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A 24 year old African-American male with a history of AIDS with a recent CD4 count of 57/uL, is admitted to the hospital with substernal chest pain and shortness of breath for the past two weeks. Dyspnea is mostly on exertion, and the patient denied productive cough or hemoptysis, fevers, chills, or night sweats. Three weeks prior to presentation, the patient underwent esophagogastroduodenoscopy, which revealed an esophageal ulcer. Biopsies did not show any specific pathology and cultures were negative. Outpatient medications include prednisone, rabeprazole, fluconazole, clarithromycin, and ethambutol, bactrim.

Vitals on admission were as follows: temperature 97.2, pulse 80/min, and respiration rate 26/min. On physical exam, no crackles or wheezing were found. Computerized tomography scan of the chest revealed multiple bilateral nodules, without pleural effusions or mediastinal/hilar lymphadenopathy. Bronchoscopy was performed with transbronchial biopsy; cultures obtained were negative. Transbronchial lung biopsy showed an interstitial infiltrate of mononuclear cells, predominantly lymphocytes, consistent with a diagnosis of nonspecific interstitial pneumonitis. The patient was subsequently referred to infectious disease clinic for highly active antiretroviral therapy.

Nonspecific Interstitial Pneumonitis

Interstitial pneumonitis in HIV-infected patients is most commonly caused by Pneumocystis carinii (PCP). PCP occurs in up to 50% of patients with acquired immune deficiency syndrome (AIDS) in the last 6 months of their lives[1]. Sputum induction for diagnosis of PCP is associated with variable sensitivity of 50 to 95%.[2-3]. Because the test can have a negative predictive value as low as 39%, the absence of Pneumocystis carinii in induced sputum does not reliably exclude the diagnosis of PCP. Other patients may be too ill to undergo bronchoscopy. Thus, many HIV-infected patients with pneumonitis are empirically treated without a confirmed diagnosis[3]. In some cases, however, pneumonitis cannot be ascribed either to known infectious agents or to malignancy. These disorders are believed to be inflammatory in origin and are grouped into two entities: lymphoid interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NSIP)[4]. In one study on 351 HIV-positive patients with pneumonitis, NSIP was the most common histologic diagnosis in patients without PCP[3]. Because treatment and prognosis of PCP and NSIP are different, it is important to differentiate these entities.

Nonspecific interstitial pneumonitis (NSIP) is a term applied to conditions in which there are abnormal mononuclear cell infiltrates of the lung without other explanations for the abnormality, including previous infection, malignancy, LIP or exposure to pulmonary toxic drugs[4-7].

Prevalence

NSIP occurs in 5 to 11% of HIV-infected adults who present with respiratory disease[3-6]. NSIP was detected in 24% of 67 symptomatic patients without PCP, using bronchoalveolar lavage (BAL) and transbronchial biopsy (3 NSIP prevalence has been reported to be as high as 38%. In this study, 41 out of 110 AIDS patients had NSIP[3,6]. Subclinical NSIP can also occur. Evidence of NSIP was found in 50% asymptomatic HIV-infected patients with normal chest radiograph and CD4 count below 200 cells/mm3 on transbronchial biopsies[6].

Clinical Manifestations

Symptoms include dyspnea with or without cough, fever, and hypoxia[4,8]. Certain clinical descriptors are helpful in distinguishing NSIP from PCP. Patient with NSIP are more likely to have less advanced HIV infection with higher body mass, serum albumin levels, and CD4 counts[3,8]. These patients tend to have less lung inflammation, normal LDH values, and fewer involved lobes on chest radiographs (CXR)[3]. CXR findings may vary from normal to increased interstitial markings. Reticulonodular infiltrates have been reported in occasional cases[5-6,9]. Mediastinal and hilar lymphadenopathy or associated pleural effusions have not been reported in NSIP.

Pathology

NSIP is defined by the presence of chronic interalveolar septal inflammation in the absence of a specific microorganism, identified through standard histopathologic, histochemical, cytologic, and culture

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techniques (methenamine silver for P. carinii, Ziel-Neelsen method for mycobacteria, nuclear inclusions for CMV pneumonia)[3]. Pathologic findings include interstitial infiltration predominantly consisting of lymphocytes and plasma cells, fibrosis, edema, pneumocyte hyperplasia, alveolar hyaline membranes, bronchial inflammation, and thickened alveolar septae[3-4]. In one retrospective review of seven patient with NSIP, interstitial pneumonitis consisted of a patchy lymphocytic infiltrates composed of B cells in focal aggregates and T cells in a more diffuse distribution. The T cell population was a mixture of CD4 and CD8 lymphocytes. These findings contrast with the more extensive infiltrates of predominantly CD8 lymphocytes seen in lymphocytic interstitial pneumonitis (LIP), which occur mainly in children[8].

Etiology

The etiology of NSIP is uncertain. The cytokine profile of BAL fluid samples from patients with NSIP differs from that with PCP, suggesting that NSIP is a distinct entity[3,10]. In 15 NSIP patients, in-situ hybridization did not show evidence of Epstein-Barr virus (EBV) or Cytomegalovirus (CMV) infection. Whether HIV causes NSIP is uncertain. Polymerase chain reaction (PCR) testing for HIV gag and env DNA is usually positive in NISP, but also positive in HIV control patients with normal lung histology[3]. The role of Human herpes virus type 6 (HHV-6) is also unclear.

Course and Therapy

NSIP runs a subacute and generally benign course. Spontaneous improvement in 7-10 days has been reported[3]. There is no published data available on treatment modalities, although some patients have anecdotally responded to oral steroids. Long-term survival is less than three years, prognosis primarily determined by other infective or neoplastic complications. NSIP does, however, appear to mark a clinical decline in the progression of HIV infection. The role of HAART in the treatment of this disorder is unknown[4,8].

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