CHEST Special Feature

Diagnosis and Treatment of Tuberculous Pleural Effusion in 2006*

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Tuberculous (TB) pleural effusion occurs in approximately 5% of patients with *Mycobacterium tuberculosis* infection. The HIV pandemic has been associated with a doubling of the incidence of extrapulmonary TB, which has resulted in increased recognition of TB pleural effusions even in developed nations. Recent studies have provided insights into the immunopathogenesis of pleural TB, including memory T-cell homing and chemokine activation. The definitive diagnosis of TB pleural effusions depends on the demonstration of acid-fast bacilli in the sputum, pleural fluid, or pleural biopsy specimens. The diagnosis can be established in a majority of patients from the clinical features, pleural fluid examination, including cytology, biochemistry, and bacteriology, and pleural biopsy. Measurement of adenosine deaminase and interferon-γ in the pleural fluid and polymerase chain reaction for *M tuberculosis* has gained wide acceptance in the diagnosis of TB pleural effusions. Although promising, these tests require further evaluation before their routine use can be recommended. The treatment of TB pleural effusions in patients with HIV/AIDS is essentially similar to that in HIV-negative patients. At present, evidence regarding the use of corticosteroids in the treatment of TB pleural effusion is not clear-cut.

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Abbreviations: ADA = adenosine deaminase; AFB = acid-fast bacilli; CXCR3 = receptor 3 for CXC chemokines; EPTB = extrapulmonary tuberculosis; IFN = interferon; IL = interleukin; PCR = polymerase chain reaction; TB = tuberculosis; Th1 = T-helper type 1

Tuberculosis (TB) is a leading cause worldwide of preventable morbidity and mortality from an infectious agent. The interaction of HIV with *Mycobacterium tuberculosis* has lead to its resurgence in developed nations and has increased the burden of TB cases in developing countries.[1] TB pleural effusion, considered as a form of extrapulmonary TB (EPTB), constitutes a frequent clinical problem[2] and is particularly important in the present era of HIV infection, when EPTB is more commonly encountered in clinical practice.[3] A pleural effusion occurs in approximately 5% of patients with TB.[4]

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Epidemiology

A total of nine million new cases and approximately two million deaths from TB were reported in 2004.[1] Although the African region has the highest estimated incidence (356 per 100,000 population per year), the majority of patients with TB live in the most populous countries of the Asian subcontinent, which accounts for nearly half of the new cases that arise yearly.[5] The frequency of pleural involvement

in TB has been variably reported (4% in United States to 23% in Spain).[6,7]

TB pleural effusion is the second most common form of EPTB, only less frequent than lymph node TB. TB pleural effusion is being increasingly recognized, even in developed nations,[2] as the incidence of EPTB has more than doubled following the HIV pandemic. The incidence of TB pleural effusions in HIV/AIDS has been variably reported from 15 to 90%,[8,9] with an effusion being more common in patients with higher CD4+ counts.[10,11]

Pathogenesis

TB pleural effusions can manifest as primary or reactivated disease. Rupture of a subpleural caseous focus in the lung into the pleural space is considered the initial event in the pathogenesis of primary TB pleural effusions.[12] The entry of mycobacterial antigens into the pleural space is followed by an interaction with predominantly CD4+ T-lymphocytes resulting in a delayed hypersensitivity reaction.[13] The accumulation of fluid in pleural cavity results predominantly from increased capillary permeability and secondarily from impairment of lymphatic clearance of proteins and fluid from the pleural space because of occlusion of pleural stomata.[14,15]. In contrast, reactivation disease is frequently associated with parenchymal lesions.

The delayed hypersensitivity reaction responsible for the pathogenesis of TB pleural effusions is mediated by T-helper type 1 (Th1) cells that activate macrophages to switch on mechanisms responsible for the killing of mycobacteria. A strong Th1-like immunity (interferon [IFN]-γ dominant) is essential for the containment of *M tuberculosis*, while these protective effects are antagonized by T-helper type 2 cytokines, primarily interleukin (IL)-4. The predominance of Th1 immunity in TB pleural effusions is demonstrated by the significantly higher levels of IFN-γ in pleural fluid compared to peripheral blood of the same patient.[16] Flow cytometry and *in vitro* polyclonal stimulation studies have also demonstrated high levels of Th1 cells, which are predominantly of memory phenotype ($CD45RA^-$). The memory T cells in TB pleural effusions typically display a surface phenotype $CD62L^-$ $CD11a^{high}$ consistent with a Th1-like cytokine profile. Therefore, selective homing of IFN-γ–biased memory T cells in TB pleural effusion is evident. The mononuclear cells infiltrating the pleura are predominantly $CD4^+$ $CD45RO^+$ T cells expressing C-C chemokine receptor 5 and receptor 3 for CXC chemokines (CXCR3). A strong expression of their ligands was observed in the pleural tissue of patients with TB pleural effusions. Intercellular adhesion molecule-1 (CD11a-ligand) was overexpressed on capillary endothelium, and chemokines like RANTES (regulated and normal T-cell expressed and secreted), macrophage inflammatory protein-1α (C-C chemokine receptor 5 ligands), and IFN-γ–inducible protein-10 (macrophage inflammatory protein-10) [CXCR3 ligands] were detected on mesothelial cells and/or fibroblasts. A hierarchical role of CXCR3 in controlling the inflammatory reaction in TB pleural effusions was demonstrated by *in vitro* human umbilical vein endothelial cell T-cell adherence assays.[17] This denotes the importance of effector cell homing at disease sites resulting in containment of infection and emphasizes that the IFN-γ response, although critical for controlling TB infection, does not always correlate with protection.[16,17]

Clinical Features

In contrast to pulmonary TB, most TB pleural effusions manifest as an acute illness, with approximately one third of patients being symptomatic for < 1 week and two thirds for < 1 month.[18] The most common presenting symptoms are pleuritic chest pain (75%) and nonproductive cough (70%).[19] TB pleural effusion was considered a disease of the young, with a mean age of 28 years, compared to 54 years for parenchymal tuberculosis.[20] However, Epstein and colleagues[21] demonstrated a rise in the median age (56 years) at presentation of TB pleural effusions with 19% of patients having reactivation disease. Therefore, pleural tuberculosis should be considered in any adult or elderly patient with a unilateral pleural effusion.

TB pleural effusions, typically unilateral and small to moderate in size, usually occupy less than two thirds of a hemithorax.[22] HIV-positive patients with TB pleural effusions tend to be older, are more likely to be pleural fluid smear and culture positive for *M tuberculosis*, have a higher propensity for positive pleural biopsy,[23] and show a higher incidence of disseminated disease.[24] Fever, dyspnea, night sweats, fatigue, diarrhea, marked tachypnea, hepatosplenomegaly, and lymphadenopathy are more common in HIV-infected patients. These patients tend to have a negative tuberculin skin test results, lower hemoglobin, and higher β_2-microglobulin; their pleural fluid shows low albumin and high globulin levels.[24]

Chronic TB empyema, an entity distinct and much less common than tuberculous pleural effusion, represents chronic, active infection of the pleural space. TB empyema can occur in several settings: (1) progression of a primary tuberculous pleural effusion