Review Article
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Extrapulmonary tuberculosis

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Extrapulmonary involvement can occur in isolation or along with a pulmonary focus as in the case of patients with disseminated tuberculosis (TB). The recent human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) pandemic has resulted in changing epidemiology and has once again brought extrapulmonary tuberculosis (EPTB) into focus. EPTB constitutes about 15 to 20 per cent of all cases of tuberculosis in immunocompetent patients and accounts for more than 50 per cent of the cases in HIV-positive individuals. Lymph nodes are the most common site of involvement followed by pleural effusion and virtually every site of the body can be affected. Since the clinical presentation of EPTB is atypical, tissue samples for the confirmation of diagnostic can sometimes be difficult to procure, and the conventional diagnostic methods have a poor yield, the diagnosis is often delayed. Availabiity of computerised tomographic scan, magnetic resosnance imaging laparoscopy, endoscopy have tremendously helped in anatomical localisation of EPTB. The disease usually responds to standard antituberculosis drug treatment. Biopsy and/or surgery is required to procure tissue samples for diagnosis and for managing complications. Further research is required for evolving the most suitable treatment regimens, optimal duration of treatment and safety when used with highly active antiretroviral treatmenrt (HAART).

Key words Abdominal tuberculosis - bone and joint tuberculosis - disseminated tuberculosis - extrapulmonary tuberculosis - genitourinary tuberculosis - laryngeal tuberculosis - lymph node tuberculosis - miliary tuberculosis - neurological tuberculosis - pericardial tuberculosis - tuberculosis in otorhinolaryngology - tuberculosis meningitis - tuberculosis pleural effusion

Tuberculosis can involve any organ system in the body. While pulmonary tuberculosis is the most common presentation, extrapulmonary tuberculosis (EPTB) is also an important clinical problem[1-3]. The term EPTB has been used to describe isolated occurrence of of tuberculosis at body sites other than the lung. However, when an extrapulmonary focus is evident in a patient with pulmonary tuberculosis, such patients have been categorized under pulmonary tuberculosis as per the guidelines of the World Health Organization (WHO)[4]. Since tuberculosis can virtually involve any organ system and a detailed description regarding EPTB at each of these sites is too exhaustive, an attempt is made to provide a critical overview of the more commonly encountered forms of EPTB in this review.

Epidemiology

In the era before the human immunodeficiency virus (HIV) pandemic, and in studies involving immunocompetent adults, it has been observed that EPTB constituted about 15 to 20 per cent of all cases of TB (Fig.1a)[1,5-13]. In HIV-positive patients, EPTB accounts for more than 50 per cent of all cases of TB (Fig.1b)[14-22]. The diagnosis of EPTB, especially

involving deeply located inaccessible areas is very difficult. Sparse literature is available regarding the relative contributions of pulmonary and extrapulmonary disease to the total number of tuberculosis cases from India as reliable epidemiological data are lacking[13]. Considering the stigma associated with and the reluctance to perform invasive procedures especially in HIV-positive patients in the Indian setting, even notified estimates of EPTB under the Revised National Tuberculosis Control Programme (RNTCP) are often based on presumptive diagnosis and are an overestimate of the problem[23]. Though it is estimated that EPTB constitutes 15 to 20 per cent of tuberculosis cases in general practice among HIV-negative adults in India[13], a higher proportion of EPTB cases have been documented in tertiary care centres. For example, at the Tuberculosis Clinic at the All India Institute of Medical Sciences, (AIIMS), New Delhi (n=1137) and the Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati (n=612), patients with EPTB constituted 53 and 30.4 per cent respectively during the period 1994-2002 (unpublished observations). Since several patients are referred to tertirary care centres for confirmation of diagnosis, these high figures could be a result of referral bias.

Impact of human immunodeficiency virus infection: HIV infected persons are at increased risk for primary or reactivation tuberculosis[24-27] and for second episodes of tuberculosis from exogenous reinfection[28,29]. CD4+ T-helper (Th) cells, upon antigenic challenge, are thought to differentiate along the separate pathways resulting in cell populations with different cytokine production profile termed Th1 and Th2[30-32]. In murine models, Th1 cells that produce interferon-γ (IFN-γ) and interleukin-2 (IL-2) confer resistance to infection with mycobacteria[32,33]. Th2 cells that produce interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6) and interleukin-10 (IL-10), do not contribute much to antimycobacterial immunity[24,32]. It has been observed that when peripheral blood lymphocytes from HIV-positive patients with tuberculosis are exposed *in vitro* to *Mycobacterium tuberculosis*, they produce less IFN-γ but similar amounts of IL-4 and IL-10 as compared with lymphocytes from tuberculosis patients who are HIV-negative[34]. Thus, reduced Th1 response observed in HIV-infected patients is thought to increase their susceptibility to tuberculosis[24,34].

The risk of tuberculosis increases as immunosuppression progresses[2,14,19,35]. The most common extrapulmonary site in HIV-positive individuals is the lymph node. However, neurological, pleural, pericardial, abdominal involvement has been described and virtually every site in the body can be involved in HIV-positive patients[1,2,14,19,35]. In studies reported from India, EPTB constituted 45 to 56 per cent of all the cases of tuberculosis in persons with AIDS[36,37].

Constitutional symptoms

Patients with EPTB may manifest constitutional symptoms such as fever, anorexia, weight loss, malaise and fatigue. In India patients with EPTB especially when the disease is located at an obscure site, may present with pyrexia of unknown origin (PUO) and this may be the only diagnostic clue in them. In addition, patients with EPTB manifest sympyoms and signs related to the organ system involved and these are discussed under the repective anatomic sites.

Lymph node tuberculosis

Historically, lymph node tuberculosis (LNTB) has been called the “King’s evil” referring to the divine benediction which was presumed to be the treatment for it. It was also referred to as “scrofula” meaning “glandular swelling” (Latin) and “full necked sow” (French)[38]. Peripheral lymph nodes are most often affected and cervical involvement is the most[38-40].

In India and other developing countries LNTB continues to be the most common form of EPTB and lymphadenitis due to non-tuberculous mycobacteria (NTM) is seldom seen[41-43]. On the other hand, NTM are the most common cause of lymphadenopathy in the developed world[44,45]. In patients with mycobacterial lymphadenitis in the USA, *M. tuberculosis* has been the most common pathogen among adults whereas NTM were the most common

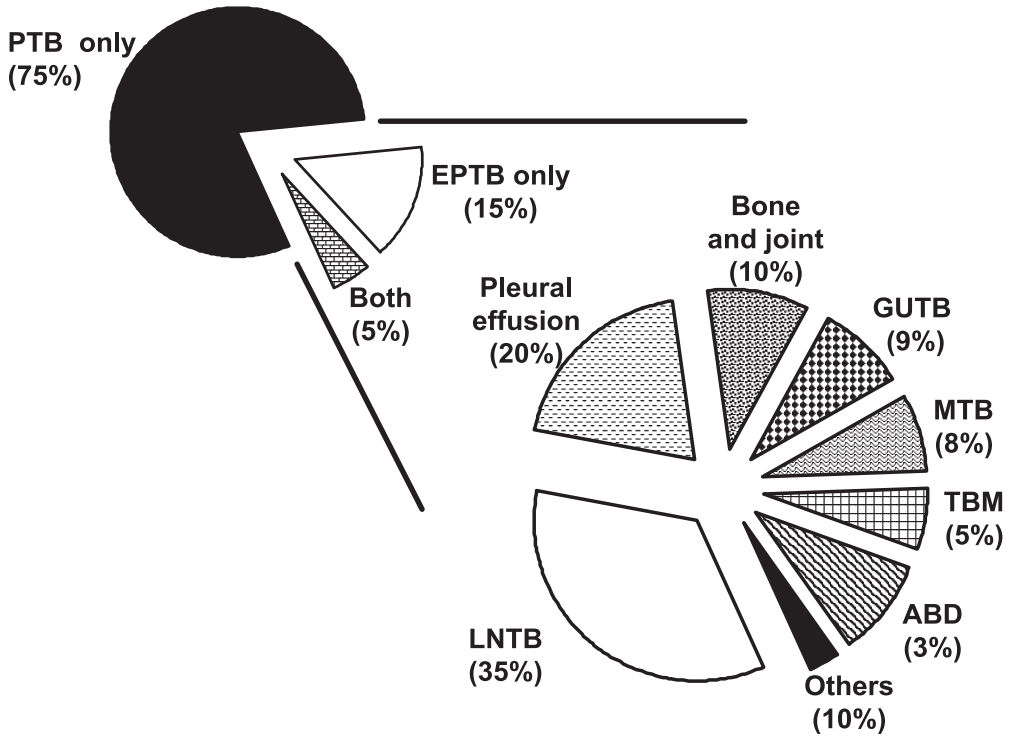

Fig.1a. Distribution of tuberculosis cases by anatomical site in HIV-negative patients. Data derived from references 3,5,6,10,11. PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; GUTB, genitourinary tuberculosis; MTB, miliary tuberculosis; TBM, tuberculosis meningitis; ABD, abdominal tuberculosis; LNTB, lymph node tuberculosis.

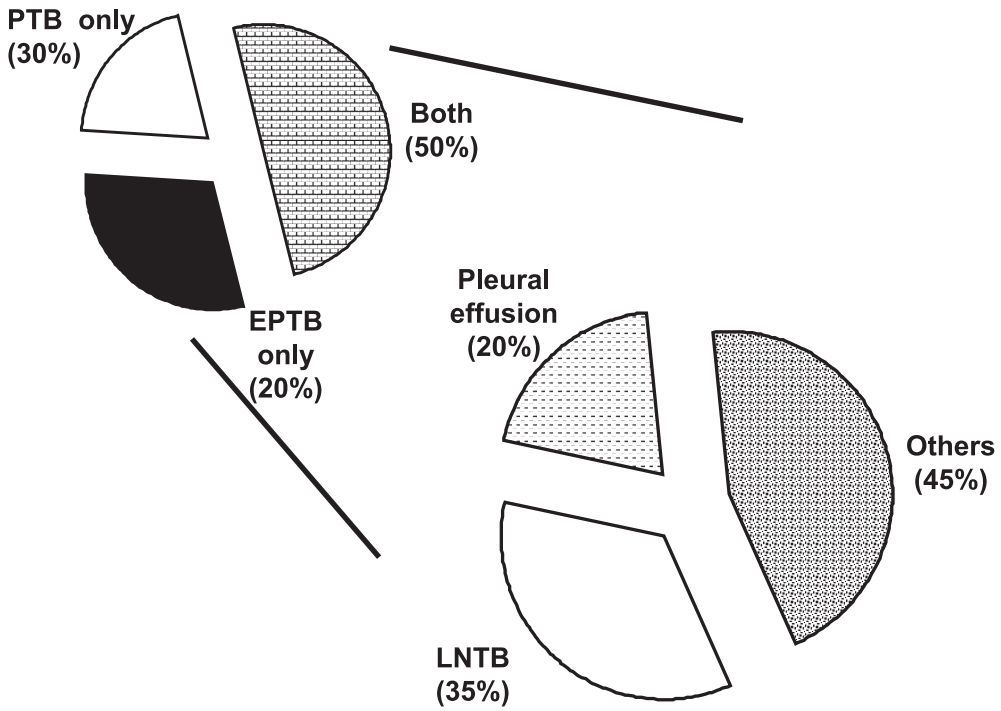

Fig.1b. Distribution of tuberculosis cases by anatomical site in HIV-positive patients data derived from references 14-22. PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; LNTB, lymph node tuberculosis.

pathogens among children[46]. In England, there has been a decline in LNTB and a rise in NTM lymphadenitis[47], and persons of Indian ethnic origin were more often affected than the local residents[40,47]. Similar results have been reported among native Americans and in persons originating from south east Asia and Africa[48,49]. Asians and Hispanic patients and African American also seem to have a high predilection for developing mycobacterial lymphadenitis[48,49].

Pathogenesis: LNTB is considered to be the local manifestation of a systemic disease whereas NTM lymphadenitis is thought to be a truly localised disease. *M. tuberculosis* gains entry into the body via the respiratory tract and undergoes haematogenous and lymphatic dissemination. Hilar and mediastinal lymph nodes are initially involved. This may occur at the time of primary infection or may occur later in life due to reinfection or reactivation of previous infection. Sometimes, tonsil is an important portal of entry. The infection then spreads via the lymphatics to the draining cervical lymph nodes. Initially, the nodes are discrete. Periadenitis results in matting and fixation of the lymph nodes. The lymph nodes coalesce and break down due to formation of caseous pus. This may perforate the deep fascia and present as a collar-stud abscess. Overlying skin becomes indurated and breaks down, resulting in sinus formation which may remain unhealed for years. Healing may occur from each of the stages with calcification and scarring. In contrast NTM, gain entry into the lymph nodes directly via oropharyngeal mucosa, salivary glands, tonsils, gingiva or conjunctiva[46,50], and lymph node involvement represents a localised disease.

Clinical presentation: LNTB often affects children and young adults[40-42]. Female predilection has been reported in some studies[40-42,51,52]. Patients usually present with slowly enlarging lymph nodes and may otherwise be asymptomatic. In HIV-negative patients, isolated cervical lymphadenopathy is most often seen in about two-thirds of the patients[40-42,51,52]. Bem *et al*[53] observed that among HIV-negative as well as HIV-positive patients, cervical lymph nodes were most commonly affected followed by axillary and inguinal lymph nodes. Multifocal involvement was observed in 39 and 90 per cent among HIV-negative and HIV-positive patients respectively. In HIV-positive patients, multifocal involvement, intrathoracic and intraabdominal lymphadenopathy and associated pulmonary disease are more common[40-42,53,54]. Some patients with LNTB may manifest systemic symptoms and these include fever, weight loss, fatigue and occasionally night sweats. Patients with mediastinal lymphadenopathy (Fig.2a and 2b) may present with cough and dysphagia[40-42,51-58]. With wider availability of computerised tomographic (CT) scan, it is expected that more cases of intrathoracic and intraabdominal lymphadenopathy and other associated lesions (Fig.2c and 2d) may be reported.

Peripheral tuberculosis lymphadenopathy has been classified into five stages[59]. These include: (*i*) stage 1, enlarged, firm mobile discrete nodes showing non-specific reactive hyperplasia; (*ii*) stage 2, large rubbery nodes fixed to surrounding tissue owing to periadenitis; (*iii*) stage 3, central softening due to abscess formation; (*iv*) stage 4, collar-stud abscess formation; and (*v*) stage 5, sinus tract formation. Physical findings depend upon the stage of the disease. The enlarged lymph nodes may be of varying size, are usually firm and may be discrete or matted. If necrosis and abscess formation have taken place they may become cystic in consistency. The lymph nodes are usually not tender unless secondary bacterial infection has occurred. Physical examination may be unremarkable but for palpable lymphadenopathy. Occasionally, lymph node abscess may burst leading to a chronic non-healing sinus and ulcer formation. Classically, tuberculosis sinuses have thin, bluish, undermined edges with scanty watery discharge. Uncommon manifestations observed in patients with mediastinal lymph node involvement include dysphagia[60,61], oesophago-mediastinal fistula[62-64], and tracheo-oesophageal fistula[65]. Upper abdominal and mediastinal lymph nodes may cause thoracic duct obstruction and chylothorax, chylous ascites or chyluria[66,67]. Rarely, biliary obstruction due to enlarged lymph nodes can result in obstructive jaundice[68]. Cardiac tamponade has also been reported due to mediastinal lymph node tuberculosis[69].

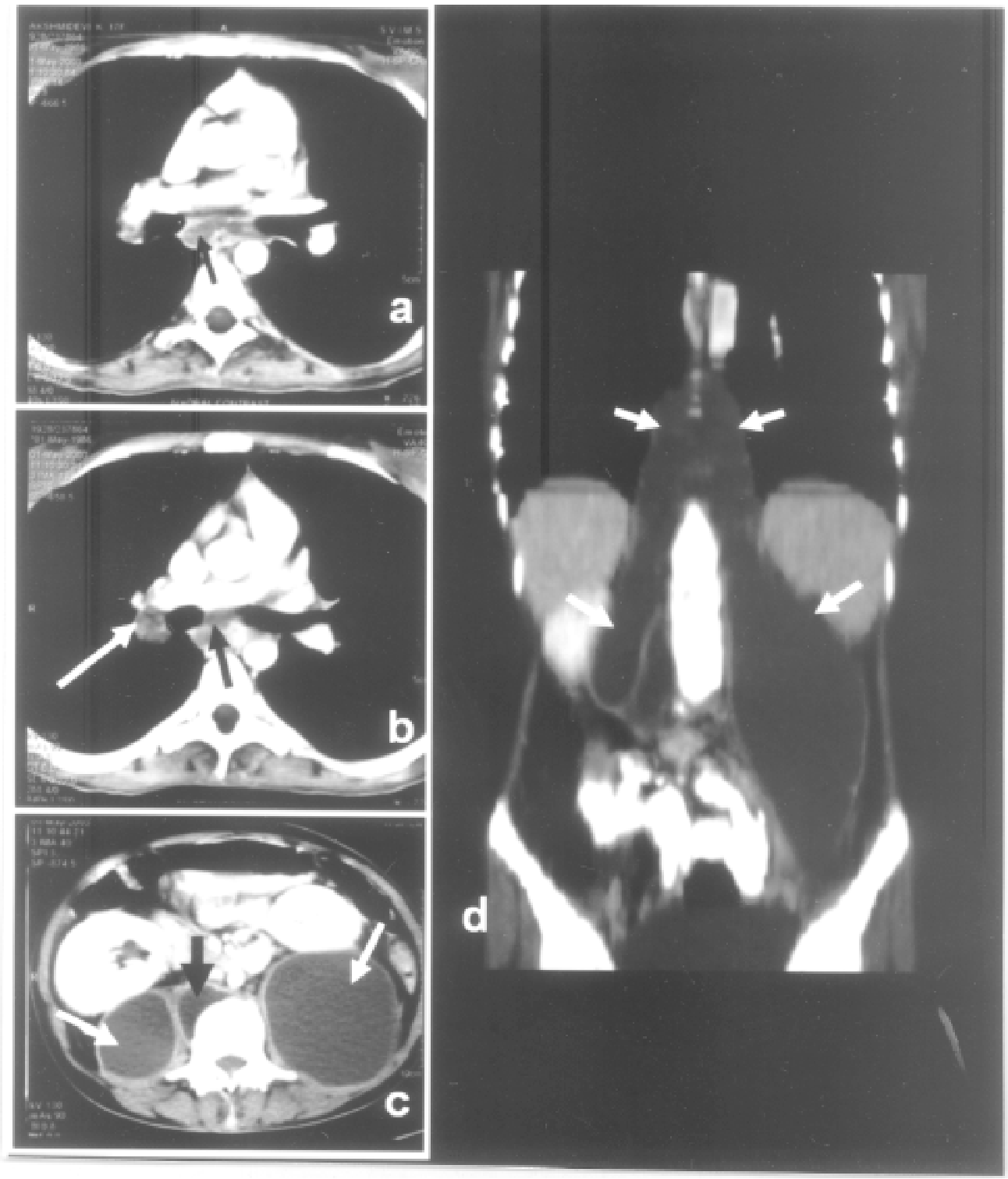

Fig.2. Contrast enhanced computerized tomographic (CECT) scan of the chest of a young woman who presented with low grade fever for 3 months, cough and dysphagia showing subcarinal **(a)** and right hilar (**b)** lymph nodes. Arrows points to hypodensity which indicates necrosis in the lymph node. CECT scan of the abdomen of the same patient showing bilateral psoas abscesses **(c)** (arrows). Coronal reconstruction of the CECT scan of the abdomen of the same patient showing bilateral psoas abscesses **(d)** (arrows). CT guided fine needle aspirate from the psoas abscess revealed numerous acid-fast bacilli.

Nontuberculous mycobacterial lymphadenitis: Very little is known regarding lymphadenitis due to NTM from India. In the western literature, NTM lymphadenitis has often been described in children. Both sexes are equally affected[48,50,59,70]. Constitutional symptoms seldom develop and the disease generally remains localised to the upper cervical area. If untreated, the nodes often progress to softening, rupture, sinus formation, healing with fibrosis and calcification[48,50,59,70].

Pleural effusion and empyema thoracis

Tuberculosis pleural effusion is categorised as extrapulmonary despite an intimate anatomic relationship between pleura and the lungs[71-75].

Pathogenesis: It is thought that a small subpleural focus ruptures into the pleural space, setting up an interaction between the tubercle bacilli or their specific components inducing a delayed hypersensitivity reaction. Recent evidence suggests that patients with TB pleural effusion have significantly higher levels of IFN-γ in the pleural fluid as compared to peripehral blood thus exhibiting localisation of predominantly Th1-type immunity in the pleural fluid[75]. Rupture of a cavity containing caseous material into the pleural space results in empyema thoracis. Less often, rupture of caseous paratracheal lymph nodes, paravertebral abscess or osteomyelitis of the ribs can result in empyema thoracis.

Clinical features: TB pleural effusion usually presents as an acute illness and the symptom duration ranges from a few days to few weeks. Most patients complain of pleuritic chest pain, non-productive cough and dyspnoea. Majority of the patients manifest fever, though a few may not have fever. Occasionally, the onset may be less acute, with only mild chest pain, low-grade pyrexia, cough, weight loss and loss of appetite.

Patients with tuberculosis empyema present with chest pain, breathlessness, cough with expectoration, fever, and toxaemia. Anaemia and hypoproteinaemia are often present. Physical examiantion may reveal digital clubbing, clinical findings suggestive of effusion and intercostal tenderness. Occasionally, tuberculosis empyema may present as a chest wall mass or draining sinus tract (tuberculosis empyema necessitatis).

Abdominal tuberculosis

Abdominal tuberculosis is the term used to encompass TB of the gastrointestinal tract, peritoneum, omentum, mesentery and its nodes and other solid intra-abdominal organs such as liver, spleen and pancreas[76]. Peritoneal and intestinal TB have been covered in another review article published in this issue of the journal[77]. Hence, TB at other abdominal sites such as hepatobiliary, pancreatic and splenic tuberculosis will be covered.

Hepatobiliary, pancreatic and splenic tuberculosis

Hepatobiliary and pancreatic TB are rare and are often associated with miliary tuberculosis, and occur more often in immunocompromised patients[78]. The clinical manifestations are non-specific and depend on the site and extent of disease. Anorexia, malaise, low grade fever, weight loss, night sweats, malaena, pancreatic mass or abscess or obstructive jaundice have all been described[79,80]. Pancreatic TB may present as acute or chronic pancreatitis or may mimic malignancy[79,80]. Isolated splenic tuberculosis is very rare in immunocompetent persons. Splenomegaly can occur in patients with disseminated/miliary tuberculosis. Splenic tuberculosis presents as hypersplenism or splenic abscess or as a solitary splenic lesion[81]. Multiple tuberculosis abscesses have been described in patients with HIV infection[82,83]. Pre-operative diagnosis of tuberculosis at these obscure sites is difficult and the diagnosis is often confirmed on histopathological examination of excised specimen.

Neurological tuberculosis

Neurological tuberculosis may be classified into three clinico-pathological categories: tuberculosis meningitis (TBM), tuberculoma, and arachnoiditis[84-86].

Tuberculosis meningitis

TBM accounts for 70 to 80 per cent of cases of

neurological tuberculosis[84-86]. A majority of cases of TBM are caused by *M. tuberculosis*. Isolated cases of meningitis caused by NTM have also been documented[86]. Neurological tuberculosis is invariably secondary to tuberculosis elsewhere in the body. In the bacteraemic phase of primary lung infection, metastatic foci can get established in any organ, which can become active after a variable period of clinical latency. The critical event in the development of meningitis is the rupture of a subependymally located tubercle (Rich focus) resulting in the release of infectious material into the subarachnoid space[87]. Whether the critical subependymal tubercle develops during primary haematogenous dissemination or due to secondary haematogenous spread from an area of extracranial extrapulmonary tuberculosis is not clear. The following features comprise the salient pathological features of TBM: (*i*) inflammatory meningeal exudate; (*ii*) ependymitis; (*iii*) vasculitis; (*iv*) encephalitis; and (*v*) disturbance of cerebrospinal fluid (CSF) circulation and absorption.

Clinical features: In the developing world, TBM is still a disease of childhood with the highest incidence in the first three years of life[86]. The disease usually evolves gradually over two to six weeks. However, acute onset has also been described. The prodromal phase lasts for two to three weeks and is characterised by a history of vague ill-health, apathy, irritability, anorexia and behavioural changes. With the onset of meningitis, headache and vomiting become evident and fever develops. Focal neurological deficits and features of raised intracranial tension may precede signs of meningeal irritation. Focal or generalised seizures, are encountered in 20 to 30 per cent of patients. Cranial nerve palsies can occur in 20 to 30 per cent of patients, the sixth nerve involvement being the most common[86,88]. Complete or partial loss of vision is a major complication of TBM. Various mechanisms postulated for the loss of vision include presence of exudates around the optic chiasma, arteritis, compression of the anterior visual pathways due to hydrocephalus or tuberculoma, and ethambutol toxicity among others. In untreated cases, progressive deterioration in the level of consciousness, pupillary abnormalities and pyramidal signs may develop due to increasing hydrocephalus and tentorial herniation. The terminal illness is characterised by deep coma and decerebrate or decorticate posturing. Without treatment, death usually occurs in five to eight weeks.

According to the severity of the illness, patients with TBM can be categorised into three clinical stages. The clinical staging helps to optimise therapy and to predict the prognosis. The prognosis of TBM is determined by the clinical stage at the time of initiation of treatment. The Medical Research Council[89] and Kennedy and Fallon systems[90] stage the patients into three categories: stage 1, patients are conscious and oriented with or without signs of meningeal irritation, but no focal neurological deficit; stage 2, patients with altered sensorium or focal deficits; and stage 3, patients are comatose and have dense deficits. During the last two decades, the clinical presentation of TBM has changed[91,92]. Atypical presentations include acute meningitic syndrome simulating pyogenic meningitis, progressive dementia, status epilepticus, psychosis, stroke syndrome, locked-in-state, trigeminal neuralgia, infantile spasm and movement disorders[86,88,93].

Intracranial tuberculomas and single, small, enhancing brain lesions

Tuberculoma is a mass of granulation tissue made up of a conglomeration of microscopic small tubercles[84]. The size of cerebral tuberculomas is highly variable. In most cases their diameters range from a few millimetres (mm) to three to four centimeters (cm)[94]. Intracranial tuberculomas in patients under the age of 20 yr are usually infratentorial, but supratentorial lesions predominate in adults. Solitary tuberculomas are more frequent than multiple lesions. Although their frequency has decreased in the last two to three decades, tuberculomas still constitute about 5 to 10 per cent of intracranial space occupying lesions in the developing world[86,95]. Patients with epilepsy who showed ring enhancing single CT lesions have been described almost exclusively from India[96-100]. The enhancing lesion is < 2 cm, but may show considerable oedema around it. Tuberculosis has been

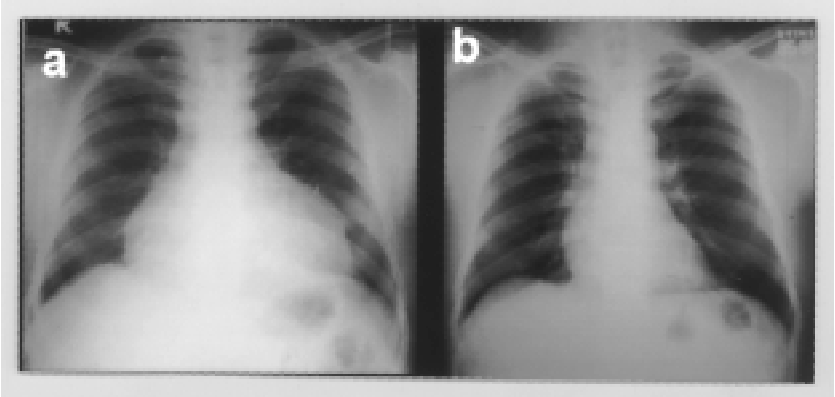

Fig.3a and **3b.** Chest radiograph (postero-anterior view) of a patient with tuberculosis pericardial effusion showing a globular heart shadow **(a)** before treatment. Chest radiograph taken 9 months after antituberculosis treatment **(b)** reveals considerable resolution of the pericardial effusion.

implicated as one of the causes for this form of presentation.

Neurological involvement is five times more frequent in HIV-positive compared to HIV-negative patients[101,102]. HIV infected patients account for over 50 per cent of the cases of TBM seen in the industrialised nations[101,102]. Bishburg *et al*[102] reported that intravenous drug abusers with AIDS exhibited increased risk of developing neurological tuberculosis and brain abscesses. Yechoor *et al*[103] found that 20 of the 31 patients (65%) identified as definite or probable TBM over a 12 yr period were infected with HIV. In general, HIV status does not alter the clinical manifestations, CSF findings and response to therapy[103]. However, HIV-positive subjects with TBM can have normal CSF more frequently[101-103].

Pericardial tuberculosis

Pericardial involvement in tuberculosis may result in acute pericarditis, chronic pericardial effusion, cardiac tamponade or pericardial constriction[104-107]. In India, TB accounts for nearly two-thirds of the cases of constrictive pericarditis[104-106]. TB has been reported to be the cause of acute pericarditis in four per cent of patients in the developed world and 60 to 80 per cent of the patients in the developing world[104-110]. TB pericarditis has been estimated to occur in one to eight per cent patients with pulmonary tuberculosis[111,112]. In industrialised countries TB pericarditis is not so common except in patients with HIV infection and AIDS[104].

Pericardial involvement most commonly results from direct extension of infection from adjacent mediastinal lymph nodes, or through lympho-haematogenous route from a focus elsewhere. TB pericarditis has the following stages: (*i*) dry stage; (*ii*) effusive stage; (*iii*) absorptive stage; and (*iv*) constrictive stage[112]. The disease may progress sequentially from first to fourth stage or may present as any of the stages. Sometimes, pericardial TB can persent as fever with no clinical localisation. Presence of cardiomegaly on the chest radiograph may be the only diagnostic clue and echocardiography may reveal pericardial effusion.

Clinical features: TB pericarditis occurs most commonly in the third to fifth decade of life. The disease has an insidious onset and presents with fever, malaise and weakness. The patients may manifest pericardial rub, vague chest pain or cardiomegaly on a chest radiograph (Figs.3a and 3b). Acute onset has been reported in 20 per cent of patients and some patients can present with cardiac tamponade[106,107]. Dyspnoea, cough, and weight loss are common symptoms. Chest pain, orthopnoea and ankle oedema occur in nearly 40 to 70 per cent of patients[113-116].

Pericardial effusion: Patients with TB pericarditis usually present with chronic pericardial effusion[104,113,115,116]. Patients may also present acutely with cardiac tamponade and may manifest severe distress, retrosternal compression, tachycardia and

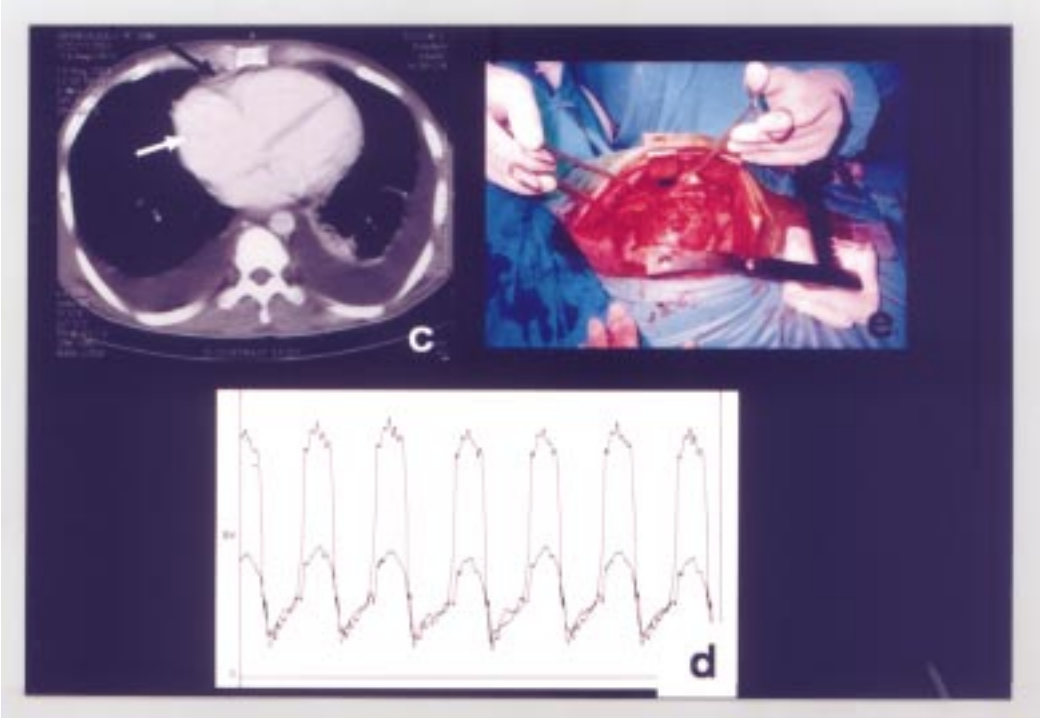

Fig.3c, 3d and **3e.** Contrast enhanced CT scan of the chest of a patient with constrictive pericarditis showing thickened pericardium (black arrow) and dilated right atrium (white arrow) **(c)**. Right and left ventricular pressure tracings (paper speed 100 mm/sec and 100 mm Hg gain) of the same patient showing markedly elevated and equal diastolic pressures with mild elevation of right ventricular systolic pressure (45 mm Hg) **(d)**. Operative photograph showing thickened pericardium **(e)**.

raised jugular venous pressure (JVP) with blunt γ descent[113,115,116], distant heart sounds, pericardial rub and pulsus paradoxus may be evident.

Effusive constrictive pericarditis: In patients with effusive constrictive pericarditis, constriction can be due to thickening of either the visceral or the parietal pericardium. Cardiomegaly, pedal oedema and raised JVP with a blunt γ descent may be present. After removal of fluid, JVP is still raised with a prominent γ descent. This stage could occur within few weeks of TB pericarditis. With effective antituberculosis treatment, some cases may resolve. Commonly, chronic constriction ensues[107,117,118].

Chronic constrictive pericarditis: In patients with chronic constrictive pericarditis, the inflow of blood is impeded due to thickened unyielding pericardium, especially in the late diastole (Figs 3c, 3d and 3e). Consequently, these patients have systemic as well as pulmonary venous congestion and manifest exertional dyspnoea, orthopnoea, ankle oedema and ascites. Cardiac output is mildly reduced at rest. Tachycardia, raised JVP with a prominent *y* descent occur. The JVP may rise further on inspiration (Kussmaul's sign). Pulsus paradoxus is seen in less than one-third of cases and signifies presence of some fluid or a relatively elastic pericardium. Cardiac size is normal. A systolic retraction of apex can be evident[104]. A pericardial knock may be present but murmurs are not common. The ascites is disproportionate to the oedema (ascites praecox)[104]. Severe elevation of venous pressure may result in congestive splenomegaly and protein losing enteropathy resulting in hypoalbuminaemia. After many years of hepatic venous congestion cardiac cirrhosis may develop in some patients. The disease worsens gradually and in chronic cases, significant myocardial atrophy occurs due to extension of inflammation and possibly disuse of the muscle. Such patients have suboptimal improvement and higher mortality with pericardiectomy[104].

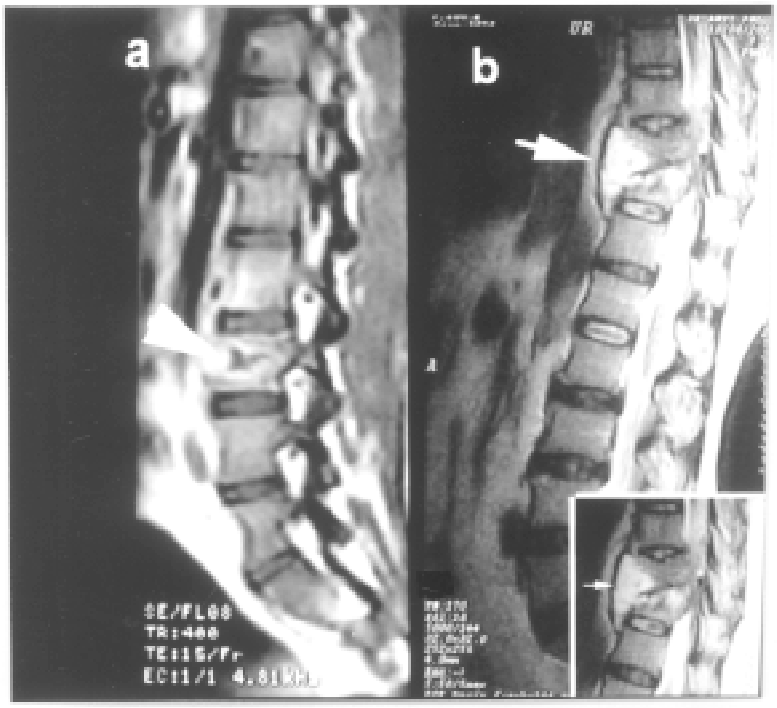

Fig.4. Magnetic resonance imaging (MRI) scan of the dorsolumbar spine, (sagittal view, T1 weighted image) showing central hypointense lesion (arrow) with reduced vertical height of the vertebra **(a)**. MRI scan of the dorsolumbar spine (sagittal view, T2 weighted image) showing destruction of D10 and D11 vertebrae (arrow), reduction in the intervening disc (inset, arrow) with anterior granulation tissue and cord compression **(b)**.

Bone and joint tuberculosis

Skeletal tuberculosis is a haematogenous infection and affects almost all bones. Tuberculosis commonly affects the spine and hip joint[119,120]. Other sites of involvement include knee joint, foot bones, elbow joint and hand bones. Rarely, it also affects shoulder joint. Two basic types of disease patterns have been observed: granular and exudative (caseous). Though both the patterns have been observed in osseous and synovial tuberculosis infection, one form may predominate.

Spinal tuberculosis (TB spine) is the most common form of skeletal tuberculosis. Majority of patients are under thirty years of age at the time of diagnosis. Constitutional symptoms such as weakness, loss of appetite and weight, evening rise of temperature and night sweats generally occur before the symptoms related to the spine manifest. Lower thoracic and lumbar vertebrae are the most common sites of spinal tuberculosis followed by middle thoracic and cervical vertebrae. Usually, two contiguous vertebrae are involved but several verebrae may be affected and skip lesions are also seen. The infection begins in the cancellous area of vertebral body commonly in epiphyseal location and less commonly in the central or anterior area of vertebral body (Figs 4a and 4b). The infection spreads and destroys the epiphyseal cortex, the intervertebral disc and the adjacent vertebrae (Fig.4b). It may spread beneath the anterior longitudinal ligament to reach neighbouring vertebrae. The vertebral body becomes soft and gets easily compressed to produce either wedging or total collapse. Anterior wedging is commonly seen in the thoracic spine where the normal kyphotic curve accentuates the pressure on the anterior part of vertebrae. The exudate penetrates the ligaments and follows the path of least resistance along fascial planes, blood vessels and nerves, to distant sites from the original bony lesion as cold abscess. In the cervical region, the exudate collects behind prevertebral fascia and may protrude forward as a retropharyngeal abscess. The abscess may track

down to the mediastinum to enter into the trachea, oesophagus or the pleural cavity. It may spread laterally into the sternomastoid muscle and form an abscess in the neck[119,120].

In the thoracic spine, the exudate may remain confined locally for a long time and may appear in the radiographs as a fusiform or bulbous paravertebral abscess and may compress the spinal cord. Rarely, a thoracic cold abscess may follow the intercostal nerve to appear anywhere along the course of nerve. It can also penetrate the anterior longitudinal ligament to form a mediastinal abscess or pass downwards through medial arcuate ligament to form a lumbar abscess. The exudate formed at lumbar vertebrae most commonly enters the psoas sheath to manifest radiologically as a psoas abscess or clinically as a palpable abscess in the iliac fossa. Abscess can gravitate beneath the inguinal ligament to appear on the medial aspect of thigh. It can spread laterally beneath the iliac fascia to emerge at the iliac crest near anterior superior iliac spine. Sometimes an abscess forms above the iliac crest posteriorly. Collection can follow the vessels to form an abscess in Scarpa's triangle or gluteal region if it follows femoral or gluteal vessels respectively[119,120].

Retropharyngeal abscess can present with local pressure effects such as dysphagia, dyspnoea, or hoarseness of voice. Further, dysphagia may also occur due to mediastinal abscess. Flexion deformity of hip develops due to psoas abscess. The abscesses may be visible and palpable if they are superficially located. Therefore, neck, chest wall, groin, inguinal areas and thighs where cold abscesses occur frequently must be carefully examined in addition to the location of a bony lesion[119,120].

Paraplegia (Pott's paraplegia) is the most serious complication of spinal tuberculosis and its occurrence is reported to be as high as 30 per cent in patients with spinal tuberculosis[119,120]. Early onset paraplegia develops during the active phase of infection. Paraplegia of late onset can appear many years after the disease has become quiescent even without any evidence of reactivation. Most commonly paraplegia develops due to mechanical pressure on the cord, but in a small number of patients cord dysfunction may occur due to non-mechanical causes[119,120].

Clinical presentation of tuberculosis of the hip and knee joints depends on the clinicopathological stage and each stage has a definite pattern of clinical deformity. Pain, circumferential reduction of movements at the joint are evident. "Night cries" may develop due to relaxation of muscle spasm and unguarded movements at the joint[121,122]. Tuberculosis osteomyelitis may mimic chronic mosteomyelitis of other causes[119,120].

Genitourinary tuberculosis

Genitourinary tuberculosis (GUTB) complicates three to four per cent of patients with pulmonary tuberculosis[121-124]. Haematogenous dissemination from an active site of infection results in GUTB. Initially metastatic lesions (tubercles) are formed in the kidneys. Macroscopic progression of the disease is often unilateral[125]. Usually, these lesions heal spontaneously or as a result of treatment. However, they may enlarge even after years of inactivity and rupture into the nephrons producing bacilluria. There is descending spread of infection, inflammation and scarring.

Active GUTB usually develops 5 to 25 yr after the primary pulmonary infection and is usually encountered between the second and fourth decades of life[121]. Patients present with dysuria, haematuria which may be painless, flank pain, renal mass, sterile pyuria, and recurrent urinary tract infection. Rarely, acute presentation mimicking pyelonephritis has also been described. Other uncommon presentations include: non healing wounds, sinuses or fistulae, haemospermia among others[121].

Female genital tuberculosis

Primary female genital tuberculosis has rarely been described in female partners of males affected by active GUTB[125-128]. More often, female genital tuberculosis is secondary to tuberculosis infection elsewhere in the body. Haematogenous or lymphatic spread is the most common method of spread. Infection may also spread from the contiguous intraabdominal sites through the fallopian tubes[125-128].

Female genital tuberculosis is an important cause of infertility. Patients may also present with chronic lower abdominal or pelvic pain, or alterations in the menstrual pattern. Sympotms of tuberculosis toxaemia may not be evident and physical examination may be unremarkable[126-128].

Cutaneous tuberculosis

Cutaneous tuberculosis accounts for 0.11 to 2.5 per cent of all patients with skin diseases[129-133]. Several clinical types of cutaneous tuberculosis have been described. In those not previously exposed to *M. tuberculosis,* miliary tuberculosis of the skin and tuberculosis chancre have been described. Previously sensitised hosts develop lupus vulgaris, scrofuloderma, tuberculosis verrucosa cutis[129]. Other lesions seen are tuberculids which include lichen scrofulosorum; papulonecrotic tuberculid; erythema induratum; and erythema nodosum. Lupus vulgaris is the most common variety seen in India followed by tuberculosis verrucosa cutis and scrofuloderma[129,133]. The other types are distinctly rare. Localised and generalised skin complications due to Bacille Calmette-Guerin (BCG) vaccination have also been described[134,135].

In patients with HIV infection and AIDS, the lesions may not fit into the above described categories and usually present as papules, nodules, vesicles or induration[129]. Ulceration and discharge from the surface of the lesions may occur. The diagnosis is usually not suspected clinically and it has been suggested that all atypical cutaneous lesions developing in immunosuppressed individuals should be biopsied and subjected to mycobacterial culture[133,136-140].

Tuberculosis in otorhinolaryngology

Before the advent of antituberculosis treatment, patients with active pulmonary tuberculosis very often developed laryngeal, otological, nasal and paranasal sinus involvement and deteriorated progressively. Laryngeal involvement was a dreaded consequence and was considered to be a harbinger of death[141]. With the advent of effective treatment the incidence of otorhinolaryngological TB had come down significantly. Otorhinolaryngological TB constitutes less than five per cent of all cases of EPTB. Focus has shifted on to otorhinolaryngological TB with the advent of HIV infection and AIDS[142].

Tuberculosis of larynx

In the present era, in countries where TB is highly endemic, almost all patients with laryngeal tuberculosis have been found to have radiological evidence of pulmonary TB and many of them may be sputum smear-positive[142,143]. On the contrary, in countries with a low prevalence of tuberculosis, associated pulmonary tuberculosis is rarely seen in patients with laryngeal TB[144,145]. In a study of 500 patients with pulmonary tuberculosis from India[145], laryngeal involvement was observed in four per cent of them.

Clinical features: Patients often present with hoarseness of voice. Pain is also an important feature which may radiate to one or both ears and may lead to odynophagia. Occasionally, patients may present with rapid onset of hoarseness of voice similar to that encountered in acute viral laryngitis. Laryngeal tuberculosis may co-exist with carcinoma. Clinical features of these conditions may overlap and the lesions may look similar[143,144].

Tuberculosis of the pharynx oral cavity and salivary glands

Tuberculosis involvement of the tonsils and pharynx is uncommon. The presenting features include: (*i*) ulcer on the tonsil or oropharyngeal wall; (*ii*) granuloma of the nasopharynx; and (*iii*) neck abcess. The oral cavity is an uncommon site of involvement by tuberculosis. Infection in the oral cavity is usually acquired through infected sputum coughed out by a patient with open pulmonary tuberculosis or by haematogenous spread. Tongue is the most common site of involvement and accounts for nearly half the cases. The lesions are usually found over the tip, borders, dorsum and base of the tongue. They may be single or multiple, the lesions may or may not be painful. Other sites of involvement include floor of mouth, soft palate, anterior pillars and uvula[146,147]. Secondary involvement of the draining lymph nodes may occur. Majority of these patients also have pulmonary tuberculosis[144,147-151].

TB sialitis is usually secondary to tuberculosis infection of the oral cavity or primary pulmonary tuberculosis[151]. Primary infection of the salivary glands is also known, but, is rare. Parotid gland is most commonly involved. Clinical presentation can be acute or chronic. Acute presentation may resemble acute non-tuberculosis sialitis and clinical differentiation may be difficult. Occasionally, the diagnosis of tuberculosis may be a surprise following surgery performed for a suspected salivary gland tumour[151]. Unsuspected tuberculosis parotid abscess may be wrongly drained mistaking it to be a pyogenic abscess. This may lead to the formation of a persistent sinus.

Tuberculosis of the ear

Tuberculosis of the external ear is uncommon. However, lupus vulgaris of the external ear has been reported[152]. Tuberculosis of the ear develops when the bacilli invade the eustachian tube while the infant is being fed, or, by haematogenous spread to the mastoid process. The focus in the middle ear cleft may present as painless otorrhoea. Pale granulation tissue may be present in the middle ear with dilatation of vessels in the anterior part of the tympanic membrane. Multiple perforations of tympanic membrane may occur as a result of caseation necrosis. Facial nerve palsy may sometimes develop.

Tuberculosis of paranasal sinuses and nasopharynx

Tuberculosis of nose, paranasal sinuses and nasopharynx is uncommon. However, occasionally maxillary sinus may be involved[153,154]. Other sites which can be involved include inferior turbinate, septal mucosa and the vestibular skin. Nasal discharge, mild pain and partial nasal obstruction are important presenting features. Involvement of nasolacrimal duct can rarely occur. Tuberculosis of the nose can cause complications like septal perforation, atrophic rhinitis and scarring of nasal vestibule.

Ocular tuberculosis

Ocular involvement has described in 2 to 30 per cent of patients with tuberculosis[1,7,12,155], and usually develops as a result of haematogenous dissemination. While tuberculosis can affect all the part of the eye, choroid is the most commonly affected structure. Primary ocular tuberculosis though has been described is extremely rate[155]. Tuberculosis affects the eyelids infrequently. Lupus vulgaris may spread to the face and involve the eyelid. Conjunctival tuberculosis and lupus vulgaris are the common manifestations of primary tuberculosis while tuberculids and phlyctenulosis occur in post-primary tuberculosis. Phlyctenulosis can involve conjunctiva, cornea or lid margin. Tuberculosis has also been implicated in the causation of Prinaud's oculoglandular syndrome and Eale's disease[155]. Tuberculosis uveitis can present as panuveitis or as chronic granulomatous iridocyclitis. Choroidal tubercles, when present, can provide valuable diagnostic clues to life threatening forms of disseminated tuberculosis such as miliary tuberculosis. These may be single or multiple and vary in size from quarter of a disc diameter to several disc diameters and are most frequently situated at the posterior pole[155].

Tuberculosis of the breast

Tuberculosis mastitis can occur as primary disease or can be secondary to tuberculosis elsewhere in the body. Primary tuberculosis mastitis is extremely rare and is thought to occur due to direct inoculation of the breast by *M. tuberculosis* through skin abrasions or duct openings in the nipple. Secondary involvement of breast is more common. The organisms may reach the breast through lymphatic route or haematogenous routes, or by contiguous spread from the ribs, pleural space. Lymphatic spread by retrograde extension from the axillary lymph nodes is considered to be the most common mode of spread though spread from cervical and mediastinal lymph nodes has been occasionally reported[83]. Clinical presentation is atypical and often, histopathological evidence suggests the diagnosis.

Disseminated/miliary tuberculosis

Disseminated tuberculosis (DTB) refers to involvement of two or more non-contiguous sites. Dissemination can occur during primary infection or after reactivation of a latent focus/re-infection. During primary infection, small numbers of tubercle bacilli gain access to the circulation through the lymphatics and disseminate to visceral sites which have rich vascular supply and good oxygenation such

as the liver, spleen, bone marrow and the brain. These foci heal by calcification in a majority of the patients. In the post-primary period, acute miliary tuberculosis (MTB) can occur when these foci fail to heal and progress. Later in life, reactivation of these latent foci, caseation and erosion into blood vessels can result in haematogenous embolisation and the development of MTB. Rarely, MTB can also develop due to caseation of an extrapulmonary site into the portal circulation and initial hepatic involvement with the classical pulmonary involvement occurring late.

Clinical presentation: Clinical manifestations of DTB/MTB are protean[36,156-171]. Even in areas where TB is highly endemic, the diagnosis of MTB can be difficult as the clinical symptoms have been subacute and non specific and the chest symptoms can be obscure till late in the disease. Fever and inanition are relatively common. Cough and dyspnoea are often present. Chills and rigors, usually seen in patients with malaria, or, sepsis and bacteraemia have often been described in patients with MTB[156-171]. Organomegaly is also a frequent physical finding. Choroidal tubercles are bilateral pale greyish white oblong patches which occur less commonly in adult patients with MTB than children. When present, they can be a valuable diagnostic clue[160,167]. Skin involvement in the form of erythematous macules and papules and unusual manifestations such as ulcerative lesions have also been described[156-171]. Signs of hepatic involvement may be evident in the form of icterus and hepatomegaly. Neurological involvement in the form of meningitis or tuberculomas is common. Clinically significant cardiac or renal involvement are uncommon in patients with MTB[160,172]. Overt adrenal insufficiency at presentation, or during treatment has also been described[173]. In some studies, headache and abdominal pain when present are supposed to have specific implications in MTB, headache signifying the presence of meningitis and abdominal pain signifying abdominal involvement[167,168].

Though the association of MTB and acute lung injury (ALI) and acute respiratory distress sydnrome (ARDS) is well known, only a few cases of this association have been published[160,164,174,175]. Severe pulmonary vascular damage has been implicated to be the pathophysiological basis for the development of ARDS in patients with MTB[176]. Immune reconstitution disease is a well known complication of highly active antiretroviral therapy (HAART). Recently, ARDS developing as a manifestation of severe immune reconstitution disease secondary to pulmonary tuberculosis has been reported[177]. Increases in CD4+ T- lymphocytes induced by HAART with subsequent inflammation in tissues affected by ongoing infection have been postulated to be the mechanism rsponsible for this. The mortality in ARDS of any cause is high, ranging from 40 to 60 per cent[171,178,179]. Therefore, identification of the primary cause is vital to initiate the appropriate therapy early. In patients with MTB complicated by ARDS, the classical miliary mottling occurs less commonly and bilateral diffuse interstitial or alveolar infiltrates similar to those described in ARDS of other causes occur nearly in all patients[160,162,164] which make the diagnosis even more difficult.

Diagnosis

Methodological issues

Definitive diagnosis of tuberculosis involves demonstration of *M. tuberculosis* by microbiological, cytopathological or histopathological methods. Clinical presentation of EPTB is atypical. Especially when the disease involves obscure occult sites, EPTB may not even be considered in the initial list of differential diagnosis. Further, invasive methods may have to be employed to secure tissue/body fluids for analysis. Many times representative tissue/body fluid may not be accessible. Even when adequate tissue is procured, the pathological findings may be suggestive of "granulomatous infection" which encompasses a wide range of differential diagnoses rather than "definitive tuberculosis". Therefore, the clinicians more often rely upon the clinical impression, radiological and endoscopic appearances and non-conventional diagnsotic methods as evidence to diagnose EPTB.

Principles of diagnosis

When EPTB is suspected as a possible diagnosis, every attempt should be made to procure tissue/relevant body fluid for diagnostic testing.

Most accessible tissue should be procured for histopathological, cytopathological and micrbiological diagnosis. For example, when working up a patient with suspected lymph node tuberculosis, the most easily accessible representative peripheral lymph node should be excised and subjected to diagnostic testing. Similarly, cerebrospinal fluid (CSF) and ascitic fluid examination provide most valuable diagnostic clue in patients with neurological and peritoneal tuberculosis respectively.

With the advent of ultrasound scan and subsequently CT scan and the magnetic resonance imaging (MRI) and widespread availability of upper gastrointestinal endoscopy, colonoscopy, laparoscopy, cystoscopy and biopsy under visual guidance and other invasive investigations such as hysterosalpingography and colposcopy, tremendous progress has been achieved in precise anatomical localisation of the lesions of EPTB antemortem. If no accessible tissue/fluid is available for analysis, radiologically guided fine needle aspiration and cytopathology (FNAC) or biopsy may be required to secure tissue for diagnosis.

Tuberculin skin test: In countries like India where tuberculosis is higly endemic, tuberculin skin test result alone is not sufficient evidence to diagnose EPTB in adult patients. Tuberculin positivity in patients with various forms of EPTB is shown in Table I.

Histopathological, cytopathological and microbiologial examination of tissue specimens and body fluids

Fine needle aspiration cytopathology (FNAC), biopsy: In patients with lymph node tuberculosis, FNAC, excision biopsy of the most accessible peripheral lymph node confirms the diagnosis most of the times. CT scan is helpful in localising intrathoracic and intraabdominal lymphadenopathy and radiologically guided FNAC and biopsy[192-200]. When available, video-assisted thoracoscopic surgery (VATS) can be a valuable minimally invasive procedure to procure tissue for diagnostic testing in patients with intrathoracic lymphadenopathy and pleural disease[201]. Transporting the collected lymph node specimen in Kirschner's transport medium is helpful in increasing the microbiological yield[202]. In patients with DTB/MTB, various invasive methods have been employed to ascertain the diagnosis their relative diagnostic yield is shown in Table II.

Laparoscopy will facilitate visual inspection of the lesions and faciliatate procurement of tissue for histopathological confirmation of the diagnosis[76]. These details are discussed in elsewhere in this issue[77].

Table I. Tuberculin positivity in various forms of extrapulmonary tuberculosis

Site	Tuberculin positive (%)
Lymph node tuberculosis[33,34,36,180,181]	74-98
Pleural effusion[75,180,182-184]	73-93
Abdominal tuberculosis[185-189]	58-100
Pericardial[115,190]	75-100
Cutaneous tuberculosis[133]	67
DTB/MTB[156,166,169,180,191]	21-62

Numbers in superscript indicate reference numbers
DTB, diseminated tuberculosis
MTB, miliary tuberculosis

Table II. Method of confirmation of diagnosis in patients with disseminated/miliary tuberculosis*

Variable	Maartens *et al*[166]	Sharma *et al*[160]	Prout and Benatar[191]	Biehl[169]	Kim *et al*[165]	Cumulative yield (%)
Sputum †	29/75	10/88	31/39	13/26	25/33	41.4
Bronchoscopy‡†	38/95	2/37	3/3	ND	12/19	35.7
Gastric lavage †	7/11	ND	ND	20/35	6/8	61.1
CSF†	14/44	ND	1/31	15/45	0/26	20.5
Urine†	5/28	ND	3/17	7/29	18/27	32.0
Bone marrow§†	18/22	3/11	20/21	ND	9/22	58.1
Liver biopsy	11/11	6/9	12/13	ND	11/12	88.9
Lymph node biopsy	9/9	16/19	ND	3/3	ND	90.3

*Data are shown as number positive/number tested. Criteria for subjecting the patients to these tests not clearly defined in any of thestudies. Often, more than one test have been performed for confirming the diagnosis. For histopathological diagnosis, presence of granulomas, caseation and demonstration of acid-fast bacilli have been variously used to define a positive test
†yield from smear and culture
‡includes yield from bronchoscopic aspirate, washings, brushings, bronchoalveolar lavage and transbronchial lung biopsy
§yield from aspiration and/or trephine biopsy
CSF, cerebrospinal fluid; ND, not described
Superscript numerals denote reference numbers

Table III. Characteristic body fluid findings in patients with various forms of extrapulmonary tuberculosis

Variable	Pleural fluid	Pericardial fluid	Cerebrospinal fluid
Appearance	Straw coloured	Straw coloured or serosanguinous	Clear early; Turbid with chronicity
*p*H	7.3-7.4 Rarely <7.3 Never >7.4	Not well described	Not well described
Cell count			
Total count	1000-5000	Not well described	100-500
Differential count	50-90% lymphocytes, eosinophils <5% Few mesothelial cells	Leukocyte count is usually increased. PMN preponderant early. Later,	Rarely >1000 PMN preponderant early. Later, up to 95%
Cytology		up to mononuclear cells predominate	Mononuclear
Protein	Usually high (>2.5g/dl)	Usually high	Usually high (100-500 mg/dl) Can be very high with blockage or extreme chronicity
Glucose	Usually less than serum concentration	Low	Usually 40-50 mg/dl (about 50% of blood glucose)

PMN, polymorphonuclear leukocytes
Data derived from references 71-75,84-86,88,104,113,115,117,180
Details regarding ascitic fluid are described in reference 77

Table IV. Yield of various tissues and body fluid specimens by the conventional smear and culture methods in patients with extrapulmonary tuberculosis

Variable	Pleural fluid	Pericardial fluid	Cerebrospinal fluid
Smear microscopy	< 10%	< 1%	5-37%
Mycobacterial culture	12-70%	25-60%	40-80%
Data derived from references	71-75,84-86,88,104,113,115,117,180		

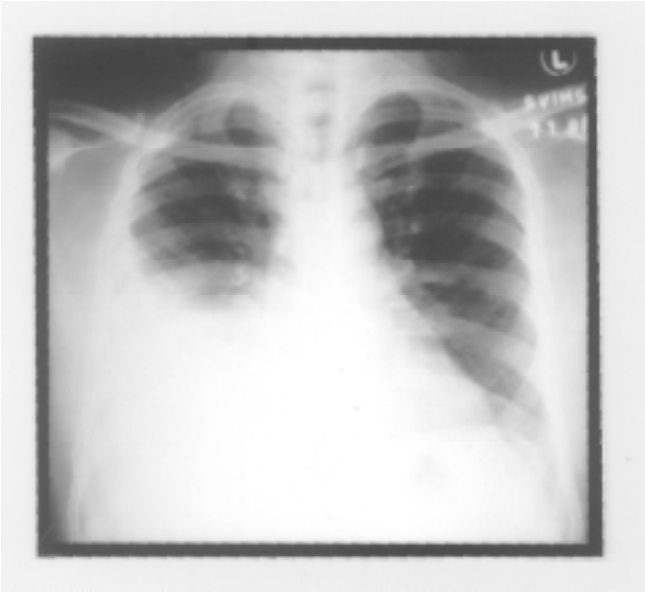

Fig.5. Chest radiograph (postero-anterior view) showing right sided pleural effusion.

Examination of body fluids and other biochemical tests

The characteristic features of various body fluids and their yield by the conventional microbological, histopathological, cytopathological, and non-conventional methods in patients with EPTB is shown in Tables III-VI.

Pleural fluid: The pleural fluid is typically clear or straw coloured, but cloudy or serosanguinous fluid may also be obtained. The pleural fluid is exudative and lymphocyte rich. Early in the disease, the pleural fluid may reveal predominantly neutrophils, but on serial thoracocenteses, lymphocytosis may become evident[71-75]. Presence of a large number of mesothelial cells (> 1% of white blood cells) is a strong evidence against the diagnosis of tuberculosis, though, a few cases with numerous mesothelial cells in the fluid have been reported[71-75] .

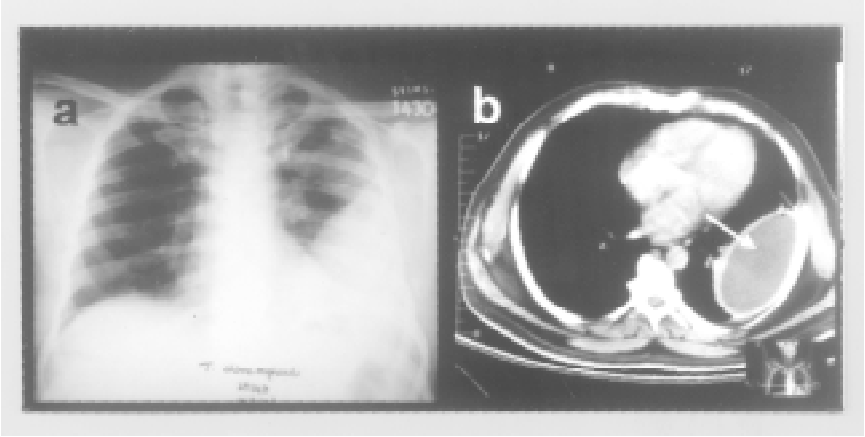

Fig.6. Chest radiograph (postero-anterior view) showing left sided encysted pleural effusion **(a)** Contrast enhanced CT scan of the chest of the same patient **(b)** showing left sided loculated empyema surrounded by thick enhancing pleura (arrow).

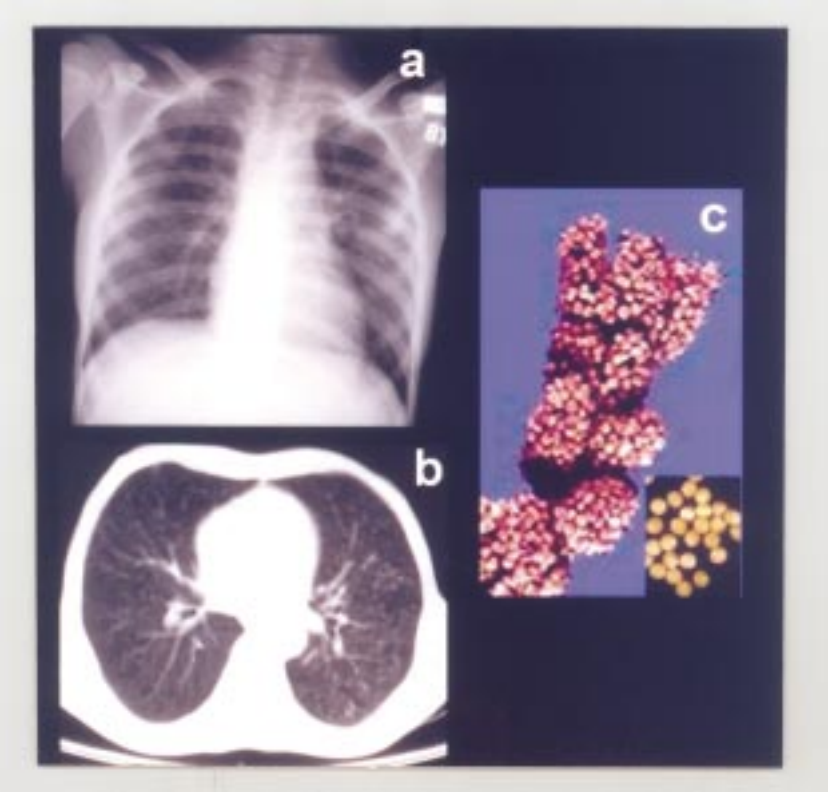

Fig.7. Chest radiograph (postero-anterior view) showing classical miliary pattern **(a)**. Contrast enhanced CT scan of the chest **(b)** showing classical miliary pattern. Branching nodular (2 to 3 mm) and linear opacities resulting in a tree-in-bud appearance can also be discerned. These nodules resemble millet seeds **(c)**.

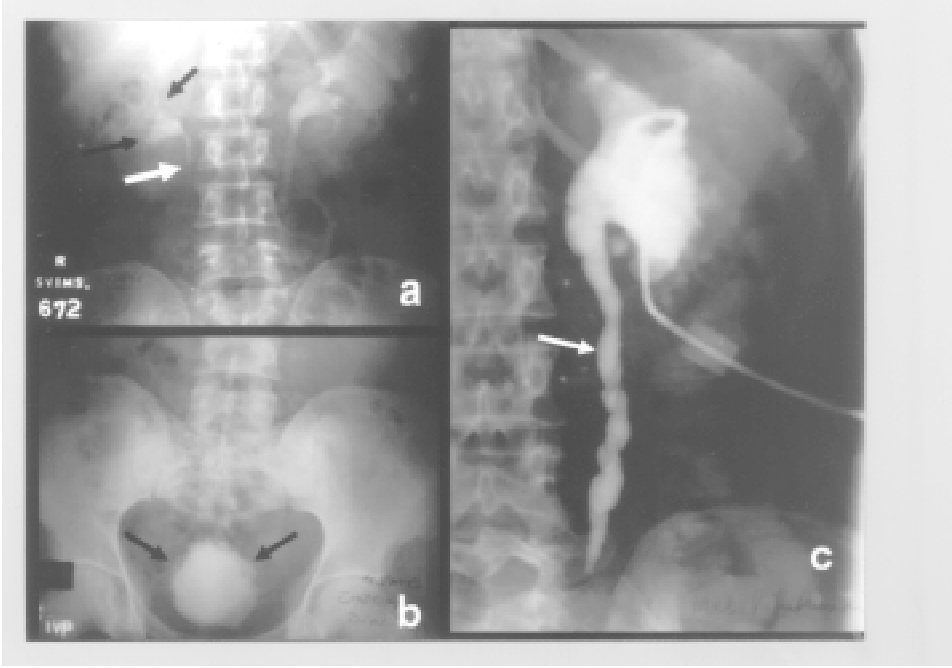

Fig.8. Intravenous pyelogram showing calyceal cut-off sign black arrow and ureteral narrowing (white arrow) **(a)** thimble bladder (black arrows) **(b).** Percutaenous nephrogram showing irregularity, narowing and stricture of ureter (white arrow) **(c)**.

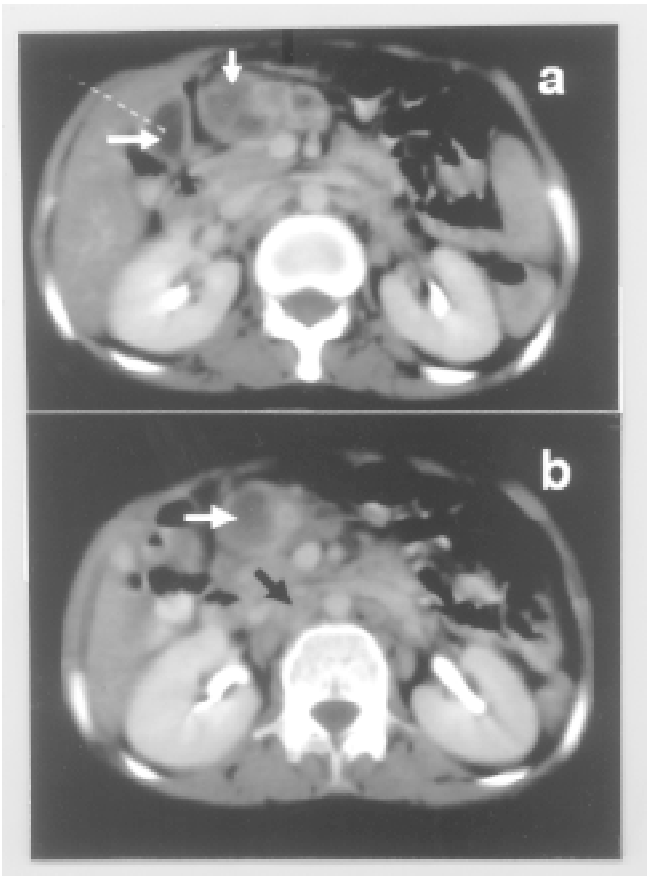

Fig.9. Contrast enhanced CT scan of the abdomen showing intraabdominal **(a)** and retroperitoneal **(b)** lymphadenopathy (arrows). Both the white and black arrows point to hypodensity which indicates necrosis in the lymph node. This central attenuation with peripheral rim enhancement is considered classical (though not pathogenomic) for tuberculosis.

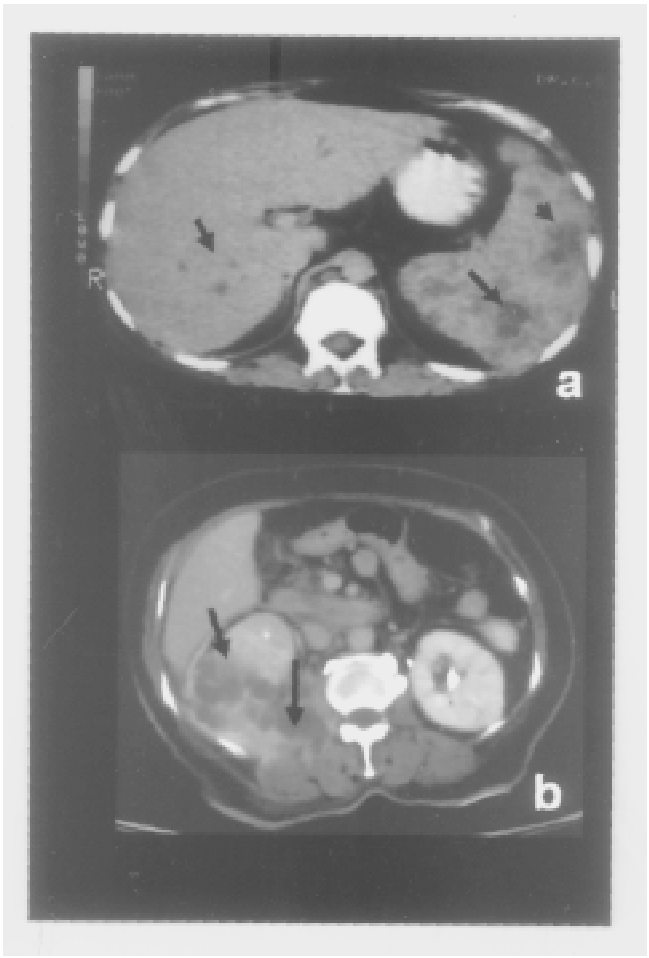

Fig.10. Contrast enhanced CT scan of the abdomen showing multiple hypointense areas in the liver and spleen (arrows) **(a)**, hypodense lesions in the right kidney (arrow) with extension into the poas and paraspinal muscles (arrow) **(b)** CT guided fine needle aspiration confirmed the diagnosis of tuberculosis.

Details about ascitic fluid examination are described eleswhere[77].

Cerebrospinal fluid: Clear CSF with moderately raised cells and protein and low glucose constitute the typical CSF picture of TBM. However, these characteristics are shared by other forms of chronic meningitis and partially treated pyogenic meningitis. In the presence of coexisting spinal meningitis and spinal block the CSF may be xanthochromic. If allowed to stand, a pellicle or cobweb may form, indicating the presence of fibrinogen. The pellicle is highly suggestive but not pathognomonic of TBM. CSF protein has been reported to be normal in some patients with AIDS and TBM[84]. CSF glucose levels are abnormal in the majority of cases, being less than 40 per cent of the corresponding blood sugar level. However, CSF glucose levels are never undetectable as in patients with pyogenic meningitis.

Pericardial fluid: Echocardiography, pericardiocentesis and examination of pericardial fluid can help in confirming the diagnosis of pericardial tuberculosis. The characteristic pericardial fluid findings in patients with tuberculosis pericarditis are shown in Table III.

Urine: The yield of urine examination by smear and culture for detecting the tubercle bacillus is low

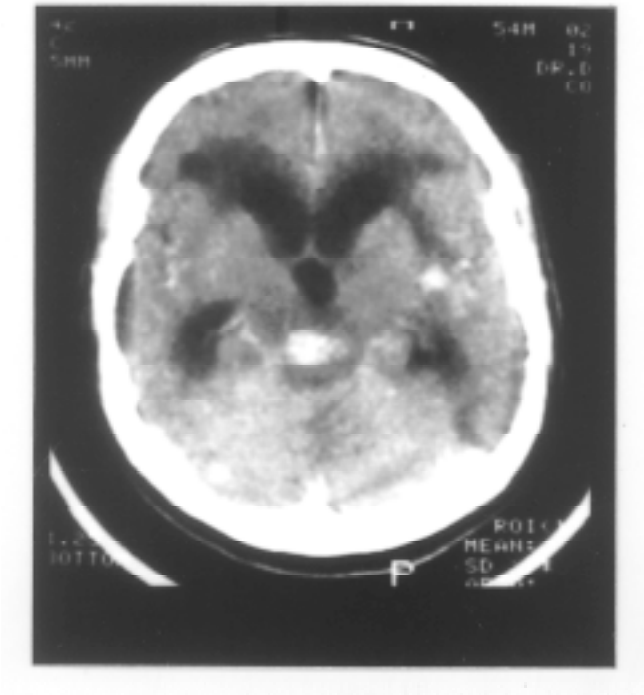

Fig.11. Contrast enhanced (CE) CT head showing basal meningitis, ventricular dilatation.

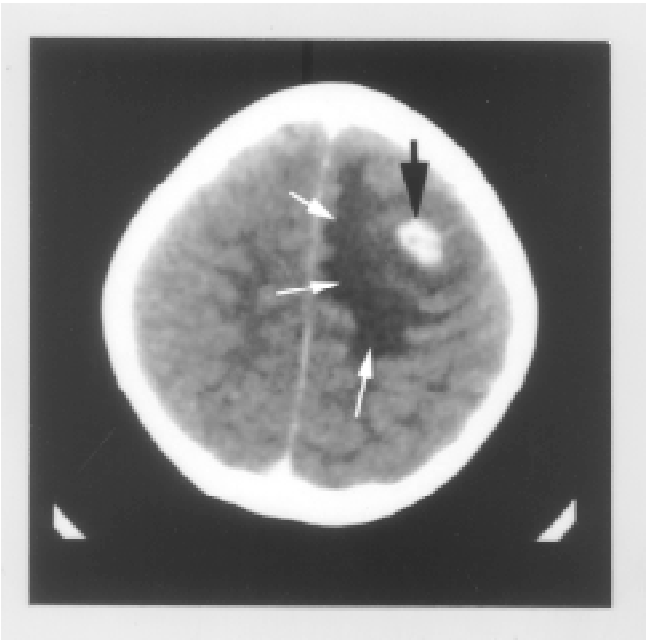

Fig.12. Contrast enhanced (CE) CT head showing intracranial tuberculoma (black arrows) and perilesional oedema (white arrows).

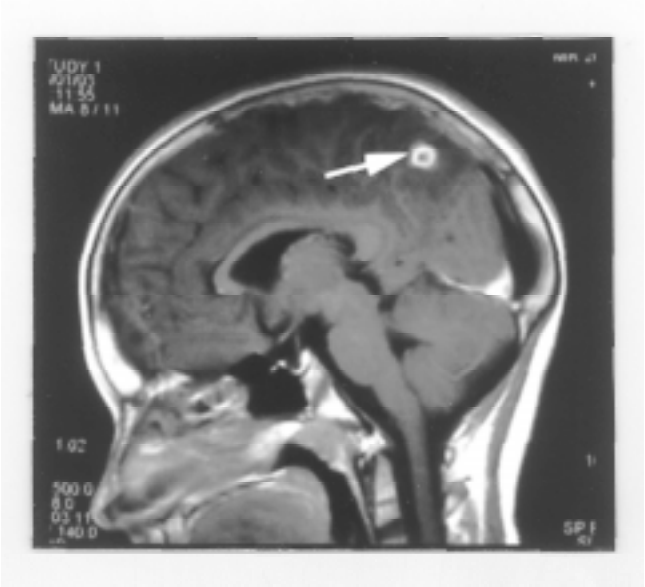

Fig.13. Contrast enhanced MRI of the brain (sagittal view, T1 weighted image) showing solitary enhancing ring lesion (arrow).

probably because of the intermittent shedding of the baclli. Nevertheless, in patients with suspected genitourinary tuberculosis, urine examination is mandatory.

Cold abscess pus: Smear and culture examination of the pus aspirated from cold abscesses either directly or under radiological guidance can be rewarding and must be attempted whenever feasible.

Imaging

Plain radiograph: The association of pulmonary tuberculosis assessed by the chest radiograph in patients with various forms of EPTB is depicted in Table VII. In patients with pleural tuberculosis, the chest radiograph usually reveals a unilateral pleural effusion (Fig.5). Sometimes the pleural effusion or empyema can be encysted or multiloculated (Fig. 6a and 6b). Encysted effusion may be confused with a mass lesion of the pleura, mediastinum, chest wall and lungs. Most often encystment occurs in the costoparietal regions, usually along the posterior parietal pleural surface on the right side. A lateral decubitus film may be useful in dstinguishing subpulmonic encystment from subpulmonic collection of free fluid as both these conditions

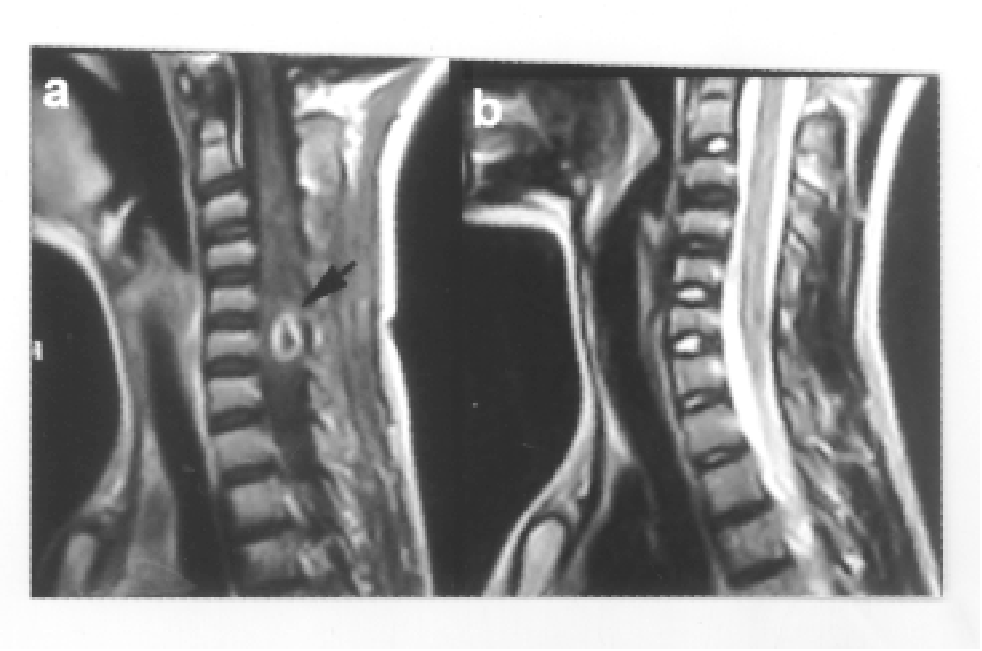

Fig.14. Contrast enhanced MRI of the brain (sagittal view, T1 weighted image) showing intramedullary enhancing ring lesion (arrow) opposite C6 vertebral body **(a)** before treatment. The lesion resolved completely following nine months of antituberculosis treatment **(b)**.

present with a raised hemidiaphragm with convexity lateral than usual with or without a blunted costophrenic angle. Very rarely, encysted mediastinal pleural effusion can present as an unexplained bulge of the mediastinum.

The hallmark of acute disseminated MTB is the miliary pattern on the chest radiograph (Figs. 7a, 7b and 7c). The term miliary refers to the "millet seed" size of the nodules (2-3 mm) seen on classical chest films[158,160]. Some patients with MTB, however, may have normal chest radiographs and some may have patterns that are indistinguishable from interstitial pneumonia[160]. Some of the patients may manifest coalescent opacities. When patients with MTB develop ARDS, the chest radiograph may be identical to that seen in ARDS due to other causes[160]. In a large study of HIV-negative MTB patients from New Delhi, majority of the patients (88%)[160] had chest radiographs consistent with MTB, and in some these classical radiological changes evolved over the course of the disease. The diagnosis of MTB is easier when the patient presents with classical miliary shadowing on chest radiograph in an appropriate setting. However, the diagnosis may be difficult in those situations where chest radiograph does not show classical miliary shadows.

Intravenous pyelography (Figs.8a and 8b) and percutaneous nephrogram (Fig.8c) are useful in imaging GUTB.

Ultrasonography: Ultrasonography of the chest may be helpful in demonstrating winding structures of different lengths which may represent fibrin bands, mobile delicate septations, regular pleural thickening, and occasional nodularity amidst the effusion. Ultrasonography and CT scan (Fig.6b) are useful in the diagnosis of encysted and multiloculated pleural effusions.

Computerised tomography and magnetic resonance Imaging: In patients with pleural effusion and empyema, contrast enhanced (CE) CT scan of the thorax may be useful in identifying the underlying pulmonary lesion, mediastinal, hilar or paratracheal lymphadenopathy (Figs.2a and 2b) and assessing the pleural loculation and thickening (Fig.6b). Sometimes, CECT of the thorax has also been used to assess pericardial thickening in patient with pericardial effusion (Fig.3c).

Abdominal CT scan scores over ultrasonography for detecting high density ascites[238-241]. Retroperitoneal, peripancreatic, porta hepatis and mesenteric/omental lymph node enlargement may be evident (Figs9a and 9b). Abdominal CT scan also detects caseous necrosis of lymph node which appears as low attenuating, necrotic centres and thick, enhancing inflammatory rim[238-241]. Granulomas or abscesses in the liver, pancreas and spleen may be seen (Figs.10a and 10b). In addition to ascites, mesenteric infiltration, omental masses, peritoneal enhancement/thickening and disorganised masses of soft tissue densities may be seen.

In patients with DTB/MTB, CT scan and MRI scan may reveal evidence of neurotuberculosis, intraabdominal lymphadenopathy, infiltrative lesions in liver, spleen and kidney (Fig.10b).

CT scan or MRI of the brain may reveal thickening and enhancement of basal meninges, hydrocephalus, infarction, periventricular oedema, and mass lesions due to associated tuberculoma or tuberculosis abscess (Figs11 and 12). Common sites of exudates are basal cisterna ambiens, suprasellar cistern and sylvian fissures. Serial CT scans are very helpful in assessing the course of tuberculomas and hydrocephalus. Gadolinium enhanced MRI is superior to the CT scan in detection of basal meningeal enhancement and small tuberculomas (Figs13,14a and 14b). Contrast enhanced MRI has been found to be superior to the contrast enhanced CT scan in detection of diffuse and focal meningeal granulomatous lesions, in delineating focal infarcts of the basal ganglia and diencephalon. Further, MRI is superior to CT in defining the presence, location and extent of associated brainstem lesions. MRI of the spine is also useful in the diagnosis of lesions of spinal tuberculosis (Figs 4a and 4b).

If there is a high index of suspicion of the diagnosis of MTB and the chest radiograph is atypical, it is suggested that high resolution computed tomographic scan (HRCT scan) (Fig.7b) be done to support the diagnosis. HRCT scan is superior to the conventional CT scan in defining the parenchymal detail. Further, HRCT of the chest with contrast can also be useful in detecting lymph nodal enlargement, calcification and pleural lesions.

Details regarding various imaging modalities in the diagnosis of abdominal tuberculosis are described elsewhere[77].

Echocardiography and cardiac catherisation

Echocardiography is useful for detecting the presence of pericardial fluid and features such as collapse of right atrial or right ventricular free wall in diastole which are diagnostic of cardiac tamponade. In fact, these features may sometimes precede the other clinical evidence of pericardial tuberculosis. Echocardiogram, however, is not an accurate test to detect pericardial thickening. Indirect echocardiographic signs such as flat posterior left ventricular wall motion in the diastole, premature opening of the pulmonary valve, may suggest chronic constrictive pericarditis[104].

In cardiac tamponade, cardiac catherisation revelas a prominent γ descent in the right atrial tracing. In chronic constrictive pericarditis, a prominent γ descent in the atrial pressure tracing and a dip-plateau ventricular pressure tracing are characteristic of chronic constrictive pericarditis. Cardiac tamponade as well as chronic constrictive pericarditis produce a similar elevated right and left atrial, right and left ventricular end-diastolic pressures[104] (Fig.3d).

Serologial, molecular and other non-conventional methods

A number of non-conventional diagnostic methods are often resorted to for diagnosing EPTB. These test results are relied upon as "concrete evidence" to initiate or withold antituberculosis treatment. When many of these non-conventional methods are validated at the time of initial introduction, the criteria employed to define the "gold standard" for diagnosis against which these methods are standardised would include "a clinical presentation compatible with tuberculosis" and "good response to antituberculosis treatment". Subsequently, the same diagnostic tests are recommended for substantiating the clinical diagnosis. Further, the small sample size and the

Table V. Sensitivity and specificity of immunodiagnostic and molecular methods applied to the pleural fluid and cerebrospinal fluid

Diagnostic method	Pleural fluid	Cerebrospinal fluid
ELISA:		
Detection of antibody in the fluid		
Sensitivity	0.22 - 0.68[a]	0.60 - 0.90[b]
Specificity	0.90 -1.00[a]	0.58 - 1.00[b]
Detection of antigen in the fluid		
Sensitivity	0.48 - 1.00[c]	0.61 - 0.79[d]
Specificity	0.98 - 1.00[c]	1.00[d]
Molecular methods :		
Polymerase chain reaction		
Sensitivity	0.22 - 0.81[e]	0.50 - 0.90[f]
Specificity	0.77-1.00[e]	1.00[f]

[a]Data derived from references 203-207
[b]Data derived from references 208-210
[c]Data derived from references 205,211-213
[d]Data derived from references 214-216
[e]Data derived from references 217-220
[f]Data derived from references 221-223

Table VI. Sensitivity and specificity of some commonly used non-conventional diagnostic tests in the diagnosis of extrapulmonary tuberculosis

Test	Pleural fluid			Pericardial fluid			Cerebrospinal fluid		
	Cut-off ≥	Sensitivity	Specificity	Cut-off ≥	Sensitivity	Specificity	Cut-off ≥	Sensitivity	Specificity
ADA (IU/l)									
Villegas *et al*[224]	45.5	0.88	0.86	-	-	-	-	-	-
Reechaipichitkul *et al*[225]	48	0.8	0.81	-	-	-	-	-	-
Sharma *et al*[226]	35	0.83	0.67	-	-	-	-	-	-
	100	0.40	1.00						
Perez-Rodriguez *et al*[227]	40	0.89	0.92	-	-	-	-	-	-
Ocana *et al*[228]	45	1.00	0.97	-	-	-	-	-	-
Burgess *et al*[229]	50	0.91	0.81	-	-	-	-	-	-
Dogan[230]	-	-	-	50	1.00	0.83	-	-	-
Burgess *et al*[231]	-	-	-	30	0.94	0.68	-	-	-
Aggeli *et al*[232]	-	-	-	72	1.00	0.94	-	-	-
Gambhir *et al*[233]	-	-	-	-	-	-	8	0.44	0.75
Mishra *et al*[234]	-	-	-	-	-	-	5	0.89	0.92
IFN-γ									
Villegas *et al*[224]	6*	0.86	0.97	-	-	-	-	-	-
Wongtim *et al*[235]	240†	0.95	0.96	-	-	-	-	-	-
Sharma *et al*[180]	134†	0.89	0.97						
Burgess *et al*[231]	-	-	-	200†	1.00	1.00	-	-	-

***** U/ml
† pg/ml
ADA, adenosine deaminase; IFN-γ, interferon-γ

Table VII. Associated pulmonary/pleural disease in patients with various froms of extrapulmonary tuberculosis

Site	Abnormal chest radiograph (%)
Lymph node tuberculosis[40-42,52,180]	5-44
Pleural effusion[71,74,180,182]	30-50
Abdominal tuberculosis[186,236,237]	20-28
Pericardial[113]	32

Table VIII. Treatment regimens for patients with extrapulmonary tuberculosis

Treatment category	Intensive phase (daily or three times a week)	Continuation phase
Severe forms of EPTB	2HRZE (2HRZS)	6HE
(category I)	$2H_3R_3Z_3E_3$ ($2H_3R_3Z_3S_3$)	4HR
		$4H_3R_3$
Less severe forms of	2HRZ	6HE
EPTB (category III)	$2H_3R_3Z_3$	4HR
		$4H_3R_3$

EPTB, extrapulmonary tuberculosis; R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol; S, streptomycin
The number before the letters refers to the number of months of treatment. The subscript refers to the number of doses per week. Some authorities advocate a seven-month continuation phase with daily isoniazid and rifampicin (7HR) for category I patients with tuberculosis meningitis, military tuberculosis and spinal tuberculosis with neurological signs
Adapted from reference 4

lack of reproducibility of the tests in most studies render the information generated by these tests inconclusive[242]. It should be remembered that a positive non-conventional test may perhaps "rule in" a diagnsosis, but certainly a negative test cannot "rule out" a diagnosis of tuberculosis Thus, it is not suprising that the diagnosis of EPTB is often delayed or missed.

Immunodiagnostic methods

Applied to body fluids: Most often, enzyme linked immunosorbent assay (ELISA) for detecting mycobacterial antigens, antibodies and immunecomplexes in the blood and body fluids have been used in the diagnosis of EPTB. Some workers have advocated testing for a panel of antigens rather than single antigens[243]. There are numerous publications regarding the application of immunodiagnositc methods for the diagnosis of every form of tuberculosis ranging from sputum positive pulmonary tuberculosis to smear and culture negative EPTB at inaccessible body sites. However, ELISA based methods for the detection of mycobacterial antigens in body fluids have been resorted to most often for the diagnosis of neurological (CSF) and pleural tuberculosis (pleural fluid). The diagnostic yield of ELISA methods in the CSF and pleural fluid EPTB is listed in Table V.

Applied to blood: The diagnostic utility of serodiagnostic methods applied to the blood samples in patients with EPTB is controversial. In a study from India[244], the utility and efficacy of detection of antimycobacterial antibodies to A60 antigen in serum and/or CSF was analysed in 100 patients with various forms of EPTB such as neurotuberculosis, abdominal tuberculosis and others. The overall positivity rate for the test was 75 per cent . The positivity rate of the test in serum and/or CSF was 79.2 per cent in neurotuberculosis and 62.5 per cent for other forms of EPTB.

Table IX. Summary of recent randomised controlled trials of additional corticosteroid treatment in patients with extrapulmonary tuberculosis

Study	Patients	Treatment regimen employed	Comments
Pleural effusion:			
Wyser *et al* (1996)[251]	Prednisone (n=30) Placebo (n=36)	Rifampicin (10 mg/kg), isoniazid (8 mg/kg), pyrazinamide (25 mg/kg) and pyridoxine (25 mg/kg) daily for 6 months Oral prednisone (0.75 mg/kg/day) for up to 4 wk with gradual reduction over an additional 2 wk by 5 mg/day	Standard ATT and early complete drainage is adequate Addition of prednisone does not relieve symptoms earlier nor influence residual pleural thickening
Galarza *et al* (1995)[252]	Prednisone (n=57) Placebo (n=60)	Isoniazid 5 mg/kg and rifampicin 10 mg/kg daily for six months Oral prednisone (1 mg/kg/day), tapered off over 30 days	Corticosteroids do not influence the rate of reabsorption of the pleural fluid, the pleural sequelae, as well as lung capacity
Lee *et al* (1988)[253]	Prednisolone (n=21) Placebo (n=19)	Isoniazid 300 mg/day, rifampicin 450 mg/day, ethambutol 20 mg/kg/day for > 9 months oral prednisolone 0.75 mg/kg/day tapered gradually over the next 2 to 3 months	Corticosteroids, in conjunction with ATT will resolve the clinical symptoms more quickly and hasten the absorption of pleural effusion
Tuberculosis meningitis:			
Girgis *et al* (1991)[254]	Dexamethasone (n=75) Placebo (n=85)	Standardised ATT Adults: dexamethasone 12 mg/day; children: 8 mg/day tapered over 6 wk	The fatality rate, development of neurologic complications and permanent sequelae were significantly lower in dexamethasone group
Kumaravelu *et al* (1994)[255]	Dexamethasone (n=24) Placebo (n=23)	Standardised ATT Oral dexamethasone 16mg/day for 7 days; then 8mg/day for 21 days	Trend towards survival and milder sequelae with desamethasone treatment though the difference was not statistically significant
Pericardial tuberculosis:			
Strang *et al* (1987)[107]	Prednisolone (n=53) Placebo (n=61)	Daily streptomycin, isoniazid, rifampicin, and pyrazinamide for 14 wk followed by isoniazid and rifampicin for total a period 6 months	In the absence of a specific contraindication, ATT should be initially supplemented by steroids
Hakim *et al* (2000)[256]	Prednisolone (n=29) Placebo (n=29)	Rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months, followed by rifampicin and isoniazid for a further 4 months in standard doses Prednisolone (60 mg/day) tapered by 10 mg/week until completion at the end of the sixth week	Adjunctive prednisolone produced a pronounced reduction in mortality No difference in the rate of radiologic and echocardiographic resolution of pericardial effusion

ATT, Antituberculosis treatment

Table X. Complications and sequelae of extrapulmonary tuberculosis

Lymph node tuberculosis
Scars, sinuses
Tracheo-oesophageal fistula
Oesophageo-mediastinal fistula
Chylothorax
Chylous ascites
Chyluria
Pleural effusion
Pleural thickening, fibrothorax
Empyema thoracis
Empyema necesstantis
Neurological tuberculosis
Raised intracranial tension, cerebral oedema, stupor
Basal meningitis with cranial nerve palsies
Focal neurological deficits
Hydrocephalus
Tuberculoma
Cerebral abscess
Visual loss
Arteritis leading to stroke
Endocrine disturbances
Hypothalamic disorders
Diabetes insipidus
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Internuclear ophthalmoplegia
Hemichorea
Spinal block
Spinal arachnoiditis
Abdominal tuberculosis
Subacute intestinal obstruction
Perforation and peritonitis
Haemorrhage
Fistula, sinus formation
Pericardial tuberculosis
Cardiac tamponade
Chronic constructive pericarditis
Bone and joint tuberculosis
Compressive myelopathy, paraplegia
Genitourinary tuberculosis
Infertility
Hydronephrosis
Pyonephrosis
Ureteric stricture, stenosis
Urinary bladder related abnormalities (thimble bladder)
Ocular tuberculosis
Visual Loss
Secondary glaucoma
Optic atrophy

In another study[245], the utility of detecting immunoglobulin G (IgG) and immunoglobulin A (IgA) against A60 antigen was studied in 42 patients with confirmed EPTB, none had clinical or radiological evidence of pulmonary involvement. In addition, 24 subjects with healed pulmonary or EPTB, 44 patients with a defined disease other than tuberculosis, and 88 healthy volunteers were studied. In patients with EPTB, the sensitivity and specificity of IgG and IgA tests were 0.738 and 0.961; and 0.69 and 0.936 respectively. When both the results were combined, the sensitivity was 0.809 and the specificity was 0.923[245]. Detection of lipopolysaccharide antigen (LPS) has also been found to be useful in the diagnosis of EPTB[207].

Adenosine deaminase: Adenosine deaminase (ADA) is an enzyme of purine metabolism which catalyses adenosine into inosine and is found in most human tissues particularly in the lymphoid tissues. ADA estimation has been found to be useful in the diagnosis of tuberculosis pleural effusion and ascites. High ADA levels have also been reported in effusions due to rheumatoid arthritis, lymphoma, chronic lymphatic leukaemia, empyema, parapneumonic effusions, and mesothelioma[74,228]. The sensitivity and specificity of ADA estimation in the diagnosis of EPTB is shown in Table VI.

ADA exists as two isoenzymes, ADA1 and ADA2, each with unique biochemical properties. The ADA1 isoenzyme is found in all cells with the highest activity in lymphocytes and monocytes, whereas ADA2 isoenzyme appears to be found only in monocytes[74,228]. In tuberculosis pleural effusion, ADA2 isoenzyme is considered to be primarily responsible for total ADA activity, while in parapneumonic effusions, the ADA1 isoenzyme is the major isoenzyme of ADA[77,229,246]. Thus, measurement of individual isoenzyme of ADA can enhance the diagnostic utility of ADA estimation in pleural effusions.

Interferon-γ: Interferon-y (IFN-γ) is a cytokine produced by activated T-lymphocytes. It plays a fundamental role in the immune response to tuberculosis. High levels of IFN-γ have been reported in tuberculosis pleural effusions[75,180,226,235], possibly related to *in situ* stimulation of CD4+ T

lymphocytes by tuberculosis antigens. A few studies have shown a better sensitivity and specificity of pleural IFN-γ levels as compared to ADA levels[180,226,235]. The sensitivity and specificity of IFN-γ in the diagnosis of pleural tuberculosis are shown in Table VI.

Other non-conventional tests: Lysozyme, a bacteriolytic protein which is widely distributed in body fluids and many cells is a marker of general inflammatory response. Lysozyme estimation has been found to help in identifying tuberculosis pleural effusion[74].

Molecular methods: Many of the molecular methods are research tools and are not widely available. Of these, polymerase chain reaction (PCR) has often been applied to the CSF and pleural fluid to detect various sequences representing the DNA of *M. tuberculosis* (Table V). Though the diagnostic utility of PCR in blood, other body fluids such as ascitic fluid, urine, pericardial fluid, pus from cold abscesses, and tissue biopsy specimens has been studied, available evidence is far from convincing. These test results must be interpreted in the appropriate clinical situation with caution. PCR alone must not be the sole evidence on which antituberculosis treatment is initiated or withheld.

Treatment

Antituberculosis drugs

Antituberculosis treatment is the mainstay in the management of EPTB. However, the ideal regimen and duration of treatment have not yet been resolved. While the RNTCP and other National Tuberculosis Programmes worldover which follow the World Health Organization's guidelines, directly observed treatment, short-course (DOTS) approach, advocates the use of short-course intermittent chemotherapy for patients with EPTB also, the reality seems different. According to the DOTS guidelines[4], patients with less severe forms of EPTB are categorised under treatment category III and those with severe form of EPTB are categorised under treatment category I. Antituberculosis treatment regimens for these categories are listed in Table VIII. While the six months treatment may be sufficient for many patients, each patient has to be individually assessed and, where relevant, treatment duration may have to be extended for a given patient[247]. Large scale prospective controlled trials with a large sample size are requried to sort out these issues. Patients receiving antituberculosis treatment should be carefully monitored for adverse drug reactions, especially drug induced hepatotoxicity[248,249].

Corticosteroids

The usefulness of corticosteroids in the treatment of EPTB is not well established and controversial[250]. When the diagnosis of tuberculosis is established with certainity, additional oral corticosteroid treatment may be helpful in selected patients with life threatening forms of EPTB. Evidence from randomised controlled trials regarding the usefulness of adjunctive corticosteroid administration along with antituberculosis drugs for the treatment of EPTB is depicted in Table IX.

Methodological issues such as varying antituberculosis drug regimens used, dosage schedule of corticosteroids, differences in the disease severity render meaningful comparison of the results from various studies difficult. In a recent publication, Prasad *et al*[257] critically evaluated the effect of corticosteroid administration along with antituberculosis drugs for the treatment of TBM. In their report, results of six randomised controlled trials involving 595 patients were evaluated. It was observed that steroids were associated with fewer deaths [relative risk (RR) 0.79; 95% confidence interval (CI) 0.65 to 0.97] and a reduced incidence of death and severe residual disability (RR 0.58, 95% CI 0.38 to 0.88). The authors concluded that adjunctive steroids might be of benefit in patients with TBM.

In a systematic evaluation of evidence from randomised and quasi-randomised trials evaluating the effects of adjunctive corticosteroids in patients diagnosed with tuberculosis pleural effusion published recently[258], three small trials (n=236) conducted in HIV-negative patients were studied. There was no difference in residual lung function between patients with tuberculosis pleural effusion who received corticosteroid treatment and those who did not at completion of treatment. The authors felt

that there is insufficient evidence to know whether adjunctive corticosteroid treatment is effective in patients with tuberculosis pleural effusion[258]. Prospective studies with large sample size involving HIV-positive and HIV-negative patients are required to clarify these issues.

Antiretroviral drugs

If co-existent HIV infection is there, the CD4+ and CD8+ T lymphocyte counts must be estimated and highly active antiretroviral treatment (HAART) must be administered when indicated[259]. Patients with EPTB especially those who are co-infected with HIV may develop paradoxical reactions[260] while on ATT. The paradoxical worsening and the immune reconstitution syndrome[177] when HAART treatment is started must be distinguished from poor response due to treatment failure, drug resistance or due to an alternate diagnosis.

When rifampicin is co-administered along with antiretroviral drugs, by inducing the hepatic P450 pathway, rifampicin may result in dangerously low levels of the antiretroviral agents. In this situation, the available therapeutic options include deferring HAART until standard antituberculosis treatment is completed; or, discontinuing HAART and treating with a standard short-course regimen; deferring or discontinuing HAART during the initial two month intensive phase when rifampicin is used; using a non-rifampicin containing regimen for the maintenance phase and using HAART among others[2,247].

Surgery

Surgery is often required to procure specimens for diagnostic testing and to ameliorate complications such as intestinal perforation and hydrocephalus where it may be life saving. Details regarding surgical management of EPTB is beyond the scope of this review.

Complications

Complications commonly seen in patients with EPTB are listed in Table X. High index of clincal suspicion and early institution of specific antituberculosis treatment can help in reducing the occurrence of these complications

In conclusion, high index of clinical suspicion, timely judicious use of invasive diagnostic methods and confirmation of the diagnsosis, early institution of specific antituberculosis treatment and close clinical monitoring for adverse drug reactions are the key to the successful management of EPTB.

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