Pulmonary Disease in the Acquired Immune Deficiency Syndrome

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The acquired immunodeficiency syndrome (AIDS) is the most recent addition to the long list of primary and secondary immune deficiencies. Unfortunately, it has rapidly become the most common immune deficiency diagnosed in the United States today. Between the first report in 1981 and early 1984, over 3,000 cases of AIDS were recorded by the Centers for Disease Control. This article reviews the major features of the immune deficiency in AIDS, as well as the diagnosis and treatment of pulmonary manifestations occurring in the setting of this newest immune deficiency state.

AIDS is defined by the Centers for Disease Control as the occurrence of a disease indicative of underlying cellular immune deficiency in persons without prior history of immunologic abnormality. The most common diseases which fit this definition are Kaposi's sarcoma before age 60, Pneumocystis carinii pneumonia, and one or more other opportunistic infections. Pneumocystis pneumonia is the presenting manifestation in over 50 percent of AIDS cases. The overall case-fatality rate for AIDS is approximately 40 percent; however, the two-year mortality for patients who have experienced one or more opportunistic infections is in excess of 90 percent.

While most cases have occurred in the United States, many cases have been reported from Western Europe, mostly in homosexual and bisexual males with the past history of sexual contacts from the United States. In addition, cases of AIDS are being reported with increasing frequency among heterosexual males and females in Haiti and Zaire. Groups recognized to be at increased risk include homosexual and bisexual males, intravenous (IV) drug users, hemophiliacs, Haitian immigrants, and sexual contacts of the above groups. The nature of the groups recognized to have an increased risk for developing AIDS suggests strongly that this immune deficiency has an infectious etiology. The available epidemiologic evidence points to an infectious agent transmissible by sexual contact, shared needle use, or blood. The putative AIDS agent has not been identified to date, recent studies point to involvement of double-stranded RNA viruses (retroviruses) of which the human T cell leukemia virus is the prototype of man. In view of its probable viral etiology, AIDS should be classified as a secondary immune deficiency.

Patients with AIDS may have Pneumocystis pneumonia, Kaposi's sarcoma, or other serious opportunistic infections. Fever of unknown origin (FUO) associated with diarrhea and 9-kg weight loss is a common presenting syndrome. In many patients with FUO, thrush or Pneumocystis develops within several weeks or months. It is well recognized that patients with AIDS who have Kaposi's sarcoma often subsequently have opportunistic infections. Thus, a high index of suspicion for Pneumocystis pneumonia is warranted in AIDS-Kaposi sarcoma patients in whom cough and dyspnea develop.

Another syndrome designated as the lymphadenopathy syndrome or AIDS-related complex (ARC) has recently been identified in the same population groups at increased risk for AIDS. Most patients are homosexual or bisexual males with chronic lymphadenopathy, sometimes associated with low-grade fevers and night sweats. Mild to moderate immunologic abnormalities are usually present, linking the syndrome with AIDS. It is clear that some patients with the ARC syndrome have progressed to AIDS during prospective follow-up; however, the true incidence of such progression will require many years of study. Two other illnesses that appear to be related to AIDS include idiopathic thrombocytopenic purpura (ITP) in young males, non-Hodgkin's lymphoma, and possibly Hodgkin's disease.

Numerous functional and phenotypic abnormalities of the immune system are found in AIDS. The most significant defects involve cell-mediated immunity as evidenced by the spectrum of viral, fungal, protozoan, and mycobacterial infections. The most characteristic feature in established AIDS is depletion of helper T cells, as enumerated with the monoclonal antibodies OKT4 or Leu 3. The numbers of suppressor/cytotoxic cells are normal to increased. Elevated levels of IgG and IgA are frequently observed; however, primary antibody responses may be defective, a point...
which complicates serologic diagnosis of infection. Initial useful laboratory studies include the complete blood cell count with differential, from which an absolute lymphocyte count is calculated. Patients with an opportunistic infection of FUO may have leukopenia or lymphopenia (<1,500/cu mm). Delayed hypersensitivity skin tests represent a useful screening procedure for disorders of cellular immunity of clinical significance. With rare exceptions, patients with AIDS are anergic. Determination of helper and suppressor T cell numbers are of value in the evaluation of selected patients. While not essential in biopsy-proved Kaposi's sarcoma or Pneumocystis infection, the tests are useful in the setting of FUO, prominent weight loss, and "minor" infections such as oral thrush or herpes zoster. Marked reduction in the helper subset with relative preservation of the suppressor subset is suggestive of evolving AIDS. While numerous common viral infections produce transient inversion of T cell subset ratios, persistent low T helper numbers over several months can narrow the differential diagnosis in symptomatic patients.

Pulmonary involvement is common in AIDS and usually takes the form of single or sometimes multiple opportunistic infections. Most patients with Pneumocystis pneumonia present have cough, dyspnea, fever, and x-ray film findings of bilateral interstitial and alveolar infiltrates. In some cases initial chest x-ray films have been normal; thus, Pneumocystis should be included in differential diagnosis of pulmonary symptoms despite a normal x-ray film, especially in members of the population groups at increased risk for AIDS. An abnormal diffusing capacity and gallium scan may provide the basis for proceeding with flexible bronchoscopic study in such patients. Bronchoalveolar lavage and transbronchial biopsy have established the diagnosis of P carinii pneumonia in 95 percent of AIDS patients with this infection.

Cytomegalovirus, Mycobacterium avium intracellulare, and M tuberculosis are other common pulmonary pathogens in AIDS. Less common are Cryptococcus neoformans, Aspergillus, Nocardia, and the enteric protozoan Cryptosporidium. Concurrent CMV and Pneumocystis infection is associated with a poor prognosis. Mycobacterium tuberculosis is most common in Haitian and African patients with AIDS. While M avium intracellulare is a common pathogen in AIDS and may be cultured from lung specimens, the most severe manifestations are usually at extrapulmonary sites, notably liver and bone marrow. The documentation of this organism in a pulmonary specimen should prompt further studies to assess extrapulmonary involvement. As a general principle, pulmonary biopsy specimens from patients with AIDS or suspected AIDS should be evaluated for multiple opportunistic pathogens. Kaposi's sarcoma frequently occurs in the lung, most commonly in patients with advanced cutaneous disease. The diagnosis is rarely established by fiberoptic bronchoscopy, and open lung biopsy is often necessary.

The therapy for Pneumocystis pneumonia in the setting of AIDS has not been uniformly successful. In most instances the initial therapy has consisted of IV trimethoprim-sulfamethoxazole (TMP-SMX) per 24 hours, with the dose calculated on the basis of the trimethoprim content (20 mg/kg of body weight). In many instances substitution of pentamidine has been required because of drug eruptions, severe neutropenia, or apparent drug-related fevers. Most such patients have recovered from the episode of Pneumocystis infection. In other patients deterioration of clinical and gas exchange status has occurred despite TMP-SMX therapy, and pentamidine has been substituted for TMP-SMX after four to ten days. Despite modification of treatment, 90 percent of such patients die during that episode. Combined TMP-SMX and pentamidine therapy is not recommended, since there are no studies to indicate benefit, and their toxicities may be additive. Thus, at present, TMP-SMX administered by the IV route remains the recommended therapy for first episodes of Pneumocystis in the setting of AIDS. Additional drugs with anti-Pneumocystis activity are currently under investigation in animal models.

In summary, AIDS is a secondary immune deficiency of presumed viral etiology which involves major defects in the T cell arm of the immune system. Pneumocystis carinii pneumonia is the most common treatable pulmonary manifestation. While antimicrobial therapy may lead to resolution of individual episodes of infection, recurrent infections with multiple organisms most often occur. Studies have been initiated aimed at the development of regimens of immunotherapy using interleukins and other biologic agents to attempt correction of the underlying immune defects in AIDS. Advances in our understanding of the etiology and pathogenesis of AIDS will help direct that search.

References