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Chapter

Thoracic Extrapulmonary Tuberculosis in the Millennial Era

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Abstract

Mycobacterium tuberculosis is one of the most pathogenic infectious organisms, usually known for causing cavitary lung infection. But this mycobacterium is also capable of causing masked involvement in any organ of the body. Its clinical manifestation can mimic other conditions according to the organ affected. Extrapulmonary infection is defined as any manifestation caused by tuberculosis in tissues outside the airway or the pulmonary parenchyma. Despite it being a well-known infectious organism throughout decades, tuberculosis continues to be causing great morbidity and mortality in this millennium. This chapter will discuss the clinical manifestations of extrapulmonary tuberculosis (EPTB), when the mycobacteria invade extrapulmonary tissues inside the thorax. We discuss and review the literature about the clinical manifestations, diagnosis and evaluation, and general treatment.

Keywords: tuberculosis, extrapulmonary, thoracic

1. Introduction

Mycobacterium tuberculosis is one of the most pathogenic infectious organisms. As a single agent, it has caused more morbidity and mortality around the world than any other organism, despite being known for years and the emergence of effective antibiotic therapy. The most common form of active disease is pulmonary parenchymal involvement. However, with the emergence of longer life expectancy of immunosuppressed patients with human immunodeficiency virus and cancer, these mycobacteria have shown its pathogenicity causing infection outside the lungs, involving a great variability of extrapulmonary tissue and other organ systems.

Extrapulmonary tuberculosis (EPTB) occurs when the tuberculous mycobacterium invades areas outside the pulmonary parenchyma, including other thoracic structures, and any other organ outside the lungs. Cases of extrapulmonary tuberculosis have been reported involving organs from the central nervous system throughout the abdominal organs and even the bone and skin. Clinical presentation will vary according to the organ involved, and its pathogenicity can mimic other infectious and noninfectious diseases. Extrapulmonary infection can be fatal and often requires extensive work-up for proper diagnosis. It often requires invasive interventions as culture of sterile body fluids and biopsies, for evaluation of pathognomonic changes and identification of the mycobacteria. Also, the diagnosis is time-consuming, and delay in identification can occur due to its variable clinical presentation.

Outside the pulmonary parenchyma, tuberculosis can invade any structure of the thorax, causing significant clinical disease. Involvement of any thoracic tissue, outside the airways and alveoli, is considered an extrapulmonary disease. Thoracic extrapulmonary tuberculosis includes involvement of the pleural tissue, the lymph nodes, the heart and blood vessels, the bone and skin, and even the complete chest wall. Also, tuberculosis can cause significant disease if it reaches the thoracic spine. This illustrates the ample spectrum of the pathology of this mycobacterium when it invades tissue outside the lung. Many times, therapy for thoracic extrapulmonary tuberculosis is similar to exclusive pulmonary involvement. However, the fact that extrapulmonary tuberculosis can mimic other diseases, identification of this mycobacteria as the culprit of a thoracic pathology, requires a vast knowledge to include it in the differential diagnosis. Also, thoracic extrapulmonary tuberculosis would require additional diagnostic and therapeutic interventions during patient's management.

In this chapter, we will discuss the most important clinical manifestations of thoracic extrapulmonary tuberculosis. It will include the most common clinical presentations, and a review of the literature is its diagnostic and therapeutic approach.

2. Pathophysiology of thoracic extrapulmonary tuberculosis

The most common presentation thoracic extrapulmonary tuberculosis is lymphadenitis [1]. When the mycobacterium is inhaled into the lungs, it is engulfed by macrophages that activate specific T cells that protect the organism causing mostly latent infection. The lung natural immunity creates a granuloma around infected alveolar macrophages where the mycobacteria can be dormant or can proliferate. Depending of the bacterial load and inflammatory host response, some patients cannot contain the infection in the granulomas, leading to mycobacterial proliferation outside the granulomas, causing active disease [2]. The mycobacteria can also escape the lung throughout blood vessels and the lymphatic system invading other organs. In the same way, mycobacteria can invade extensively the alveolar spaces and reach extrapulmonary tissues after rupture of caseous foci in the proximity [3].

It is thought that most of the extrapulmonary tuberculosis occurs during primary infection rather than reactivation [4–6], especially tuberculous pleurisy [1]. However, in the immunosuppressed population, other extrapulmonary findings are more common after activation of latent disease [2].

3. Epidemiology of thoracic extrapulmonary tuberculosis

When we talk about extrapulmonary tuberculosis, we refer to any invasion of the mycobacteria outside the pulmonary tissue. Invasion of the pleura, thoracic lymph nodes, and structures of the chest wall is part of the spectrum of extrapulmonary disease.

The most common extraparenchymal invasion of the mycobacteria in the thorax is invasion of the supraclavicular, mediastinal, and hilar lymph nodes [1]. Depending of the world location and endemicity of the infection, lymph node infection has been identified between 8 and 30% of the patients [1]. Almost 30% of those patients present with concomitant extra nodal disease [1]. Variability in diagnosis techniques and available resources must probably influence in the lymph node infection being underdiagnosed.

Tuberculous pleural involvement is the second most frequent thoracic extrapulmonary manifestation. Almost 25% of patients with tuberculosis present with

pleuritis. The incidence is higher in immunosuppressed patients secondary to human immunodeficiency virus [7]. The incidence of tuberculous pleural involvement can be higher, but its epidemiological data is limited based on world location, patient population, and diagnostic resources. Pleural fluid culture has a low diagnostic yield, and pleural biopsy, which is the most common way for identification, many times is not readily available for most patients.

Heart and thoracic blood vessel involvement by tuberculosis is a rare disease. Diagnosis of direct cardiac tissue involvement is made in only around 2% of patients [8]. However, pericardial effusions are more common, and tuberculosis can be the culprit of most of the pericardial effusions of patient with a lack of adequate immune system response, reaching almost 70% of them [9]. Aortic tuberculous involvement is also extremely rare and can occur secondary to infection in adjacent tissue and blood dissemination.

Bone and chest wall infection by tuberculosis is also a rare presentation, accounting for approximately 2% of all tuberculosis cases reported [10]. The most common site of musculoskeletal involvement is the spinal bones, but tuberculosis can also invade the ribs, muscles, sternum, and sternoclavicular joints [10]. Most of the infections are also related to adjacent tissue invasion but can also occur secondary to hematogenous and lymphatic dissemination.

4. Tuberculous lymphadenitis

After the mycobacterium is inhaled into the lungs, it is engulfed in macrophages after activation of nonnatural immune system occurs. The immune system forms granulomas that can rupture and infect the adjacent tissue. Mycobacteria can also enter in the lymphatic duct and travel to the lymph node in the proximity. Inside the lymph nodes, the mycobacteria can cause active inflammation and abscesses. Tuberculous lymph node involvement can present as a mass-like lesion but also can cause fissures and ulcers [11]. Thoracic lymphadenitis occurs in the mediastinum and hilar nodes, but lymphadenopathy can also occur in the supraclavicular area and migrate to the neck and face. More common symptoms are those associated to pulmonary tuberculosis but in some patients can present with pain and mass effect. Other patients can present with ulceration of the skin as the nodules progress to an abscess and cause a fistula.

Diagnosis is made by culture and tissue evaluation. Fine needle aspiration is the most common diagnostic evaluation, but other techniques include surgical node excision. Aspiration of the lymph nodes can be done guided by ultrasound or CAT scan. Also, ultrasound- or non-ultrasound-guided bronchoscopic approach can also be done. Fine needle aspiration or direct nodal biopsy has shown similar diagnostic yields in the present literature [1].

Identification of the mycobacteria by acid-fast staining, cultures, and genetic testing has been the principal method of diagnosis. Histologic evidence of granulomatous disease can also help in the diagnosis of negative culture patients in the proper clinical setting.

Treatment for tuberculous lymphadenitis is similar to pulmonary disease: antituberculous antibiotic with isoniazid, rifampin, and ethambutol for 2 months [12], followed by 4–7 months of isoniazid and rifampin. Total duration of disease is about 6–9 months, and length and type of therapy can be affected by other organ involvement, immunosuppressive level of the patient, and culture sensitivities. Surgical and percutaneous drainage can assist in treatment when abscess and fistulas are formed and mass effect is caused by the enlarged nodes.

5. Tuberculous pleurisy

Pleural tissue manifestations of tuberculosis are the second most common finding of thoracic extrapulmonary disease, and it competes with lymphadenitis as the most common extrapulmonary disease presentation. The mycobacteria can reach the pleural cavity by direct parenchymal tissue rupture but also can travel to pleural tissue by the lymphatic system. When the mycobacteria reach the pleural tissue, it can cause a hypersensitivity reaction that produces a lymphocytic inflammatory proliferation that decreases pleural fluid resorption [7]. Also, the inflammatory reaction increases the permeability of the pleural capillaries to proteins and increases the oncotic pressure inside the cavity, increasing the rate of pleural fluid formation [13]. The pleural fluid, rich in cells and protein, obstructs the lymphatic ducts of the parietal pleura and decreases fluid clearance from the pleural space [13]. So, a high rate of fluid formation and the decreased pleural fluid removal lead to the accumulation of pleural fluid and development of pleural effusions. Also, the inflammatory reaction and granuloma formation affect directly the pleural tissue, causing pleural thickening and fibrosis.

Common clinical presentations include symptoms of concomitant pulmonary parenchymal infection as cough, hemoptysis, fever, and weigh loss. Other patients present with pleuritic and nonspecific pain or dyspnea as fluid accumulation causes compression of the lung tissue. Chest wall pain can occur as the parietal pleura is involved and a pleural inflammatory reaction causes abscesses and empyema. The most severe presentation is when the pleural abscess fistulizes to the chest wall, esophagus, main bronchus, and or abdominal cavity, seen as empyema necessitans. Rare cases present without symptoms [14] but have been reported.

Chest images can usually present with a unilateral moderate to large pleural effusion, and almost 90% of patient have concomitant pulmonary parenchymal findings [7]. So, it is always important to rule out active pulmonary disease when pleural tuberculosis is suspected. Nodules, abscesses, and pleural thickening are also common findings on imaging.

Pleural fluid analysis during tuberculous pleurisy shows usually an exudative effusion. As the clinical presentation is usually subacute and chronic inflammation and due to the common immune reaction, the pleural fluid usually presents with lymphocytic cells. Pleural fluid lymphocytic predominance is mostly of more than 50% of the total cell count, and a ratio of lymphocytes to neutrophils is in the range of more than 75% [15]. Cells rarely seen in pleural fluid with tuberculous involvement are mesothelial cells that are present in less than 5% of the total cell count, and eosinophils are rarely in a proportion of more than 10% [7].

Other pleural fluid analyses show increased fluid proteins and low pH and glucose. Lactate dehydrogenase levels are usually high in tuberculous pleurisy, often higher than concomitant blood levels [7].

Pleural fluid stains for tuberculosis as the acid-fast bacillus stains are rarely positive. However, in immunosuppressed patients, for example, HIV positive, it can be positive if it is around 20% of the pleural fluid analysis [16]. Cultures from pleural fluid have slightly higher yield than stains, around 35%, but in concomitant pulmonary tuberculosis, the combination of sputum and pleural fluid culture can have a diagnostic yield of almost 80% [16]. Genetic testing has low sensitivity but good specificity [16], so a positive test is indicative of pleural fluid *Mycobacterium tuberculosis* presence, but a negative test does not rule out the pleural involvement.

Adenosine deaminase (ADA) is a lymphocyte-produced enzyme for metabolism of the components of the DNA. ADA helps during T-cell differentiation and proliferation, and knowing the usual immune reaction activated by the tuberculous

bacilli, it is expected that ADA would be high during pleural tissue involvement. Levels of this enzyme have been available during years, and its use has been extensively discussed. In high prevalent populations, a high level is almost diagnostic despite negative cultures of the mycobacterium [17]. The contrary is also considered correct: pleural cavity involvement can be ruled out when a patient in low-prevalence population has low levels of ADA in the pleural fluid. Suggested cutoff values for diagnosis for highly suggested disease are 65–70 IU/L. Levels of less than 35 IU/L have a high negative predictive value for disease in low-incidence populations [17].

Other tests that can be done for identification of tuberculous pleural effusion include genetic testing with polymerase chain reaction, measurement of γ-interferon levels, and interferon release assays. However, those tests have not been readily available and standardized for general use.

Pleural biopsy has the highest diagnostic yield until this time. Biopsy can be done using blind or image-guided percutaneous needle pleural cut. Images used to guide biopsy include ultrasound and CAT scan. Thoracoscopic and surgical pleural biopsy are more invasive alternatives. Tissue evaluation of the parietal pleural tissue can show caseous granuloma and the presence of acid-fast bacilli. Cultures of the pleural tissue have shown the highest yield (75–90%), increasing the diagnosis rate when the biopsy is guided by images [15].

The most efficient way of establishing a diagnosis for pleural tuberculous involvement is throughout a compressive and progressive evaluation. First, ruling out pulmonary parenchymal involvement should be done. Evaluation of the sputum for acid-fast bacilli and cultures is the first step. If pulmonary involvement is ruled out, in the presence of a lymphocytic predominant pleural effusion, pretest probability of pleural tuberculous infection must be taken into account. In low-prevalence populations, a low ADA (less than 35 IU/L) almost rules out the disease. In high-prevalence populations, a high ADA (more than 65 IU/L) is highly suggestive of pleural disease, and treatment can be considered. In a patient with ADA levels in between 35 and 65 IU/L, pleural biopsy can be done, and if typical granulomas are seen, therapy can be considered even with negative cultures. A positive culture would warrant an antibiotic therapy.

Therapy for tuberculous pleural involvement often is similar to pulmonary active infection, as it usually presents with concomitant disease. Usually it includes isoniazid, rifampin, ethambutol, and pyrazinamide for the first 8 weeks or until sensitivities are obtained, and then 16 weeks of isoniazid and rifampin are completed to a total of 6 months. Direct observe therapy is recommended during the completion of treatment [7].

Adding systemic steroids for pleural tuberculosis is not recommended as no benefit has been seen [18], and usually complications of immunosuppressive therapy add morbidity and mortality to the patients. In some patients with persistent pain and fever symptoms, systemic steroids can be considered [7] for a short period of time, until symptoms subside. Surgical evacuation with simultaneous antituberculosis antibiotics is the treatment option for empyema. It usually requires complex decortication and debridement of tissue and abscess area, with reconstruction of the surrounding tissue as in the case of empyema necessitans.

6. Cardiac and pericardial disease

Tuberculous involvement of the heart can include infection of the pericardium (most common), the cardiac muscle, and the large blood vessels as the aorta.

Pericardial involvement is similar to pleural tuberculosis. The pericardium acquires the infection by lymphatic or hematogenous spread of the bacteria, as well

as rupture of granulomas on an adjacent tissue. Once the mycobacteria reach the tissue, it causes similar hypersensitive reaction inside the pericardium leaded by T cells. This inflammatory process induces a granulomatous reaction that progresses to a fibrinous and serosanguineous effusion and produces pericardial thickening and fibrosis [18]. Impaired lymphatic drainage can worsen the process and cause rapid accumulation of fluid.

Clinical presentations can vary from systemic symptoms due to pulmonary and other organ infection to chest pain and congestive heart failure. Rapid fluid accumulation can cause vascular collapse due to cardiac tamponade. Asymptomatic pericardial effusion is very uncommon.

Diagnosis of pericardial involvement is made by similar mechanisms as pleural disease. Analysis of pleural fluid aspirated using direct visualization with ultrasound or CAT scan can be done. Also, surgical exploration is an alternative when those methods are not available, and other diseases are also considered. Pericardial fluid analysis findings are similar to tuberculous pleural fluid, including lymphocytic cellular predominance, low glucose and pH, high LDH levels, and similar levels of ADA. Biopsies usually show granulomas and AFB, and culture for mycobacteria can be positive. Empiric treatment response can be highly suggestive of diagnosis in high-risk populations with no conclusive diagnosis, but confirmation of infection is the recommended evaluation.

Other cardiac involvement presentation is direct invasion of the myocardial tissue and endocarditis. This is a very rare presentation and is usually fatal. Clinical findings include symptoms similar to a cardiomyopathy with heart failure, arrhythmias, conduction blocks, cardiac output blocks, valvulopathy, and aneurysms [8]. Diagnosis is usually done with an autopsy due to the severity of the cases.

The aorta can also be involved after hematogenous involvement or due to proximity in concomitant cardiac disease. In nonfatal cases, diagnosis is done after reviewing tissue from repaired aneurysms [19].

Therapy for cardiac tuberculosis includes drainage of pericardial effusions, by surgical or percutaneous methods, with simultaneous antituberculous antibiotics for 6–9 months. Systemic steroids during pericardial effusion have not demonstrated less progression to fibrosis in the pericardium or less requirement of surgical interventions, but some studies suggest a decrease in mortality [20]. Antituberculous therapy has an initial regime of four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) and then two drugs, as sensitivities become available. Surgical interventions are indicated in some cases of valvular or large vessel involvement.

7. Bone and musculoskeletal involvement

The most common presentation of musculoskeletal involvement is vertebral and chest wall invasion secondary to hematogenous, lymphatic, and adjacent tissue infection spreading. When the spine is involved, it is known as Pott's disease. The name originated from the description of tuberculous infection of the spine by Sir Percivall Pott, a British surgeon, in 1779 [21]. The tuberculous bacilli invade the bone and vertebral disk with an inflammatory and mass-like process that destroys the tissue causing fractures and can progress to cord compression.

Clinical presentation will vary according to deepness of tissue invasion and localization. Images usually show the lesions and guide the tissue diagnosis. Confirmation of tuberculosis involvement is done by tissue diagnosis and cultures. The treatment includes a similar antituberculous drug regime to other sites and surgery to correct possible mechanical damage.

8. Conclusion

Thoracic extrapulmonary tuberculosis is a disease characterized for *Mycobacterium tuberculosis* involvement outside the pulmonary parenchyma and inside the chest cavity. It has a variety of presentations according the tissue affected. More common presentations include the lymph nodes and pleural tissue, but rare cases present with myocardial and chest wall invasion. Cases can be fatal. Therapy usually is mainly based on antituberculous therapy, but some patients require percutaneous and surgical procedures. Clinical suspicion and the correct work-up usually led to the diagnosis.

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