Clinical manifestations of pulmonary and extra-pulmonary tuberculosis

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The clinical manifestations of tuberculosis are dependent on a number of factors: age, immune status, co-existing diseases, immunization status to the bacillus Calmette-Guerin (BCG); virulence of the infecting organism and host-microbe interaction.

Before the advent of the HIV epidemic, approximately 85% of reported tuberculosis cases were pulmonary only, with the remaining 15% being extra-pulmonary or both pulmonary and extra-pulmonary sites [1]. One large retrospective study [2] of tuberculosis in patients with advanced HIV infection reported:

- Pulmonary involvement alone 38%,
- Extrapulmonary sites alone 30%,
- Both pulmonary and nonpulmonary 32%

Extrapulmonary involvement tends to increase in frequency with worsening immune compromise [3].

A. Systemic effects of tuberculosis

Tuberculosis involving any site may produce systemic (i.e. not organ specific) symptoms. The frequency of fever ranges from 37 to 80% [4, 5]. Loss of appetite, weight loss, weakness, night sweats, and malaise are also common [4].

The most common haematologic manifestations are increases in the peripheral blood polymophonuclear leukocyte count and anaemia. Each occurs in approximately 10% of patients with apparently localized tuberculosis [6, 7]. In some instances, anaemia or pancytopenia may follow direct involvement of the bone marrow.

Hyponatremia, which may occur in 11% of patients [8], is caused by the production of an antidiuretic hormone-like substance in affected lung tissue [9].

Tuberculosis is associated often with other serious disorders including:

- HIV infection,
- alcoholism,
- drug abuse
- chronic renal failure,
- diabetes mellitus,
- neoplastic diseases.

The clinical features of these diseases and complications may modify those of tuberculosis and so hinder diagnosis [10].

B. Pulmonary tuberculosis

Clinical features

Cough is the commonest presentation. Initially it may be nonproductive, but as inflammation and tissue necrosis ensue, sputum is produced. Haemoptysis is occasionally a presenting symptom but usually results from previous disease and may not indicate active tuberculosis. It may arise from tuberculous bronchiectasis, rupture of a dilated vessel in the wall of a cavity (Rasmussen's aneurysm), bacterial or fungal infection (especially Aspergillus mycetoma) in a cavity or erosion into an airway (broncholithiasis). Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic pain. Dyspnoea is unusual unless there is extensive disease and may result in respiratory failure [11, 12]. Rales or crackles may be heard in the area of involvement and bronchial breathing indicating consolidation.

Radiographic features

Chest X-ray abnormalities are nearly always found. However in the presence of HIV infection, a normal X-ray is more common. In primary tuberculosis the process is generally seen as a middle or lower lung zone infiltrate, often with associated ipsilateral hilar adenopathy. Compression of airways by enlarged lymph nodes may cause atelectasis and is more common in children. If the primary process persists beyond the time when specific cell-mediated immunity develops, cavitation may occur ("progressive primary" tuberculosis) [13].

Tuberculosis developing as a result of endogenous reactivation of latent infection usually causes abnormalities in the upper lobes and cavitation is common (See figure 1). In the immunocompetent adult intrathoracic adenopathy is uncommon but may occur with primary infection. In contrast, intrathoracic or extrathoracic lymphatic involvement is quite frequent in children. As tuberculosis progresses, infected material may be spread via the airways into other parts of the lungs, causing a patchy bronchopneumonia. Erosion of a parenchymal focus of tuberculosis into a blood or lymph vessel may

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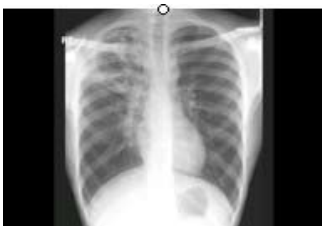


Figure 1. Chest radiograph Right upper zone cavity

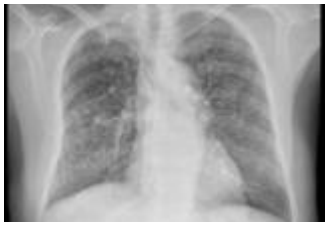


Figure 2. Chest radiograph Miliary tuberculosis

lead to dissemination of the organism and a "miliary" (evenly distributed small nodules) pattern on the chest X-ray see figure 2). Disseminated tuberculosis can occur in primary disease and may be an early complication of tuberculosis in children (both immunocompetent and immunocompromised). When it occurs in children, it is most common in infants and the very young (<5 year).

Healed tuberculosis presents a different radiologic appearance. Dense pulmonary nodules, with or without visible calcification, may be seen in the hilar area or upper lobes. Bronchiectasis of the upper lobes sometimes occurs from previous pulmonary tuberculosis. Pleural scarring may also appear [13, 14].

In patients with HIV infection, the nature of the radiographic findings depends to a certain extent on the degree of immunocompromise. Tuberculosis that occurs relatively early in the course of HIV infection tends to have the typical radiographic findings [15, 16]. With more advanced HIV disease the findings become more "atypical" - cavitation is uncommon, and lower lung zone or diffuse infiltrates and intrathoracic adenopathy are frequent.

C. Extrapulmonary tuberculosis

Extrapulmonary tuberculosis usually presents a more difficult diagnostic problem. It is less common and, therefore, less familiar to most clinicians [17, 18].

Extrapulmonary tuberculosis in HIV-infected patients. The high frequency is related to the failure of the immune response to contain M. tuberculosis, thereby enabling haematogenous dissemination and subsequent involvement of single or multiple non-pulmonary sites.

Disseminated tuberculosis occurs because of the inadequacy of host defenses in containing the infection. The organism proliferates and disseminates throughout the body ("miliary" tuberculosis"). The presenting features are generally nonspecific and characterized by the following systemic effects [19, 22]:

- fever,
- weight loss,
- night sweats,
- anorexia,
- weakness.

Physical findings are also variable and in descending order of frequency are:

- fever,
- wasting,
- hepatomegaly,
- pulmonary findings,
- lymphadenopathy,
- splenomegaly.

A finding strongly suggestive of disseminated tuberculosis is the choroidal tubercle, a granuloma in the retinal choroid [23].The chest X-ray is abnormal in most patients at the time of diagnosis approximately 85% of patients have the characteristic radiographic findings of miliary tuberculosis. Other abnormalities may be present including upper lobe infiltrates with or without cavitation, pleural effusion and pericardial effusion.

Lymph node tuberculosis. Tuberculous lymphadenitis usually presents as painless swelling of one or more lymph nodes. The nodes most commonly involved are those of the posterior or anterior cervical chain or those in the supraclavicular fossa. Frequently the process is bilateral and other noncontiguous groups of nodes can be involved [24]. With continuing disease the nodes may become matted and the overlying skin inflamed. Rupture of the node may result in formation of a sinus tract, which is slow to heal. Intrathoracic adenopathy may compress bronchi, causing atelectasis leading to lung infection and perhaps bronchiectasis being particularly common in children.

Pleural tuberculosis. There are two mechanisms by which the pleural space becomes involved in tuberculosis. Early on a few organisms may gain access to the pleural space and, in the presence of cell-mediated immunity, cause a hypersensitivity response [25, 26]. Commonly, this form of tuberculous pleuritis goes unnoticed, and the process resolves spontaneously. In some this involvement of the pleura is manifested as an acute illness with fever and pleuritic pain. If the effusion is large, dyspnoea may occur but effusions generally are small and rarely bilateral. In approximately 30% of patients there is no radiographic evidence of involvement of the lung parenchyma even though parenchymal disease is nearly always present [27, 28].

The second variety of tuberculous involvement of the pleura is empyema. This is much less common than tuberculous pleurisy with effusion and results from a large number of organisms spilling into the pleural space, usually from rupture of a cavity or an adjacent parenchymal focus via a bronchopleural fistula [29]. A tuberculous empyema is usually associated with evident pulmonary parenchymal disease on chest X-ray and air may be seen in the pleural space.

Genitourinary tuberculosis tends to present with local symptoms with systemic symptoms being less common [30, 31]. Dysuria, hematuria and frequency of micturition are common. Flank pain may be noted. However, often there is advanced renal destruction by the time of diagnosis [32]. In women genital involvement is more common without renal tuberculosis and may present with pelvic pain, menstrual irregularities and infertility [31]. In men a painless or only slightly painful scrotal mass is probably the most common presenting symptom of genital involvement.

Symptoms of prostatitis, orchitis or epididymitis may also occur [30]. The finding of pyuria in an acid urine with no bacterial organisms isolated from a routine culture should prompt the possibility of an evaluation for tuberculosis by culturing the urine for mycobacteria. Acid-fast bacillus (AFB) smears of the urine should be done, but the yield is low. The suspicion of genitourinary tuberculosis should be heightened by the presence of abnormalities on the chest film. In most series, approximately 40% to 75% of patients with genitourinary tuberculosis have chest radiographic abnormalities; although in many these may be the result of previous, not current, tuberculosis [30, 31].

Skeletal tuberculosis. The usual presenting symptom is pain [33]. Swelling of the involved joint may be noted with limitation of motion and occasionally sinus tracts. Systemic symptoms of infection are not common. Since the epiphyseal region of bones is highly vascularized in infants and young children, bone involvement is much more common in these groups. Approximately 1% of young children with tuberculosis will develop a bony focus [34]. Delay in diagnosis can be especially catastrophic in vertebral tuberculosis, where compression of the spinal cord may cause severe and irreversible neurologic sequelae, including paraplegia. Early in the process the only abnormality noted may be soft tissue swelling. The initial changes may be particularly difficult to detect by X-rays of the spine, but in advanced cases a fusiform paravertebral abscess is visible. Computed tomographic (CT) scans and magnetic resonance imaging (MRI) of are more sensitive and should be obtained when there is a high index of suspicion of tuberculosis - see figure 3.

Bone biopsy may be needed to obtain diagnostic material if the chest radiograph is normal and the sputum smear and culture are negative.

Central nervous system tuberculosis. Meningitis can result from direct meningeal seeding and proliferation during a tuberculous bacillaemia either at the time of initial infection or at the time of breakdown of an old pulmonary focus. It may result from breakdown of an old parameningeal focus with rupture into the subarachnoid space. The consequences of subarachnoid space contamination are diffuse meningitis or localized arteritis. In tuberculous meningitis the process is located primarily at the base of the brain (35).

Symptoms include those related to cranial nerve involvement as well as headache, decreased level of consciousness and neck stiffness. In most series more than 50% of patients with meningitis have abnormalities on chest film, consistent with an old or current tuberculous process and often miliary tuberculosis.

Physical findings and screening laboratory studies are not particularly helpful in establishing a diagnosis. In the presence of meningeal signs on physical examination, lumbar puncture is usually the next step. If there are focal findings on physical examination or if there are suggestions of raised intracranial pressure, a CT scan of the head, if it can be obtained expeditiously, should be performed before the lumbar puncture. With meningitis, the scan may be normal but can also show diffuse oedema or obstructive hydrocephalus. The other major central nervous system form of tuberculosis, the tuberculoma, presents a more subtle clinical picture [36]. Tuberculomas are generally seen as ring-enhancing mass lesions. The cerebrospinal fluid is usually normal. The diagnosis is established by CT or MRI and subsequent resection, biopsy or aspiration of any ring-enhancing lesion (See figure 4).

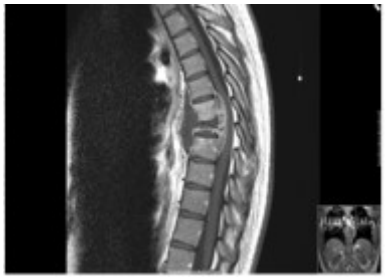
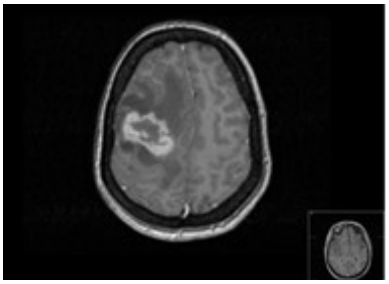


Figure 3. Magnetic resonance image (MRI) showing destruction of T12/L1 vertebrae

Figure 4. MRI head: Tuberculoma with surrounding oedema (differential diagnosis cerebral toxoplasmosis, lymphoma



Abdominal tuberculosis. Tuberculosis can involve any intra-abdominal organ and the peritoneum. The clinical manifestations depend on the areas of involvement. Tuberculosis may occur in any location from the mouth to the anus, although lesions proximal to the terminal ileum are unusual. The most common sites of involvement are the terminal ileum and caecum [37]. In the terminal ileum or caecum the most common manifestations are pain, which may be misdiagnosed as appendicitis or intestinal obstruction. A palpable mass may be noted that, together with the appearance of the abnormality on barium enema or small bowel films can easily be mistaken for a carcinoma. Rectal lesions usually present as anal fissures, fistulae or perirectal abscesses.

Tuberculous peritonitis frequently presents with pain often accompanied by abdominal swelling [37-40]. Fever, weight loss, and anorexia are also common. The combination of fever and abdominal tenderness in a person with ascites should always prompt an evaluation for intra-abdominal infection and a paracentesis should be performed. However, this is often not diagnostic, and laparoscopy with biopsy is recommended if tuberculosis is suspected.

Pericardial tuberculosis. The symptoms, physical findings, and laboratory abnormalities may be the result of either the infectious process itself or the pericardial inflammation causing pain, effusion and eventually haemodynamic effects. The systemic symptoms produced by the infection are nonspecific. Fever, weight loss and night sweats are common [41-43]. Cardiopulmonary symptoms tend to occur later and include cough, dyspnea, orthopnea, ankle swelling and chest pain. The chest pain may occasionally mimic angina but usually is described as being dull, aching, and affected by position and inspiration. Apart from fever, the most common physical findings are those caused by the pericardial fluid or fibrosis–cardiac tamponade or constriction. In the absence of concurrent extracardiac tuberculosis, diagnosis of pericardial tuberculosis requires aspiration of pericardial fluid or, usually, pericardial biopsy.

All figures from the author.

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