidosis.**
- **Clinical and radiological findings, BAL data and outcome for sarcoidosis are similar to those observed for the patients receiving HAART and for HIV-uninfected patients.**