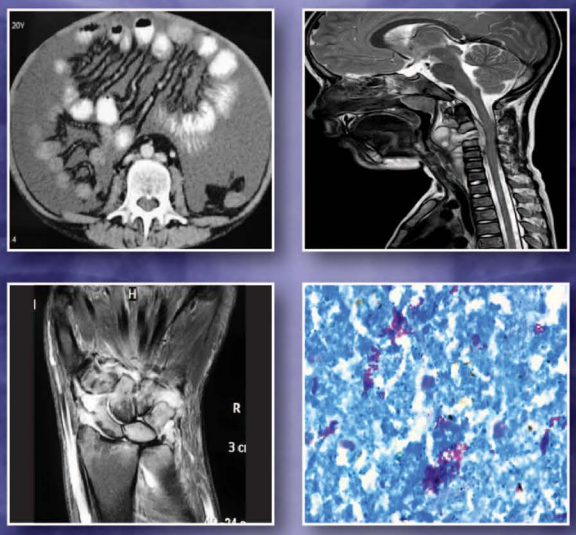
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Imaging in Tuberculosis

Clinicopathological Correlation



Editors
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Foreword
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2 CHAPTER

Tuberculosis: Clinical Features

Krishan Chugh, Neetu Talwar

INTRODUCTION

Tuberculosis (TB) is one of the most common infectious diseases worldwide, affecting almost a third of the global population. It is caused by *Mycobacterium tuberculosis*. Although any organ in the body can get affected, pulmonary infections are the most common.

KEY FACTS ON CLINICAL FEATURES IN TUBERCULOSIS

- Tuberculosis may remain completely asymptomatic till the disease is quite advanced
- The usual symptoms of TB, like low-grade fever, loss of weight, poor appetite, and productive cough can either go undetected both by the patient as well as the physician or wrongly attributed to some other disease
- Delay in diagnosis leads to silent transmission of the disease
- The estimated lifetime risk of a young child developing TB infection as diagnosed by positive Mantoux test is about 10%[1]
- Of these infected children, approximately 5% are likely to develop the disease in the first year after infection and the remaining 5% during their lifetime.[1] Thus, in TB, infection and disease are two different entities—an infected child may never develop symptoms (i.e., disease) in his lifetime
- About 40% of the untreated children infected below 1 year of age, develop radiologically significant lymphadenopathy or parenchymal lesions in contrast to 24% of children between 1 and 10 years and 16% of children with 11–15 years of age[2]
- Older children and adults who develop the disease, often have reactivation of the infection acquired earlier.

WHO IS AT HIGH RISK?

The risk factors for developing TB are young age (<3 years), malnutrition, unvaccinated [Bacillus Calmette-Guerin (BCG)] population, rural area, exposure to biomass cooking fuel, smoking, and a history of contact with a known TB case. Immunocompromised patients such as those with human immunodeficiency virus (HIV), malnutrition, or diabetes are not only at risk of developing the infection but are also more likely to develop a severe and disseminated infection.[3]

DISEASE PROGRESS

The clinical presentations of childhood TB have undergone significant variations due to widespread BCG vaccination. There is a decreased incidence of disseminated and severe disease, but a higher rate of localized illness like localized central nervous system (CNS) infection. The progress of the disease has been described in table 1.

CLINICAL FEATURES

Primary Infection

Usually this phase passes off unrecognized with no specific clinical or radiological manifestations. The only way to diagnose is by a positive Mantoux test.

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Table 1: Tuberculosis march (of clinical features)

Phase	Mantoux test	Chest X-ray	Time after primary infection	Point to note
Phase I	Positive	Primary complex seen	After 3–8 weeks	–
Phase II	Positive	–	After 1–3 months	Highest risk of developing tuberculous meningitis and miliary tuberculosis
Phase III	Positive	Present	After 3–7 months	Period of pleural effusion over 5 years, period of bronchial disease below 5 years
Phase IV	Positive	Present	Lasts 1–3 years after primary infection and continues till the primary complex is calcified	Phase of development of osteoarticular tuberculosis in children below 5 years
Phase V	–	Present	Occurs more than 3 years after primary infection	Late manifestations of tuberculosis including pulmonary reactivation disease occur

PULMONARY TUBERCULOSIS

This is the most common manifestation of TB. Symptoms vary according to the site of involvement, whether it is the parenchyma, endobronchial tree or the pleura. Accordingly clinical features have been described.

Clinical Presentations of Pulmonary Tuberculosis

Pulmonary Primary Complex

Pulmonary primary complex (PPC) is the most common presentation of TB. Symptoms are vague-like cough, low-grade fever with an evening rise of temperature, lethargy, poor appetite and even these symptoms may not always be present. Radiological features may also be absent or may be nonspecific like a doubtful shadow persisting despite a course of antibiotics. In such a clinical setting, history of a contact especially a sputum positive contact should be actively elicited.

Progressive Primary Disease

Progressive primary disease is because of the progression of the PPC. Now the symptoms may be the presence of moderate to high-grade fever and cough. Productive cough and hemoptysis would be the signs of advanced disease and are indicative of formation of cavity or ulceration of bronchus.[4] These symptoms are usually present in adolescents and adults. If they are seen in the younger age group, HIV and other immunodeficiencies must be ruled out.

Endobronchial Tuberculosis

When the spread is to the endobronchial tree, the child will develop persistent fever and cough, expectoration may be present and breathlessness. Respiratory distress, wheezing, and cyanosis could be present. Radiological presentation is usually in the form of broncho-pneumonia. However, X-ray may not show any significant abnormality (Fig. 1). Airway compression would be indicated by emphysema (if partial compression) and collapse (with complete compression).

Miliary Tuberculosis

Miliary TB results from hematogenous spread of the disease leading to seeding throughout the body with progressive, innumerable small foci. The age groups most affected are infants and small children. Onset is usually sudden with the symptoms of high-grade fever, cyanosis, and breathlessness. Respiratory system examination reveals bilateral, fine crepitations. In addition, significant systemic findings are the presence of hepatosplenomegaly.

On the contrary, the other presentation of this alarming condition may be a slow, insidious onset with a lethargic child, low-grade persistent fever, and sick looking with a loss of weight and appetite.

Miliary TB may spread to the brain and meninges resulting in TB meningitis.

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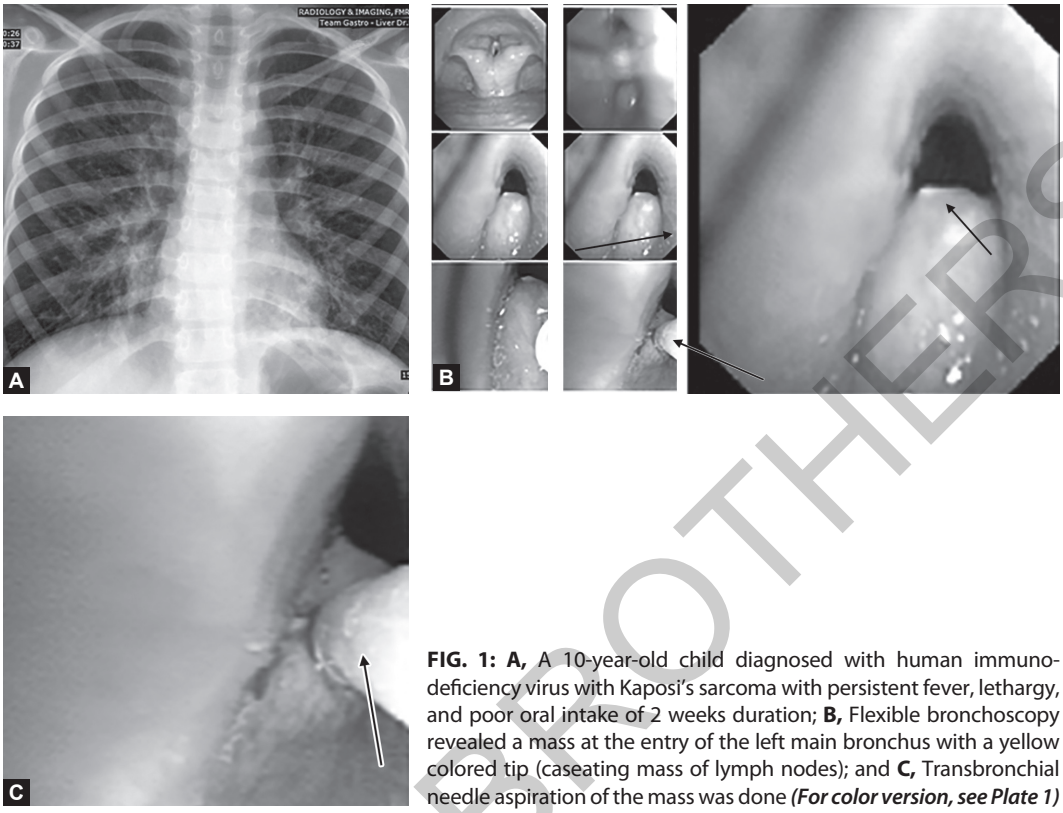


FIG. 1: A, A 10-year-old child diagnosed with human immunodeficiency virus with Kaposi's sarcoma with persistent fever, lethargy, and poor oral intake of 2 weeks duration; **B,** Flexible bronchoscopy revealed a mass at the entry of the left main bronchus with a yellow colored tip (caseating mass of lymph nodes); and **C,** Transbronchial needle aspiration of the mass was done ***(For color version, see Plate 1)***

Pleural Effusion

Pleural effusion may result from primary complex in young persons. The patient may have respiratory distress and breathlessness. Fever is commonly present.[4] On the contrary, the patient may appear to be quite comfortable despite a massive pleural effusion.

Diagnosis

Following important points help in the diagnosis of pulmonary TB:

- Clinical features
- Presence of TB contact in family or neighborhood
- Positive tuberculin skin test (TST)
- Radiological features
- Demonstration of possible acid-fast bacilli (AFB) remains the gold standard for diagnosis, but may not always be present.

Specimen Collection

Specimens to be collected for the diagnosis of pulmonary TB are sputum, gastric lavage, bronchoalveolar lavage collected by flexible bronchoscopy, and pleural fluid.

Laboratory Tests

Tables 2 and 3 list the site-specific investigations to be done in a case of pulmonary TB.

LATENT TUBERCULOSIS

Latent tuberculosis infection (LTBI) occurs when there is a persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without any evidence of clinically manifested active TB. Almost a third of the world's population has LTBI, and have a risk of developing TB later, a process called as "TB reactivation".[5]

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Table 2: Diagnostic investigations for pulmonary tuberculosis

Suspected site of disease	Possible imaging techniques	Specimen	Routine test	Additional tests
Pulmonary (adult)	• X-ray • Lung ultrasound	• Three respiratory samples—preferably spontaneously produced, deep cough sputum samples, otherwise induced sputum or bronchoscopy and lavage • Preferably one early morning sample	• Microscopy • Culture • Histology	• Cartridge-based nucleic acid amplification test (CBNAAT)
Pulmonary (young people aged 16–17 years)	• X-ray • Computed tomography thorax	• Three respiratory samples—preferably spontaneously produced, deep cough sputum samples, otherwise induced sputum or gastric lavage • Preferably one early morning sample	• Microscopy • Culture • Histology	• CBNAAT
Pulmonary (children aged 15 years or younger)	• X-ray • Computed tomography thorax	• Three respiratory samples: preferably spontaneously produced, deep cough sputum samples, otherwise induced sputum or gastric lavage • Preferably one early morning sample	• Microscopy • Culture • Histology • CBNAAT (one per specimen type)	• Interferon-γ release assay and/or tuberculin skin test (with expert input)

Table 3: Site-specific investigations for pleural tuberculosis

Suspected site of disease	Possible imaging techniques	Specimen	Routine test	Additional tests on primary specimen
Pleural	• X-ray • Broncho-scopy	• Three respiratory samples: preferably spontaneously produced, deep cough sputum samples, otherwise induced sputum or gastric lavage • Preferably one early morning sample • Pleural biopsy	• Microscopy • Culture • Histology • Cartridge-based nucleic acid amplification test	–
		• Pleural fluid	–	Adenosine deaminase assay

Diagnosis of Latent Tuberculosis Infection

The traditional method of diagnosing LTBI is the TST. However, newer diagnostic tests are now available commercially, e.g., QuantiFeron®-TB Gold In-Tube (QFT-IT) and the T-Spot, TB.

TUBERCULOUS LYMPHADENITIS

Tuberculous lymphadenitis is the most common form of extrapulmonary TB in children and is usually due to *M. tuberculosis*. One or more lymph nodes may be affected. The affected lymph nodes may be a localized group (regional

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adenopathy) or at multiple sites. These may be unilateral or bilateral.

Clinical Features

Tuberculous lymphadenitis most frequently involves the cervical lymph nodes followed by mediastinal, axillary, mesenteric, porta hepatis, perihepatic, and inguinal lymph nodes (Table 4). Symptoms usually develop gradually and insidously.[6-8] The three characteristic features of tuberculous lymphadenitis are:

1. Affection of multiple nodes
2. Matting
3. Caseation.

Lymph nodes affected by TB are usually nontender, hence the terminology—"cold abscess".

NEUROTUBERCULOSIS

Tuberculous involvement of the brain and spinal cord is more common in children below 5 years of age.

Clinical Picture of Central Nervous System Tuberculosis

Tuberculous meningitis (TBM) is the most common type of neurotuberculosis in our country.[9] Different stages of CNS tuberculosis can be differentiated on the basis of clinical features as follows:[10]

- Stage I (early): Conscious, nonspecific symptoms without any neurological symptoms
- Stage II (intermediate): Signs of meningeal irritation are present, with or without affection of the sensorium, with or without minor neurological deficits like cranial nerve palsy or limb paresis
- Stage III (advanced): Severe clouding of the sensorium, convulsions and focal neurological deficits, involuntary movements.

Laboratory Diagnosis

This is based on the findings in the cerebrospinal fluid (CSF). But, these tests are neither sensitive nor specific (Table 5).

Table 4: Site-specific investigations for lymph node tuberculosis

Suspected site of disease	Possible imaging techniques	Specimen	Routine test	Additional tests on primary specimen
Lymph node (including intrathoracic mediastinal adenopathy)	• Ultrasound • Computed tomography • Magnetic resonance imaging	Biopsy	• Microscopy • Culture • Histology	Cartridge-based nucleic acid amplification test
		Aspirate	• Microscopy • Culture • Cytology	

Table 5: Site-specific investigations for central nervous system tuberculosis

Suspected site of disease	Possible imaging techniques	Specimen	Routine test	Additional tests on primary specimen
Central nervous system	• CT • MRI	Biopsy of suspected tuberculoma	• Microscopy • Culture • Histology	• CBNAAT
		Cerebrospinal fluid	• Microscopy • Culture • Cytology • CBNAAT	• Adenosine deaminase assay
Meningeal	• CT • MRI	Cerebrospinal fluid	• Microscopy • Culture • Cytology • CBNAAT	• Nucleic acid amplification test • Adenosine deaminase assay

CT, computed tomography; MRI, magnetic resonance imaging; CBNAAT, cartridge-based nucleic acid amplification test.

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Molecular Diagnostic Tests

Detection of *M. tuberculosis* antigens and antibodies in the CSF has no value.[11]

Recent data shows that commercial nucleic acid amplification tests for the diagnosis of TBM show a combined average sensitivity of 56% and specificity of 98%. Hence, due to the high specificity, a positive commercial nucleic acid amplification tests is regarded as a definite test in cases of suspected TBM. It is of particular value in those patients who have already received TB treatment.[12]

Radiological Evidence

Radiology has an established role in the diagnosis of CNS tuberculosis. Hydrocephalus and basal meningeal enhancement are the most common findings.

Computed Tomography Findings in Tuberculous Meningitis

Combination of infarcts, hydrocephalus, and basal meningeal enhancement has a 100% specificity in the diagnosis of TBM. Basal meningeal enhancement is the most sensitive finding.[13]

Magnetic Resonance Imaging in Tuberculous Meningitis

Magnetic resonance imaging (MRI) is very useful in the detection of abnormalities like meningeal enhancement, infarcts and tuberculomas especially in the area of the brain stem. In patients with coinfection of HIV and TBM, hydrocephalus and basal meningeal enhancement are not very frequently seen. The positive findings in such cases are infarcts, gyral enhancement, and mass lesions. Cerebral atrophy is also commonly present.[14]

Spinal TB is diagnosed by CSF examination and MRI of the spine.[15] One should actively rule out TB elsewhere in the body, especially in all cases of TBM.

Parenchymal Neurotuberculosis

Parenchymal tuberculous affection results in the formation of a tuberculoma or tuberculous granuloma. Tuberculoma usually occurs in solid organs.

Clinical Features

The clinical presentation is determined by the size and location of the tuberculoma as well as the concurrent absence or presence of meningitis. The child usually presents with seizures without any meningeal signs and without any evidence of TB elsewhere in the body. If the location of the neurotuberculoma is infratentorial then the child will present with features of raised intracranial tension.

ABDOMINAL TUBERCULOSIS[16]

Clinical Features

Usually the symptoms are vague and non-specific. In children peritoneum and abdominal lymph nodes are more commonly involved as compared to the intestine per se. Contiguous extension is common, especially tuberculous salpingitis and TB of the spine.

Peritoneal Tuberculosis

The presenting features of this type of TB are abdominal distension and ascites. Constitutional symptoms like fever and night sweats may be present. Abdominal examination reveals a diffuse tenderness with a doughy feeling. Enlarged mesenteric lymph nodes may be the other presentation.

Small Intestinal and Ileocecal Tuberculosis

Older children and adults are more commonly affected. The various types are:

- Ulcerative: Presenting with chronic diarrhea and features of malabsorption
- Stricturous: May present with subacute intestinal obstruction
- Hypertrophic: May also present with the earlier feature as well as a vague lump in the abdomen. Involvement of other sites like colorectal and anal areas is rare. In disseminated disease, spleen, pancreas, and the hepatobiliary region can be involved.[17]

Diagnosis of Abdominal Tuberculosis

Diagnosis is achieved by demonstration of the AFB.

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The following samples can be tested (Table 6):

- Ascitic fluid: The yield is usually low for smear[18,19] as well as for culture.[20] However, if the sample is concentrated, the yield of culture can be increased by approximately 80%
- Fine-needle aspiration cytology: Fine-needle aspiration cytology from an intra-abdominal mass can give a quick diagnosis. Mass could either be a lymph node mass, rolled up omentum or intestines. Ultrasound and computed tomography (CT)-guided aspiration can be done if the mass is deep-seated. This sample can further be tested for smear, culture or histopathology[20]
- Biopsy: Biopsy material can be obtained by upper or lower gastrointestinal endoscopy, peritoneal biopsy, laparoscopy, peritoneoscopy, laparotomy, liver biopsy, and splenic aspirate.
- Gastric aspirate
- Stool
- Sputum
- Urine.

Other Investigations

Other tests to prove the diagnosis of TB are Mantoux test, chest X-ray, family screening, plain X-ray abdomen, abdominal ultrasound, percutaneous fistulogram, barium meal and follow through, and a barium enema.

Enzyme-linked immunosorbent assay tests for antigens and antibodies are not recommended for the diagnosis. Polymerase chain reaction (PCR) and certain newer seromarkers such as C-X-C motif chemokine IP-10 (CXCL-10) are being investigated for the diagnosis.[21,22]

GENITOURINARY TUBERCULOSIS

Genitourinary tuberculosis (GUTB) often presents insidiously and with nonspecific complaints. This very often leads to the diagnosis being missed or delayed. The risk is of a rapid progression to a nonfunctioning kidney. Investigations which are helpful in the diagnosis of GUTB are given in table 7.[23]

SKELETAL TUBERCULOSIS

Tuberculous arthritis usually involves only one joint. Although any joint may be involved, the hips and knees are affected most commonly, followed by the ankle, elbow, wrist, and shoulder.[24] Pain may precede radiographic changes by weeks to months. Tubercular osteomyelitis is often diagnosed late, as the onset is insidious and the acute symptoms of pyogenic osteomyelitis are generally not present (Table 8).

Table 6: Site-specific investigations for gastrointestinal tuberculosis

Suspected site of disease	Possible imaging techniques	Specimen	Routine test	Additional tests on primary specimen
Gastrointestinal	• Ultrasound • Computed tomography • Laparoscopy	• Biopsy of omentum • Biopsy of bowel • Biopsy of liver	• Microscopy • Culture • Histology	–
		• Ascitic fluid	• Microscopy • Culture • Cytology	• Cartridge-based nucleic acid amplification test • Adenosine deaminase assay

Table 7: Site-specific investigations for genitourinary tuberculosis

Suspected site of disease	Possible imaging techniques	Specimen	Routine test	Additional tests on primary specimen
Genitourinary	• Ultrasound • Intravenous urography • Laparoscopy	• Early morning urine	• Culture	–
		• Biopsy from site of disease, such as endometrial curettings or renal biopsy	• Microscopy • Culture • Histology	–

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Table 8: Site-specific investigations for bone and joint tuberculosis				
Suspected site of disease	**Possible imaging techniques**	**Specimen**	**Routine test**	**Additional test on primary specimen**
Bone or joint tuberculosis	• X-ray • Computed tomography • Magnetic resonance imaging	• Biopsy or aspirate of paraspinal abscess • Biopsy of joint • Aspiration of joint fluid	• Culture • Cartridge-based nucleic acid amplification test	–

DISSEMINATED TUBERCULOSIS

Disseminated TB or miliary TB is a potentially lethal condition and often goes undetected due to the nonspecific symptoms. An underlying immune deficiency or HIV status should always be investigated. Table 9 lists the investigations, which help in the diagnosis of this condition.[25] In addition, evaluation of the fundus should be done.

LOCALIZED TUBERCULOSIS

Localized tuberculous abscess can be evaluated in table 10.

HUMAN IMMUNODEFICIENCY VIRUS AND TUBERCULOSIS

Recent data suggests that HIV infection is probably one of the most important factors leading to increased incidence of TB in adults as well as in the children.[26]

Two mechanisms serve to lead to an increased incidence of TB in patients infected with HIV:

1. Individuals coinfected with HIV-TB can transmit the *Mycobacterium tuberculosis* infection to others, thus putting them at high risk for developing significant disease including drug-resistant TB

Table 9: Site-specific investigations for disseminated tuberculosis				
Suspected site of disease	**Possible imaging techniques**	**Specimen**	**Routine test**	**Additional tests on primary specimen**
Disseminated	• Computed tomography of the thorax and head • Magnetic resonance imaging • Ultrasound of the abdomen	• Biopsy of site of disease, including lung, liver, and bone marrow	• Microscopy • Culture • Histology	• Additional tests appropriate to site • Cartridge-based nucleic acid amplification test
		• Aspirate bone marrow • Bronchial wash • Cerebrospinal fluid	• Microscopy (if sample available) • Culture • Cytology	
		• Blood	• Culture	

Table 10: Site-specific investigations for localized tuberculous abscess				
Suspected site of disease	**Possible imaging techniques**	**Specimen**	**Routine test**	**Additional tests on primary specimen**
Abscess outside of the lymph nodes	Ultrasound or other appropriate imaging	Aspirate	• Microscopy • Culture • Cytology	Cartridge-based nucleic acid amplification test
		Biopsy	• Microscopy • Culture • Histology	

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2. Individuals of populations with a high incidence of HIV infection are at higher risk of developing HIV and subsequently more prone to developing TB.

There is no difference in the clinical features of TB in HIV-infected children, however, as mentioned before they are at a higher risk of developing more severe and disseminated disease.[27]

CONCLUSION

Diagnosis of childhood tuberculosis continues to remain a challenge, especially in immunocompromised and those with HIV co-infection. The spectrum of the disease may range from a latent or an asymptomatic presentation to a rapidly progressive disseminated or miliary TB.

This review sums up the clinical, radiological, and bacteriological approaches to diagnose the diverse presentations of TB infection and disease in children.

Fever which is low grade and intermittent, weight loss or failure to thrive, and cough persisting for more than 2 weeks remain the most useful symptoms for diagnosing pulmonary tuberculosis. Extrapulmonary TB, which is not so uncommon, would present with additional specific symptoms or signs. Index of suspicion should be high in the evaluation of certain groups of patients, since they may not have a typical presentation. These patients are children below 5 years, unvaccinated children, poor nutritional status, contact history of pulmonary TB, and those on immunosuppressive drugs. Evidence of an adult TB index case is clue for diagnosis of childhood TB in low-endemic countries.

Although Mantoux test remains in the forefront of laboratory tests, other investigations, relevant to system affected should be performed. Bacteriological confirmation should be aggressively sought and fluids and tissues obtained whenever possible and sent for CBNAAT, culture for mycobacteria, and drug sensitivity. Chest radiographs provide important information in many patients and advanced imaging can be applied in case of (and should be restricted to) inconclusive diagnosis.

Continuous assessment and evaluation of the patient, along with appropriate investigations in suspected cases would definitely march us towards a TB free India.

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Imaging in Tuberculosis
Clinicopathological Correlation

Key Features

- The book is a compilation of various facets of imaging in tuberculosis with special emphasis on its clinicopathological correlation
- Also covers important aspects of tuberculosis like epidemiology, clinical perspective and management
- Includes designated chapters on extrapulmonary tuberculosis involving the central nervous system, spine, head and neck, lymph nodes, abdomen, urogenital system and bones and joints
- Written by experts well known for their academic inclination and capability
- The book is a valuable resource for pulmonologists, physicians and postgraduate students.

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