Extrapulmonary tuberculosis, part 1: Pleural and lymph node disease

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Abstract: Pleural tuberculosis and lymph node involvement are the most common extrapulmonary manifestations of tuberculosis. Most patients with pleural involvement complain of pleuritic chest pain, nonproductive cough, and dyspnea. The pleural effusion is usually unilateral and small to moderate in size. The diagnosis depends on the demonstration of acid-fast bacilli in pleural fluid or biopsy specimens, or the presence of caseous granulomas in the pleura. The gold standard for the diagnosis of lymph node tuberculosis is the identification of mycobacteria in smears on fine-needle aspiration cytology, histopathology, or mycobacterial culture. On ultrasonography and CT, the lymph nodes show enlargement with hypoechoic/hypodense areas that demonstrate central necrosis and peripheral rim enhancement or calcification. Treatment involves the combination of 4 antituberculosis drugs for 2 months, followed by 2-drug therapy for 4 months. (J Respir Dis. 2005;26(8):326-332)

In the past decade, there has been a significant increase in the prevalence of tuberculosis and its extrapulmonary manifestations worldwide. Factors that have contributed to this include the rising number of immunosuppressed persons, the development of drug-resistant strains of Mycobacterium tuberculosis, aging-population demographics, and an increase in the number of health care workers who are exposed to tuberculosis. The incidence of extrapulmonary manifestations is approximately 50% in patients who have both AIDS and tuberculosis, compared with 10% to 15% in HIV-negative patients with tuberculosis.

Tuberculosis that involves the lymph nodes, bone (excluding the spine), peripheral joints, or skin is classified as a less severe form of disease. The severe forms include meningitis, abdominal involvement, miliary tuberculosis, pericarditis, bilateral or extensive pleural effusion, spinal involvement, and genitourinary involvement.

In some patients, it can be difficult to make the diagnosis of extrapulmonary tuberculosis. Although imaging studies or a positive tuberculin skin test may support the diagnosis, negative results do not exclude extrapulmonary tuberculosis. However, recognition of the common and uncommon radiologic findings can be helpful.

In a series of articles, we will focus on the more common forms of extrapulmonary tuberculosis. In this article, we will review the presentation and diagnosis of pleural and lymph node (peripheral and mediastinal) involvement. In coming issues of The Journal of Respiratory Diseases, we will discuss CNS, abdominal, and skeletal manifestations of tuberculosis.

PLEURAL TUBERCULOSIS

Lymph node involvement and pleural tuberculosis are the 2 most common extrapulmonary manifestations of tuberculosis. Most cases are caused by M tuberculosis; a few cases caused by other mycobacteria, including Mycobacterium bovis, have been reported.

Tuberculous pleural effusion is usually seen in children and young adults. It characteristically occurs 3 to 7 months after initial infection with M tuberculosis. An upward shift in the age spectrum and a more frequent association with reactivation disease have been reported in many series in the past decade.

Underlying pulmonary parenchymal disease is also being documented, thereby confounding the classification of pleural disease as extrapulmonary tuberculosis. In general, patients who have tuberculous pleural effusion are younger than patients who have parenchymal tuberculosis.

Pathogenesis

Neutrophils appear to play a key role in the initiation of inflammatory reactions in tuberculous effusion. In addition, pleural mesothelial cells produce a neutrophil chemotactic cytokine, interleukin (IL)-8, and a mononuclear cell chemotactic cytokine, monocyte chemotactic peptide-1 (MCP-1). MCP-1 is produced by inflammatory macrophages and endothelial cells. This cytokine may be at least partly responsible for the recruitment of macrophages.
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Transforming growth factor-13 (TGF-13) is an immunosuppressive cytokine and a potent modulator in tissue repair. It suppresses the release of tumor necrosis factor (TNF)-a and TNF-g by inflammatory cells. Levels of TGF-13 are significantly elevated in tuberculous pleural effusion compared with nontuberculous pleural effusion. This may play an important role in regression of granulomatous inflammation and promotion of pleural fibrosis by stimulating mesothelial cells and fibroblasts.

The traditional explanation for the development of a tuberculous pleural effusion is that a small subpleural focus of M tuberculosis ruptures into the patient's pleural space, initiating an interaction between the bacilli and CD4+ T lymphocytes. The clinical syndrome reflects an in situ delayed hypersensitivity reaction. A significant decrease in the removal of protein from the pleural cavity has been documented, contrary to an anticipated augmentation in the formation of protein resulting from inflammation. The intense inflammatory reaction obstructs the lymphatic pores in the parietal pleura, resulting in accumulation of protein in the pleural cavity.

The pleural fluid may become loculated as a result of adhesions. The formation of these adhesions depends on pH, cellular components, and fibrinogen content of the fluid; it usually occurs during antituberculosis treatment.

Clinical features
Most patients with pleural involvement complain of pleuritic chest pain followed by nonproductive cough and dyspnea. Although tuberculosis is generally a chronic disease, tuberculous pleural effusion most often manifests as an acute illness. Infrequently, the onset may be less acute, with mild chest pain, low-grade fever, cough, weight loss, and anorexia.

Tuberculous pleural effusion is almost always unilateral and is usually small to moderate in size, although massive effusion can occur. The loculation of effusion prolongs the recovery. In India, tuberculosis is the most common cause of loculated effusion.

Diagnosis
The diagnosis of tuberculous pleural effusion depends on the demonstration of acid-fast bacilli (AFB) in pleural fluid or pleural biopsy specimens, or the presence of caseous granulomas in the pleura. Other supportive findings include tuberculin skin test results and the erythrocyte sedimentation rate.

Radiologic investigations: The chest radiograph usually demonstrates a unilateral pleural effusion (Figure 1). Ultrasonography of the pleural cavity may be helpful when suspected tuberculous pleural effusion is not detected on radiography; it demonstrates septations and pleural thickening. Ultrasonography and CT scanning are also useful in the diagnosis of an encysted effusion. Most often, loculated effusions occur on the right side along the posterior parietal pleural surface. Subpulmonic encystment needs to be distinguished from subpulmonic collection of free fluid, since they present with an identical radiologic picture. A lateral decubitus radiograph usually provides the correct diagnosis.

Enzymes and cytokines: The pleural fluid adenosine deaminase (ADA) has long been used as a marker of pleural tuberculosis. The sensitivity and specificity range from 93% to 100% and 76% to 100%, respectively. False-positive results can be caused by pyothorax, lung cancer, lymphoma, or pleural mesothelioma. False-negative results can occur in patients who have an inadequate immune response or early-stage disease.

A ratio of ADA to lysozyme is reported to be useful in differentiating tuberculosis from pyogenic empyema effusion. A threshold value above 3.3 is highly specific for tuberculous pleural effusion. Studies have suggested that elevated pleural fluid interferon (IFN)-g can be used as a marker for the diagnosis of tuberculosis. It is now well documented that a significantly higher ratio of IFN-g to IL-4 in the pleural fluid than in the peripheral blood suggests sequestration of T\textsubscript{\gamma}1 cells in the pleural fluid and is consistent with the presence of pleural tuberculosis.

IL-8 has been shown to be significantly elevated in patients with empyema and parapneumonic effusion, compared with those who have tuberculous pleural effusion. Marked elevation of soluble IL-2 receptors in pleural fluid and serum is found in patients with tuberculous pleural effusion and helps distinguish tuberculosis from malignant pleural effusion.

Pleural fluid examination: On thoracocentesis, pleural fluid is typically straw-colored. The characteristic observation is a high protein content with marked lymphocytosis, although lower protein content may be found in patients with AIDS. The presence of a large number of mesothelial cells (more than 1% of white blood cells) and eosinophils (more than 10%) is strong evidence against the diagnosis of tuberculosis.

Pleural fluid pH is usually higher than 7.3, and pleural fluid glucose concentration is not significantly decreased. Pleural fluid culture yields M tuberculosis in 13% to 70% of cases. The yield is the same with conventional culture methods and with the rapid diagnostic system. The detection of mycobacterial DNA by polymerase chain reaction has a sensitivity of 61% to 90% and a specificity of...
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78% to 100%. Until the gene amplification tests have proved reliable and quality-control procedures have been established, the clinical validity of these tests remains controversial.

Pleural biopsy: The combination of culture and histopathologic examination of pleural biopsy specimens has been described as the most sensitive diagnostic test for pleural tuberculosis. The histologic finding of granulomatous inflammation is used as a diagnostic criterion for tuberculosis and is seen on pleural biopsy in 50% to 80% of cases. However, caution must be exercised in interpreting the presence of granuloma, because other diseases, especially sarcoidosis and fungal infection, can produce similar findings.

The demonstration of AFB on stained smears of pleural fluid, with histopathologic evidence of granulomas, is the gold standard for diagnosis. The combined yield of direct AFB stains of pleural fluid and biopsy tissue, coupled with mycobacterial culture, exceeds 90%.

The pleural biopsy has potential disadvantages, such as pneumothorax and needle breakage. Moreover, patchy involvement of pleura may result in an inconclusive finding on biopsy. Ultrasonography-guided needle biopsy and video-assisted thoracoscopic pleural biopsy are being used to increase sensitivity. The higher sensitivity of these procedures is related to the delineation of focal pleural abnormalities.

Since there is a greater burden of bacilli as a result of the impaired host response in patients with HIV infection, the yield of AFB in pleural tissue is significantly higher in these patients than it is in HIV-negative patients.

Treatment

Short-course chemotherapy (3 or 4 drugs for 2 months, followed by 2 drugs for the next 4 months) has been found to be highly effective in patients with tuberculous pleural effusion. Corticosteroid therapy has been proposed as a way of decreasing pleural inflammation, and the addition of corticosteroids has been reported to result in a quicker improvement in symptoms (fever, chest pain, anorexia) and resorption of pleural fluid; however, there is insufficient evidence to establish whether corticosteroid therapy is useful in the management of pleural tuberculosis.

Complications

The most frequent sequela is residual pleural thickening, which occurs in more than 50% of patients. The presence of residual pleural thickening is not affected by administration of antituberculosis drugs or repeated therapeutic thoracocentesis. However, it has been suggested that a therapeutic thoracocentesis may decrease the incidence of this complication.

Another potential complication is empyema thoracis, which is especially common in developing countries. It most often results from rupture of a superficial tuberculous cavity into the pleural space or, occasionally, from rupture of a caseous paratracheal lymph node or paravertebral abscess into the pleural cavity.

Patients with empyema thoracis have clinical features of pleural effusion but have a more toxic appearance, and they have clubbing and intercostal tenderness. Rarely, empyema thoracis may manifest as a draining sinus tract. In addition to antituberculosis therapy, management includes intercostal chest tube drainage and antibiotics for superimposed infection. Nonetheless, conventional surgical procedures, such as decortication, rib resection, or thoracoplasty, may have to be performed for complete cure.

Lymph Node Tuberculosis

Peripheral lymph node involvement is the most common form of extrapulmonary tuberculosis. M. tuberculosis is the most common cause of tuberculous lymphadenopathy in developing countries, such as India. However, nontuberculous mycobacteria are increasing in prevalence as causes of lymphadenitis. In the United States, M. tuberculosis was the pathogen in 95% of adults with mycobacterial lymphadenitis, but nontuberculous mycobacteria were the cause in 92% of pediatric patients with this disease.

Pathogenesis

M. tuberculosis gains access through the respiratory tract and is disseminated via lymphatic and hematogenous pathways. The organism first reaches the mediastinal lymph nodes during lymphatic spread from the lung parenchyma as a result of primary infection or reactivation of latent infection. The tonsillar gland is also an important portal of entry. Subsequently, infection from the mediastinum or tonsils disseminates to the cervical lymph nodes via the lymphatics. The lymph nodes are clinically discrete in the early stages. Subsequently, perilymphadenitis causes matting of the nodes. If untreated, the lymph nodes coalesce to form caseous pus. The swelling in the neck may present as a "collar-stud" abscess (cold abscess), or the overlying skin may indurate and lead to the formation of a sinus. The typical tuberculous sinus has thin, bluish, undermined edges with caseous discharge. There is calcification and/or scarring on healing.

Clinical features

Tuberculous cervical lymphadenopathy presents more often in young adults, especially females. Patients complain of progressively enlarging lymph nodes, most commonly in the cervical group. The axillary and inguinal lymph nodes may also be involved. The lymph nodes are nontender, except when secondary bacterial infection has occurred.
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Some patients do not present with constitutional features. Occasionally, cough is a prominent symptom in patients who have mediastinal lymphadenopathy. Unusual presentations of mediastinal lymphadenopathy include dysphagia caused by compression of the esophagus, esophago-mediastinal fistula, tracheo-esophageal fistula, chylothorax resulting from thoracic duct obstruction, and pericardial effusion (including cardiac tamponade). Peripheral and mediastinal lymph node tuberculosis is commonly seen in patients with HIV infection. In these patients, tuberculosis lymphadenopathy presents as lymph node enlargement at multiple sites; in HIV-negative patients, it manifests as a focal cervical lymphadenopathy and other groups of lymph nodes are rarely involved. Diagnosis

The differential diagnosis in this setting includes reactive lymphadenopathy (secondary to viral and bacterial infections), lymphoma, and metastatic deposits. Sarcoidosis is an important diagnostic consideration in patients with mediastinal lymphadenopathy. The gold standard for the diagnosis of lymph node tuberculosis is demonstration of mycobacteria in smears on fine-needle aspiration cytology, histopathology, or mycobacterial culture. FNAC has replaced the conventional lymph node excision biopsy. Although excision biopsy is a simple procedure, it has been associated with morbidity. FNAC is a relatively noninvasive, pain-free outpatient procedure. It should be the first diagnostic procedure for peripheral lymphadenopathy. The characteristic cytopathologic features include epithelioid cell granuloma with or without multinucleate giant cells and caseation necrosis. Supportive tests include the Mantoux tuberculin test and conventional chest radiography. However, a negative tuberculin test result does not exclude tuberculosis. Paratracheal, hilar, and mediastinal lymphadenopathy has been observed on chest radiographs in fewer than 10% of patients with peripheral tuberculous lymphadenitis. Therefore, other radiologic studies, such as CT scanning of the chest (Figures 2 and 3) and ultrasonography of the abdomen, may be useful. However, these studies should be performed only if there is a strong clinical suspicion of the diagnosis. On an ultrasonogram and CT scan, the lymph nodes show enlargement with hypoechoic/hypodense areas with central necrosis and peripheral rim enhancement or calcification. In patients with mediastinal lymphadenopathy, cytopathologic/histologic diagnosis requires invasive techniques such as ultrasonographic/CT-guided percutaneous biopsy, mediastinoscopy, video-assisted thoracoscopic surgery, or endoscopic transbronchial or transesophageal biopsy. Treatment

Currently, short-course chemotherapy with 4 drugs (rifampin, isoniazid, ethambutol, pyrazinamide) is recommended for the first 2 months, with rifampin and isoniazid administered for the subsequent 4 to 7 months, depending on the response (Table). The enlargement of lymph nodes and the appearance of new nodes during or after antituberculosis therapy have been documented by various authors. These nodes show histopathologic features of tuberculosis but are sterile on culture. They usually represent a transient hypersensitivity phenomenon and normally regress in size without alteration in therapy. Another important feature observed during therapy is the appearance of fluctuation caused by "cold pus" in lymph nodes, which should be aspirated under strict aseptic conditions. Drainage and appropriate broad-spectrum antibiotics may be required, in addition to antituberculosis treatment, for complete cure.

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