UNIVERSITY OF KHARTOUM
Faculty of Medicine
Postgraduate Medical Studies Board

PATTERNS OF EXTRA-PULMONARY TUBERCULOSIS IN ADULT SUDANESE PATIENTS

By

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قال الله تعالى:

(وقل ربي زدني علماً)

صدق الله العظيم
Dedication

To

my parents
ACKNOWLEDGMENT

I would like to express my sincere thanks and gratitude to my supervisor Prof. Abdel Gadir Mohammed Yousif Alkadaru, Dean of Faculty of Medicine University of Khartoum, for his meticulous supervision, continuous guidance, encouragement and for his very valuable advice throughout all stages of the study.

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I am also grateful for Mr. Hassan Ali for data analysis and Miss Widad A/Magsood for typing the thesis.
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tr>
<td>$^{99}$TC-MDP</td>
<td>$^{99}$Technitium-methylene diphosphonate</td>
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<tr>
<td>AD</td>
<td>Adenosine deaminase</td>
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<tr>
<td>ARI</td>
<td>Average risk of infection</td>
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<tr>
<td>BC</td>
<td>Before christ</td>
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<tr>
<td>BCG</td>
<td>Bacillus Calmette Guerin</td>
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<tr>
<td>C.T</td>
<td>Computed Tomography</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest X-ray</td>
</tr>
<tr>
<td>DOTs</td>
<td>Directly observed treatments</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>EX. Pul-TB</td>
<td>Extra-pulmonary tuberculosis</td>
</tr>
<tr>
<td>FMOH</td>
<td>Federal Ministry of Health</td>
</tr>
<tr>
<td>FNA</td>
<td>Fine needle aspiration</td>
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<tr>
<td>GIT</td>
<td>Gastrointestinal tract</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<tr>
<td>INH</td>
<td>Isoniazid</td>
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<tr>
<td>IUAT-LD</td>
<td>International Union Against Tuberculosis and Lung Disease</td>
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<td>MTB</td>
<td>Mycobacterium tuberculosis</td>
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<td>NTP</td>
<td>National Tuberculosis Program</td>
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<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PDD</td>
<td>Purified protein derivatives</td>
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<tr>
<td>PZH</td>
<td>Pyrazinamid</td>
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<tr>
<td>S1</td>
<td>Sacroiliac joint</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
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<td>WHO</td>
<td>World Health Organization</td>
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ABSTRACT

Tuberculosis is found worldwide, but it is particularly common in Africa and Asia. The prevalence of tuberculosis increases with poor social conditions, inadequate nutrition and over crowding. The impact of tuberculosis in the developing world has been magnified in the past 20 years by the emergence of HIV pandemic\(^\text{(10)}\).

This study is carried out as trial to evaluate the clinical presentations of extra pulmonary tuberculosis, to
assess methods used in the diagnosis, and to identify factors that may predispose to the disease.

In this study 100 patients of different types of extra-pulmonary TB were enrolled. Abdominal TB was found to be the commonest (37%), followed by tuberculous lymphadenitis (20%). TB of the skeleton and that of the pleura accounted to (19%) and (9%) respectively, while CNS TB was found in (4%) of the study. Genitourinary, pericardial and miliary TB each was observed in (3%) of the cases. Cutaneous TB was the least encountered, occurring in only 2 of the 100 patients.

Clinical manifestations generally depend on the organ involved in addition to the general symptoms such as fever, weight loss and night sweat. Ascites was the commonest presentation of abdominal TB whereas enlarged lymph nodes with or without sinus formation were the commonest presentation of tuberculous lymphadenitis.
Affection of the dorsal spine with or without kyphos formation was the remarkable feature of spinal TB. Pleural tuberculosis presented mainly with unilateral pleural effusion. Signs of space occupying lesion were the main mode of presentation of CNS tuberculosis as well as tuberculous meningitis. Pericardial tuberculosis presented with effusion in two patients while in one patient it presented with constrictive pericarditis.

In most patients the diagnosis was made on clinical grounds in addition to the presence of a high ESR and a positive Mantoux test as well as other specific investigations such as ascitic, pleural, pericardial and cerebrospinal fluids analysis. Tissue histopathology was obtained in a minority of patients (38%) and in all of them it showed the specific features of tuberculosis. Most patients did not receive BCG vaccination. HIV screening test was done for 56 patients and it was positive in 18 of them. Pulmonary tuberculosis can co-exist although not commonly with extra-pulmonary TB and in fact
sputum for acid alcohol fast bacilli was positive in 4 of the enrolled cases.
لا يمكنني قراءة النص العربي بشكل طبيعي.

يرجى تقديم نص يمكنني قراءته بشكل طبيعي.
إصابة الفقدان أفضل إذا كان مادة الأكسجين قاعداً.

وقد يحدث احتمال مع الظهير الألم في القلعة.

وقد يكون في الصراع الرئيسي السريري الصورة تتمثل الظهير الفقدان العظمي بالسل.

والبولير السريري يتألف من النازحي والتهاب الرأس ضغط ارتفاع الجهاز اللبلي في الأندية.

والصدب SCOPE اللفحة الإصابة الرئيسي السريري الصورة.

الدم ترسب ارتفاع والسفيرة الحالة على التشخيص استناداً إلى الأنواع هذه كل في المناعي الفحص و(In)

مثل الفحص البصري، ال]? (إلى الاضفية، الإشعال،

السائلى تحليل الظهير والإشعال،

البريتوني،

الكوسيلة الرضمية.

وقد يكون في القدرة بالمرض.

قبل مدة تطعيم المرضي معتوم.

فادي الإيدز الفحص 38 المرضى حيث شاعة غير فقط المرضي أربعة في وجدت 18 الريوي بالمتزامنة الإصابة، المرضي حديثاً إفادة الريوي النازحي للتهاب الياكسينة.

15.5 أخذ SCOPE وظائف وFPD

U 38 المريض أحدث البصري 05، وحولية لبي جأشودا ودبي دودج

1.40 لتعرض له في فادي الاضفية، ويعود SCOPE 8 المريض عليه كمية

وسية بعد النزاع.
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INTRODUCTION

1.1. Definition

Tuberculosis is a communicable systemic disease caused by the tubercle bacillus, “mycobacterium tuberculosis”. Most infections are caused by inhalation of droplet nuclei containing virulent human strains of the tubercle bacillus. Infection by mycobacterium bovis through ingestion of unpausterlized cow’s milk is less common. Almost every organ in the body can be affected but involvement of the lungs accounts for more than 80% of tuberculosis cases. (1)

1.2. Brief history of Tuberculosis

Mycobacterium tuberculosis has been present in the human population since before christ as antiquity- fragments of the spinal column from Egyptian mummies 2400 before christ (BC) show definite pathological signs of tubercular decay.

Exact pathological and anatomical descriptions of the disease began to appear in the seventeenth century. In his Opera Medica of 1697, Sylvius was the first to identify that actual tubercles are consistent and characteristic changes in the lungs and other areas of consumptive patients. He also described their progression to abscesses and cavities. Magnet described the pathological features of miliary tuberculosis in 1702. (2)
In 1720, the English physician Benjamin Markn was the first to guess, in his publication, a new theory of infection, that TB could be caused by “wonderfully minute living creatures”, which, once they had gained a foothold in the body, could generate the lesions and symptoms of the disease.

In 1865, the French military doctor Jean-Antoine Villemin single handedly demonstrated that infection could be passed from humans to cattle and from cattle to rabbits.\(^{(2)}\)

In 1882, Robert Koch discovered a staining technique that enabled him to see Mycobacterium tuberculosis. These efforts were reinforced by the observation of the Italian Forlanini, that lung collapse tended to have a favorable impact on the outcome of the disease. With the introduction of artificial pneumothorax and surgical methods to reduce the lung volume, the depressing era of helplessness in the face of advanced TB was over, and active therapy had begun.

Another important development was provided by the French bacteriologist Calmette, who together with Guerin, used specific culture media to lower the virulence of the bovine TB bacterium, creating the basis for BCG vaccine, which is still widely used today. Then in the middle of world war II, came the final breakthrough, the chemotherapy the greater challenge to the bacterium that had threatened humanity for thousands of years.\(^{(2)}\)
1.3. Epidemiology:

Tuberculosis (TB) continues to be a devastating disease worldwide and is believed to be present in about one third of the world population. It is estimated that about 8 million new cases of TB and 2.6 to 2.9 million deaths from this disease occur annually around the world.\textsuperscript{(3)}

1.4. Tuberculosis in Sudan:

In Sudan the first published reports about TB were done by Cummins (1908 –1911) who studied TB in the Egyptian Army. He noticed that the incidence of TB among Sudanese soldiers was 3.7/100, which was higher than that for Egyptian soldiers. Cummins observation was accompanied by an almost complete absence of the disease among Sudanese tribes in their natural habitat, and by corresponding absence of TB in Sudanese cattle.\textsuperscript{(5)}

With the onset of the 2\textsuperscript{nd} world war (1940) the incidence of tuberculosis started to increase as a result of increased incidence among troops serving abroad. The disease was more common in Eritrea and Ethiopia, which had more contact with Sudan during the war than before. The disease was detected among farmers and unemployed groups, it was also dominantly detected in young adults and middle age people.\textsuperscript{(6)} By the end of 1950 the Sudan association for prevention of tuberculosis was formed to provide some voluntary assistance in domiciliary care.
The best indication of the magnitude of tuberculosis in Sudan is the average annual risk (ARI) which is the proportion of the population that is likely to be newly infected over a period of one year.

The ARI derived from the studies of the prevalence of tuberculin positivity, was at 1.9% and 1.8% in 1976 and 1986 respectively.(1)

The reported ARI of 1.8% represent the average, that can be used at the central level for program planing and treatment. Thus the estimated number of total new cases per year is supposed to be 50,218 as the estimated population of Sudan 1998 is 27,8900,000 while the detected cases in 1998 were 22,762 with detection rate coverage of 43.6%. This low rate of detection is an alarming parameter which high lights the need of a lot of effort for case detection and treatment in different areas in Sudan.(7)

1.5. National Tuberculosis Program (NTP):

Because of its extent, TB is categorized as a major health problem in Sudan. According to the Federal Ministry of Health (FMOH) statistics tuberculosis as a leading cause of morbidity, ranking the fourth of causes of out patients visits, third reason for hospital admission, fourth cause of hospital deaths and accounting for 16% of all hospital deaths. (8)

For the above-mentioned reasons, the national tuberculosis programs (NTP) was first Launched in 1996 following the WHO support of this concept.
Before 1990 Sudan national tuberculosis control existed but it was hospital based and poorly implanted. Cure rate was 30% and case detection was 38%. Up to 1993 regular monitoring of treatment was limited to pilot areas. The program with other International Union Against tuberculosis and Lung Disease (IUAT-LD) collaborative programmers has fully adopted the WHO policy package of tuberculosis control. The cure and case detection rates rose to 92% and 44% respectively.

Directly observed treatment short course (DOTs) has been initiated in 1995 covering 66% of patients, with conversion rate of 91% and cure rate of 87%. The aim of NTP is to reduce the incidence of tuberculosis until it is no longer a health problem, by diagnosing and treating effectively as many tuberculous patients as possible, especially those with sputum positive.

Pathology and Immunity:

Human response in tuberculosis may be either protective leading to resolution of disease or tissue destroying leading to pathological characteristic of active disease.\(^9\) While the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually, fewer the 10 percent) reach the alveoli. There, non-specifically activated alveolar macrophages ingest the bacilli.\(^{10}\) The initial lesion of tuberculosis occurs at the site of implantation of the bacillus, usually the lung, skin or alimentary tract including the tonsils. Implanted bacilli are ingested as mentioned by polymorphs, and macrophages some of which migrate to the draining lymph nodes where secondary lesions develop causing nodal enlargement. The initial pulmonary lesion the Ghon focus together with hilar lymph adenopathy form, the primary complex of Ranke.\(^{9,10}\)
characteristic histological lesion of tuberculosis is the granuloma which consists of a chronic compact aggregation of activated macrophages (epitheliod cells), some of which fuse to form, multinucleated giant cells. The primary complexes often heal with calcification. (9,10,11,12,13)

**Post primary tuberculosis:**

This results from reactivation of quiescent, endogenous, primary infection or from exogenous reinfection. Reactivation usually occurs in the upper lobes of the lungs perhaps because of a higher oxygen tension at that site. (9,11) In contrast to primary disease extensive caseous necrosis occurs in the lesions, due in part to release of tumor necrosis factor from activated macrophages and may lead to the development of large tumor like masses termed tuberculomas. It has been shown that sequential activation of macrophages by interferon and calcitriol prime them for release of tumour necrosis factor that a potent trigger for such release is lipoarbinomannan, amycobacterial cell wall component. Being anoxic and acidic, the tuberculomas contain very few acid fast bacilli. Release of proteases by macrophages softens or liquefies the caseous material so that if the lesion erodes into a bronchus, the liquefied material is discharged and a cavity will be formed. (9)

Dissemination of bacilli to regional lymph nodes and more distant organs is uncommon in post primary disease, but bacilli may spread directly via air passage from cavities to other parts of the lung and larynx. Bacilli in swallowed sputum may cause an undetermined lesion in the alimentary tract. (9,12)

**Types of Extra-Pulmonary Tuberculosis:**

1. **Pleural tuberculosis:**

Pleural tuberculosis is a major treatable cause of exudative pleural effusion. (14) Among extrapulmonary presentation of TB, pleural effusion is second only after TB lymphadenitis. (15) In one study, the frequency of pleural effusion in TB patients was approximately 31%. (16,17)

Pleural tuberculosis is more common among men. The effusion occurred on average at young age, with no preference for either the right or left side. It normally affects no more than two thirds of the hemithorax, and it is generally unaccompanied by pulmonary infiltrates. (19)

The pleura may be affected in three different ways:

1. Effusion which develops within a few months of primary infection in children and young adults.
2- Effusion developing as a result of lung disease in older adults. Rarely may this go on to purulent effusion (empyema).

3- Rupture of tuberculous cavity and escape of air into the pleural space, with resultant hydropneumothorax.

**Primary pleural tuberculosis:**

Traditionally, pleural TB has been considered a manifestation of primary TB seen largely in children and even some authors used this finding as a criterion for primary tuberculosis.\(^{(14,15,22)}\)

The current hypothesis for pathogenesis of primary pleural effusion is that sub pleural caseous focus in the lung ruptures into the pleural space within 6 – 12 weeks after primary infection.\(^{(14,16,19,20,22)}\) Mycobacterial antigens enter the pleural space and interact with T- cells previously sensitized to mycobacteria, resulting in a delayed hypersensitivity reaction and accumulation of fluid.\(^{(16)}\) The fluid is generally exudate but may be serousanguineous and usually contains few tubercle bacilli.\(^{(14)}\)

Commonly, effusion in primary TB pleuritis goes unnoticed and resolves spontaneously in 90% of cases.\(^{(14,18,22)}\) 65% of untreated patients develop active pulmonary or extra-pulmonary disease within five years, if not treated.\(^{(14,19,22,23)}\)

**Post- primary (reactivation) TB pleurisy:**

TB pleurisy can occur from reactivation at any time after infection.\(^{(16)}\) Reactivation may occur if the patient’s immunity is lowered.\(^{(20)}\) Coexisting underlying disease such as pleural malignancy which can commonly produce pleural effusion may hamper establishment of the correct diagnosis.\(^{(14)}\) The chest-x-ray shows a unilateral, small to moderate pleural effusion, although massive effusion have been noted.\(^{(24)}\) Parenchymal disease can be detected radiographically and by CT scan in most patients. Infiltration may be seen in the upper lobes or superior segments of the lower lobe. Parenchymal scaring may exist in the upper lobe and that is typical of TB reactivation. The effusion is almost always ipsilateral to the infiltrate and is a mark of active parenchymal disease.\(^{(24)}\)

**Pleurisy with effusion complicating miliary TB:**
Heamatogenous dissemination occurs in miliary TB.\textsuperscript{(20)} TB pleural effusion may rarely result from heamatogenous dissemination or contamination by adjacent lymph node.\textsuperscript{(14)} Pleural effusions occur in 10 to 30\% of cases of miliary tuberculosis. These may be associated with other progressive extra-pulmonary foci and involvement of other serous membranes. There is usually a history of gradual onset of fever, malaise and weight loss over week’s.\textsuperscript{(20)} Sometimes there is enlargement of the liver and the spleen. Chest x-ray may show diffuse, evenly distributed, small shadows. The effusions may be massive or bilateral in miliary TB.\textsuperscript{(22)} TB skin test may be negative and sputum smear is usually negative too.\textsuperscript{(20)}

\textbf{Tuberculous empyema:}

TB empyema represents a chronic, active infection of the pleural space.\textsuperscript{(25)} The inflammatory process may be present for years with a paucity of clinical symptoms. It is a rare complication of TB and characterized by the presence of thick pus, and the visceral pleura is usually calcified.\textsuperscript{(16)}

TB empyema is usually associated with evidence of pulmonary parenchymal disease on chest films.\textsuperscript{(18)} The fluid is thick and cloudy and may contain cholesterol, causing the fluid to look like chyle. (pseudochylous effusion).\textsuperscript{(18)} This is a rare complication in patients with chronic TB pleuritis.\textsuperscript{(16)}

Analysis of pleural fluid usually demonstrates triglycerides level below 110 mg/dl but the cholesterol level is usually elevated about 200mg/dl and frequently there are cholesterol crystals. TB chylothorax should be treated with anti TB regimen even if there is no evidence of active TB. The pleural fluid is grossly purulent.\textsuperscript{(25)} and usually has a high TWBC count nearly all of them lymphocytes.\textsuperscript{(18)} Acid fast smear and mycobacterial cultures are usually positive which makes pleural biopsy unnecessary. \textsuperscript{(16, 17, 18, 23)}

The clinical presentation of TB pleurisy may be subtle or abrupt and severe.\textsuperscript{(22)} The symptoms most commonly reported are cough (71-94\%), fever (71-100\%), chest pain (78-82\%) and dyspnea.\textsuperscript{(17)} The cough is usually non-productive particularly when active pulmonary lesions are not present.\textsuperscript{(26)} Night sweats, chill sensation, dyspnea, weakness and weight loss are common complaints. The average duration of symptoms before presentation is about 14 days for primary TB and 60 days in reactive disease.\textsuperscript{(27)} The patients with TB pleural effusion and HIV are symptomatic for a longer period and have additional symptoms such as tachypnea, night sweats, fatigue, diarrhea and have more chance
for hepatomegaly, spleenomegaly and lymphadenopathy. Negative skin test has been reported in up to 30% of immuno-competent and in up to 50% of HIV infected patients. Physical examination reveals findings related to pleural involvement including splinting due to pain and reduced breath sounds and percussion dullness overlying the effusion. Pleural friction rub is reported in 10% of patients.

Tuberculous pleural effusion may resolve over a period of several months (2-4) without treatment.\(^{15,22}\) Treatment of hypersensitive variety of T.B pleural effusion consists of a standard antituberculous drug regimens. The current recommendations for all pulmonary and extra-pulmonary T.B is a six month regimen with first phase of isoniazid (INH), rifampin (R) and pyrazinamide (Z),\(^{15}\) and a second phase of INH and (R) for the next four months.\(^{16}\)

**Abdominal tuberculosis:**

**Abdominal tuberculosis accounts for 0.8-10% of all hospital admission.**\(^{28}\) Any portion of the gastrointestinal tract may be affected by tuberculosis. Various phagocytotic mechanisms are involved such as swallowing of sputum with direct seeding or (rarely) ingestion of milk from cows affected by bovine tuberculosis.\(^{10}\) In adults gastrointestinal tract tuberculosis accounts for two-thirds of abdominal tuberculosis. In children however, the involvement of peritoneum and lymph nodes is more common than gastrointestinal tuberculosis.\(^{29}\) 85-90% of patients have tuberculosis affecting caecum. Abdominal pain, at times similar to that associated with appendicitis, diarrhoea,
constipation and palpable mass in the abdomen are common findings at presentation.\(^{(30)}\) Fever, weight loss and night sweats are also frequent.

Secondary involvement of the appendix from iliocecal tuberculosis is uncommon and forms 1.5 – 3\%.\(^{(31,32,33)}\) Multiple sites in the same patient may be involved.\(^{(34)}\) Involvement of the GIT may occur in absence of any discernible tuberculosis lesion in chest x-ray. There are three clinical types of tuberculous appendicitis, which have been described in the literature.\(^{(31)}\) The first type presents as an acute form. Indistinguishable from pyogenic appendicitis, until histopathologically proved. The second clinical type is a chronic form, presenting with vague pain, vomiting, diarrhoea and a mass at the iliac fossa. The third type is a latent one found accidentally on histopathologic examination. Differential diagnosis from other conditions such as Crohn’s disease and lymphoma may be difficult even with experienced observers.\(^{(35,36)}\)
The presence of granuloma with Langhan’s cells, epitheliod cells, and response of the patient to treatment is also suggestive. Though tuberculosis is a common cause of intestinal stricture in the developing counties, the incidence of associated enteroliths as reported in the literature is very low.\(^{(38)}\)

Tuberculous peritonitis is the 6\(^{th}\) most common site of extrapulmonary TB in the United States, followed by lymphatic, genitourinary, bone, joints, miliary and meningeal involvement.\(^{(39)}\) It results from reactivation of latent tuberculosis foci in the peritoneum, seeded previously from haematogenous spread from a primary infection in the lungs. Tuberculous peritonitis is associated with active tuberculosis in 4\% to 21\% of cases.\(^{(40)}\) The contiguous spread from tuberculous lesions in the intestine and fallopian tubes is relatively infrequent. Tuberculous peritonitis is divided into three-types.\(^{(41)}\) First, the wet type which is the most common type is characterized by large amounts of free or loculated viscous fluid. Second, the fibrotic fixed is less common, has large omental masses, matted and tethered bowel loops and mesentery, and, occasionally, loculated ascites. Third, the dry or plastic type is characterized by caseous nodules, fibrous peritoneal reaction and dense adhesions.\(^{(41)}\)

Peritoneal tuberculosis can be seen at any age and slightly more prevalent in women. Its onset is insidious with symptoms for several weeks to months.\(^{(40)}\) These include abdominal swelling due to ascites (65-100\%), fever (54-100\%), abdominal pain (36 – 96\%), weight loss (37 – 87) and diarrhoea (36 – 96\%).

The ascitic fluid is oxidative in nature (protein > 3 g/dl) and serum ascitic albumin difference is <1.1 g/dl.\(^{(40)}\) The total white blood cells count is usually 1.5-4.0×1.000/mm\(^3\) with lymphocytic predominance.\(^{(40)}\)

The available diagnostic tests for tuberculous peritonitis include paracentesis with acid-fast smear and culture, laparoscopy with directed biopsy, blind percutaneous peritoneal biopsy and diagnostic laparotomy. A new test measuring adenosine deaminase activity in the ascitic fluid has been
described, but it is not commonly available.\textsuperscript{(42)} This enzyme catalyzes the break down of purine bases from adenosine to inosine. The response of cell mediated immunity to M. Tuberculosis in the ascitic fluid results in stimulation of lymphocytes. The T. Lymphocyte increases adenosine deaminase level $>33\text{ u/l}$ in the ascitic fluid with a sensitivity and specificity of 100% and 95% respectively.\textsuperscript{(42,44,45)} A cut off $>33\text{ u/l}$ eliminates false positive tests resulting from cirrhosis or malignancy.\textsuperscript{(48)} In cirrhotic patients, the adenosine deaminase concentration is significantly lower $(14+10.6\text{ u/l})$.\textsuperscript{(42)} The value of adenosine deaminase testing patients with acquired immuno-deficiency syndrome who have extra pulmonary tuberculosis needs to be evaluated.

The finding on CT and ultrasonography of the abdomen are non-specific and include high-density ascites, adenopathy and mesenteric thickening.\textsuperscript{(43)} The overall sensitivity of CT for predicting tuberculous peritonitis was 69%. The ultrasonographic finding suggesting tuberculous peritonitis are the presence of fine fibrous strands in the ascitic fluids, localized ascites, and caseous or calcified lymph nodes.\textsuperscript{(41)}

Polymerase chain reaction (PCR) is another technique that may be helpful in the diagnosis of peritoneal tuberculosis.

The diagnosis of tuberculous peritonitis is made in less than 3% of cases by using acid fast stained smear of ascitic fluid.\textsuperscript{(49)} The ascitic fluid culture for M. Tuberculosis provided diagnosis in less than 20% of the cases in several trials.\textsuperscript{(40)} However, one series reported a diagnostic yield of 66% and furthermore the ascetic fluid culture may take as long as 4 to 8 weeks.\textsuperscript{(40)} The yield of ascetic fluid culture can be increased to 83% by culturing one litre of ascetic fluid concentrated using centrifugation.\textsuperscript{(40)}

Blind percutaneous peritoneal biopsy is not as accurate as laproscopy with directed biopsy. Fatality has been reported with blind peritoneal biopsy.\textsuperscript{(40)} However, the overall complication rate is low.\textsuperscript{(40)} Laproscopy with directed biopsy can provide presumptive diagnosis in 85% to 95% of patients.\textsuperscript{(40)} The peritoneal biopsies during laproscopy detect caseating granulomas in 85% - 95% of cases.\textsuperscript{(40)} Laproscopy is a safe procedure with a complication rate of 3%. The complications include bowel perforation, intraperitoneal bleeding requiring transfusion, subcutaneous haematoma and death.\textsuperscript{(40)} A patient with unknown large volume ascites is the easiest and safest to laprooscope. Using mini- laproscope, a bedside procedure with instantaneous return can be done. The finding of a
granuloma is characteristic of tuberculous peritonitis. Specimens are readily available for biochemical, microbiologic and histological evaluation. Besides, the low yield of an acid-fast stained smear, culture of the ascitic fluid may take from 4 to 8 weeks. High yield procedures, like blind peritoneal biopsy, laparoscopy with directed biopsy and minilaparotomy with peritoneal biopsies, are expensive, require expertise, have associated morbidity and mortality and may not be easy to do in critically ill patients.

Early recognition of peritoneal tuberculosis is the key to successful management of this entity. Patients with clinical presentation suggestive of peritoneal tuberculosis should have either a diagnostic work up using high yield tests or trial of a tuberculosis therapy with periodic clinical evaluation.

**Tuberculous lymphadenitis: Scrofula:**

The word scrofula comes from Latin for glandular swellings and from French for full necked sow.\(^{(46,47)}\)

Tuberculous lymphadenitis is the most common cause of lymph adenopathy in developing countries.\(^{(48,49,50)}\) This is the most common type of extrapulmonary TB. Cervical lymph nodes are most frequently affected (75%).\(^{(51)}\) Patients classically present between 20-40 years of age and there is slight female predominance, F : M (1.2-2 : 01). HIV infection increases the likelihood of developing active TB and lymph node involvement. Tuberculous lymphadenitis was seen in 23/65 (39%) HIV-positive TB cases versus 0/65 HIV negative cases in one study from Spain.\(^{(52)}\)

Most cases are thought to represent a reactivation of the initial lymphatic spread of primary pulmonary infection, although this assumption has not been confirmed even using newer molecular epidemiological tools. The disease is usually unilateral (60%), and cervical in location (75%). The most common site is along the upper border of sternocleidomastoid muscle where it presents as painless firm masses growing over months. Draining sinuses are uncommon (5%). Classically patients with tuberculous lymphadenitis are described as having systemic symptoms such as fever, weight loss, fatigue and malaise. However, a review of the recent literature suggests that many patients are asymptomatic. The purified protein derivatives (PPD) is almost always positive (74% – 100%).

The differentiation between cervical lymphadenitis due to *Mycobacterium tuberculosis* versus atypical mycobacterium is important because treatment strategy differs (medical, surgical). Atypical mycobacterium (*Mycobacterium scrofulaceum, M. avium* intercellular and *M. kansassi* in US)
frequently causes cervical lymph-adenitis, 95% to 98% of mycobacterial lymphadenitis in U.S adults is
due to *Mycobacterium tuberculosis*, whereas 86-92% of mycobacterial lymphadenitis in U.S
children is due to atypical mycobacteria. Using the size of PPD reaction has been suggested as
means of differentiating, but this is not recommended based on recent data describing non-
tuberculous mycobacterial lymphadenitis in healthy Israeli children associated with a median PPD of
15.5 mm.

Excisional biopsy has traditionally been the standard for making a diagnosis of tuberculous
lymphadenitis. However, it can be associated with significant morbidity as well as delay in diagnosis
since it involves surgical consultation. Over the last few years, fine needle aspiration (FNA) has been
established as the initial diagnostic test of choice based on its low morbidity and high clinical yield. Specimens are evaluated by cytopathology, AFB smear and mycobacterial culture. The cytological
criteria typically include either the presence of mycobacteria and/or epithelioid granulomas ±
multinucleate giant cells and caseating necrosis.

Prior to antituberculous chemotherapy, surgical excision of all involved lymph nodes was
the only treatment available. The relapse rate without medical therapy was greater than 80%. Incision and drainage (as opposed to complete excision) of tuberculous lymph nodes even with
chemotherapy may lead to chronic drainage fistula formation in approximately three quarter of cases,
even with medical therapy and therefore, should be avoided. Antituberculous drugs, when first
introduced, were used to supplement surgical excision. Case series reported up to one third of patients
“failed” medical management alone and required surgery in the prerifampin era. Medical therapy with
a regimen that includes INH and rifampin has now been shown to obviate the need for surgery in
almost all patients. Lymphadenitis due to atypical mycobacteria requires surgical excision.

In all forms of TB, therapy needs to be individually guided based on the sites of infection,
the organism burden, and the underlying immuno-competence of the host. Given that the relative
organism burden in tuberculous lymphadenitis is much lower than that seen in pulmonary disease, a 6
months regimen should suffice. The recommended regimen is INH/rifampin for 6 months, PZA for the
first 2 months, ethambutol until susceptibilities are known. This recommendation is based on small,
retrospective studies showing six months treatment regimen to be equivalent to nine months
regimens. HIV infected patients with cervical lymph node disease seem to be at higher risk for
relapse or recurrence, and therefore, may warrant empiric treatment for 9 months.\(^{(60)}\) Node enlargement
with pain, suppuration, and even sinus formation, as well as appearance of new nodes can occur in up
to 25-30% of cases, both during and after chemotherapy, and does not indicate failure of drug
treatment.

These events are thought to represent reactions to retained tuberculous antigens rather than
to controlled infection, and they usually subside spontaneously. Extending treatment duration or even
short courses of corticosteroids may be beneficial.\(^{(61)}\) Surgical excision of involved lymph nodes should
be reserved as a last resort for symptomatic relief. Up to 20% of patients will have residual, < 1 cm
lymph node 2 years after successful treatment.\(^{(58)}\)

**Genitourinary tuberculosis:**

Genitourinary tuberculosis is typically a late manifestation of previous pulmonary
infection. It develops in 3 to 5% of cases of pulmonary tuberculosis.\(^{(9, 62)}\) Rarely the primary infection is
derived from the gut. Spread via blood stream results in tuberculosis of the urinary tract. It involves the
kidneys, ureter, bladder or genital organs. Genitourinary tuberculosis frequently leads to the formation
of strictures in the urinary tract.\(^{(63,64)}\) These may lie within the renal pelvis, in the ureter or more rarely
in the prostate gland or urethra. By far the commonest site of obstruction is at or near the lower end of a
ureter.\(^{(62,63,64,65)}\) Antegrade spread from proximal urethral focus and tuberculous ureteritis cause
obliteration of the ureteric lumen by oedema and fibrosis.\(^{(66)}\) Genital urethral tuberculosis presents as a
superficial tuberculous ulcer on the penis or in the female genital tract, secondary to exposure to
mycobacteria during sex. The penile ulcer may cause cavenositis that extends to the urethra. This form
of TB involves the urethra and fallopian tube causing strictures.
Genitourinary tuberculosis often produces few symptoms until the bladder is involved. Then most patients develop irritative voiding symptoms and dysuria.\textsuperscript{(6)} Macroscopic haematuria and renal pain, occur in minority of patients. Fever, weight loss, anorexia and fatigue are uncommon.

Patients with genitourinary tuberculosis will usually have a positive tuberculin test.\textsuperscript{(62)} Serial early morning urine for acid fast smear (of at least 3 days) is specific but less sensitive tool. Serial urine cultures are still considered as gold standard for evidence of active disease with 100% specificity. The polymerase chain reaction (PCR) test has been extensively studied and proved highly sensitive and quick. Chest and spine radiograph may show older active lesions. Intravenous urogram shows abnormalities in about 90% of cases.\textsuperscript{(62)} Some degree of ureteric hold up dilatation is a common finding on intravenous urography. Inability to pass a ureteric catheter through the obstructed segment is considered as a definitive evidence of a fibrous stricture.\textsuperscript{(67)}

Antituberculous drug treatment regimens for pulmonary and genitourinary tuberculosis are similar.\textsuperscript{(62)} Steroids may also be used in an attempt to reduce fibrosis and prevent stricture formation.\textsuperscript{(68)} Sometimes results are exceptionally good, but more often they are disappointing.\textsuperscript{(9-65)} If a fibrous stricture is already present, it is unrealistic to expect much benefit from steroids. Transluminal balloon dilatation has been recommended if the stenosis can be negotiated by a guidewire.\textsuperscript{(66)} In cases where it is not possible, the obstruction can be relieved only by excision of the stricture and reimplantation of the ureter directly into the bladder using a non-refluxing technique.\textsuperscript{(68)}

**Miliary tuberculosis:**

Miliary tuberculosis is defined as the haematogenous dissemination of *Myobacterium tuberculosis* from an established focus, producing numerous lesions of approximately the same age and size, which usually progress to necrosis and caseation in multiple organs.\textsuperscript{(69)} The granulomas are linked to millet seed in appearance, hence the term miliary.\textsuperscript{(70)} In the prechemotherapy era, the disease was usually fatal and was most often an early complication of primary TB in children who seem to have decreased resistance to haematogenous spread.\textsuperscript{(71,72)} As well, it also followed recrudescence of an old primary lesion that discharged tubercle bacilli intravascularly.\textsuperscript{(70)} Five different reports have indicated and ever-increasing number of elderly patients affected by this kind of TB, in many of these aged patients.\textsuperscript{(73,74)} The diagnosis was made only at autopsy, since either concomitant illness masked the
clinical picture, or the disease presented in an insidious fashion unassociated with the typical hallmarks of the miliary TB. (73) Proud Foot et al., termed these later cases “cryptic” tuberculosis. (74)

The incidence of TB has increased in recent years. (75) In the developed countries, this has been linked to the human immunodeficiency virus infection. (76)

Presenting nonspecific symptoms such as: fever, anorexia, sweats and weight loss were most frequent. (77,78) Tachypena, rales, and altered mental status were the most commonly associated signs. (77,78) The mean duration of symptoms was 10.5 weeks. (78) Munt determined the mean duration of symptoms in his series to be 15.7 weeks, (79) while that of Biehl was 7.5 weeks. (80)

The laboratory findings are abnormal but non-specific. Haematological abnormalities are common in patients with miliary tuberculosis. The spectrum varies from pancytopenia with or without an aplastic bone marrow to rare leukemoid reactions, some were mistaken for leukaemia. (81,82) The haematological abnormalities observed included anaemia, thrombocytopenia, thrombocytosis, leukopenia and lymphopenia. (78,81) Elevated alkaline phosphatase and a significantly elevated ESR were seen in 67% and 39% respectively. Purified Protein Derivatives (PPD) was positive in almost half of the patients. (78) The demonstration of miliary lesions in chest radiography is an important clue for the clinical diagnosis of miliary TB. Sputum smear for AAFB is rarely positive, however, culture may be positive in 54% - 76% of patients. (79,83,84) Urine cultures may be positive in 25% of patients. (84) Lumber puncture should be done when indicated. Abnormal CSF is a strong pointer to the diagnosis. AFB can often be seen if large volumes are examined. Smears of body fluids are frequently negative for AAFB, however, routine cultures allow microbiological diagnosis in a significant proportion of patients. (78)

Routine cultures for MTB takes up to 8 weeks to become positive. Tissue biopsies are frequently needed to establish the diagnosis. The most frequent biopsy sites were bone marrow, followed by lymph node, transbronchial and liver. Identification of AFB in these biopsies was uncommon, however culture was more frequently positive. (78) Biopsy sample are often abnormal histologically. In patients with miliary TB lymph node biopsy is the invasive procedure with the highest yield. (69,86,87) Several authors have investigated the role of fibreoptic bronchoscopy in the diagnosis of miliary TB and found conflicting results.

The treatment of miliary TB has evolved dramatically over the past 50 years. Before the development of an effective antituberculous chemotherapy, the disease was fatal. Amberson was
quoted as saying in regards to miliary TB that “the prognosis is uniformly hopeless and treatment unavailing”. However, with the introduction of streptomycin, and later on isoniazid, rifampin, and the use of combination therapy, the mortality has dropped markedly in recent years. The American Thoracic Society (ATS) recommended 12 months therapy for patients with military TB. The regimen consists of isoniazid, rifampin and pyrazinamide for two months, followed by isoniazid and rifapin for 10 months. It is further recommended that ethambutol or streptomycin should be included in the initial regimen unless the results of drug susceptibility studies are available.

Gelb, et al, associated the poor outcome in patients with miliary tuberculosis with stupor and meningismus, to increasing age, cirrhosis, leukopenia and leukocytosis. Although no statistical tests were performed.

**Tuberculosis of the heart:**

Tuberculous infection of the pericardial membrane (pericardium) covering the heart is becoming more. The infection can result in accumulation of fluid around the heart and later on fibrosis of the pericardium. In industrial nations, the incidence of tuberculous pericarditis has decreased within the past three decades, but it remains a rare, but dangerous, disease with mortality of 20-40%. The incidence of tuberculous pericarditis among patients with pulmonary tuberculosis ranges from about 1% to 8%. Tuberculosis was diagnosed in only 4% of acute cases of pericarditis. Tuberculous pericarditis usually develops by retrograde spread from peribronchial, peritracheal or mediastinal lymphnodes. Less commonly, it occurs during miliary tuberculosis, but it may also develop from a focus in the spine or sternum.

The onset is abrupt, resembling acute idiopathic pericarditis, with weight loss, cough, dyspnea, chest pain, ankle oedema, fever, tachycardia, weakness, anoxia and night sweats.

Physical examination usually shows fever, tachycardia, pericardial friction rub, hepatomegaly, ascites, peripheral oedema and weak heart sounds. Tuberculous pericarditis in HIV infected patients, usually appears in situation of advanced immunosuppression and usually in the context of disseminated tuberculosis and as a first opportunist infection. Its presentation with cardiac tamponade is unusual and its high morbidity and mortality demand early diagnosis and therapy. Constrictive pericarditis is a relatively rare clinical manifestation nowadays.
The appropriate diagnostic work up and optimal therapeutic management of tuberculous pericarditis are not well defined.\(^{(98)}\) Traditional diagnostic tests for pericardial tuberculosis are insensitive and often require long culture periods and this has led to a more emphasis being placed on biochemical tests such as pericardial fluid adenosine deaminase (AD) and interferon (IFA) gamma levels. A cutoff point of 200 Pg/L for IFN-gamma results in sensitivity, and specificity of 100% for the diagnosis of pericardial TB\(^{(99)}\). The diagnosis of pericardial tuberculosis also can be made by detection of mycobacterium tuberculosis complex DNA in the pericardial fluid using a nested PCR assay.\(^{(100)}\)

Twelve-lead ECG is of supportive, but of not diagnostic value in cardiac tamponade resulting from tuberculous pericarditis.\(^{(101)}\) The chest x-ray shows cardiomegaly.\(^{(94)}\) Sometimes a pleural effusion may be detected in about half of the patients. However, the apices and hila of the lung are usually normal and pulmonary infiltrates or calcification are only present in a minority of patients. The tuberculin skin test (PPD) may be negative in as 30% of patients with tuberculosis.\(^{(90,93,102)}\)

The optimal management of tuberculous pericarditis includes an open pericardial window with biopsy, both for the diagnosis and to prevent reaccumulation of fluid. If a thickened pericardium is found during window procedure, early pericardiectomy is strongly encouraged.\(^{(103)}\) Corticosteriods probably offer some benefit in preventing fluid reaccumulation as well.\(^{(98)}\) No studies have addressed these issues specifically in HIV-positive patients.\(^{(98)}\)

Tuberculous involvement of the myocardium is relatively rare. Three district forms of myocardial involvement are recognized: nodular tubercles (tuberculoma) of the myocardium, miliary tubercles of the myocardium and an uncommon diffuse infiltrative type. The myocardium is involved by a haematogenous route, by lymphatic spread or contiguously from the pericardium. The diagnosis can be made by endomyocardial biopsy if clinical suspicion is strong and echocardiographic findings are suggestive. Antituberculous drugs may be curative.\(^{(104)}\)

Skeletal tuberculosis:

Skeletal tuberculosis constitutes 35% of extrapulmonary disease with the spine affected in 30-60% of cases.\(^{(105)}\) The thoracolumbar spine is most often affected with less frequent involvement of cervical and sacral spine.\(^{(105)}\) Unilateral sacroiliac (S1) joint involvement is not uncommon.\(^{(105,106)}\) Potts
disease presents in the mid thoracic spine and thoracolumbar junction. It results from the hematogenous spread of *M. tuberculosis*. The prevalence of spinal TB is likely to rise as the number of those infected with HIV rises. The primary focus for infection is different for different age groups. In a series of 499 patients, 31% showed a radiographically demonstrated source in the lung. Of these 78% were children. The remaining 69% showed a normal chest X-ray and were mostly adults. In the adult, silent foci such as kidneys, gut, and tonsils were the primary source.

Owing to the distribution of the vertebral arterial supply, involvement of adjacent vertebra are possible. When large vertebral segments or multiple segments with intervening normal zone are present, the paravertebral venous plexus of Batson is implicated. Bony changes are seen two to five months after infection. Usually the subchordral regions of the vertebral body are affected when the anterior and lateral portions of the vertebral body are affected, vertebral collapse occurs resulting in kyphosis and gibbus deformity. Involvement of the posterior vertebral body results in cavitation and an extradural mass. Kyphosis occurs in the thoracic spine while the lumber spine telescopes on its self as it collapses. The diseased spine is eventually destroyed, but at a lower rate than in cases of pyogenic infection. Tuberculosis can spread from spinal focus by direct extension through the disc space. Once a paravertebral abscess is formed, the disease can spread via anterior posterior longitudinal ligaments and extend to the pleural space. From the cervical vertebrae the disease can travel to the posterior triangle of the neck or retropharynx. The abscesses can also tract along fascial planes to create a psoas abscess or can extend posteriorly to form an extradural abscess. Clinically patients present with pain over the affected vertebrae, low grade fever, weight loss and chills. Duration of symptoms range from 2 weeks – 3 years with a mean of one year. The ESR may be elevated, and a positive skin test in 77 –100%. Significant number of smears and cultures of spinal biopsies may be negative.

A neurological deficit also occurs and affects 13% of patients. Years after resolution of the initial infection, stretching of the spinal cord over bony deformity can lead to paraplegia. Symptoms of tuberculous infection are distinct from those of pyogenic infection in that patients may be afebrile with a normal white blood cell count.
Plain films and tomography are useful for assessing vertebral destruction but they may be normal.\textsuperscript{(107)}

Technetium –99m methylene diphosphonate (MDP) bone scintigraphy, though invaluable, can remain positive for a very long time, which limits the value of this modality for following the response to therapy. Radio neucleotide imaging is valuable in detection and follow up of this disease. When it imaging is normal, one should obtain tissue specimen to confirm or exclude presence of disease.\textsuperscript{(110)}

The scientific basis for the clinical management of spinal tuberculosis has been well established by the British Medical Research Council Group and Hong Kong Surgeons. It is believed, however, that well-controlled basic and clinical studied are required if the incidence of unwanted complications of spinal tuberculosis is to be reduced further. Antituberculous agents are the main stay of management, with chemotherapy for 12 months preferred to short courses.

The standard is a combination of isoniazid, rifampin, and pyrazinamide, with or without ethambutol. Anterior surgery consisting of radical focal debridement without fusion does not prevent vertebral collapse. The major advantage of anterior arthrodesis is the decreased tendency for progression of the deformity.\textsuperscript{(108)} Patients who present late with deformity are candidates for anterior debridement and stabilization with corrective instrumentation. Posterior stabilization with instrumentation has been found to help arrest the disease and bring out early fusion. Posterior instrumented stabilization to prevent kyphosis in early spinal tuberculosis is indicated, however, only when anterior and posterior elements of the spine are involved particularly in children.\textsuperscript{(108)}

Tuberculosis can affect any joint, hips and knees being frequently affected. It may present as gradually worsening arthritis but is often mistaken for some other form of arthritis, such as monoarticular rheumatoid arthritis. Unlike most forms of arthritis, joint TB is most often monoarticular and the joint space will often be maintained.\textsuperscript{(111)} Tuberculosis of the foot and ankle is an uncommon presentation of skeletal tuberculosis. The uncommon site, lack of awareness, and the ability to mimic other disorders clinically and on radiography, leads to diagnostic and therapeutic delays.\textsuperscript{(112)} In early stages and when the disease is limited to bone, medical treatment leads to excellent healing and limited residual disabilities. Joint involvement occurs because of spread from a periarticular bony focus, and in the mid-foot may result in residual deformities. The most common radiologic findings is
that of osteoporosis, which may be intense: cancellous bone involvement may present as a cystic lesion with or without sequestrum. Computed tomography scans and magnetic resonance imaging are helpful examinations. Because the disease is paucibacillary, a positive acid-fast bacilli culture is rare and the diagnosis usually is confirmed by obtaining granulomatous tissue on biopsy. The treatment basically is medical, with surgical interventions being reserved for patients with intractable disease and as a salvage procedure for patients with deformed hind foot joints.\(^{(112)}\)

**Tuberculosis of the central nervous system (CNS):**

Tuberculosis of the central nervous system is a granulomatous infection, which predominantly involves the brain and meninges, but occasionally, it affects the spinal cord.

The development of CNS tuberculosis is a two step process. Initially, haematogenous spread from a primary focus, usually in the lungs allows the bacilli to seed in the meninges or brain parenchyma, resulting in the formation of small subpial or subependymal foci of metastatic granulomatous caseous lesions termed Rich foci after the original pathologic studies of Rich and MC Cordic.\(^{(113)}\) The second step is increase in the size of Rich focus until it ruptures into the subarachnoid space. The location of the expanding tubercle (i.e. Rich focus) determines the type of CNS involvement. Tubercles rupturing into the subarachnoid space
cause basal leptomenigitis. Those deeper in the brain or spinal cord parynychyma cause tuberculomas or abscesses. While an abscess or heamatoma can rupture into the ventricle, a Rich focus does not. Other manifestations of tuberculosis are tuberculous cerebritis, and pachymeningitis.⁽¹¹³⁾

The meningitis, usually causes communicating hydrocephalus, but it may also cause obstruction of the foramina of Luschka and Magendie, resulting in obstructive hydrocephalus. Vasculitis involving the lenticulostriate and thalamoperforating arteries may occur and cause small infarcts in the deep gray nuclei and deep white matter.⁽¹¹⁴⁾

Spinal cord infection is less common, but it results owing to spread of infection from intracranial meningitis, primary spinal meningitis in isolation as a result of a tuberculous focus on the surface of the cord rupturing into the subarachnoid space, or transdural extension of infection from caries of the spine. Sequele include arachnoiditis, or uncommonly, focal intramedullary
tuberculosis. In addition, a gross granulomatus exudate fills the subarachnoid space and extends over several segments. Vasculitis involving arteries and veins occurs, sometimes resulting in ischemic spinal cord infarction.

The main symptoms of tuberculous meningitis are fever, headache, seizures, meningism, drowsiness and confusion. Headache, meningism and mental status changes are much more common in the elderly while seizures are less frequent.\textsuperscript{(115)}

The British Medical Research Council developed a method for staging the severity of the disease:\textsuperscript{(116)}

- Stage I describes the early non specific symptoms and signs, including apathy, irritability, headache, malaise, fever, anorexia, nausea and vomiting, without any alterations in the level of consciousness.
• Stage II describes altered consciousness without coma or delirium but with minor focal neurological signs. Symptoms and signs of meningism and meningitis are present, in addition to focal neurological deficits, isolated cranial nerve palsies, and abnormal involuntary movements.

• Stage III describes an advanced state with stupor or coma, severe neurological deficits, seizures, posturing, and or abnormal movements.

Visual symptoms include visual impairment or blindness. Papilloedema is the most common visual effect of tuberculous meningitis.\(^{(114)}\) In adults, papilloedema may progress more commonly to secondary optic atrophy, provided the patient survives long enough. Other causes of visual impairment include chorioretinitis, optic neuritis, interneuclear ophthalmoplegia and occasionally, abrupt onset of painful ophthalmoplegia. Apart from papilloedema, fundus examination occasionally might reveal the presence of a retinal tuberculoma or a small grayish-white choroidal nodule, highly suggestive of
tuberculosis. These lesions are believed to be more common in miliary tuberculosis than in other forms of tuberculosis.\(^{(117)}\)

Patients with parynychmal tuberculomas often present with space occupying lesion.\(^{(117)}\) Tuberculomas have been reported in unusual sites such as cerebellopontine angle where they can closely mimic tumors leading to diagnostic confusion and sometimes inappropriate therapy. Tremors is the most common movement disorder seen in the course of tuberculous meningitis. Less commonly abnormal movements, including choreoathetosis and hemiballismus, have been observed, more so in children than adults. In addition myoclonus and cerebellar dysfunction have been observed. Deep vascular lesions are more common among patients with movement disorders.\(^{(116)}\)

The clinical picture in primary spinal meningitis is often characterized by myelopathy, with progressive ascending paralysis, eventually resulting in basal meningitis and associated sequele. A recent study in
India reported 10 cases diagnosed radiologically over a period of 16 years (1985-2000) of which 8 cases were confirmed histologically. All cases presented with motor and sensory involvement. Most common site of involvement was the dorsal cord followed by cervical, cervico dorsal and dorsalumber regions.\(^{(119)}\)

Hydrocehalus occurs in most patients who survive the first 4-8 weeks and is usually communicating due to obstruction of the cerebral aqueduct or fourth ventricular foramina by tuberculous exudate in the acute phase and be pachymeningitis in the chronic phase of the disease.\(^{(116)}\)

Infarction is common (>50% of patients) in the acute phase\(^{(114)}\) and results from a vasculitis that involves the pontine perforator, lenticulostriate, and thalamoperforator arteries. Small infarcts are common in the basal ganglia and brain stem, where they are responsible for the morbidity associated with the disease. These infarcts lead to mental retardation, stroke, and
blindness. Ventriculitis is a common complication and a major cause of morbidity resulting in hydrocephalus.

Mild to moderate hyponatremia is a common complication reported in up to 73% of cases of tuberculous meningitis, in some cases constituting a true syndrome of inappropriate secretion of antidiuretic hormone (SIADH). (120) The presence of hyponatremia combined with a negative Gram stain should strongly suggest a tuberculous cause in a patient with meningitis. (120)

The cerebrospinal fluid (CSF) is typically clear or slightly turbid and if left to stand, a fine clot resembling a pellicle or cobweb may form. This faintly visible “spider web clot” is due to a very high level of protein in the CSF (i.e. 1-8 g/L) typical of this condition. Haemorrhagic CSF also has been reported. (116) It typically shows elevated protein level, marked hypoglycemia and a pleocytosis, initially polymorphs then lymphocyte. (117)

Clinical diagnosis can be difficult, therefore, imaging has an important role in establishing the diagnosis of tuberculosis of the CNS. Skull radiographic findings
are usually normal. Rarely in healed tuberculous meningitis, faint parynchymal calcification is evident but this of course is a non specific finding. Chest x-ray shows evidence of old tuberculosis or a miliary pattern in more than half of the cases.\textsuperscript{(117)}

Although CT scan and MRI of the brain lack specificity they currently play pivotal role in the diagnosis of CNS tuberculosis and a lot of research is currently underway to improve both sensitivity and specificity. CT and MRI also help in monitoring complications that require neurosurgery.\textsuperscript{(121)} The characteristic CT-scan finding is a nodular enhancing lesion with a central hypodense lesion.\textsuperscript{(122)} Contrast enhancement is essential. Parynchymal cerebritis may cause hypoattenuation with little or no enhancement. Non caseating granulomas are homogeneously enhancing lesions. Caseaing granulomas are rim enhancing, if these have a central calcific focus, they may form a target like lesion. Granulomas may also form a miliary pattern with multiple finy nodules scattered
throughout the brain. All lesions are surrounded by hypoattenuating oedema. The differential diagnosis includes fungal infections, bacterial infections, neurocysticercosis and cerebral metastases. MRI gadolinium-enhanced T1-weighted images demonstrate prominent leptomeningeal and basal cistern enhancement. Deep grey matter and pontine infarction resulting from vasculitis are hyperintense on T-2 weighted images. Paranchymal cerebritis may show hyperintensity tuberculomas demonstrate various pattern.\(^{(122)}\)

It is important to note that conventional MRI may miss an early infarct and no MRI findings are pathognomic for tuberculosis. Electroencephalogram (EEG) findings were found to correlate with severity of meningitis and the degree of coma.\(^{(123)}\) Brain stem audiometry evoked potentials may be helpful in objective documentation of respective motor and sensory functions in patients with tuberculous meningitis and altered sensorium.\(^{(116)}\)
Antibodies against mycobacterium tuberculosis antigens were detected in the CSF of 87% of patients with clinical (culture –ve) tuberculous meningitis.\textsuperscript{124} Adot-immunobinding assay (Dot-ibe) has been standardized to measure circulating antimycobacterial antibodies in CSF specimens for the rapid laboratory diagnosis of tuberculous meningitis.\textsuperscript{125}

Excitatory amino-acids, aspartic acid and glutamic acid, GABA, glycine and tryptophan all were increased significantly in both tuberculous and pyogenic tuberculosis, whereas levels of taurine were decreased and levels of phenylalanine, nitrite and its precursor arginine were significantly higher in patients with tuberculous meningitis whereas they were unchanged in patient with aseptic meningitis.\textsuperscript{126}

The best antimicrobial agent in the treatment of TBM include isoniazid (INH) rifampin (RIF), pyrazinamide (PZA) and streptomycin (SM), all of which enter CSF readily in the presence of meningeal inflammation. Ethambutol (EMB) is less effective in meningeal
disease unless used in high doses. Usually intrathecal
drugs are not necessary. Treatment is best started with
INH, RIF and PZA. The addition of a fourth drug is
left to the choice of the local physicians and their
experience with little evidence to support the use of
one over the other.\(^\text{(127)}\)

Evidence concerning the duration of treatment is conflicting.
The duration of conventional therapy is 6-9 months,
though some investigators still recommended as many
as 24 months of therapy.\(^\text{(127)}\) The use of corticosteriods
in adult is controversial, they may be indicated in the
presence of increased intracranial pressure, altered
consciousness, focal neurological findings, spinal
block, and tuberculous encephalopathy.\(^\text{(127)}\)

Hyaluronidase has been used in spinal arachnoiditis with good
results.\(^\text{(128)}\)

In patients with evidence of obstructive hydrocephalus and
neurological deterioration who are undergoing
treatment for tuberculosis meningitis (TBM),
placement of a ventricular drain or
ventriculoperitoneal or ventriculoatrial shunt should not be delayed unless a mass effect is compromising vital structures. Surgical intervention is rarely required in the treatment of tuberculomas.\(^{(113)}\)

Prediction of prognosis is difficult but various clinical indices are used for predicting the outcome, such as level of consciousness, stage of meningitis, BCG vaccination, CSF findings and evidence of raised intracranial pressure.

**Cutaneous tuberculosis:**

Although 1 of 3 individuals on this planet is infected with *Tubercle bacillus*, the incidence of cutaneous TB appears low. In areas such as India or China where TB prevalence is high, cutaneous manifestation of TB (overt infection or tuberculids) are found in fewer than 0.1% of individuals seen in dermatology clinics.\(^{(129)}\)

In a 10-yeas (1983-1992) retrospective survey of patients seen in governmental dermatology clinics in Hong Kong, the detected incidence of cutaneous TB among patients was 179 per 267,089 (0.07%). Among patients with cutaneous TB, 15% had classic cutaneous TB (approximately 5% each of lupus vulgaris, TB verrucosa cutis, and
scrofuloderma), and 85% had tuberculids.\(^{(130)}\) Among the tuberculids, erythema induratum accounted for 93.3%.

**Clinical variants of cutaneous TB:**

- **Tuberculous chancre:**

  Primary-inoculation TB results from direct introduction of mycobacteria into the skin or mucosa of an individual who was not previously infected with TB or was immunized with the *M. bovis* strain bacille calmette-Guein (BCG). Since mycobacteria do not penetrate intact skin, initiation of infection almost always follows an injury, usually in children. Common sites include the face and other exposed skin. Tuberulous chancre are reported after ritual circumcision, tattooing, ear piercing, veni puncture, sexual intercourse, tooth extraction and after ingestion of milk contaminated with *M. bovis*\(^{(129)}\)

- **TB verrucosa cutis:**

  Is an indulent warty plaque that occurs after direct inoculation of TB into the skin of individuals perviously infected with *M. tuberculosis*. Farmers, butchers and veterinarians contract this form of re-infection TB from tuberculous cattle. Lesions most commonly occur on the hands and, in children lower extremities. Infection starts as an asymptomatic warty papule often mistaken for *Veruca vulgaris*. Lesions usually are solitary
and regional nodes are not affected unless secondary bacterial infection occurs—lesions may evolve and persist for years.(129)

- **Miliary TB of the skin:**

  It is a rare manifestation of fulminated miliary TB resulting from hematogenous spread of mycobacteria to multiple organs, including skin. The initial site of infection is usually pulmonary or meningeal. Tuberculin sensitivity is absent and bacillary load is high, which is consistent with an overwhelming infection. Currently, numorous instances of miliary TB of the skin are reported in immuno-suppressed individuals infected with HIV.(131)

- **Scrofuloderma:**

  This results from breakdown of the skin overlying a tuberculous focus, usually of lymph node, but also at the skin over infected bones or joints. Lesions present as firm, painless, subcutaneous nodules that gradually enlarge and suppurate then form ulcers and sinus tracts in overlying skin. Tuberculin sensitivity is usually marked. Spontaneous healing can occur but often takes years and is accompanied by the formation of hypertrophic scars.(129)

- **TB cutis orificialis:**

  This results from autointroduction of mycobacteria into the periorificial skin and mucous membranes in patients with advanced TB. Underlying disease can be pulmonary, intestinal or genitourinary TB.
Tuberculin sensitivity is strong. The tip and lateral margins of the tongue are affected most frequently; however, hard and soft palate lesions are also common. Auto-inoculation of tooth sockets can occur after extraction. Perianal skin, vulva, the urinary meatus, and glans penis are also described sites. Lesions start as red papules that evolve into painful, soft, punched out, shallow ulcers.\(^{(129)}\)

- **Lupus vulgaris:**

  This is a chronic and progressive form of cutaneous TB that occurs in tuberculin-sensitive patients. In most series it is the most common form of cutaneous TB and has the most variable presentation. Lesions appear in normal skin as a result of direct extension of underlying tuberculous foci, of lymphatic or haematogenous spread, after primary inoculation, BCG vaccination, or in scars of old scrofuloderma. Lesions are usually solitary, and in more than 90% of cases involve the head and neck. Small, sharply marginated, red brown papules of gelatinous consistency (apple gelly nodules) slowly evolve by peripheral extension and centreal atrophy into large plagues. Reappearance of new nodules within previously atrophic or scarred lesions is characteristic. Cartilage (nose, ears) within the affected area is progressively destroyed (lupus vortex) and bone is usually spared.

  Clinical variants are numerous and are seen in plague, ulcerating, vegetative, and nodular forms.\(^{(132)}\) In long standing lupus vulgaris,
squamous cell carcinoma can occur and be confused with the disease itself.

- **Tuberculids:**

  Tuberculids are symmetric generalized exanthemas in the skin of tuberculous patients, possibly resulting from hypersensitivity reaction to tubercle bacillus. Typically patients with tuberculids are relatively in good health and show positive tuberculin test.\(^{(129)}\)

- **Erythema induratum (Bazin disease):**

  Erythema induratum is a persistent or recurring condition associated with past or active TB lesions. It arises in small numbers as tender indurated plagues and nodules that may progress to ulceration and scarring. Erythema induratum often recurs for years.\(^{(129)}\)

- **Papulonecrotic tuberculid:**

  Papulonecrotic tuberculid occurs as a chronic and recurrent symmetric eruption of necrotizing skin papules appearing in clusters and healing with varioliform scars\(^{(129)}\)

- **Lichen scrofulosorum:**

  Lichen scrofulosorum is an eruption of asymptomatic, perifollicular, lichenoid papules affecting children and young adults with TB.\(^{(129)}\)
• **Histopathology:**

   All types show chronic granulomatous changes. The majority is infiltrated with epitheloid cells, with Langerhans and neutrophils in ulcerated lesions. Increased numbers of mast cells were seen in upper and lower dermis in two thirds of cases. Caseating necrosis was visible in half of the specimens while Ziehl-Neelsen stain was negative in most of cases\(^{(133)}\)

• **Treatment:** -

   Combination dug therapy should be given to all true cutaneous tuberculosis such as lupus vulgaris, tuberculosis verrucosa cutis and scrofuloderma. Contraversery exists about wheather tuberculids should receive multiple drug treatment or not.\(^{(134)}\)
OBJECTIVES

The aims of the study are:

1- To evaluate the clinical presentation of extra-pulmonary tuberculosis in adult Sudanese patients.

2- To assess methods used in the diagnosis of extra-pulmonary TB.

3- To identify the possible risk factors such as past history of pulmonary tuberculosis, contact with TB patients, previous BCG vaccination, immune status of the patient (HIV, DM), that may predispose to extra-pulmonary TB.
Chapter Two
PATIENTS AND METHODS

Study design:

This is a hospital based descriptive study carried out from January to December 2003 in Khartoum Teaching Hospital, Shaab Teaching Hospital, Omdurman Teaching Hospital and Omdurman Hospital for Tropical Diseases.

Study population:

Hundred patients diagnosed as having extra-pulmonary tuberculosis were enrolled in the study. All the cases are in patients.

Materials and methods

To be enrolled in this study, the patients should fulfill the following criteria:

1- Being an adult Sudanese.

2- Diagnosed as having any type of extra-pulmonary tuberculosis.

3- On antituberculous treatment.

Clinical history:
Each individual of these patients was seen by the investigator. A
detailed history was obtained, concerning the patient's age, sex, residence, and symptoms of his current illness. The patient's past medical history of previous attacks of pulmonary tuberculosis, history of contact with tuberculous patients, history of BCG vaccination were recorded.

Coinciding other chronic or debilitating illnesses such as diabetes mellitus, HIV were also noted.

Physical examination:

Each patient was subjected to meticulous clinical examination.

Investigations:

Investigations were done by the treating staff and all patients had ESR, CXR, Mantoux test and sputum examination for AAFB. No further investigations were done by the investigator.

Analysis:

Finally the collected data from patients were analysed to achieve the objective of the study.
The data were entered and analysed using Statistical Package for Social Science Software (SPSS) on IMB computer. Simple statistics frequency distribution and cross-tabulation were done to explore the pattern of variables and percentages.
Chapter Three
RESULTS

Hundred patients who were diagnosed as having extra-pulmonary tuberculosis were enrolled in this study.

Abdominal TB was found to be the commonest type (37%), followed by tuberculous lymphadenitis (20%), spinal TB (19%) and to less extent by TB of the pleura (9%), CNS (4%), genitourinary tract (3%), pericardiam (3%), miliary (3%) and the skin (2%) (Fig. 1).

In abdominal TB, 20 (54%) patients were males and 17 (46%) were females (Table 5). Twenty-three (62%) patients fall in the age group between (16-45) years, 14 (37%) patients fall in the age group between (46-70) years (Table 6). General symptoms were common, fever was found in 32 (86%) of cases of abdominal TB, weight loss in 29(78%) patients, and night sweats in 12(32%) patients (Table 1). The main abdominal symptoms and sings were ascites in 29(78%) patients, chronic diarrhoea in 7(19%), abdominal masses in 4(11%) and abdominal pain in 7(19%) patients (Fig. 2). Past history of pulmonary TB was not recognized in all
these patients, however, 12 (32%) had history of contact with patients of TB. Three (8%) of the patients with abdominal TB had BCG vaccination previously (Table 2). HIV screening test was done in 19 (51%) patients, and it was found to be positive in 6 (16%) of them (Table 3). Thirty-four (92%) patients had an ESR >80 mm/h. Mantoux test was positive in 26 (70%) patients. Sputum examination for AAFB was positive in one patient. Significant CXR findings (calcification, cavitation, fibrosis and consolidation) were found in 4 (11%) patients (Table 4). Abdominal U/S was done for all patients with abdominal TB and it had suggested findings (presence of fine fibrous strands in the ascitic fluid, localized ascites and caseous or calcified lymph node) in 34 (92%) of the patients. Ascitic fluid analysis was done for all patients and it was found to be significant (being exudate with predominant lymphocytosis). Ascitic fluid ZN-staining was positive in only one patient. Ascitic fluid was not cultured. Peritoneal biopsy was done in 13 (35%)
patients and it showed caseating granuloma in all specimens (Fig. 3).

Lymph node tuberculosis (LN TB) was the second common type in the study and constituted 20% of cases, 11(55%) patients were males, and 9(45%) were females (Table 5). Eleven (55%) patients fall in the age group between (16-45) years and 9(45%) in the age group between (46-70) years.

The cervical group of lymph nodes was the most common site involved in 12(60%) patients. Supraclavicular LN was involved in 7(35%) and axilary lymph nodes in one patient (Fig. 4).

The general non specific symptoms observed were fever, which occurred in 15(75%) patients, weight loss in 13(65%) patients, night sweat in 6(30%) patients, and cough in 6(30%) patients (Table 1).

Past history of pulmonary TB was present in one patient, 5 patients had history of contact with patients of TB, 2 patients had BCG vaccination previously, and 3 patients of the cases of LN-TB were diabetic (Table 2).
HIV screening test was done in 15(75%) and it was found to be positive in 4(20%) (Table 3), 18(90%) had an ESR >80% mm/h. Sputum for AAFB was done for all patients and it was found to be positive in one patient. Suggestive CXR findings (consolidation, fibrosis, calcification) were found in 3(15%) patients. Mantoux test was positive in 11 (55%) patients (Table 4). LN biopsy was done for all patients and in all of them it had show caseating granuloma.

The spine was the third commonest site of extra-pulmonary TB in the study, It constituted 19% of all cases of extra-pulmonary TB (Fig. 1), 10 (53%) of them were females and 9 (47%) were males (Table 5). Ten (53%) patients fall in the age group between (16-45) years and 9 (47%) patients fall in the age group between (46-70) years.

All patients with the spinal TB had backache, tenderness and deformity in the spine. When examined 15(78%) of them had paraparesis, only one had quadriplegia, and 3 patients had no apparent weakness (Fig. 5). 15
(78%) patients with spinal TB had fever, 13 (68%) had weight loss, 6 (32%) had night sweats, and cough was present in 2 patients (Table 1).

Past history of pulmonary TB was found in 3 (16%), contact with patients of TB was found in 9 (47%), only one patient had BCG vaccination in the past, and 4 (21%) patients were diabetics (Table 2).

HIV screening was done only in 7(37%) patients and found to be positive in 3 (16%) patients (Table 3).

All patients had an ESR >80mm/h, Mantoux test was found to be positive in 14 (74%). Suggestive CXR findings were found in 3 (16%) patients, sputum examination for AAFB was negative in all patients (Table 4).

X-ray spine was done for all cases of spinal TB and suggestive findings (vertebral collapse) were seen in 15(79%) patients mainly affecting the dorsal spine.

MRI of the spine was done in 15 patients and according to its findings and x-ray findings, thoracic vertebrae were affected in 13 patients, Lumbar vertebrae in 5
patients, cervical vertebrae affected in one patient (Fig. 6).

Pleural TB was the fourth common site of extra-pulmonary TB in the study affecting 9 patients (Fig. 1). All of them were males (Table 5). Eight (89%) patients fall in the age group between (16-45) years and one patient was 54 years old age. The main presenting sign was pleural effusion, which was detected in all nine patients. All of them developed fever and chest pain, 8 had cough and 4 had night sweating (Table 1).

No patient had past history of pulmonary TB, 3 patients had a history of contact with tuberculous patients, 6 of them were diabetics and only one patient had BCG vaccination (Table 2).

HIV screening was done for 5 patients and was found to be negative in all of them (Table 3).

All patients had an ESR >80mm/h, CXR in all cases showed pleural effusion. The effusion was unilateral in 7 (78%) of them and 2 patients had bilateral pleural effusion (Fig. 7).
Sputum examination for AAFB was positive in 2 patients. Mantoux test was positive in all patients (Table 4).

Pleural fluid analysis was done in all cases and it was found to be suggestive (protein >3mg and predominant lymphocytosis). Pleural fluid ZN stain for AAFB was positive in 2 patients. Pleural biopsy was done for 3 of the 9 patients and it showed caseating granuloma in all of them (Fig. 8).

Tuberculosis of the central nervous system (Fig. 1) was the fifth common site of extra-pulmonary TB in the study. It was encountered in 4 patients. Two were males and 2 were females. Three of the 4 patients were less than 45 years and 1 patient was 60 years of age. The main presenting features were those of raised intracranial pressure (disturbed level of consciousness, headache, convulsions and focal signs) and 3 of them had signs of meningitis as well. Other symptoms such as chest pain, and haemoptysis were not detected (Table 1). No one of them had past history of pulmonary TB. Two had a history of contact with tuberculous patients and only
one was diabetic. No patient had BCG vaccination before (Table 2). HIV screening was done for 3 and it was found to be positive in one patient (Table 3). High ESR >80 was found in 3, sputum examination for AAFB found to be positive in only one patient. Suggestive CXR findings (consolidation, fibrosis, calcification) was detected in 3 patients and a positive Mantoux test in 2 patients (Table 4). Cerebrospinal fluid (CSF) was obtained from 3 of the 4 patients and its analysis showed suggestive findings (protein >3g, low glucose, predominant lymphocytes) in all of them. Two of the patients with CNS tuberculosis had C.T brain with features suggestive of tuberculoma (Fig. 9).

Pericardial tuberculosis occurred in 3% of the cases of extrapulmonary TB (Fig. 1). Two were males and one was a female (Table 5). All 3 patients were less and 45 years of age. Fever, and shortness of breath were found in all 3 patients and 2 of them had cough as well. Two patients showed signs of pericardial effusion and one
patient showed signs of constrictive pericarditis (Fig. 10).

One patient had chest pain and another was febrile. No patient had weight loss, haemoptysis, or night sweats (Table 1). One patient gave a history of pulmonary TB, another one had a history of contact with tuberculous patients. One patient was diabetic and no patient had BCG vaccination (Table 2). HIV screening was done in 2 patients and found to be positive in both of them. ESR >80mm/h was found in one patient, sputum examination for AAFB showed negative result in all cases. Mantoux test was positive in all cases. Suggestive CXR findings (globular enlargement of the heart ± pericardial calcification) was present in all cases (Table 4).

ECG was done for all patients and it showed low voltage and T wave changes suggesting pericardial effusion. The presence of pericardial effusion was documented by echocardiography in all patients.
Pericardiocentesis was done in 2 patients and its analysis showed features suggesting tuberculosis (protein > 3g and predominant lymphocytes). Pericardial biopsy was not done to any of them (Fig. 11).

Miliary tuberculosis constituted 3% of cases of extra-pulmonary tuberculosis (Fig. 1), 2 were males and one was a female (Table 5). Two of the 3 patients were less than 45 years and the third was 50 years of age. All cases had more than one organ involvement simultaneously. Fever, night sweats, weight loss, cough, and chest pain were detected in all cases (Table 1). Disturbed level of consciousness was found in all cases.

No patient had a past history of TB, but all of them had history of contact with tuberculous patients, no patient received BCG vaccination before and only one patient was diabetic (Table 2).

HIV screening was done for all patients and it was found to be positive in two of them (Table 3). All three patients had an ESR >80mm/h. Sputum examination for AAFB was positive in one of the 3 patients and suggestive CXR
findings (mottling) was found in all of them. Mantoux test was positive in 2 patients (Table 4).

Tuberculosis affecting the genitourinary system constituted 3% of cases (Fig. 1). It was mainly affecting the renal system, 2 were males and one was a female. Two patients were less than 45 years and one patient was 60 years of age.

All 3 patients presented with dysuria and loin pain and two of them were febrile. One patient complained of night sweats. Other symptoms such as cough, chest pain, weight loss and haemoptysis were not detected (Table 1). One had a past history of pulmonary TB and one patient gave a history of contact with tuberculous patients. All patients did not receive BCG vaccination before. Two of the 3 patients were diabetics (Table 2). HIV screening was not done for any of them (Table 3). All patients had an ESR >80mm/h. Sputum examination was negative in all patients, and CXR was normal in all of them. The Mantoux test was positive in all cases (Table 4). Microscopic examination of urine
sample showed uncountable pus cells in all cases, early morning sample (3 times) was done for all patients and it was found to be negative. Urine culture for AAFB was not done for any patient. U/S examination was done for all patients and it showed no abnormalities. Intravenous urogram was done for all patients and showed features suggesting renal tuberculosis in all cases.

Cutaneous tuberculosis constituted 2% of the cases of extrapulmonary tuberculosis in the study. The 2 patients were males and they were less than 45 year of age (Table 5). The main presentation was skin lesions (ulcers) mainly located on the face. The two were febrile and one had night sweats as well. Other symptoms such as cough, weight loss, and chest pain were not detected in any patient (Table 1). No patient had past history of pulmonary tuberculosis, and one had history of contact with tuberculous patients. Non of the 2 patients received BCG vaccination before, and both of them were diabetics (Table 2). They were not
screened for HIV (Table 3). Both patients had ESR >80m/h and the Mantoux test was positive in one patient. Sputum examination for AAFB was negative in both of them and a significant CXR findings (consolidation, fibrosis, calcification) was not detected in any of them (Table 4). In both patients the diagnosis was made by biopsy from skin lesions which showed chronic granulomatous changes with infiltration of epitheliod cells and caseating necrosis.

Table 1: Frequency of general symptoms in each type of extra-pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Tuberculosis type</th>
<th>Total No. of patients</th>
<th>Fever</th>
<th>Cough</th>
<th>Night swea t</th>
<th>Weight loss</th>
<th>Chest pain</th>
<th>Haemoptysis</th>
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</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>37</td>
<td>32</td>
<td>12</td>
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<td>29</td>
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<tr>
<td><strong>Pleural</strong></td>
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<td>8</td>
<td>4</td>
<td>8</td>
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<tr>
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<td>2</td>
<td>6</td>
<td>12</td>
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<td>----</td>
<td>----</td>
<td>----</td>
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<td>----</td>
</tr>
<tr>
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Table 2: Risk factors in each type of extra-pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Tuberculosis type</th>
<th>Total No. of patients</th>
<th>Past history of pulmonary TB</th>
<th>Contact with <em>tuberculous patients</em></th>
<th>BCG</th>
<th>Diabetes mellitus</th>
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<tr>
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Table 3: HIV status in different types of extra pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Tuberculosis type</th>
<th>Total No. of patients</th>
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<th>Negative</th>
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<td>Spinal</td>
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Table 4: General investigations of the different types of extra-pulmonary tuberculosis

<table>
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<tr>
<th>Tuberculosis type</th>
<th>Total No. of patients</th>
<th>ESR &gt; 80</th>
<th>Positive sputum for AAFB</th>
<th>Significant CXR</th>
<th>Positive Mantoux test</th>
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Table 5: Distribution of gender in the different types of extra-pulmonary tuberculosis in the study.

<table>
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<tr>
<th>Type of tuberculosis</th>
<th>Male</th>
<th>Female</th>
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<td>9</td>
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<tr>
<td>Lymph node</td>
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<td>2</td>
<td>4</td>
</tr>
<tr>
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<td>1</td>
<td>3</td>
</tr>
<tr>
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<td>0</td>
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</tr>
<tr>
<td>Pericardial</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
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Table 6: Distribution of age in the different types of extra-pulmonary tuberculosis in the study.

<table>
<thead>
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<th>Type of tuberculosis</th>
<th>(16-45) years</th>
<th>(46-70) years</th>
<th>Total No. patients</th>
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<td>8</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Lymph node</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal</td>
<td>23</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>Spine</td>
<td>10</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pericardial</td>
<td>3</td>
<td>0</td>
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<tr>
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Fig. 1: Frequency of different types of extra-pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Type of tuberculosis</th>
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<tr>
<td>Abdominal</td>
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<tr>
<td>Pleural</td>
<td>9.00%</td>
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<tr>
<td>Lymph node</td>
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<tr>
<td>Spinal</td>
<td>19.00%</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>4.00%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>3.00%</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>2.00%</td>
</tr>
<tr>
<td>Pericardial</td>
<td>3.00%</td>
</tr>
<tr>
<td>Miliary</td>
<td>3.00%</td>
</tr>
</tbody>
</table>
Fig. 2: Symptoms and signs in abdominal tuberculosis

- Abdominal pain: 15%
- Chronic diarrhoea: 15%
- Ascites: 61%
- Masses: 9%
Fig. 3: investigations used in the diagnosis of abdominal tuberculosis
Fig. 4: lymph node groups involvement in lymph node tuberculosis

- Cervical lymph nodes: 60%
- Supraclavicular lymph nodes: 35%
- Axillary lymph nodes: 5%
Fig. 5: Symptoms and signs in patients with spinal tuberculosis

- Backache: 100%
- Back tenderness: 100%
- Back deformity: 100%
- Paraparesis: 78.94%
- Quadriplegic: 5.20%
Fig. 6: Sites of lesions according to the clinical and MRI findings

- Thoracic: 69%
- Lumbar: 26%
- Cervical: 5%
Fig. 7: X-ray findings in pleural effusion

Bilateral
22%

Unilateral
78%
Fig. 8: Investigations used in diagnosis of pleural tuberculosis
Fig. 9: Investigations used in the diagnosis of CNS tuberculosis
Fig. 10: Symptoms and signs in patients with heart tuberculosis

Signs of pericardial effusion 67%

Signs of constrictive pericarditis 33%
Fig. 11: investigations used in diagnosis of heart tuberculosis

- ECG: 100%
- Echo: 100%
- Pericardial fluid analysis: 67.00%
- Pericardial biopsy: 0%
Chapter Four
DISCUSSION

Tuberculosis is a widely extended disease in Sudan and according to the Federal Ministry of Health (FMOH), it is categorized as a major health problem and considered to be a leading cause of morbidity and mortality all over the country.\(^{(1)}\)

100 patients with extra-pulmonary tuberculosis were included in this study, 57% of them were from different parts of the country and 43% from Khartoum State.

Abdominal tuberculosis was found to be the commonest type of extra-pulmonary tuberculosis and it forms 37% of the cases. This does not go with the literature findings as it was found to be the 6\(^{th}\) commonest site in USA studies\(^{(39)}\). This could be explained by the fact that tuberculosis is still a major problem in developing countries and some Sudanese people had the behaviour of drinking raw milk. In this study TB peritonitis was the most commonest type of abdominal TB where as in the USA TB entities is the commonest\(^{(29)}\). The main presenting symptoms were fever, abdominal distention due to ascites, weight loss, night sweat, chronic diarrhoea and abdominal masses. No patient with abdominal tuberculosis had a past history of pulmonary tuberculosis, but significant CXR findings (consildation, fibrosis, calsification) were found in 4 (11%)
patients, and this could be explained by the fact that, abdominal tuberculosis occurred as a primary infection in most patients. HIV screening was done in 21 (56%) patients with abdominal tuberculosis and it was found to be positive in 6 of them and negative in 15. This in contrast to the findings in the literature, which showed increased incidence of abdominal tuberculosis among HIV positive patients. This could be explained by the presence of factors other than HIV increasing the likelihood of having abdominal TB such as malnutrition.

The study showed that the methods used for diagnosing abdominal tuberculosis, were abdominal ultrasound, ascitic fluid analysis in addition to the general investigations such as the ESR and Mantoux test. These were done for all patients. Whereas internationally the available diagnostic methods of tuberculous peritonitis include paracentesis with acid-fast smear and culture, laparoscopy with direct biopsy, blind percutaneous peritoneal biopsy and diagnostic laparatomy. In this study blind peritoneal biopsy was done for (17%) patients and all of them showed caseating granuloma. This seems to be a good method with high yield and should be performed in all such cases. A new test had been introduced to facilitate the diagnosis of tuberculous peritonitis by measuring the adenosine deaminase activity of the ascitic fluid. But this was not done for any patients probably because it was not available.
Tuberculous lymphadenitis is the second most common site of extra-pulmonary tuberculosis in the study and it is regarded as the commonest type of extra-pulmonary tuberculosis in another study done by Talavera W, Miranda R.\textsuperscript{(51)} It constituted 20\% of cases of extra-pulmonary tuberculosis in the study. The cervical group of lymph nodes was the commonest site and this goes with the finding in the literature.\textsuperscript{(51)} Fever, weight loss and night sweat were detected in most cases, however, a review on a recent literature suggested that many patients were asymptomatic, again this may be attributed to small sample of our study. Significant CXR findings (consolidation, fibrosis, calcification) were found in 15\% of cases, however, most cases were thought to represent a reactivation of an initial lymphatic spread according to the literature. This can be explained by the fact that, normal CXR could not exclude past history of pulmonary tuberculosis and also we are not using newer molecular epidemiological tools in the diagnosis of tuberculosis. HIV screening test was done on 15 (75\%) patients and it was found to positive in 4 (27\%) patients and negative in 11 (73\%) patients. This is in contrast to the literature as it is known that HIV infection increases the likelihood of developing active tuberculosis and LN involvement. This may be explained by the presence of factors other than HIV such as malnutrition, which increases the likelihood of having LN tuberculosis. All cases were diagnosed using excisional biopsy and this is a standard tool for making
diagnosis of tuberculous lymphadenitis worldwide. All biopsies showed caseating granuloma, which is the typical picture of tuberculosis.

Tuberculosis of the spine constituted 19% of cases of extra-pulmonary tuberculosis, whereas in a study done in 1988 it constituted 35% of cases. This study showed that the thoracic spine is most commonly affected and this is goes with the literature.

Clinically patients presented with pain over the affected vertebrae, low grade fever and weight loss, such findings were reported by D. Bush and L Schnieder J. in study about skeletal TB. All patients had a deformity in the back, and this may be explained by delayed presentation of most patients. Most patients neither had past history of pulmonary tuberculosis, nor their CXR showed significant finding and this goes with the findings of a review of 499 cases where 69% of them showed normal CXR. Positive Mantoux test was detected in 74% and similar results were reported from the literature. Plain films of the spine showed destructive changes in 79% and again this could be explained by the delayed presentation in most patients.

Pleural tuberculosis is the 4th common type of extra-pulmonary tuberculosis in this study, however, in other studies it ranked second to tuberculous lymphadenitis. This could be explained by the fact that effusion in primary TB pleuritis goes unnoticed and resolved spontaneously in 90% of cases. The clinical presentation of TB pleurisy
included fever, cough, chest pain and dyspnoea. These findings are similar to those in the literature. No patient in the study had past history of pulmonary tuberculosis, this could be attributed to the fact that most patients had primary pleuritis, which passed unnoticed. Also most patients were not vaccinated against TB. The screening test for HIV was done only for 5 patients and found to be negative in all of them and this in contrast with literature, which showed increased incidence of pleural TB among HIV positive patients. But this could be attributed to the small number of cases which were screened for HIV and the small number of cases which enrolled in the study. The effusion is mainly unilateral and a similar finding was reported in the literature. Parenchymal lung disease was seen in a minority of patients in contrast to the literature where parenchymal lung disease was found in most of patients. In most cases the main tool of diagnosis was analysis of the pleural fluid (straw colour, high lymphocyte and protein > 3g). Pleural biopsy was done only in 33% of patients, and showed caseating granuloma, in spite of the small number of patients who underwent this procedure it seems sensitive and it should be done in such cases. Culture of pleural fluid for AAFB was not done for any patient. And in fact this investigation is very sensitive but it tooks long time.

TB of the CNS constituted 4% of the cases in the study. The main presenting symptoms were fever, headache, seizure, altered level of
consciousness, focal neurological signs and night sweat. These findings are consistent with those reported in a study about tuberculous meningitis.\textsuperscript{(117)} All patients denied any history of pulmonary tuberculosis before, despite that 3 (75\%) of them showed significant CXR findings (consolidation, calcification and fibrosis) and this is probably due to a primary pulmonary TB, which had passed unnoticed as it healed spontaneously. Only one patient was diabetic. All patients did not receive BCG vaccination before and again this may be an additional factor to increase the risk for CNS TB. The main method for diagnosis in addition to all mentioned above was analysis of cerebrospinal fluid which was done for 3 patients and it showed suggestive findings for tuberculous meningitis (high protein, low glucose and increased lymphocytes). CT brain was done for 2 patients and it showed features suggestive of tuberculomata, characteristicly a nodular enhancing lesion with a central hypodense area.\textsuperscript{(124)} As it is difficult to obtain a tissue for diagnosis of such cases, the above investigations may not be sufficient for establishing the diagnosis, so in addition to the above mentioned investigations detection of the mycobacterial DNA by PCR may be important to make the diagnosis.\textsuperscript{(125)} Hydrocephalous is a common complication in most patients who survive the first 4-8 weeks.\textsuperscript{(126)} This finding was not detected in this study, most probably due to the small number of cases encountered.
Pericardial TB constituted 3% of cases in the study. The main presenting symptoms were fever, cough, shortness of breath. Two patients showed signs of pericardial effusion. (diffuse apex, muffled heart sound). The same findings were detected in a study about TB of the heart done by Recli ESP in July 1997. Pericardial friction rub was not detected in any patient, and this may be due to the late presentation till effusion had developed. One patient had past history of pulmonary TB. The incidence of tuberculous pericarditis among patients with pulmonary tuberculosis was reported to be from 1-8%. No patient had BCG vaccination before and this again may be a factor in increasing the risk of infection. Only one patient was diabetic. HIV screening was done for 2 patients and it was found to be positive in both of them, therefore, immunosupression may play a role in increasing the risk of infection, however the number of cases is too small for such a comment. The helping diagnostic findings were high ESR, positive Mantoux test in addition to confirmation of presence of pericardial effusion by CXR and echocardiogram. The CXR in all patients showed cardiomegaly and did not show parynychmal diesase or pleural effusion which were reported in a minority of patients with percardial TB in study done by Orth bad, DW, Aviote LV about tuberculous pericarditis. ECG was done for all the patients and it supported the diagnosis. Pericardiocentesis and analysis of the pericardial fluid was done in 2 of the cases. Analysis of pericardial
fluid showed high protein (>3g) and increased lymphocyte count. The adenosine deaminase (AD and interferon gamma (IFN) levels were not examined in both cases. In fact these investigations had a high yield of senstivity and specificity but they are expensive.\(^{101}\) No patient had pericardial biopsy probably because it is dangerous.

Miliary tuberculosis constituted 3 cases (3%) of extra-pulmonary tuberculosis in the study. The main presenting symptoms were fever, night sweat, weight loss, cough and disturbed level of consciousness. These were detected in all cases and these clinical features were similar to those in previously reported series.\(^{79,80}\) All patients with miliary TB in this study were found to have hepatosplenomegaly, and this is in agreement with the findings in a paper written by Biehl JP about miliary TB.\(^{80}\) Two of the 3 patients with miliary tuberculosis where HIV positive and the third was negative. Although number of the cases is too small to make solid conclusion the risk of infection may be increased in immunocompromised patients. All 3 patients were found to have a high ESR and a positive Mantoux test. Sputum examination for AAFB was found to be positive in one of the 3 patients. These findings were in agreement with study about miliary TB carried in Qatar.\(^{80}\) CXR showed millet appearance in all patients and depending on these findings all patients were diagnosed. No patient had biopsy from bone marrow, lymph node or liver, which are frequently needed to establish the
diagnosis as reported in the literature.\textsuperscript{(79)} Also no patient had culture of body fluids (e.g. CSF) to make the diagnosis, and in fact it allowed microbiological diagnosis in a significant proportion of patients but it takes long time (6–8 weeks).

Genitourinary TB constituted 3\% of the cases in the study. The main presenting symptoms were those of urinary tract infection (UTI) dysuria and loin pain), no patient had haematuria. It is reported in the literature that haematuria occurred in a minority of patients.\textsuperscript{(9)} Fever and night sweat were detected in 2 patients, and in fact these findings were uncommon but this may be attributed the small number of cases. Suggestive CXR findings for old TB (fibrosis and calcification) were not detected in any patient and this may be due the small size of the sample. Examination of early urine sample for AAFB was done for all patients and it was negative in spite of the fact that it is a sensitive tool of diagnosis for renal tuberculosis. All cases were diagnosed by the above investigations in addition to sterile pyuria in culture and suggestive intravenous urogram findings. Polymerase chain reaction (PCR) was not done for any patient and this investigation is highly sensitive and quick. Genital tuberculosis was not detected in any patient and this may be attributed to the fact that such patients usually go to venereal disease clinics. Also female patients usually go to gynecological departments where the diagnosis of genital tuberculosis is made.
CONCLUSION

• Abdominal TB is the commonest type of extr. pul. TB and tuberculous peritonitis with ascites formation is the commonest mode of presentation of abdominal TB.

• Tuberculous lymphadenitis is the second commonest type of extra. Pul. TB. And cervical group of lymph node is the main site of involvement followed by supraclavicular and axillary.

• Thoracic spine is the commonest site of spinal TB, followed by lumber and cervical spine.

• Pleural effusion is the main presentation of tuberculous pleurisy and the effusion is mainly unilateral. Isolation of the bacilli by Z.N staining of pleural fluid is uncommon.

• The main presentation of CNS TB is by symptoms and signs of raised intracranial pressure (headache, focal neurological deficit, disturbed level of consciousness and convulsions).

• Pericardial effusion and constrictive pericarditis were the main modes of presentation of tuberculosis of the heart. newer methods such as measuring gamma IFN level and adenosine deaminase level in the pericardial fluid were not done for any patient with heart TB.
• The main clinical features of genitourinary TB are symptoms and signs of urinary tract infection. The examination of early sample urine for AAFB is specific but less sensitive tool. Most patients were diagnosed on intravenous urogram findings in this study.

• Most patients did not receive BCG vaccination.

• Histopathology for diagnosing extra-pulmonary TB was done in minority of patients.

• Serological methods such as PCR was not done for any patient.
RECOMMENDATIONS

- To make a definitive diagnosis requires a high index of suspicion and need a detailed patient work-up and considerable efforts to obtain pathological confirmation of diagnosis.

- Extra pulmonary TB has to be viewed in the context of its association with HIV and other high-risk groups and any patient with extr.pul. TB should be screened for HIV.

- BCG vaccination should be taken by those who had negative Mantoux test.

- Detection of mycobacterial DNA by PCR should be carried out when it is difficult to obtain tissue for histopathology.

- Newer methods of diagnosis of extra-pulmonary TB such as measuring ADA and interferon gama in the ascitic, pericardial and cerebrospinal fluids should be done because they have a high yield of sensitivity and specificity.

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Appendix
Questionnaire
PATTERNS OF EXTRA-PULMONARY TB IN ADULT SUDANESE PATIENTS

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Residence:

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PH:

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FH:

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- TB

**SH:**
- Social class
  - High
  - Moderate
  - Low

**DRUG HISTORY:**

**O/E:**
- Pt. looks
  - Ill
  - Unwell
  - Well
  - Wasted

**LN:**
- Cervical
- Axillary
- Inguinal

**CHEST SIGNS:**
- YES
- NO

**CVS:**
- Signs of pericarditis
- Signs of pericardial effusion

**ABD:**
- YES
- NO
  - Ascites
  - Splenomegaly
  - Hepatomegaly
  - Masses

**CNS:**
- Signs of meningitis
- Signs of cord compression
- Signs of space occupying lesion

**BACK:**
- Deformity
- Tenderness

**SKIN ULCERS:**

**INVESTIGATIONS:**
- ESR
- HB%
- Mantoux test
- Sputum for AAFB

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<td>ZN stain</td>
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</table>

- **Intravenous Urogram**
- Pleural biopsy
- Pleural fluid analysis
- Pleural fluid ZN stain
- Acitiec fluid analysis
- Acitiec fluid ZN stain
- Peritoneal biopsy
- LN biopsy
- CXR
- Abd. U/S
- X-ray spine
- MRI spine
- CT-brain
- HIV
- ECG
- CSF analysis
- ECHO findings
- Pericardial fluid analysis