4 Tuberculosis in the adult

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4.1 TUBERCULOSIS OF THE LUNG

4.1.1 Pathophysiology

The lung, primary entry site of the tuberculosis (TB) bacillus into the body, is the organ most commonly affected by clinical TB. The initial infection occurs by the inhalation of droplet nuclei which, because of their size, bypass the bronchial mucociliary protective barrier. Settling in an alveolus, a single acid-fast bacillus (AFB) carrying droplet nucleus is adequate to initiate a primary focus of infection [1].

The organisms, initially facing no immune response, multiply with a doubling time of 24 hours [2]. The host's neutrophils and macrophages ingest and destroy the multiplying bacilli, but some remain viable and even replicate within macrophages. This growth and the attraction of cellular elements results in the formation of a primary focus. The organisms spread via lymphatics to the hilar and mediastinal lymph nodes and reach the blood stream, seeding the lung and other organs. The virulence of strains of *Mycobacterium tuberculosis* can be measured by their ability to grow progressively in the lungs of mice [2a]. Avirulent strains were found to have slower doubling times, which could be shortened *in vivo* by corticosteroid administration with the strains becoming more pathogenic [2a].

Although any tissue can be involved, the upper lung fields, kidney, lymph node, brain and bone seem to provide an environment where foci with viable bacilli are likely to persist. Further spread is limited by the development of cell-mediated immunity, demonstrable by a positive tuberculin skin test within 4–10 weeks [3]. The infection is not well contained in 2–5% of recently infected individuals, resulting in overt disease within a year. In the remainder of individuals, the granulomatous foci may heal

L. I. Lutwick (ed.), *Tuberculosis*

or continue to harbor viable bacilli awaiting reactivation. The risk of reactivation is life long, but the rate declines over the years, with 10% of untreated infected individuals eventually developing active TB [3].

The site of primary infection is often the lower lung fields [2], where the ventilation is best. The primary complex consists of a lung focus with hilar or mediastinal lymph node enlargement. Pleural effusion or atelectasis may occur. These processes can occur alone or in combination and, in many cases, no primary lesions are detected on X-ray [3–5]. The hilar or mediastinal adenopathy persists longer than the parenchymal lesions and is usually a manifestation of primary TB, while parenchymal and pleural lesions develop both in primary and reactivation TB. In individuals with intact immunity, the primary lesions usually heal, some calcify and symptoms are minimal or absent. In others, the lesions may progress to overt pulmonary or extrapulmonary TB.

Post-primary TB is caused by reactivation of an old focus. Reinfection with a new strain is unusual but may occur in persons exposed to a large infective dose [6] or who have cellular immunosuppression. The latter circumstance has been reported using restriction fragment length polymorphism demonstrating exogenous reinfection with multi-drug-resistant *M. tuberculosis* [6a]. In cases of reactivation, immunosuppression, malnutrition, alcoholism or aging may contribute to the failure of containment. The upper lobe apical and posterior segments are the usual sites for reactivation. This is thought to be due to zonal variation in the ventilation–perfusion relationship with resultant higher oxygen tension in the upper lobes. A second factor may be a relative lack of lymphatic drainage from the upper fields. Both conditions provide a more favorable environment for sustaining the viability and growth of TB [4].

The inflammatory process occurring early in reactivation pulmonary TB is not different from the primary focus. As the lesions progress relatively unchecked, they enlarge and may cavitate and/or rupture into the bronchial or pleural space. An important mode of spread within the lung is bronchogenic or bronchial embolization [4,5]. The parenchymal lesions, as they caseate, spill necrotic contents into the bronchial tree, resulting in extension to areas beyond the lobar boundary. The bronchial wall may become involved, resulting in endobronchial TB characterized by mucosal ulceration, mass lesions or bronchial stenosis [7]. A cavitary lesion can communicate with the pleural space, producing empyema, broncho-pleural fistula or pneumothorax [8].

Miliary TB may be associated with primary or reactivation disease. It usually follows hematogenous dissemination from erosion of a blood vessel by a parenchymal lesion or caseating lymph node. The course is often subacute, but fatal fulminant disease can occur even before the onset of radiographic mottling [4]. Another condition with a high mortality is whole lung TB in which all five lobes are involved [9]. It may occur as a result of diffuse bronchogenic spread and/or hematogenous dissemination.

4.1.2 Clinical presentation

The patient with overt pulmonary TB may initially be relatively asymptomatic, reporting mild and nonspecific complaints. More prominent symptoms and signs develop which reflect the progression and extent of disease. Concurrent medical illness can predispose to TB, as well as altering its manifestations, making the diagnosis difficult.

The symptoms and signs of pulmonary TB are categorized as constitutional, pulmonary and other [3,10]. Some manifestations may be suggestive of primary disease and others of reactivation. The findings are not specific and asymptomatic cases may occur.

(a) Constitutional symptoms

Common symptoms include fatigue, anorexia, irritability and weight loss. Fever is initially low grade, persisting for weeks to months, being more marked with disease progression. The absence of fever, however, should not discount a diagnosis of TB. The fever often develops in the afternoon, subsiding during sleep with the characteristic night sweat [10]. A fever of unknown origin can receive an extensive diagnostic evaluation despite the presence of significant clinical clues for TB. This may result in the use of unneeded diagnostic tests and delay the institution of specific therapy [11]. It should be noted that persistent fever during TB therapy does not necessarily suggest treatment failure, particularly if the patient's sense of well being is improving.

(b) Pulmonary manifestations

A mild initial cough will progress over weeks to become more frequent, producing mucoid or mucopurulent sputum. Hemoptysis occurs in 8% of adults with active disease and may be significant in those with cavitary lesions [12]. Chest pain can be localized or generalized, may be pleuritic and can indicate more diffuse lung involvement. Dyspnea is uncommon, occurring only with massive lung involvement, large pleural effusion or concomitant cardiac disease.

The physical findings are also nonspecific. Fine rales on deep inspiration may be heard, indicating parenchymal involvement. Pleural signs may or may not be present. The pulmonary physiologic changes are also nonspecific. Arterial pO_2 is usually preserved even with extensive lung disease, unless acute respiratory distress syndrome (ARDS) occurs. Pulmonary function tests may reveal a reduction in vital capacity, lung volume and single breath carbon monoxide diffusing capacity in those with extensive disease [3].

Primary TB, previously seen mostly in children, has been noted in adults with increasing frequency, and accounts for up to 30% of adult pulmonary TB in the USA [4]. The infection is, however, commonly asymptomatic and

may not be diagnosed until an abnormal X-ray or conversion of the tuberculin test is discovered. In a study of 37 adults with primary TB [13] (assessed using the diagnostic criteria of recent tuberculin conversion and lower lobe disease with hilar node enlargement or lower lobe or anterior segment lung lesions that cleared on specific TB drug treatment) symptoms were absent to mild in 70% of patients and the remainder had moderately symptomatic illness, with the exception of one patient who had miliary TB. Cough and pleuritic chest pain were the most common symptoms and the illness may mimic acute pneumonia [14].

Reactivation TB is more common in the older individual. The symptoms may be nonspecific or masked by other illnesses, reflecting a chronic condition with fever, weight loss and cough. It requires, therefore, a high index of suspicion as the infection is potentially fatal if not treated and, if cavitary disease is present, substantial infectivity exists. In one series, the average delay in diagnosis was 10 days from time of hospital admission and 23.2 days when the diagnosis of TB was not initially included [15].

(c) Other manifestations

Certain patient populations, especially the elderly and the immunocompromised, are likely to manifest unusual clinical findings that qualify TB as 'the great masquerader' [16]. Hypertrophic osteoarthropathy, which was known to indicate non-TB intrathoracic disease, has been recently reported in patients with pulmonary TB [17]. Erythema nodosum and/or phlyctenular (vesicular) conjunctivitis may be seen in acute disease, reflecting immunological hyperreactivity [10]. These entities are discussed in Chapter 6. Certain individuals will present with TB in other organs and pulmonary involvement. These are discussed below.

4.1.3 Diagnosis

If pulmonary TB is suspected, a chest X-ray should be done, sputum sent for AFB smear and culture and a tuberculin skin test placed. Culture of the tubercle bacillus may take weeks, but it is the most definitive method of diagnosis. A presumptive diagnosis, usually based on X-ray findings with a reactive skin test (Chapter 8) and/or a positive AFB smear (Chapter 7) justifies starting specific therapy (Chapter 12) while awaiting culture results.

Pulmonary TB is now increasingly reported in patients with AIDS, a condition which predisposes to numerous other lung infections, making the diagnosis of TB more difficult (Chapter 5). It is also associated with multidrug-resistant TB (Chapters 3 and 13). In cities with a high TB incidence, the adoption of specific measures for rapid identification and treatment has been attempted [18,19]. Newer and more rapid diagnostic techniques are now available or being developed (Chapter 7 and below).

(a) Radiographic findings

The chest radiograph is usually abnormal in pulmonary TB except in some cases of endobronchial disease [10] or early in miliary disease [4]. The radiographic findings are usually categorized as primary or reactivation, but overlap occurs.

In primary TB the usual radiographic patterns include parenchymal consolidation, hilar or mediastinal lymphadenopathy with or without parenchymal involvement, pleural effusion, lobar atelectasis and miliary disease.

In primary TB the parenchymal infiltrate is located in the lower lobes in more than 50% of patients [5] (Figure 4.1). It may or may not be accompanied by lymphadenopathy or pleural effusion and may also contain cavities. Tuberculous intrathoracic lymphadenopathy is almost always due to primary infection. It may be unilateral or bilateral, hilar, mediastinal or both. The well recognized primary complex of parenchymal pneumonitis with regional adenopathy is more common in children. Isolated mediastinal lymphadenopathy is increasingly described in patients with TB and AIDS (Figure 4.2). The tuberculous pleural effusion is usually seen in

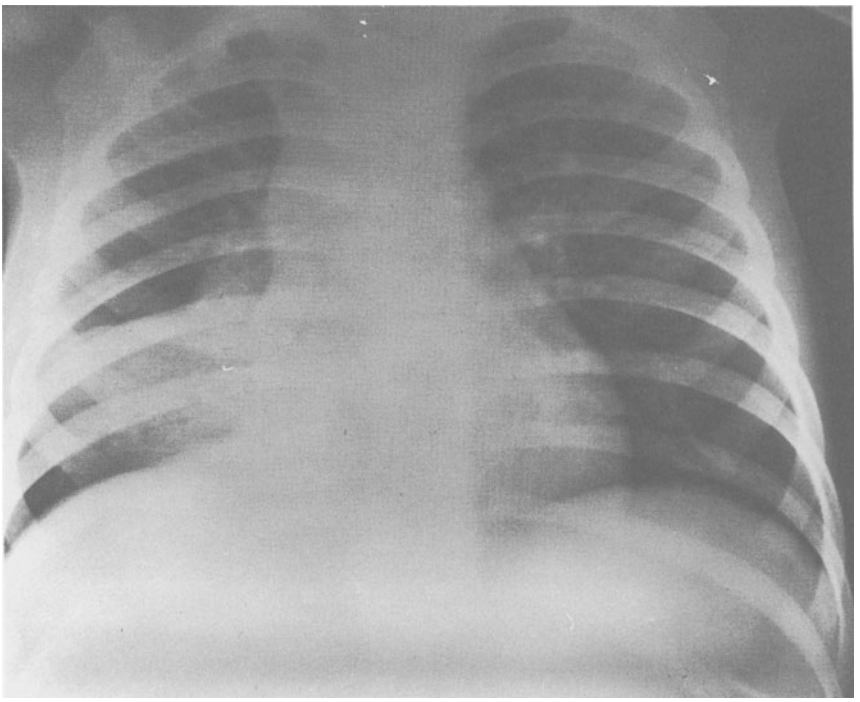

Figure 4.1 A non-upper lobe consolidation found in primary TB. Reproduced with permission from *Infectious Diseases*, 1st edn, by H.P. Lambert and W.E. Farrar, Gower Medical Publishing, London, UK, 1982.

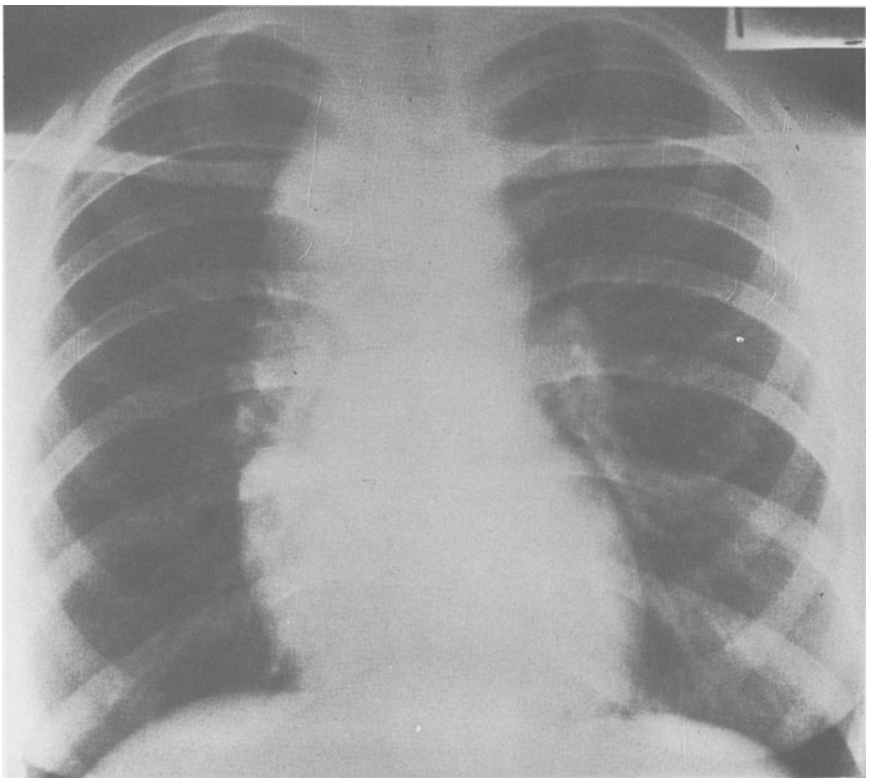

Figure 4.2 Tuberculous lymphadenopathy with right paratracheal node enlargement. Reproduced with permission from *Infectious Diseases*, 1st edn, by H.P. Lambert and W.E. Farrar, Gower Medical Publishing, London, UK, 1982.

young adults with primary disease, occurring alone or with a parenchymal infiltrate (Figure 4.3). Other radiographic manifestations of primary TB are lobar atelectasis mimicking post-obstructive pneumonia and miliary changes.

Most cases of pulmonary TB are caused by the reactivation of an old focus in the apical or posterior segments of the upper lobe. The radiographic abnormalities usually combine the elements of an acute pneumonic process, seen as patchy ill-defined opacities, and partial healing with nodular or linear fibrosis and calcifications. Cavities occur in 40% of adult patients [5]. They may be thin or thick walled, solitary or numerous and some may show air-fluid levels [20]. When a cavity is solitary, it is almost always surrounded by, or associated with, an inflammatory reaction or infiltration [5]. As the disease extends, mainly by endobronchial spread, multiple lobes and the pleural space become affected, leading to the classical radiographic picture of extensive pulmonary TB (Figure 4.4).

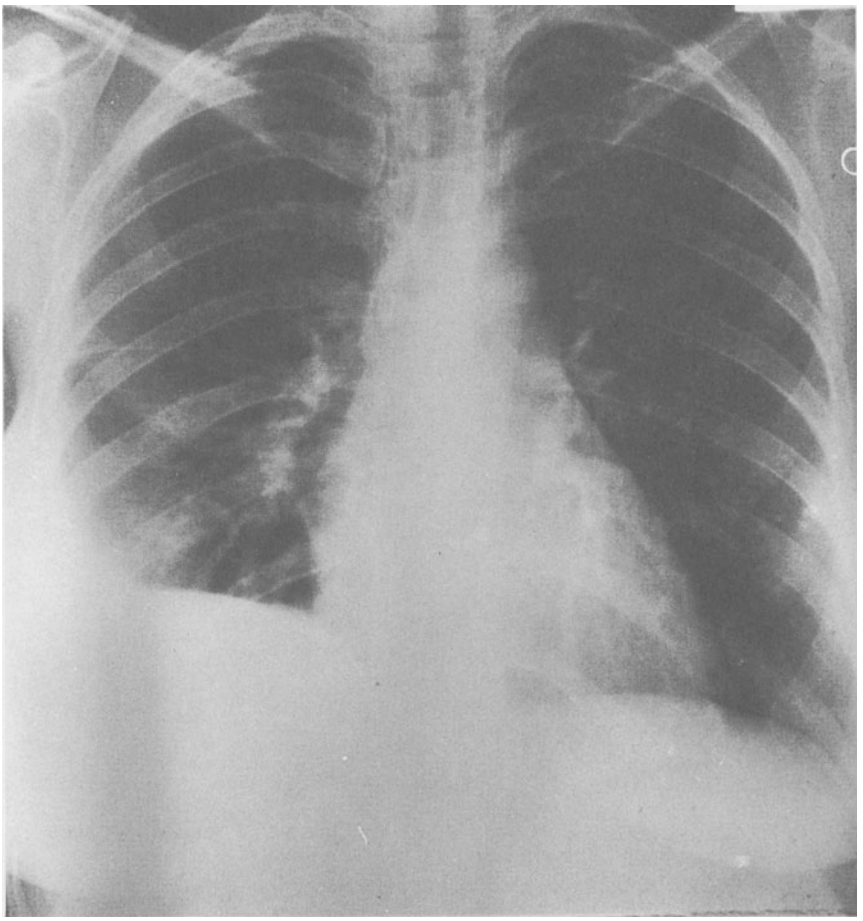

Figure 4.3 Tuberculous pleural effusion, right sided. Reproduced with permission from *Infectious Diseases*, 1st edn, by H.P. Lambert and W.E. Farrar, Gower Medical Publishing, London, UK, 1982.

Some patients may present with only linear or nodular opacities or pleural thickening. Pneumothorax may also occur. Additionally, tuberculoma, a nodular opacity ranging from less than 1 cm to 3 cm or more which may ultimately calcify, may be seen as a solitary uncalcified nodule and be difficult to distinguish from a neoplastic lesion [4].

Almost any form of pulmonary radiographic abnormality may occur in TB. Terms such as 'old changes' should be used only after reviewing previous radiographs and ascertaining that no changes had occurred during the preceding three to four months [3]. When subtle changes are suspected, further details can be uncovered using computerized tomography (CT) or magnetic resonance imaging (MRI) [3,21]. X-ray abnormalities may be

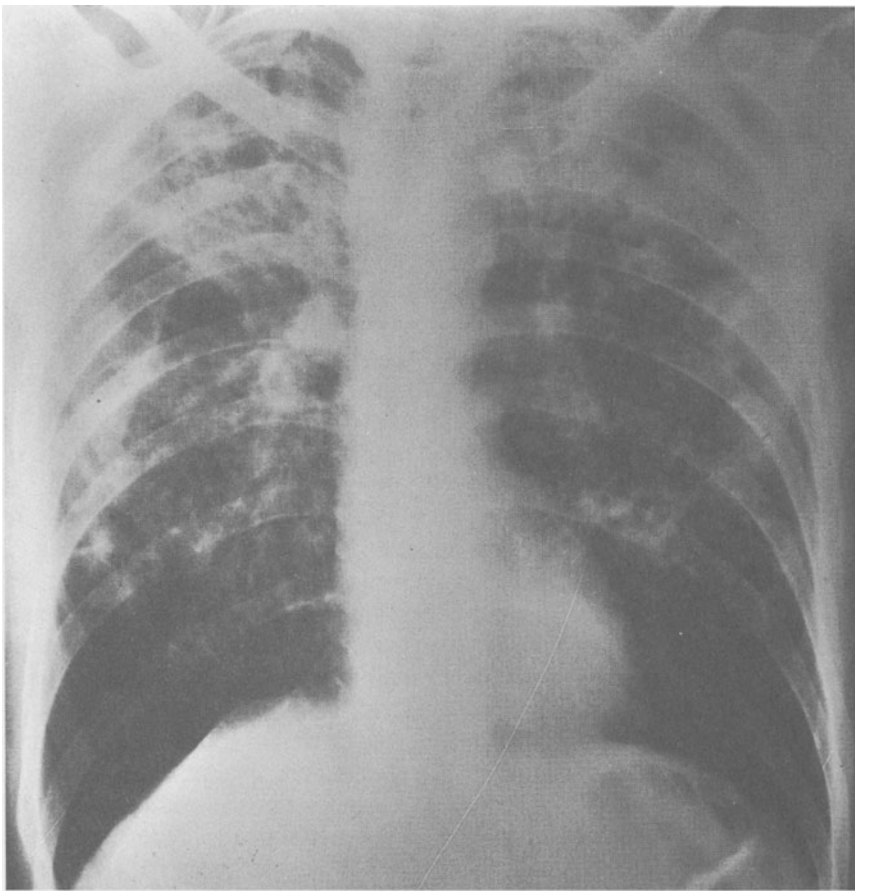

Figure 4.4 Far advanced TB with extensive nodular shadowing in both lungs, especially in the upper lung fields with contracted upper lobes and probable cavitation on the right. Reproduced with permission from *Infectious Diseases*, 1st edn, by H.P. Lambert and W.E. Farrar, Gower Medical Publishing, London, UK, 1982.

absent or nonspecific in cases of endobronchial TB. A CT scan may be useful in detecting bronchial stenosis in some of these cases [22].

(b) Microbiological diagnosis

At least three properly obtained sputum specimens containing minimal saliva or nasopharyngeal secretions should be promptly sent to the laboratory. Induction with saline solution (after taking the necessary precautions to prevent nosocomial transmission) may help in persons who are unable to produce sufficient sputum. Likewise, early morning aspiration of gastric secretions may be helpful in hospitalized, debilitated patients and in

children [3]. The presence of non-TB mycobacteria limits the value of the smear of gastric aspirates, requiring cultural confirmation of the diagnosis [10]. Gastric smears with large numbers of organisms are likely to represent *M. tuberculosis* [23]. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) should be considered when efforts to obtain sputum fail. Post-bronchoscopy sputum should also be collected. Pleural, pericardial, bone marrow or lymph node aspirates may be helpful in certain situations.

The AFB smear has significant clinical and epidemiological importance since the presence of numerous mycobacteria indicates high infectivity. Thus, the experienced microbiologist may be able to estimate the mycobacterial load accurately [3]. Other aspects of the AFB smear are discussed in Chapter 7. A review of sputum AFB smear results obtained from four studies conducted in the USA reported a sensitivity ranging from 22% to 78% with 99% specificity [24]. In a group of 47 patients with pulmonary TB, the sputum smear was positive in 34%, culture was positive in 51%, smear of BAL was positive in 68% and BAL culture positive in 92% [25]. A reported 93% sensitivity was found when cultures of both the sputum and BAL were combined [26]. The sensitivity of the latter combination was not increased significantly by using a biopsy during bronchoscopy [27]. However, transbronchial brushing with biopsy and open lung biopsy retain their diagnostic value in the remaining undiagnosed bronchial, parenchymal or lymph node lesions. Bronchoscopy is particularly valuable in endobronchial TB [28].

Sputum culture is still the gold standard for the diagnosis of pulmonary TB. As discussed in Chapter 7, a properly performed sputum AFB culture is the most sensitive and non-invasive procedure available to clinicians. It will identify infected patients with non-diagnostic radiographs and negative smears as demonstrated in an elderly nursing home population [28]. Unlike the smear, which takes a few hours to perform, the culture causes a significant delay in diagnosis. This may subject some patients to inappropriate therapy and/or delay the institution of proper therapy if TB is not appropriately considered and treated while awaiting culture results. For this reason, newer technologies are now being developed to improve on or replace existing techniques. Some of the new tests are currently marketed, while others are limited to reference or research laboratories. They may be performed on sputum, pleural fluid and other clinical specimens and are discussed in some detail in Chapter 7. The tests include radiometric growth systems [29], polymerase chain reaction [30], serum antibody tests [31,32] and adenosine deaminase activity [33].

4.1.4 Differential diagnosis

(a) Primary tuberculosis

The features of primary TB in adults, including mild to moderate constitutional symptoms and X-ray findings of parenchymal infiltrates, lympha-

denopathy and/or pleural effusion are nonspecific. Parenchymal infiltrates with or without effusions can be due to bacterial, atypical or viral pneumonia. Pulmonary TB should be considered in patients with pneumonia, especially in the setting of possible exposure to or risk factors for TB or failure to respond to antibiotics.

Intrathoracic lymphadenopathy with or without parenchymal changes may be due to sarcoidosis. A useful clue is the combination of bilateral mediastinal with unilateral hilar lymphadenopathy, which suggests TB [5]. HIV-infected persons with TB often present with hilar adenopathy [34]. The issue of TB in HIV patients is discussed further in Chapter 5.

(b) Reactivation tuberculosis

This form of TB is often encountered in the elderly or in patients with diabetes, alcoholism, HIV infection, lung cancer, sarcoidosis, silicosis, post-gastrectomy and organ transplant and those who are receiving corticosteroids or other immunosuppressive therapy [35–37]. Malignancy, sarcoidosis and silicosis may induce inflammatory or destructive pulmonary lesions which can be indistinguishable from TB or may exist with it. AIDS, immunosuppression and organ transplantation predispose to opportunistic infections involving the lung, resembling any of the forms of pulmonary TB. Table 4.1 lists some conditions which can be confused with TB on chest X-ray. Patients with diabetes or HIV and the elderly may exhibit atypical clinical or radiological findings. Lower lobe infiltrates were reported to occur in 20% of diabetic patients with reactivation TB [36]. Most diabetics will, therefore, have typical upper lobe disease with or without cavitation.

Table 4.1 Conditions that can simulate tuberculosis on chest X-ray

Non-tuberculosis mycobacteria
In particular *M. kansasii* and *M. avium-intracellulare*
Fungi
Including *Histoplasma, Coccidiodes, Blastomyces, Sporothrix, Cryptococcus* and *Aspergillus*
Bacteria
Including *Nocardia, Actinomyces* and *Rhodococcus* (*Corynebacterium*) *equi*
Purulent lung abscess
Parasitic diseases
Paragonimus westermani, Echinococcus sp. (cystic or cavitary lesions)
Pneumocystis carinii, Strongyloides stercorales (miliary type lesion)
Viral disease
Herpes simplex, Varicella-zoster, Cytomegalovirus (miliary type lesions)
Non-infectious causes
Including carcinoma, lymphoma, sarcoidosis, silicosis and other pneumoconioses

The relationship of lung cancer and TB is significant [38]. Bronchogenic carcinoma is 20 times more common in TB patients than in a population with a similar history of smoking tobacco. TB may be associated with a 'scar carcinoma' in which the malignancy develops in an old inflammatory area. Cancer should be suspected in a TB patient who has progression of one area with regression of others, hilar nodes in adult reactivation disease (Figure 4.5) or atelectasis [39].

4.1.5 Pulmonary tuberculosis in the elderly

The incidence of pulmonary TB in the elderly (those aged 65 or over) is usually higher than in younger populations. In the USA in 1987, the incidence was 20.6 cases per 100 000 in the elderly and 4.6 in younger adults [40]. A higher rate in younger people has occurred in recent years in areas of increased TB as detailed in Chapter 3. A rate of 234 per 100 000 has been found in the elderly residing in nursing homes [41]. These data indicate that while older adults often develop TB living in the community, moving into the closed setting of a nursing home places them at an even higher risk.

One report found a rate of purified protein derivative of tuberculin (PPD) reactivity of 25% in persons newly admitted to nursing homes compared with 45% in those residing there for some time [41]. The difference could not be attributed solely to the booster phenomenon (Chapter 8) and was felt to indicate that new infection occurred in some. This finding indicates that TB can be endemic in nursing homes and that institutional transmission occurs [41]. Whether advancing age itself produces an increased TB susceptibility is not clear but this appears not to be the case in a murine model [42].

The magnitude of the problem of pulmonary TB in the elderly is further expanded by the absence of typical clinical manifestations in many cases, making the diagnosis difficult and easy to miss [43]. The combination of fever, cough, night sweats and hemoptysis may not be present. In one study, the time from onset of symptoms to diagnosis was 8 weeks in the elderly compared with 3.5 weeks in a younger group [44]. Weakness was the most frequent complaint and anorexia and weight loss were common. Some elderly persons may present with cough and no other clinical findings [28]. Diseases which are more common in the elderly, such as lung cancer, mimic TB [45]. Several authors reported atypical X-ray findings as well [43]. In a prospective study [46], pure apical lesions were seen in only 7% while 48% had middle field or basal lesions and 46% had a mixed pattern. Atypical radiographic presentations are not necessarily encountered only in the elderly and have been found equally in the elderly and younger adults [47].

Guidelines exist for the prevention and surveillance of TB in chronic care facilities [48]. All persons newly admitted to a nursing home or a chronic care facility should be tuberculin tested, with chest X-rays performed on

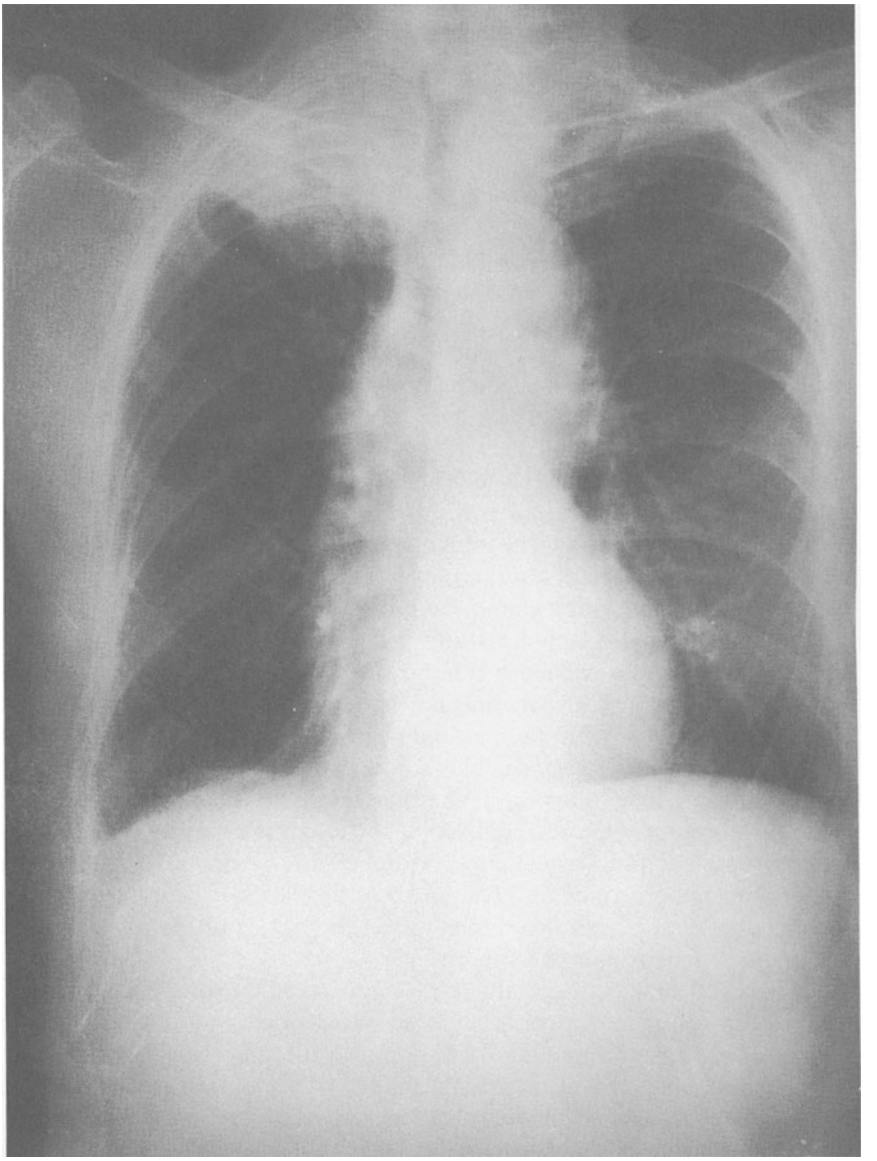

Figure 4.5 Right upper lobe reactivation TB with right hilar adenopathy subsequently found to be a lung carcinoma. Radiograph courtesy of Maimonides Medical Center Radiology Department.

those with a positive test. Those with cough, bronchitis or other symptoms of respiratory infection should have an AFB smear and sputum culture even if the skin test is negative. Those who are tuberculin negative require a repeat PPD whenever a case of active TB is identified in the facility.

Isoniazid (INH) prophylaxis and close follow-up are indicated for all persons with a recent skin test conversion (Chapter 12). A second tuberculin test is often administered 1 week after an initially negative test to evaluate for a booster phenomenon (Chapter 8).

4.1.6 Outcome

With the availability of effective therapy, continuous hospitalization for patients with active TB is not required. With clinical improvement, management can be continued at home. In fact, patients who are otherwise well with good home situations may be treated without hospitalization. Clinical indices signifying a good response include improved appetite, reduction in intensity and frequency of cough and disappearance of or decrease in the sputum count of AFB. Fever may persist for two or more months even with effective therapy owing to the infection or may be drug induced [49]. If the sputum culture is still positive after 3 months of treatment, drug resistance should be suspected [1]. The sputum AFB stain, however, may continue to be positive intermittently for up to 6 months on adequate therapy. Such organisms may not be viable by the end of the third week of therapy and often cannot be grown in culture [49].

In 1976, a 5 year follow-up study of 543 patients with TB who were treated successfully revealed a relapse rate of 11.6% [50]. This rate was lowest during the first 2 years and not influenced by the initial pattern of resistance. Patients with radiographic clearing by the end of therapy had the lowest rate of relapse. This study also concluded that there is no indication for yearly follow-up if the individuals return when appropriate symptoms occur. Of interest, only 25% of the relapse cases were detected during routine annual check ups. More recent prospective trials from 1990 found relapse rates of 1.6% and 3.5% [50a,50b]. These rates, from short course therapy protocols, may reflect the risk of relapse with current treatment regimens more accurately.

Primary TB may be associated with endobronchial complications, such as fibrostenosis or ulcerative granulomas. These occur more frequently in patients with parenchymal consolidation or local atelectasis than in those with lymphadenopathy or pleurisy. Patients with lower lobe consolidation or atelectasis should be followed closely for signs of endobronchial disease, which may have serious consequences, including permanent anatomical lung deformity and respiratory failure if not found at an early stage [51,52].

The complications of chronic pulmonary TB are related to the degree of tissue destruction and fibrosis. Fistulae to the pleural space or esophagus may develop [53]. Additionally, residual cavities can serve as a potential space for fungal colonization [54]. Respiratory failure occurred in 0.02% of TB patients in the 'pre-AIDS' era. There was a 30% mortality in those who developed this complication and most of the survivors suffered permanent restrictive lung disability [55]. ARDS and disseminated intra-

vascular coagulation (DIC) rarely occurred and were usually complications of miliary disease [56,57].

Pulmonary TB is almost always a treatable disease. Mortality remains relatively high, however, in persons with AIDS, the elderly and immunocompromised patients. Atypical clinical and X-ray findings, poor compliance with therapy and a high incidence of concurrent disease contribute to this high mortality. Multi-drug-resistant disease in AIDS patients can result in death rates as high as 93% [18]. In the USA between 1979 and 1989, 60% of deaths due to TB occurred in persons 65 years of age or older. This rate is 10 times higher than in patients 25–44 years old [1]. In cases of TB diagnosed at death, the proportion of cases increased with age from 0.7% in children less than 5 years of age to 18.6% among adults over 85 [58]. There was also a higher representation of extrapulmonary cases diagnosed at death. These observations demonstrate that difficulties in diagnosis contribute significantly to TB mortality in the elderly.

4.2 PLEURAL TUBERCULOSIS

4.2.1 Organ involvement

Pleural TB has largely been considered a consequence of primary infection [59] but may also complicate reactivation disease. The overall rate was 4.9% in a study of 1738 patients with proven TB [60]. The pathogenesis of the pleural reaction involves a delayed hypersensitivity reaction to AFB, which enter the pleural space from a ruptured caseous focus. Autopsy studies have confirmed direct continuity between the lung parenchyma and pleural space in most cases [59]. A pleural granulomatous reaction occurs with the effusion, but AFB are only found in small numbers, if at all [4]. In the classic case complicating primary TB, the effusion appears 1–4 months after exposure [15].

In industrialized countries, tuberculous pleuritis is more common in middle-aged and older individuals. In a large survey, the median age was 47 years [60]. One report [61] found that 81% of the effusions were associated with primary disease and 19% with reactivation. Most of the patients had a co-existing debilitating condition, such as chronic alcoholism, malignancy or previous gastrectomy. The epidemiology is strikingly different in undeveloped countries where TB and HIV infections are endemic. In this setting, TB is the most common cause of pleural effusion [62], with as many as 86% of pleural effusions caused by TB and 83% of patients with tuberculous pleuritis being HIV seropositive.

4.2.2 Presentation and diagnosis

Symptom onset is acute or insidious. Cough, fever, weight loss, dyspnea and chest pain are common, with chills and night sweats less frequent. In a

study of 71 patients with TB pleuritis [63], pneumonia was the initial diagnosis in most cases and cough, usually nonproductive, characteristically preceded the chest pain. Purulent sputum was uncommon. Another study revealed a longer duration of cough in those with reactivation rather than primary disease [64].

Examination reveals the signs of pleural fluid with bilateral involvement in less than 10% of cases [64]. Chest X-ray confirms the effusion. Diagnosis requires the direct evaluation of the fluid, even in the presence of a reactive tuberculin test [4,63]. If TB is suspected clinically, thoracentesis should be performed with pleural biopsy [14]. The fluid is typically clear or green tinged, but cloudy or serosanguinous fluid may be obtained [63].

Polymorphonuclear leukocytes (PMNs) may predominate in those with brief illnesses, but a lymphocytic pleocytosis is the rule [59]. Some consider all exudative lymphocytic effusions in PPD-reactive persons to be tuberculous until proved otherwise [60]. Some recommend empiric TB therapy to such patients [4]. The diagnostic value of the phenotypic analysis of fluid lymphocytes has not been proved [65], but the absence of mesothelial cells in the pleural fluid is said to be highly suggestive of TB [59], and pleural fluid eosinophilia is not generally reminiscent of infection with the tubercle bacillus [66].

Tuberculous effusions are exudative; defined as a fluid to serum protein ratio of more than 0.5, a lactate dehydrogenase (LDH) ratio of more than 0.6 and/or a pleural LDH concentration of more than 200 U/l [67]. One study found the LDH concentration was higher than 550 U/l in all cases [64]. The mean pleural fluid protein is about 5 g/dl in most series. In another study [64], pleural fluid glucose was 57 mg/dl in reactivation and 89 mg/dl in primary TB effusion. The use of fluid cholesterol [68] and alkaline phosphatase [67] assists in distinguishing exudative effusions but not in making a diagnosis of TB. Other markers such as tuberculostearic acid [69], adenosine deaminase and interferon gamma have had success diagnostically. One study [70] reported pleural adenosine deaminase levels of more than 47 U/l in all TB effusions with sensitivity of 100% and specificity of 95% while interferon gamma had a sensitivity of 94% and specificity of 92% using a 140 pg/ml threshold. Additionally, the lack of contamination and low bacillary count suggest that pleural fluid may be ideal for testing with polymerase chain reaction for the detection of mycobacterial DNA. In appropriate hands, this technology can be extremely sensitive and specific [30].

As with other forms of TB, a definitive diagnosis of pleural infection requires identification of tubercle bacilli. Pleural fluid, pleural tissue and sputum should be sent for smear and culture. The pleural fluid AFB smear was positive in 27% in reactivation infection and only 7% in those with primary disease [64] and culture was positive in 91% and 66%, respectively. Pleural biopsy [70] revealed granulomata in 25% of those with reactivation and 72% of those with primary disease, with AFB seen in 17% in both groups and culture positivity ranging between 40% and 58%. The sputum

AFB smear and culture were positive in more than 50% of those with reactivation and 0% and 23%, respectively, in primary disease. Pleural biopsy is particularly useful whenever primary pleural TB is suspected [64]. Bedside cultures of pleural fluid, repeated cultures (two or more) and/or culturing 200 ml or more have been felt to increase the diagnostic yield [71]. Imaging techniques, such as chest radiography, CT scan and MRI are useful for the detection of pleural effusion, fluid loculation and complications such as pleural thickening, calcifications and broncho-pleural fistulae. Recently, ultrasound has been evaluated for diagnosing TB pleuritis; the finding of small pleural nodularity is highly specific for pleural TB [72].

4.2.3 Outcome

Primary tuberculous pleuritis resolves spontaneously in most patients, including those with massive effusions, without specific chemotherapy [4,59]. As many as 50% of patients, however, will develop pleural thickening with no clinical or laboratory means of predicting the risk of development. Neither pleural fluid characteristics, nor the type of TB therapy or surgical drainage influenced the development of pleural thickening [73]. Further studies are needed to define this risk, however, since in another study none of the 22 patients who were treated, traced and reassessed 2 years later had significant pleural thickening or impairment of lung function [74]. Patients who do not receive chemotherapy are reported to have a 65% chance of developing pulmonary TB within 5 years [59].

When TB pleuritis accompanies reactivation disease, a protracted course with long-term morbidity may ensue. Some complications such as broncho-pleural fistula, fibrosis and calcification commonly require surgical management. Treatment with specific chemotherapy and drainage will be required during the acute stage and may be followed by a definitive surgical procedure such as staged thoracoplasty and decortication. These patients will also require long term TB chemotherapy [75].

4.3 EXTRAPLEUROPULMONARY TUBERCULOSIS

Although classically a disease of the lung, *M. tuberculosis* infection may involve any organ. Infection of the skin, middle ear, aorta, eye and breast, among others, are well described but will not be considered further. The most common sites outside the lung and its lining are shown in Figure 4.6.

4.4 LARYNGEAL TUBERCULOSIS

4.4.1 Organ involvement

In the pretherapy era, involvement of the larynx was found in 34–83% of patients with far advanced pulmonary TB [77]. The larynx was felt to be directly infected from contact with infectious sputum. Currently, upper

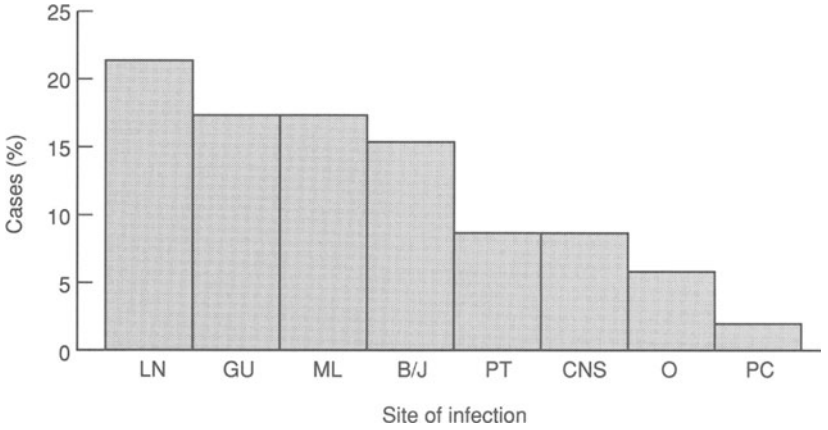

Figure 4.6 Site of involvement of 207 cases of extrapulmonary TB [76]. LN, lymph node; GU, genitourinary; ML, miliary; B/J, bone/joint; PT, peritoneal; CNS, meningitis; O, other; PC, pericardial.

respiratory tract infection is reported in 1.8% of TB patients [78]. Although most patients have co-existing pulmonary infection, reports of isolated laryngeal infection suggest infection may be an isolated reactivation event [79,80]. Beginning as an erythematous, exudative laryngitis, the infection progresses from discrete nodularity to ulceration with edema and exuberant granulation tissue [81]. Any area of the larynx may be involved but most commonly it affects the true vocal cords (47%), epiglottis (39%) and false cords (29%) [77]. Progression can involve the pharynx, the tonsils and soft palate but unlike malignant or non-TB inflammatory conditions usually does not extend to the hypopharynx or subglottic areas [77].

4.4.2 Presentation and diagnosis

Local symptoms of laryngeal TB include cough (94%), sore throat (75%), odynophagia (69%), hoarseness (50%) and otalgia (31%) [78]. Cough is not commonly conspicuous, often being of long standing duration and disregarded as a smoker's cough [82]. Symptoms averaged 4.6 months in duration and were associated with weight loss [78]. The diagnosis is made by demonstrating a granulomatous reaction and the visualization of AFB on stain and/or growth in culture. Because many cases are associated with pulmonary infection, finding AFB in the sputum with a granulomatous laryngeal reaction is adequate for a diagnosis.

The differential diagnosis is laryngeal carcinoma, though other inflammatory conditions such as sarcoidosis, Wegener's granulomatosis, syphilis and fungal infections may merit consideration. The finding of a productive cough, rales on pulmonary auscultation and the absence of cervical lymphadenopathy is supportive of TB and less of malignancy [78].

It has been generally accepted that laryngeal TB is highly infectious but since most cases are associated with far advanced cavitary pulmonary disease, the infectivity of the laryngeal process alone is not clearly proven. In two patients with laryngeal TB without pulmonary disease, no evidence of intrafamilial spread was found, suggesting that laryngeal disease in itself may not be so infectious [80].

4.4.3 Outcome

Appropriate drug treatment is adequate to treat this infection. In one report [78], two of 16 patients were left with mild, permanent hoarseness. Persistent symptoms are related to adhesions or fibrosis of the cord [81]. Progressive infection which is not recognized and treated may cause enough damage to need tracheostomy, partial laryngectomy or laryngo-tracheoplasty for respiratory insufficiency [83].

4.5 MILIARY TUBERCULOSIS

The term miliary relates to similarities between the 1–2 mm millet seed (Figure 4.7) and the nodular pulmonary infiltrates that often occur during the infection. The chest X-ray in miliary disease may be normal, have nodular shadows which are barely visible or have nodular densities several

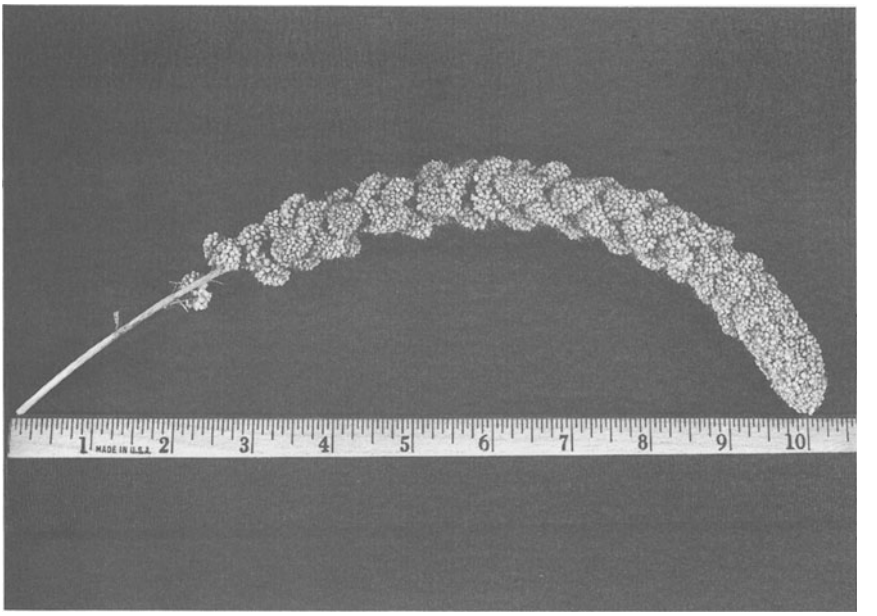

Figure 4.7 A millet seed sprig.

times or more the size of the millet seed [84]. Classically a disease of the young, over the past few years there has been a progressive increase in the age distribution of miliary TB. In Belfast, for example, of 39 autopsies of individuals dying of this entity before 1949, over half were under 20 years of age; between 1966 and 1969, none was under 30 [85].

4.5.1 Organ involvement

Miliary TB results from the acute hematogenous dissemination of tubercle bacilli. The dissemination may be associated with progressive spread following primary infection or a reactivated focus such as a lymph node. The disease process tends to be more severe and more acute in children. Sometimes, especially in the elderly, the seeding is chronic and the symptom complex more difficult to diagnose. This protracted, cryptic form is called chronic hematogenous or late generalized TB [86]. A form of miliary TB known as generalized non-reactive TB or typhobacillosis of Landouzy involves areas of necrosis surrounded by normal tissue with little or no cellular reaction and large numbers of AFB [87]. In rare cases, unusual sources of tubercle bacilli occur, as exemplified by recurrent miliary TB related to a ventriculo–atrial shunt in a patient with TB meningitis [88].

The organs that are well perfused and have reticulo-endothelial function are those with the most involvement in miliary TB. These include lungs, bone marrow, liver, kidneys, adrenals and spleen. In a South African series [89], 63% of endobronchial, 82% of bone marrow and 100% of liver biopsies revealed granulomata, with 50–60% revealing caseation and AFB seen in more than half. Bone marrow is a good source of granulomata but is a poor source of AFB on stain and culture. Slavin's review [86] from 1980 found the frequency of various commonly involved organs as follows: spleen (100%), liver (97%), lungs (86%), bone marrow (77%), kidneys (64%), adrenals (53%) and ocular choroidal lesions (50%). An autopsy survey from 1946 revealed a similar distribution [90].

4.5.2 Presentation and diagnosis

The clinical picture of miliary disease is that of a nonspecific systemic illness with weakness, anorexia, fatigue and weight loss [91]. Focal symptoms can vary depending on system involvement and include cough, headache and abdominal pain [85,92]. Physical signs on initial evaluation include fever, pulmonary rales, hepatomegaly, localized lymphadenopathy, splenomegaly and choroidal tubercles [89,91]. Choroidal tubercles have been reported in as many as 95% of miliary cases [92] and are described as gray–white oblong patches seldom greater than 1 mm. The incidence may be related to the diligence with which they are searched for.

Although the disseminated nature of this disease can produce a non-reactive tuberculin skin test, 52% had 9 mm or more induration to 5 TU

and 79% reacted if higher strengths were used [91]. Of Munt's 11 patients who were initially negative, all but one developed positivity in the course of illness [91]. The classic diagnostic finding is the miliary pattern on chest X-ray (Figure 4.8). Although it is taught that miliary lesions take up to 6 weeks to develop, one study found that of 12 chest X-rays initially reported to be normal in miliary TB, 10 had subtle lesions on review [93]. Close inspection of the intercostal and retrocardiac spaces is recommended to aid the diagnosis [84]. Most individuals with miliary disease have normal total

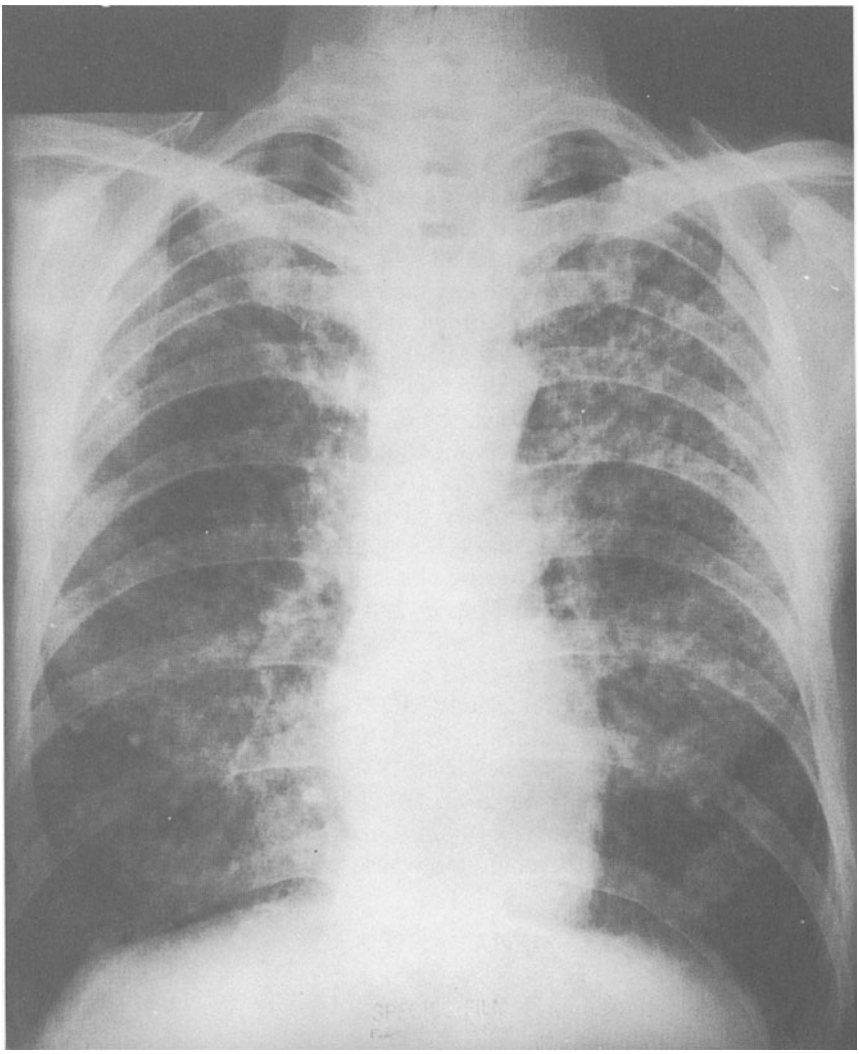

Figure 4.8 Miliary tuberculosis. Radiograph courtesy of Maimonides Medical Center Radiology Department.

white blood counts but an elevated band count and lymphopenia are both common [89,91]. Hepatic function tests often show cholestatic indices with elevated alkaline phosphatase [90].

The yield of AFB in pulmonary secretions is usually lower than in standard pulmonary TB. One large review found positive sputum AFB smears in 39% and positive cultures in 54% without lung consolidation or cavity formation [91]. Tissue examination may be of value diagnostically, including transbronchial, bone marrow and liver biopsies [89]. Both Maartens, Willcox and Benatar and Munt [89, 91] found a low yield of bone marrow examination for AFB. A diagnostic trial of TB therapy can be attempted and may be used to help diagnose TB while awaiting microbiological or histological confirmation of the disease.

4.5.3 Outcome

The return to an afebrile state in response to specific TB therapy is often slow. In Munt's review, only 14% were afebrile within 1 week and 35% within 2 weeks, with 8% requiring more than 60 days to return to a normal temperature [91]. There was often an increased sense of well being, despite persistent fever, indicating a therapeutic response. Munt did not correlate prolonged fevers with decreased survival. In a more recent series reflecting, in part, treatment regimens containing INH and rifampin, Maartens, Willcox and Benatar [89] reported the median duration of fever was 7 days after treatment began, with 76% of patients being afebrile within 2 weeks.

With appropriate therapy, chest X-ray clearing occurs substantially more rapidly than in classical pulmonary TB [94]. The resolution is generally complete without residual changes. Residual miliary calcifications on chest X-ray are most likely related to varicella or histoplasmosis. In Biehl's series [95], most cases had normal findings by 16 weeks with the time to complete resolution generally correlating with the extent of initial involvement, being slower in older patients.

Complications of miliary TB include ARDS (6%), adrenal insufficiency (less than 1%), pancytopenia and death [89]. DIC may also occur [96]. Mortality rates were 21.7% in Munt's series from 1971 [91], and 24% in the series by Maartens, Willcox and Benatar from 1990 [89]. The latter report found six predictors of death: age over 60 years, lymphopenia, thrombocytopenia, hypoalbuminemia, elevated aminotransferase levels and treatment delay.

4.6 TUBERCULOUS LYMPHADENITIS

4.6.1 Organ involvement

Superficial lymph node involvement is the most common form of extrapulmonary TB. It is often referred to as scrofula, from a latin word for brood sow, or king's evil from the practice of attempting cure by a royal touch.

Since it is often unaccompanied by disease elsewhere, scrofula has been addressed less rigorously than other forms of TB [97]. Lymph node disease is most commonly found in the cervical group (60–90%) but any lymph node group may be involved (Table 4.2) [98–100]. Multiple node groups occur in 10–20% and generalized adenopathy in less than 5% [98,99].

Table 4.2 Distribution of lymph node involvement in tuberculosis [98, 99, 103]

Site	*Percentage (%)*
Cervical	
Total	61
Anterior	23
Posterior	16
Supraclavicular	14
Submandibular	8
Axillary	17
Abdominal	7
Inguinal	5
Mediastinal	5
Hilar	3
Generalized	2

4.6.2 Presentation and diagnosis

The affected node begins as an enlarged, firm, mobile, slightly painful or non-tender mass with progression in size and the development of caseation. Node enlargement is generally slow but can be acute with accompanying pain, fever and surrounding inflammation. As the necrosis progresses, abscesses may develop with sinus formation.

The diagnosis is histologic in nature. Caseous granulomatous necrosis on biopsy was seen in 91% of cases [101], with 22% having positive AFB stains and 56% positive cultures. Others report a higher yield with AFB culture [102]. The differential diagnosis of these histologic changes [97] includes diseases with granulomatous changes and AFB (non-TB mycobacteria, lepromatous leprosy), with necrotizing granulomas without AFB (cat scratch disease, lymphogranuloma venereum, syphilis, tularemia and fungi) and with noncaseating granulomata (sarcoidosis, brucellosis and Hodgkin's disease). A clinical response to TB treatment in a patient with localized adenopathy (particularly cervical) and a reactive tuberculin test are reasonably adequate diagnostic criteria.

4.6.3 Outcome

The relapse rate following surgical treatment without TB therapy varies depending on the procedure performed. An 86% recurrence rate occurred

after node aspiration, 40% after incision and drainage, 14% after primary excision with abscess present and 3% with excision without abscess [102]. Recurrences following appropriate chemotherapy occur in less than 5% of cases [97].

The major complication of scrofula is a sinus tract which can develop either postsurgically or in unrecognized disease. These sinuses may not heal readily with treatment and surgical excision may be necessary [97]. Damage to the cervical branch of the facial or the posterior auricular nerve may occur, most likely related to surgical intervention.

4.7 NEUROTUBERCULOSIS

4.7.1 Organ involvement

Tuberculous meningitis generally develops from the breakdown of a 'Rich' focus in a subependymal location. This focus has been found, in almost all autopsies with this form of TB, communicating with and discharging caseous material into the cerebrospinal fluid (CSF) [104]. It may destabilize after many years of quiescence related to advanced age, immunosuppression, debilitation or physical factors such as head trauma. Alternatively, TB meningitis can develop during miliary disease.

The reaction to AFB and necrotic debris produces a thick exudate, most marked in the basilar area of the meninges, and may involve the exiting cranial nerves particularly III, IV and VI. A vasculitis may develop from the direct invasion by *M. tuberculosis* or from extension from the surrounding arachnoiditis. The vessels most commonly involved are branches of the middle cerebral artery, especially the perforating vessels to the basal ganglia [105] and can result in cerebral infarctions.

Similar processes can occur in the spinal subarachnoid space from a 'Rich' focus or TB vertebral osteomyelitis. The epidural space may be involved without meningeal involvement [106].

The tuberculoma, usually intracranial but occasionally in the spinal parenchyma, develops as one or multiple slowly expanding lesions. They may be associated with meningitis and can be silent. The lesions have been observed to appear and disappear on brain imaging studies during medical therapy for meningitis or miliary disease. In areas of the developing world, tuberculomas represent a significant minority of intracranial tumors [106].

4.7.2 Presentation and diagnosis

TB meningitis is a subacute disease beginning with vague complaints of weakness, low grade fever, headache and personality changes. Within several weeks, however, a more defined meningoencephalitis syndrome develops with protracted headache, meningeal signs, fever, vomiting and

confusion [105,107]. Seizures, focal neurologic signs, particularly related to cranial nerves and long tract signs may develop [108]. The presentation may be more acute and not clinically distinguishable from a pyogenic meningeal process or more chronic with dementia. Physical findings vary based on the extent of the infection. Meningeal irritation signs are present in 80–90% of cases with altered mental status in 40–60% [109]. Other neurologic signs on presentation include papilledema, extensor Babinski sign, hemiparesis and choroidal tubercles [109].

The CSF cell count is 100–400 cells/mm^3 in about 50% of cases, with 20% less than 100 and 30% more than 400 [107,109]. Although the typical CSF reveals a prominent lymphocytic predominance, early in the disease a minimal pleocytosis or a PMN cell response can be noted [106]. These can be initial pitfalls in diagnosing this potentially fatal infection. Serial lumbar punctures should show the trend towards the expected lymphocytic pleocytosis. Serial analysis during therapy, however, can show the opposite response, an initial lymphocytic response fluctuating intermittently to granulocytes. This 'therapeutic paradox' has been said to be very suggestive of tuberculous disease [110]. The CSF protein is elevated, most often at 100–500 mg/dl. In 25% of patients it will initially be less than 100 mg/dl and may be less than 40 mg/dl. In 10–20%, the CSF protein may be over 500 mg/dl, sometimes in the range 2–5 g/dl [105,109]. Marked elevation of the CSF protein is associated with a subarachnoid block. CSF glucose is less than 45 mg/dl in 80% or more of cases [105,109].

An increased yield of the AFB stain and culture is produced by the use of multiple CSF examinations. A yield on stain of 37% and culture of 56% could be increased to 87% and 83%, respectively, when up to four CSF specimens were examined [109]. In 30% of the cases, the diagnosis could still be made up to 3 days after therapy was begun so that beginning therapy does not need to be delayed. In the setting of a negative CSF AFB stain, AFB culture results will not be available for weeks. Empiric therapy is clearly indicated while awaiting culture results. A number of newer approaches to diagnosis in the CSF have been evaluated, including indirect tests, such as adenosine deaminase activity [111], and direct ones, such as *M. tuberculosis* antigen detection [112]. Reproducible data on such tests are needed, showing a high degree of sensitivity and specificity before they should be uniformly adopted.

The differential diagnosis of a subacute or chronic lymphocytic meningeal process includes infections such as cryptococcosis, coccidioidomycosis, histoplasmosis, brucellosis, syphilis, Lyme borreliosis and focal parameningeal foci. Non-infectious causes such as lymphomatous or carcinomatous meningitis, sarcoidosis and CNS angiitis may also be considered. In particularly difficult cases, meningeal biopsy has been performed but generally is not helpful, except in malignant meningitis [113].

4.7.3 Outcome

In untreated cases, death usually occurs within one or two months [105] but much more prolonged courses are well described. Complications, often related to delayed diagnosis or treatment, include seizures, hemiplegia, cranial nerve palsies, gait disturbances, blindness, deafness, dementia, hydrocephalus and a variety of hypothalamic or pituitary syndromes. The incidence of complications is greatly influenced by the stage of the disease at the onset of treatment. One study [109] found early stage disease had a mortality rate of less than 10% and minimal sequelae, but 46% with late disease died.

Hydrocephalus develops in as many as 80% of cases [104], usually related to poor CSF reabsorption by the arachnoid villi. Noncommunicating hydrocephalus may also occur from obstruction of the ventricular passages. Serial brain imaging studies [114] can be useful in alerting to the need for decompression by external or internal shunting. Adjuvant corticosteroid use can decrease cerebral edema and the risk of spinal fluid block [105]. New focal neurological signs that develop during specific TB treatment may be due to infarction from vasculitis or complications of cerebral hypertension. Tuberculomas can develop paradoxically during therapy and can require surgical decompression if medical measures to diminish intracranial pressure are not successful [115].

4.8 GASTROINTESTINAL TUBERCULOSIS

4.8.1 Ileocecal tuberculosis

(a) Organ involvement

The ileocecal area is the most common portion of the intestinal tract involved by TB. In a report of 67 cases [116], all but six (91%) involved this area. Lesions may be hypertrophic, ulcerative or mixed. After involvement of the mucosa and submucosa, intense inflammation with necrosis occurs in the bowel wall and lymphatic channels encircling it. Caseation necrosis is often found, distinguishing gastrointestinal TB from Crohn's disease. The lymphangitis and endarteritis cause circular transverse mucosal ulceration. Since longitudinal ulcers generally do not develop, the cobblestone appearance seen in Crohn's disease involving both transverse and longitudinal ulcers is rare [117].

TB in the intestinal tract can be related to swallowing sputum tubercle bacilli or the disease reactivation in periintestinal lymphatic tissue. Acquisition of bovine TB is now less common owing to tuberculin programs in cattle and milk pasteurization [118].

(b) Presentation and diagnosis

Abdominal pain is the most common symptom, occurring in 77–85% of

patients [116,119]. The pain is often located in the right lower quadrant but can be generalized or located elsewhere. It is often a chronic ache which has existed for months or years. In one series, 12% of patients had had pain for more than 5 years [116]. However, 32% of patients presented with acute abdominal pain as a surgical emergency [116]. Other symptoms include weight loss, fever, vomiting, malaise, diarrhea and constipation [116]. A palpable tumor in the right iliac fossa was found in 49 of 67 patients with intestinal TB [119]. The inflammatory mass, due to a thickened cecum, is usually firm, slightly tender and fixed to the posterior abdominal wall. Intestinal obstruction and/or ascites may occur.

The highest culture yield is from a biopsy of the intestinal wall or regional lymph node. The finding of a positive Mantoux test and/or proven pulmonary TB with compatible intestinal disease can support the diagnosis. Most series do not report stool examinations for AFB but a digested, 24 hour specimen after flotation has been used to yield the organism on stain [120]. Since 30% of patients with pulmonary TB without enteritis can yield tubercle bacilli on stool culture [121], such isolation may not be helpful diagnostically in the presence of pulmonary disease.

The diagnosis of gastrointestinal TB may be made endoscopically. Stenoses, ulcerations and ileocecal valve deformities are found and valve destruction strongly favors the diagnosis [122]. Although the X-ray picture can be indistinguishable from a malignant process or Crohn's disease, failure to fill the cecum with barium, cecal retraction and a gaping, rigid ileocecal valve with loss of the normal ileocecal angle are typical of TB enteritis [117].

(c) Outcome

Obstruction of the small or large bowel occurs in 12–60% of cases and is the most common complication requiring surgical intervention [121]. Entero-enteral and enterocutaneous fistulae may develop. Intestinal perforation is uncommon, occurring in only 10 of 734 cases in one series [123]. The low incidence of perforation is related to the marked fibrosis and thickening of the bowel wall with adherent mesentery. Overt intestinal bleeding is also uncommon.

4.8.2 Peritoneal tuberculosis

(a) Organ involvement

TB of the peritoneal surface can develop as a local reactivation or be related to active disease in the adjacent gastrointestinal or gynecological systems. The disease is manifest from the seeding of tubercles throughout the peritoneal surface. It has been described as occurring in either ascitic (exudative) or plastic (adhesive or dry) forms. The former is more common

and is characterized by obvious free fluid and the latter by fibrous adhesions and discomfort rather than overt abdominal swelling [124].

(b) Presentation and diagnosis

The most common symptoms are abdominal pain and swelling [125–127]. Other symptoms include fever and chills, anorexia, weight loss, night sweats and constipation or diarrhea. At presentation, abdominal swelling may have existed for several months with pain for a longer period [125]. Frank rigors can occur, especially with rapidly increasing ascites [128].

Physical findings include fever in 60–100% of patients, ascites in 60–90% and a palpable abdominal mass in 25–50% [125–128]. The mass is often tender and may be multiple. One of the classical findings, the 'doughy' abdomen, is relatively rare and nonspecific. There is often concomitant pulmonary infection and pleural involvement occurs in at least 30–40% [129]. Pericardial involvement may also occur.

Ascitic fluid analysis reveals a lymphocytic exudate. The cell count ranges from 150 to 1500 per mm^3 with more than 80% lymphocytes. The total protein is often greater than 3.5 g/dl. Direct AFB smear is positive in about 10% of patients and cultures positive in about 50% [124,126,127]. A higher yield (83%) with culture of 1 liter of ascitic fluid is reported [129]. The diagnostic test of choice is laparoscopy, finding the peritoneum studded with nodules (Figure 4.9) which on biopsy reveal granulomas with caseation. With the availability of laparoscopy, blind Cope needle biopsy of the peritoneum or laparotomy is rarely needed for diagnosis.

This form of TB is easily confused with other diseases. It should be considered in the differential diagnosis of inflammatory bowel disease and abdominal or pelvic malignancies. Care must be taken not to overlook TB in evaluating the patient with alcoholic cirrhosis and ascites. Significant overlap in the ascitic fluid parameters occurs [126,130].

(c) Outcome

Palpable abdominal masses and ascites disappear within several months of adequate treatment [125,126]. Intestinal obstruction owing to adhesions may be a late complication. Such fibrotic complications can occur in 5–15% of cases [125,129]. Corticosteroids may diminish this risk [129].

4.8.3 Miscellaneous gastrointestinal tuberculosis

(a) Esophageal tuberculosis

Esophageal TB is rare. It was found in 3 of 117 cases of gastrointestinal disease from South Africa and felt to be primarily due to spread from adjacent tuberculous lymph nodes [131]. Dysphagia was found in 60% of

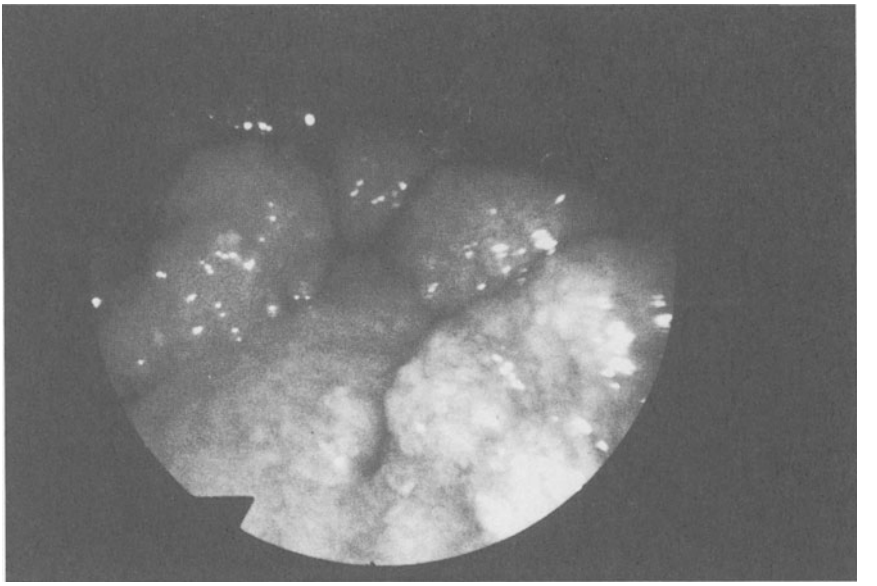

Figure 4.9 Laparoscopic view of peritoneal tuberculosis. Photograph courtesy of Dr Eliot Zimbalist, Maimonides Medical Center.

patients, weight loss in 22% and retrosternal pain in 20% [132]. It is very difficult to distinguish clinically from carcinoma without histologic confirmation. Tracheoesophageal fistulae occur.

(b) Gastroduodenal tuberculosis

Gastric ulcers may be tuberculous in origin. Infiltration of the stomach wall produces an X-ray appearance indistinguishable from linitis plastica [131]. Pyloric obstruction occurs related to ulcerative or infiltrative disease or large sub-pyloric lymphadenopathy. Isolated duodenal TB may occur, appearing similar to peptic ulcer disease with gastric outlet obstruction; it can cause duodeno-renal or duodeno-aortic fistulae [132].

(c) Pancreatic tuberculosis

Isolated pancreatic TB presents as abdominal pain, obstructive jaundice, chronic pancreatitis or splenic vein thrombosis. The biopsy of a suspected pancreatic carcinoma is needed to evaluate for the possibility of TB in the appropriate setting [133].

4.9 GENITOURINARY TUBERCULOSIS

4.9.1 Urinary tuberculosis

(a) Organ involvement

Reactivation of a renal focus may be unilateral or bilateral and begins in the cortex spreading towards the papillae and medulla [134]. As the infection progresses, the kidney lesion may caseate, cavitating to discharge material containing viable AFB into the renal pelvis and ureter. Infection produces edema and eventual fibrosis at the calyceal neck, ureteropelvic junction and ureterovesicular junction. The process can spread to the bladder producing a small capacity, thick walled, fibrotic structure.

(b) Presentation and diagnosis

Generally a disease of young adulthood, Narayana [135] reported that 75% of 66 patients were below 50 years of age. Two other reports found an average age of 30 [136] and 47 [137] years. The symptomatology of urinary TB is nonspecific. The most common complaints relate to late involvement of the bladder and include frequency (60%), dysuria (34%) and hematuria (28%) [135]. This study found that 21% of patients presented with symptoms unrelated to the urinary tract. In fact, 72% of Lattimer's cases [138] of advanced cavitary renal TB had minimal renal symptoms. Constitutional complaints are the exception rather than the rule. Other symptoms related to urinary TB include renal colic due to clots and/or debris from open cavitary kidney lesions and a cold abscess presenting as a non-tender flank mass.

The urinanalysis typically shows an acid pH, pyuria, proteinuria and hematuria and a negative routine urine culture. An abnormal urinanalysis is found in 93% of cases [139]. Routine urine cultures may be positive for enteric bacilli, especially if structural abnormalities are present. Although a direct urine AFB stain can be positive [135], saprophytic AFB are visualized as well. The microbiological benchmark is isolation of *M. tuberculosis* from culture, with first voided morning urine having replaced 24 hour urine for culture. Comparing over 3600 clinical specimens, the yield of tubercle bacilli from the morning void was equal to the 24 hour urine, more convenient and less prone to contamination [140]. Urine cultures are positive in 80–90% [136,139] with the additional cases diagnosed on reactive skin tests, characteristic X-rays and/or isolation of TB from other sites. The initial urine culture was found positive in 77% and at least one of the first two cultures in 91% [141]. Positive urine cultures may also occur with normal urinanalyses. These individuals usually have obvious disease elsewhere with subclinical renal seeding.

Radiographically, the intravenous pyelogram (IVP) can reveal calyceal

dilation, stricture, cavitary papillary disease and calcification. Multiple ureteral strictures causing a beaded appearance and a small scarred bladder may also be seen. A typical IVP is shown in Figure 4.10. Early in disease,

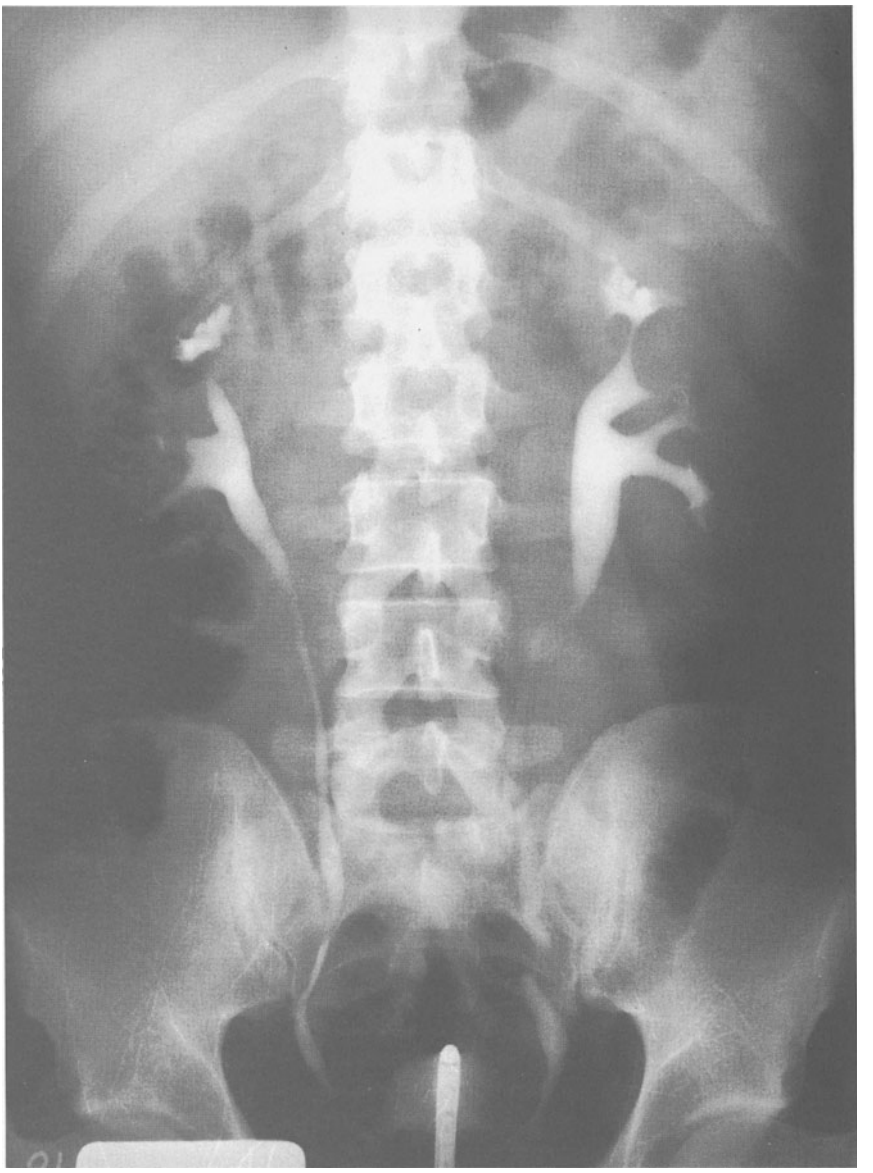

Figure 4.10 Renal tuberculosis. Pyelogram showing infundibular stenosis and calyceal scarring. There is a stricture at the left ureteropelvic junction. Radiograph courtesy of Maimonides Medical Center Radiology Department.

the pyelogram can be normal. Cystoscopy may be helpful in revealing edema, hyperemia and shallow bladder ulcers. A variety of urinary tract disorders may produce similar X-ray changes. Among systemic infections, urinary brucellosis may closely mimic TB [142].

(c) Outcome

Based on a higher than expected tuberculin reaction rate in children of individuals with urinary TB without pulmonary disease, it was suggested that transmission may have occurred via the urine [143]. No direct data exist to support this and no evidence to support this route of transmission was found in 1720 relatives of 290 urogenital TB patients [144].

Although therapy is quite effective, significant diminution in renal function is caused by this infection. Diminished creatinine clearance in 58% of 117 patients has been noted with 5% considered to be severe [145]. Azotemia may affect the dosing of antitubercular drugs. The renal disease is usually caused by granulomatous destruction but can be caused by tuberculous interstitial nephritis [146].

Although nephrectomy has been advocated for the non-functioning TB kidney, it now appears unnecessary if urine culture conversion is obtained and the drug treatment completed [139,141]. Surgical intervention is used for strictures and nephrolithiasis, which can cause obstruction and predispose to recurrent infection. Hypertension as a complication is rare [139].

4.9.2 Male genital tuberculosis

(a) Organ involvement

Involvement of multiple sites in the male genital tract is often seen. Christensen [136] reported clinical involvement of prostate in 37%, epididymis 31%, testes 23% and seminal vesicles 9%. Similar comparative rates are reported [147] in an autopsy series. Penile TB is quite rare. This form of skin TB can be acquired from sexual contact. It was a complication in ritual circumcisions in the pretherapeutic age. It can also be a manifestation of either local or hematogenous spread [148]. Because concomitant or previous renal TB occurs in many cases (44–80%) [149], genital involvement is thought to follow a descending infection from the kidney. Renal involvement, however, may be difficult to document because intravenous pyelograms can appear normal in the setting of microscopic renal disease. Clinical studies, therefore, underestimate kidney involvement. Genital TB may also occur through: hematogenous spread with late reactivation; direct extension from adjacent foci; or lymphatic spread. Female to male venereal transmission is extremely rare [150].

(b) Presentation and diagnosis

Most cases occur between the ages of 20 and 40 with few before puberty. The onset of symptoms is often insidious and constitutional symptoms are often absent. Prostatic involvement manifests as urinary frequency, urgency, hematuria or hematospermia. Digital rectal examination is often not remarkable until disease progression, when an enlarged, nodular prostate is detected [151]. If caseation occurs, soft areas that depress on digital examination may be noted. Such necrosis can perforate through the prostate capsule into the rectum or produce perineal sinuses [149]. Biopsy reveals granulomatous inflammation with AFB. Noncaseating granulomas may be seen and do not rule out *M. tuberculosis* [151]. In TB prostatitis, semen cultures are often positive [152].

Epididymitis rarely presents acutely with the rapid onset of a focal, painful scrotal swelling [153]. More commonly, it manifests as scrotal swelling, with or without pain, developing over several months. As many as 40–50% of advanced cases have scrotal fistulae [149,153]. Examination of TB epididymitis at an early stage reveals irregular nodularity. With progression, the epididymis enlarges to four or five times its usual size. Involvement of the testes, usually combined with epididymal disease, presents as progressive swelling.

As with all forms of genitourinary TB, a combination of typical signs and symptoms, a reactive Mantoux tuberculin test, AFB cultures of urine and seminal fluids and, when available, histopathologic findings and cultures of appropriate biopsy material are needed to produce an accurate diagnosis. Fine needle aspiration of mass lesions may be helpful [150]. Sonographic studies may help in distinguishing solid from cystic structures and localizing intrascrotal pathology [154].

The differential diagnosis of genital TB includes acute epididymitis due to pyogenic Gram-negative bacilli, *Neisseria gonorrheae* or *Chlamydia.* Chronic processes such as brucellosis, blastomycosis, malignancy, non-TB AFB, and sarcoidosis also need to be considered.

(c) Outcome

Early therapy may prevent fibrosis during healing, but fibrotic lesions already present will not resolve with treatment. Surgery is rarely needed but should be considered if there is no response after several months of therapy, a large caseating mass is present or there is significant obstruction. Surgery may be used diagnostically in those in whom a concern about malignancy exists [153]. Abnormal semen analysis is the rule [152], with a marked decrease in fertility and a high incidence of sterility. Among the findings are decreased volume of seminal fluid, blockage of the lumen of the epididymitis or vas deferens and decreased sperm counts.

4.9.3 Female genital tuberculosis

(a) Organ involvement

Pathologically, the fallopian tube is the most common site of involvement; it is affected in 80–100% of cases, usually bilaterally [155,156]. The tube is likely seeded during the primary infection with subsequent reactivation. The endometrium is also commonly (70–90%) involved, probably related to spread from the fallopian tubes [157]. The myometrium and myosalpinx are involved by direct spread. Conversely, involvement of the serosal uterine surface is related to local TB peritonitis from contamination of the pelvic peritoneal surface from the ends of the fallopian tubes.

Less commonly, the uterine cervix and vagina may be involved. Both of these areas are infected from endometrial involvement. Direct ovarian infection has been reported in 20–43% of cases in which the disease was severe enough to require surgery [156,157]. Female genital TB due to venereal transmission causes vulvar ulcers and inguinal adenopathy resembling lymphogranuloma venereum [158].

(b) Presentation and diagnosis

The average age at diagnosis has increased and the disease now involves more postmenopausal women [157]. Presenting symptomatology includes lower abdominal pain (often bilateral) and menstruation abnormalities, such as postmenopausal bleeding and oligo- or amenorrhea [155]. The latter is more likely to be related to general debility than any pelvic pathology. Between 7% and 13% [155,157] of women present with infertility. Many have a history of failure to respond to standard antimicrobial therapy for pelvic inflammatory disease.

Physical examination reveals lower abdominal and pelvic tenderness. On bimanual pelvic examination, unilateral or bilateral adnexal masses are often found. Pelvic pain is less than that of pyogenic pelvic inflammatory disease [155]. The patient is often afebrile with no leukocytosis, which can help to distinguish this disease from pyogenic processes.

A diagnosis can be made by endometrial curettage with AFB stain and culture. The optimal time to perform the curettage is late in the menstrual cycle [155]. Cervical biopsy and culdoscopy is also useful. TB isolation is successful in 30–65% of cases [156,157]. In as many as 65% of cases [156], no diagnosis is made until histopathologic examination of surgically removed tissue is performed. The use of endoscopy (laparoscopy and hysteroscopy) has been found to be useful diagnostically [159] with tubercles seen on the surface of the organs, nodular, thickened tubes and fibrous adhesions.

(c) Outcome

Chemotherapy is usually effective. A 97% cure rate is reported in patients

followed for an average of 2.5 years [156]. Surgical intervention should be used only if therapy is not successful from persistent large adnexal masses, recurrent endometrial infection or continued uterine bleeding. In a series of 709 cases, the need for follow-up surgical intervention dropped from 11% to 0% using modern TB regimens [156].

The chances of reversing infertility are slim because of blockage of the fallopian tubes. In an Indian study of 101 cases of pelvic TB [159], 11 (15%) subsequent intrauterine pregnancies occurred. Three patients developed ectopic pregnancies (27% of total conceptions). Another report [160] found no pregnancies in 47 cases followed for 169 patient-years in the pretherapeutic era and a 11.7% pregnancy rate after antitubercular therapy. Of these 18 pregnancies, only seven viable babies (39%) were produced with a 33% ectopic pregnancy rate. Clearly, any pregnancy in a patient who has had genital TB should be considered to be high risk.

4.10 BONE AND JOINT TUBERCULOSIS

4.10.1 Organ involvement

Bone and joint involvement with *M. tuberculosis* occurs in 1% of TB patients and 5% or more with extrapulmonary disease [161]. It is usually a late manifestation of hematogenous spread to bone from the primary pulmonary infection. Less commonly, spread from a contiguous area of activity such as pleura, kidney or periaortic lymph node occurs. Predisposing factors include trauma, race (higher incidence in Blacks), debilitating systemic diseases, intra-articular injection of steroids and intravenous drug use.

The site most frequently involved is the vertebral body, representing 36–50% of the total of bone and joint TB [161,162]. Spinal TB is known as Pott's disease after Sir Percival Pott, an 18th century physician who described the disease and its neurologic complications. Involvement of the spine occurs most commonly (48–67%) in the lower thoracic and upper lumbar areas. Weight bearing joints are involved most frequently such as the knee (12–15%) and hip (9–15%) [161,163]. Any bone or joint, however, can be involved. Rib TB is not frequent, but is the most common inflammatory lesion of the rib [164].

Invasion of the joint is direct via the blood stream to the synovium or indirect from lesions in epiphyseal bone eroding into the joint space. Initially, the synovium develops a granulomatous reaction with effusion. Fibrin debris precipitates in the effusion, forming so-called rice bodies. The pannus of inflammatory tissue begins to erode and destroy cartilage and bone ultimately leading to progressive demineralization with caseation necrosis. Cartilage is destroyed peripherally first, preserving the joint space for a considerable length of time. In far advanced disease, para-osseous abscesses develop involving tissue surrounding the bone or joint.

4.10.2 Presentation and diagnosis

The incidence of bone and joint TB has fallen dramatically during the past 30 years in developed countries such as the USA and the UK. This decline has not been shared, however, by underdeveloped nations. Today, spinal TB is a disease of children in developing nations and of the elderly in the USA and Europe. The disease most commonly involves a single joint, though it may be multifocal [165]. A recent report of four cases of multicentric TB bone disease from Canada emphasizes the difficulty of distinguishing this entity from a malignant process [166].

The commonest early evidence of illness is the insidious onset of local pain and swelling. TB should always be considered when evaluating skeletal pain. Limitation of motion can also be found along with constitutional symptoms such as fever, night sweats, anorexia and weight loss. Buttock pain occurs with sacroiliac TB which can cause gluteal abscesses [167]. Chronically swollen, infected joints may be associated with draining sinuses. Very often, patients tolerate the symptoms for many months and even years before seeking medical attention. In vertebral disease, back pain can progress to focal neurological symptoms and signs [162].

X-rays of affected joints typically show some decrease in the articular space with destruction of adjacent cartilage and bone. In Pott's disease, classical involvement is of two vertebrae with destruction of the intervening intervertebral disc (Figure 4.11). Normal radiographs, however, do not exclude the condition, particularly if the disease is of recent onset (less than 3 months). Thirteen cases of atypical spinal TB were reported [168] including: neural arch involvement only; intraspinal cold abscesses; and infection of a single vertebra with collapse. CT and MRI are important in defining spine and cauda equina involvement. Intraspinal cold abscesses as well as paravertebral (psoas) abscesses can easily be found by these means. Psoas abscess is seen in a significant number of patients with advanced Pott's disease.

The diagnosis is best made by biopsy with culture and histology. For practical purposes, a histologic appearance of granulomatous synovitis in an individual with a reactive tuberculin test is sufficient to start a patient on chemotherapy, even in the absence of positive cultures. The yield of AFB stain for joint fluid is 25%, with higher yields using synovial tissue [169]. An individual with a positive tuberculin test and a compatible spinal X-ray must be treated for Pott's disease, even in the absence of a tissue diagnosis. AFB stains on material obtained from vertebrae or disc tissue are positive in 27% and culture in 53–59% [163,170].

4.10.3 Outcome

A microbiologic cure is possible with therapy, even in far advanced disease. Failure to diagnose a bone or joint problem as tuberculous will delay

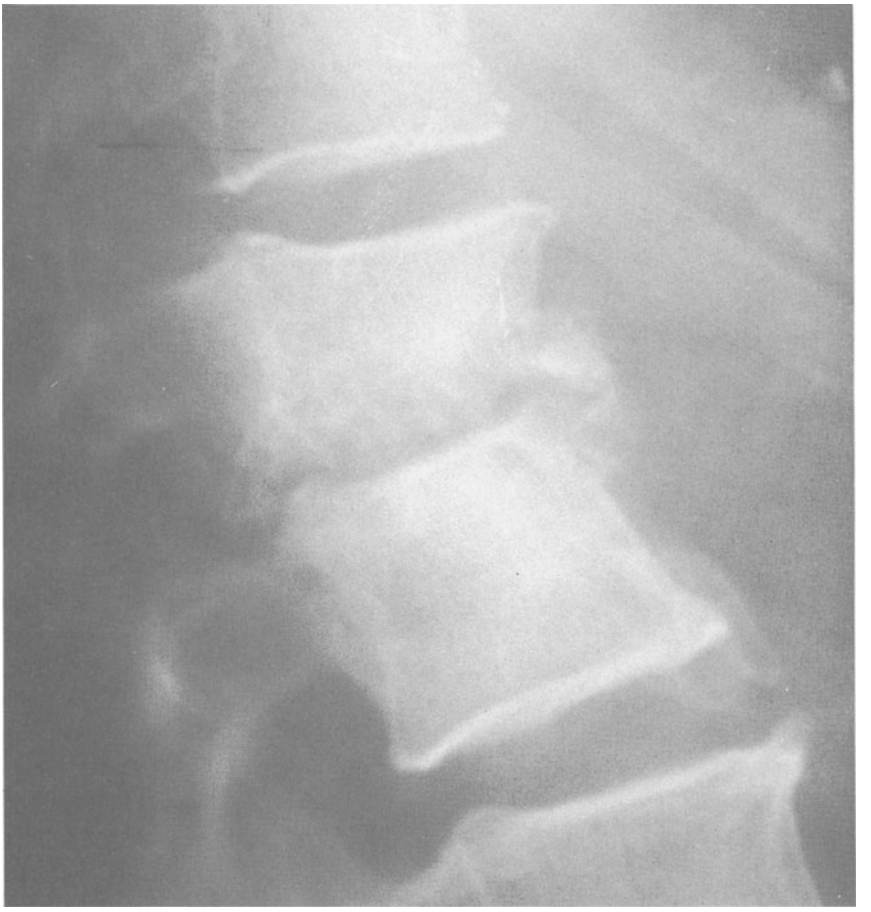

Figure 4.11 Tuberculous lumbar spondylitis. X-ray showing involvement of two adjacent vertebrae with some collapse. Radiograph courtesy of Maimonides Medical Center Radiography Department.

treatment and allow further destruction. Prompt recognition and treatment can prevent destructive arthritis or vertebral collapse with kyphosis and scoliosis (gibbus formation).

Outcome of joint TB, in general, is fair. The results of the treatment of 10 patients with wrist TB [170] were microbiologically satisfactory in that the activity of the disease was controlled throughout the period of observation. Six of these patients, however, needed arthrodesis. Eleven patients with sacroiliac TB all returned to full activity and none had significant functional impairment despite marked radiographic changes [167].

The outcome in Pott's disease changes if the infection penetrates through

the dura [171]. Spinal cord or root compression are possible complications of vertebral TB. The degree of neurologic involvement observed on the physical examination can serve as a prognostic measure. Those with complete loss of motor function have a poor prognosis while those with preservation of some voluntary muscle control, sphincter control and sensory function have a better prognosis. Surgical decompression is useful in more severe cases if carried out expeditiously. In most cases of TB of the spine, however, immobilization and/or surgery is unnecessary. Chemotherapy should provide appropriate treatment [162,169].

4.11 PERICARDIAL TUBERCULOSIS

4.11.1 Organ involvement

In countries where TB is highly endemic, tuberculous involvement is the most common form of pericardial disease. In industrialized countries, this entity may attract increased interest because of the current TB resurgence and its propensity to produce life-threatening cardiac tamponade or disabling constrictive pericarditis. In the USA, TB has been reported to cause 4% of acute pericardial disease, 5% of cardiac tamponade and 6% of constrictive pericarditis [172]. The pericardium is involved in 1–2% of cases of pulmonary TB and 5% of extrapulmonary TB [172].

Generally, the infection reaches the pericardial space directly following reactivation of TB in latent mediastinal lymph node rupturing into the pericardial space. The lymph nodes at the tracheal bifurcation are the most common source of infection. Rarely, direct extension from contiguous pulmonary, pleural or bony structures or hematogenous spread from a nearby or distant organ occurs [172,173]. In one autopsy series of 10 patients, all had concomitant mediastinal TB adenitis, nine had pulmonary and five had pleural involvement [174].

The process begins as a hypersensitivity reaction to mycobacterial proteins with the attraction of cellular elements and the deposition of fibrin. PMNs predominate at the onset but lymphocytes rapidly replace them. With the development of a granulomatous reaction, an effusive phase occurs with the collection of fluid in the pericardial sac. The amount is usually several hundred milliliters, but up to 3.5 liters has been reported [173]. The fluid is hemorrhagic in as many as 80% [172]. Despite a prominent granulomatous reaction, few AFB are noted histologically. Later, the fluid is slowly absorbed with the development of pericardial thickening, adhesions and fibrosis. The thickening is considered the hallmark of the disease as it progresses to a constrictive phase. Microscopically, the lymphohistiocytic infiltration, fibrosis and necrosis may not be limited to the pericardium, but may involve the myocardium as well [175]. The calcifications, when they occur, are patchy or form a diffuse sheet surrounding the heart.

4.11.2 Presentation and diagnosis

Affected persons are usually in their third to fifth decade with a male preponderance [174]. The disease is more common in Blacks compared with other races and the higher ratio persisted even after adjustment for the high prevalence of TB in Black populations [174]. In HIV-infected persons, the disease may be encountered as the initial manifestation of AIDS [176]. The clinical manifestations of TB pericarditis can be caused by the infective process *per se*, or reflect disability due to organ involvement with the heart and lung most commonly affected. Cough, dyspnea and weight loss are by far the most common complaints, occurring in 80% or more of the cases, followed by shortness of breath, chest pain, fever, night sweats, ankle edema and hemoptysis [172–174].

Physical examination reveals some degree of cardiomegaly in up to 95% of patients. Fever and tachycardia are also common. Other findings are pulsus paradoxus, pleural effusion, friction rub, distant heart sounds, neck vein distension and hepatomegaly [172–174]. The signs and symptoms of cardiac tamponade and constrictive pericarditis caused by TB are not different from those occurring in pericarditis from other etiologies.

The chest X-ray usually shows cardiomegaly. Concomitant evidence of pulmonary TB has been found in 72% [172]. In another report, pleural effusion was seen in about 70% and more than a third of these effusions were confirmed as TB [174].

Electrocardiographic, echocardiographic and angiographic findings are largely nonspecific. Their usefulness is retained for confirmation of the presence, size and hemodynamic significance of the effusion, but cannot establish the etiology. The electrocardiogram may show ST depression, low voltage and rarely ST elevation. Real time echocardiography offers a readily available sensitive bedside means of evaluating cardiac tamponade. Thickening of the pericardium with stranding and adhesions occurs commonly in TB pericarditis [172]. Right heart catheterization, although invasive, is also useful for evaluation of constrictive pericarditis and cardiac tamponade.

For the non-invasive diagnosis of constrictive pericarditis, CT may be the test of choice. In a study of 212 patients with impaired diastolic filling, it could clearly differentiate between constrictive TB pericarditis and restrictive cardiomyopathy. Magnetic resonance imaging is also capable of detecting pericardial thickening, but is inferior to CT because of its inability to detect pericardial calcifications [177].

The pericardial fluid is usually exudative and either serosanguinous or grossly hemorrhagic. The cells in the fluid are predominantly lymphocytes, but a significant number of PMNs is not unusual initially. The diagnosis is often based on the identification of AFB in the sputum or pleural fluid because of the common coexistence of pulmonary and/or pleural TB. In a large study of 189 proven cases of TB pericarditis, the pericardial fluid

culture was positive in 59% of the patients and pericardial biopsy was diagnostic in 70% of the patients [178]. In the same series, 11% of the patients had a positive sputum culture. DNA amplification by polymerase chain reaction is suitable for use with uncontaminated fluids, such as pericardial fluid, and can confirm a diagnosis rapidly [179].

The list of differential diagnoses includes many infectious and non-infectious conditions. Viral infections, malignancy, uremia, autoimmune disease and hypothyroidism are common causes of pericardial effusions. Some authors favor early pericardial biopsy to establish the diagnosis [173]. TB may also complicate a pre-existing pericardial disease [173].

4.11.3 Outcome

Without chemotherapy, the mortality of TB pericarditis is 90% or more [180]. With the advent of specific therapy, it has been reduced to less than 40% [174]. Major causes of death relate to the cardiac complications of tamponade, constriction and myocarditis. The patient will usually require hospitalization and observation for the initiation of diagnostic testing. It is justified to treat those with a positive tuberculin test and rapidly progressive pericardial disease empirically for 4–6 weeks while following the response if bacteriological diagnosis cannot be confirmed [172]. Emergent pericardiocentesis may be required for cardiac tamponade and pericardiectomy may be indicated if this complication recurs during therapy. A pericardial window may be tried in some cases, but if pericardial thickening is present, pericardiectomy should be performed. The surgical mortality of pericardiectomy is high if it is done at a late stage, particularly after onset of calcification.

Early surgical intervention with pericardiectomy was advocated in some older studies [181] claiming a better outcome, but recent studies reported a good clinical response to medical therapy if started in the acute phase, obviating the need for pericardiectomy in such patients [182]. Medical management is not different from other forms of extrapulmonary TB. However, corticosteroids are considered an integral part of the therapy of TB pericarditis. Adding corticosteroids to the regimen, usually 40–60 mg/day of prednisone, is reported to improve the clinical outcome [178].

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