

Case 12

U.X. is a 36-year-old male homosexual with a history of recurrent herpes simplex infections and intermittent diarrhea for three years. In the three months prior to admission, he noted fever, malaise, cervical adenopathy, and perianal ulcerations. One week prior to admission he developed a non-productive cough and shortness of breath. Physical examination was remarkable for T 101°F and a respiratory rate of 24. His oxygen saturation was 92% (low).¹ The patient appeared cachectic² and had oral thrush.³ Laboratory examination revealed mild pancytopenia (low blood count). Analysis of his peripheral blood lymphocytes by flow cytometry revealed 21% CD3⁺, 2% CD4⁺ and 17% CD8⁺ lymphocytes. The CD4 count was 140 cells/ μ l (low). A Western blot test for HIV was positive and the HIV-1 RNA was 50,000 copies/ml (indicative of either acute infection or heralding rapid disease progression). Skin tests for Mumps, *Candida*, and tuberculin were all negative. A chest X-ray is shown below (Fig. 1). *Pneumocystis carinii* pneumonia (PCP) was suspected and the patient was treated empirically with TMP-SMX (trimethoprim-sulfamethoxazole). He demonstrated rapid improvement, and was discharged on HAART⁴ and TMP-SMX prophylaxis; however, he was non-complicant.

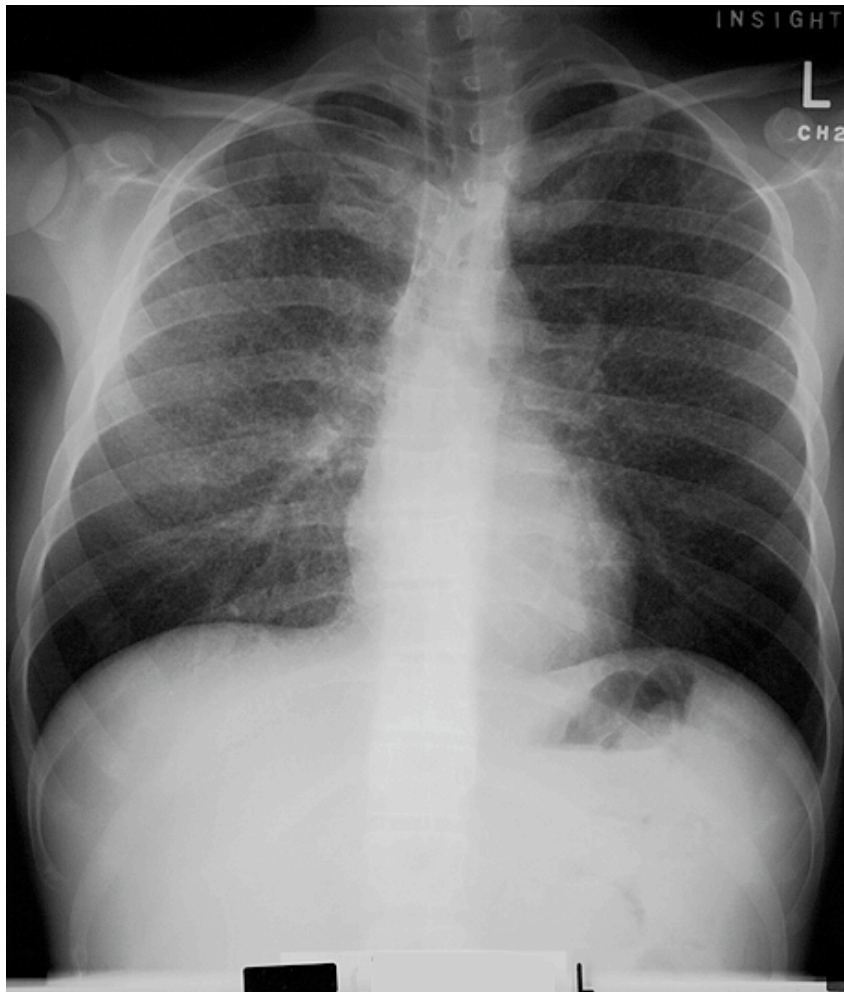


Fig. 1. PA chest X-ray of U.X. on presentation to CPMC.

Case 12, cont'd

Two months later the patient developed erosive proctitis, diarrhea, fever to T 104°F and recurrent pulmonary symptoms. The WBC count was 3200 cells/ μ l (decreased) with 42% neutrophils, 23% band forms, 23% lymphocytes, and 12% monocytes. The complement fixing antibody titer to cytomegalovirus was 1:128; antibody titer to Epstein-Barr virus capsid antigen was 1:640. A chest X-ray revealed diffuse infiltrates that had worsened since his prior study. Recurrent *Pneumocystis carinii* was suspected, but the patient did not respond to either TMP-SMX or pentamidine isethionate. Fiberoptic bronchoscopy with BAL (bronchoalveolar lavage) revealed *Pneumocystis* (Fig. 2) and CMV (Fig. 3).

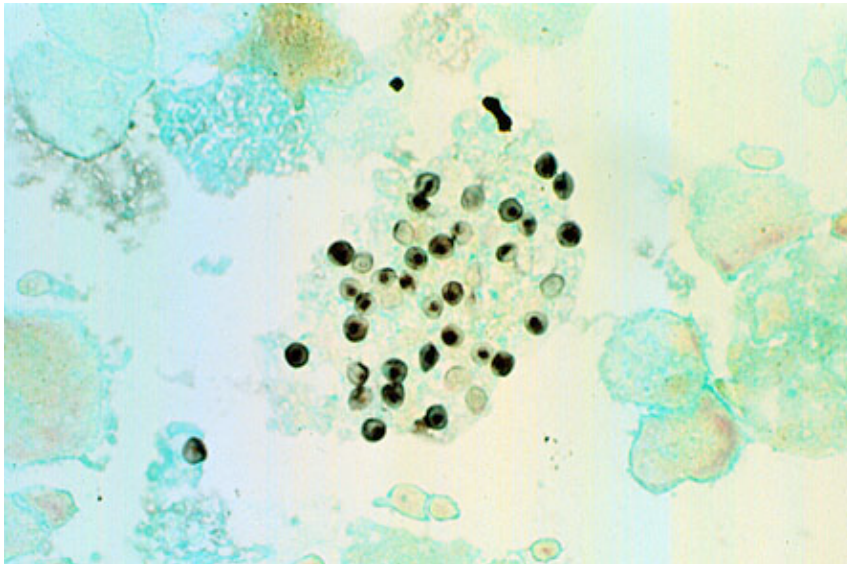


Fig. 2. Silver stain of BAL material from S.C. upon second presentation to CPMC.

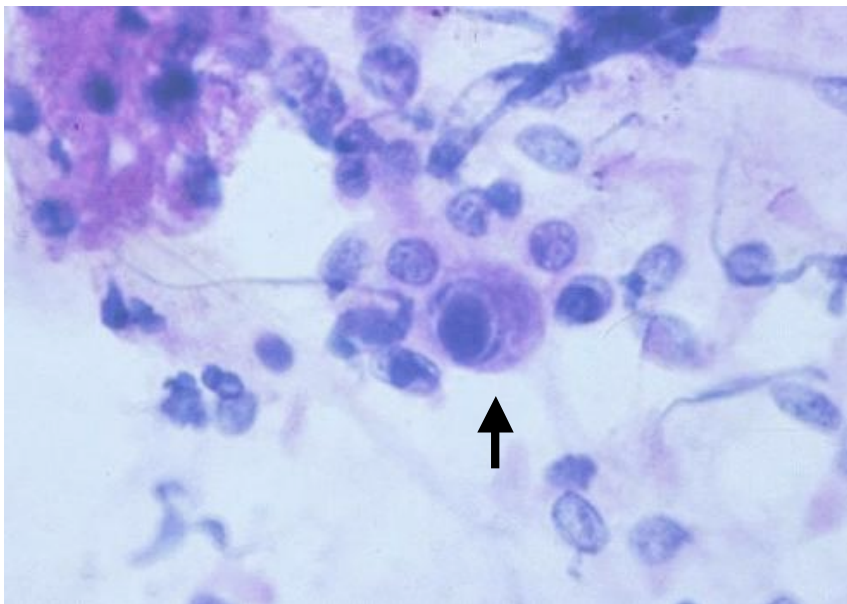


Fig. 3. H&E stain⁵ of BAL material from S.C. upon second presentation to CPMC. Note presence of typical CMV inclusion body (i.e., intranuclear inclusion surrounded by a clear halo), giving the appearance of an "owl's eye" (arrow).

Case 12, cont'd

Despite maximal therapy with trimethoprim-sulfamethoxazole, pentamidine, corticosteroids and vidarabine, the patient died of progressive respiratory failure. Postmortem examination showed extensive pulmonary cytomegalovirus and *P. carinii* infections. No lymphoma or malignancy was found.

¹Indicative of an inability to oxygenate the blood, which most often reflects lung disease

²appearing chronically ill

³Infection of the oral cavity with yeast, typically *Candida albicans*.

⁴Highly active anti-retroviral therapy

⁵Haematoxylin and eosin, a commonly used histochemical stain

Questions for Case 12

- (1) HIV is known to infect CD4⁺ T lymphocytes and monocytes. What molecular determinant of the viral envelope dictates whether there will be preferential infection of T cells or monocytes? What molecular determinants on T cells and monocytes account for this tropism?
- (2) The initial infection in HIV is usually with a monocyctotropic virus. Later in the illness, there is a switch to lymphotropic virus. What features of the virus account for this switch? What features of the host immune response account for this switch?
- (3) What human genes determine if an HIV infected individual is likely to be a rapid or slow progressor? By what mechanisms are these effects mediated?
- (4) In AIDS, the number of CD4⁺ T cells decreases progressively. Describe plausible mechanisms by which CD4 cells are reduced by HIV.
- (5) In response to HAART, patients with AIDS demonstrate an early rise in memory T cells followed by a gradual and continual rise in naïve T cells; however, levels of both cell types never become normal. What does these observations indicate about thymic function in AIDS?
- (6) Antigen triggering of CD4⁺ cells augments HIV replication. What are the mechanisms of this effect?
- (7) Why are patients with HIV particularly susceptible to mycobacteria (e.g., *M. tuberculosis* and *M. avium*) and organisms like *Pneumocystis carinii*?
- (8) *Pneumocystis carinii* is a fungus that binds to lung epithelial cells and pulmonary alveolar macrophages. Binding to epithelial cells induces secretion IL-8 from the epithelial cells and binding to macrophages results in phagocytosis of the organism. In an experimental model of infection, a scientist performed a large-scale mutagenesis of the organism and derived a stable clone whose virulence was decreased. When she examined which genes were lacking in this

clone, she identified a gene responsible for shedding of a major mannose-containing glycoprotein from its surface. How might shedding of a mannosylated glycoprotein by lead to increased virulence of *Pneumocystis carinii*? Based on interaction of *Pneumocystis carinii* with lung epithelial cells, what type of inflammation would you expect to see in the lungs of infected patients?

(9) What is the significance of the elevated antibody titers to EBV antigens in this patient?