Extra-Pulmonary Tuberculosis

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133

ABSTRACT

Tuberculosis (TB) is one of the commonest infections occurring in individuals with HIV/AIDS and TB rates have gone up in many parts of the world. Extrapulmonary TB assumes importance as clinical presentation may be diverse and a delay in diagnosis can prove fatal. The emphasis on clinical presentation may be so great that it leads to over diagnosis. There is ambiguity regarding duration of drug therapy and role of surgery. Short course chemotherapy regimen for 6-12 months has proved effective in obviating the need for surgery in majority of the cases. A high index of suspicion and early diagnosis and regular chemotherapy results in a favorable outcome.

INTRODUCTION

The clinical manifestation of tuberculosis can be pulmonary or extrapulmonary (outside the lungs). The highly vascular areas like lymph node, meninges, kidney, spine and growing end of bones are usually affected. In India, 10-15% of all forms of TB are extrapulmonary TB. A higher prevalence has been noted due to the interaction of HIV and TB. The clinical presentation is may be so much atypical that TB may not be considered in the differential diagnosis. Sputum for AFB and X-ray chest may not aid in the diagnosis. Extrapulmonary TB may require specialist care with diagnostic modalities that may not be widely available. Mantoux is useful, but its value is limited to children less than 5 years of age, as 40% or more of the Indian population is infected with TB. The PPD assumes importance as far as TB lymphadenitis is concerned. Attempts should be made to confirm the diagnosis by HPE or bacteriological smear/culture wherever possible. Studies conducted by TRC showed 33-62% culture positivity in different forms of extrapulmonary TB (Table 1). Even though a number of reports on immunologic tests like SAFA, ELISA and slide agglutination technique are available, the specificity and sensitivity are variable and need to be interpreted in the light of clinical findings. Supportive evidence from ADA of more than 9 IU and lysozyme of 2mg /litre or more could provide an indirect diagnosis in some cases like TB meningitis. Several RCT's have established the efficacy of Short Course Chemotherapy (SCC) as the main stay of management.[7] The response to intermittent regimen has been as effective as daily regimen. The International Union against TB and lung diseases and the joint tuberculosis committee of the British Thoracic society have recommended 2HRZ7/4HR7 for all extrapulmonary forms of tuberculosis except serious forms like joint and brain TB where the duration is extended upto 12 months. The cure rate was 87-99% except in Pott's paraplegia and relapse rate was less than 4%.

TB LYMPHADENITIS

It is the commonest type of TB described in hippocrates writing dating back to 460-377 B.C. It was initially thought to be cured by the touch of the king (king's evil) in Europe.

Table 1 : An overview of studies conducted by TRC in various extrapulmonary forms of TB.

Studies	No.of patients	Mx +	X-ray evidence	No. of specimens	Bac. proof	HPE proof
TB spine	304	93	13	85	50	29
TB meningitis	180	50	55	180	33	-
TB lymphadenitis	197	81	24	168	62	98
TB abdomen	193	74	48	156	40	51
Tuberculoma brain	108	44	9	13		61

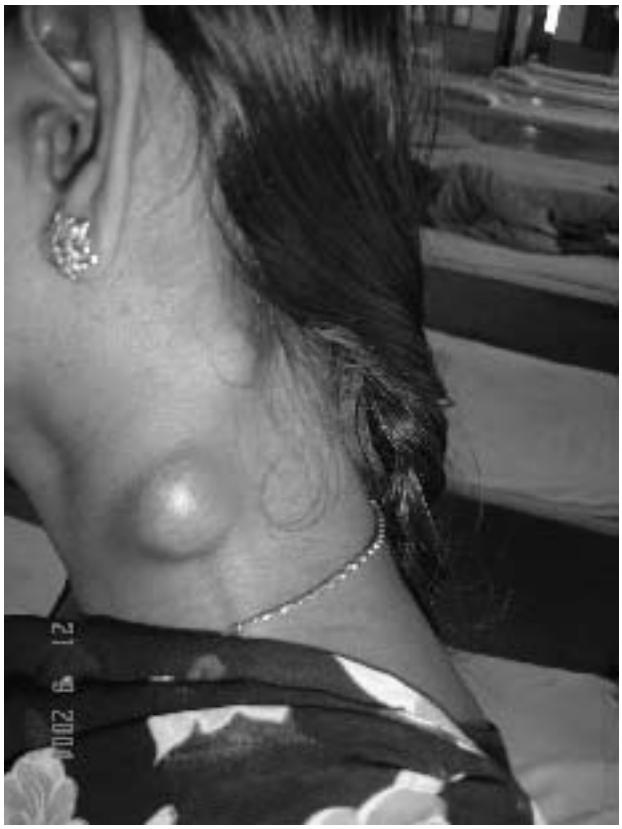

Fig 1 : Caeseating lymphnode in the cervical region with cold abscess formation

Epidemiology: Cervical region is the commonest. Risk factors include younger age group, immune status, race (more in blacks). Sex: F>M .2:1.

Pathology: It spreads from primary focus to regional draining lymph nodes. This often results in a greater volume of diseased tissue in regional lymph nodes than at the original site of infection. Further spread via lymphatic to other nodes and hematogenous spread occurs if not contained.

Bacteriology: *Mycobacterium TB* is the commonest in India followed by *M.bovis* and africanum. Non –TB mycobacteria especially MAC and scrofulaceum should be kept in mind in the HIV millennium.

Clinical features: Persons affected may have nonspecific constitutional symptoms.

Locally there may be a painless swelling with discharging sinus with or without scar. A classical presentation is multiple, matted and variable consistency of the lymph node which is painless and slow growing. Rare manifestations include chyluria, chronic abdominal pain, progressive jaundice, dysphagia and generalized lymphadenopathy.[1]

Histology: Reveals epitheloid cells, modified histiocytes, Langhans giant cells surrounded by dense, infiltrate of lymphocytes.caeseation may or may not be present.

Investigation: Mantoux is significant especially in < 5 years of age, but may not be specific. FNAC is the easiest, safe and convenient way of proving the diagnosis followed by biopsy. (Fig. 2 Xray of the chest showing lymphadenitis) CT scan of the chest/abdomen may give additional details such as mediastinal or retroperitoneal adenopathy.and can even distinguish between MTB And MAC. The presence of focal visceral lesion and low attenuation in LN suggest MTB.Marked hepatic and splenic enlargement with enlarged soft density nodes.(density> muscle suggest MAC.[8])

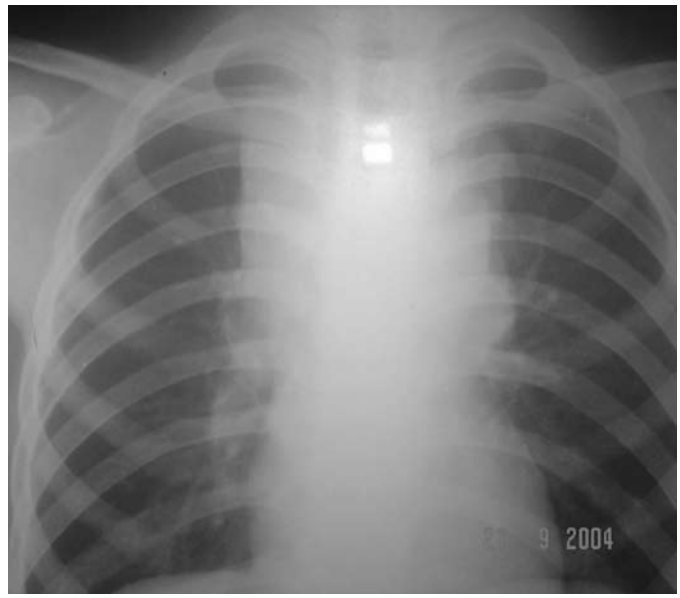

Fig. 2 : Chest X-Ray showing mediastinal adenitis

Treatment: Medical RNTCP: CAT III with 2 months of HRZ/4HR in immunocompetent patients. Four drugs in the intensive phase in immunocompromised /seriously ill patients.

Surgical indication: 1) sinus tract removal 2) Enlargement and softening in spite of treatment 3) Concomitant and suspicion of malignancy. 4) Atypical mycobacteria

TB BONE AND JOINTS

The incidence of skeletal tuberculosis is very high in children, adolescents and young adults. Higher incidence of 30% occurs in young adults. It is uncommon in old age. Among TB patients, 1-3% have skeletal TB.

Etiology: Like other infection, it is mostly a monoarthritis. MTB is the causative organism .It is secondary to another focus in the lung or contiguous nodes as a rule.

Pathology: There are two types of microscopic lesions. The ***caeseating exudative*** type with predominant necrosis and cold abscess formation.2***) the proliferating type*** where the cellular proliferation predominates with minimal or no caeseation. The extreme form occurs in TB granuloma of the shoulder "***Caries sicca***".

Clinical features: Onset is insidious with constitutional symptoms. It is succeed by localizing symptoms and signs according to the site involved.

TB spine: (Pott's spine) Fig. 3

Tuberculosis of the spine forms 50-60 % of the total incidence of skeletal tuberculosis. The most common level is the thoracolumbar region due to excessive strain of movement and weight bearing at this level. The various locations favored are 1) paradiscal

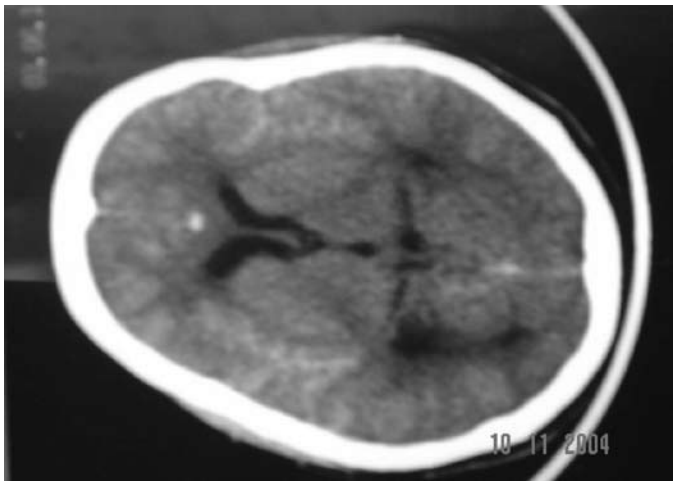

Fig. 3 : X-Ray showing caries spine with wedging of the vertebra

region 2) central body 3) anterior type 4) apppendiceal lesion 5) articular region. The lesion soon destroys the intervertebral disc and adjacent body of the vertebra, which collapse and obliterate the intervertebral space. Destruction of the framework results in an angular kyphosis called gibbus. Spreading caeseation and osteolysis leads to a cold abscess.

Clinical features: 1) pain, which can be localized or referred pain. 2) rigidity, caused by spasm of para spinal muscles demonstrated by coin test. 3) deformity can be in the form of gibbus in thoracic region and loss of normal curvature as in cervical or lumbar region. 4) cold abscess: the abscess forms in the para vertebral region and soon tracks downwards due to gravity and tracks down along the neurovascular bundle. In the cervical region, it forms a retropharyngeal abscess. In the thorax, it can track lateral, or anterior. Thoracolumbar cold abscess can point in the back or enter the psoas sheath and track down to psoas or iliac region. 5) paraplegia: occurs in 10% of cases, the higher being in the thoracic spine. Early onset paraplegia occurs in the active stage of the disease. Late onset paraplegia occurs due to deformity or sequelae. A rare gradual onset of paraplegia occurs in "Spinal cord tumor syndrome", due to granulation tissue growing inside the spinal cord.

Investigations: Specific; X-Ray spine: earliest radiological sign is narrowing of intervertebral space followed by erosion, destruction and collapse of vertebral bodies with obliteration of intervertebral space. CT of the spines is shown in Fig. 4.

Treatment: Anti-TB treatment for a period of 6-12 months. Once the lesion becomes quiescent, patient is given a spinal brace. Surgery is indicated 1) when there is no sign of recovery, 2) paraplegia getting worse in spite of treatment 3) spastic paraplegia. The randomized clinical trial conducted in Madras by TRC, in collaboration with BMRC, and orthopedic department of GGH in 1975-78 showed that SCC for 9 months is effective for spinal tuberculosis without paraplegia obviating the need for surgery. Surgery is indicated only in patients less than 15 years of age and having an initial angle of kyphosis > 30°.[2,3,7]

TB Hip joint

It is the second most common site involved in the age of 5-15 years.

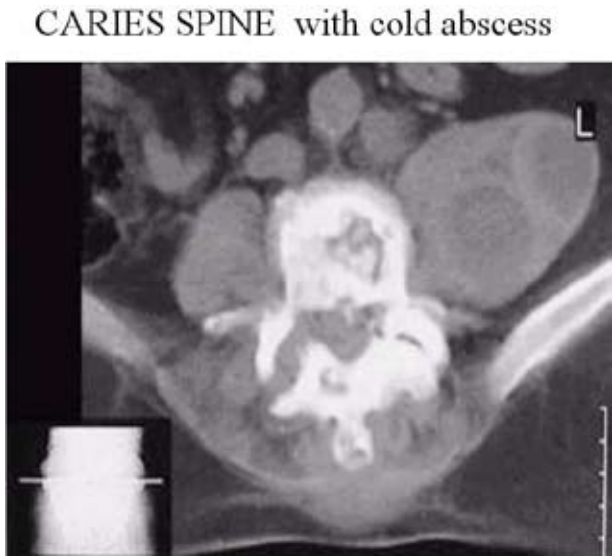

Fig. 4 : CT showing caries spine with psoas abscess

Stage 1) there is exudation into the joint cavity with the limb assuming flexion, abduction and external rotation. Stage 2) the spasm of adductors take over resulting in flexion, adduction, internal rotation. Stage 3) the neglected joint is destroyed resulting in real shortening of the limb

The cold abscess opens with sinus pouring out pus.

X-Ray of the hip joint: 1. Rarefaction of bone and joint space widening due to effusion. 2. Erosion of articular surface and narrowing of joint space. 3. Destruction of the femur with dislocation of acetabulum"traveling acetabulum". MRI and CT can reveal abnormalities in greater detail.

Treatment: SCC for 6 months. bed rest for 3 months followed by protected weight bearing.

TB Shoulder Joint: In this site, it is Caries sicca of the dry type.

TB Osteomyelitis

Occurs in children, affecting the shaft of phalanges. There is subperiostial new bone formation and thickening of the bone peculiar to TB infection of the short long bones making the fingers spindle shaped "spina ventosa"

BCG Osteomyelitis: It is a rare complication of BCG vaccine occurring in a few months to few years after BCG vaccination. The condition is benign and heals with ATT.

Poncets Osteomyelitis: It is a polyarthritis resembling rheumatoid arthritis occurring during treatment. The condition requires symptomatic management only.[3]

ABDOMINAL TUBERCULOSIS

Includes upper GI lesions, ulceration, ileocaecal, omental inflammation, mesenteric adenitis, TB peritonitis, anorectal lesion, hepatitis. Some of them are described here (Frequency distribution given in Table 2).

Intestinal TB

Its prevalence has increased in the era of HIV. It constitutes 5% of extra pulmonary TB in India. It can be primary from swallowing

Table 2 : Frequency distribution of abdominal TB :[4]

Location	Clinical reporting Percentage
Esophageal	0.3
Stomach	2
Duodenum	0.3
Jejunum Ileum	35* (*includes both)
Ileocaecal	42
Appendix	1
Colon	12
Anorectum	7

and ingestion of infected sputum or by haematogenous spread from miliary or primary pulmonary TB, (silent bacilliemia).

Anatomical distribution: It can occur anywhere from mouth to anus, ileocaecal junction being the commonest. The preponderance of lymphoid tissue, increased physiological stasis, increased rate of absorption, and electrolyte absorption, minimal digestive activity all favour the invasion of the TB bacilli at the site. The involvement of oesophagus, pancreas and appendix are common in HIV.

Pathology

1. ***Ulcerative***: Multiple small ulcers coalesce to form large ulcers that may be thickened, infiltrated or everted with skip areas. They do not penetrate the muscularis mucosa. perforation is uncommon. The ulcers heal with extensive fibrosis leading to stricture, "Napkin ring appearance".
2. **Hypertrophic** type : Inflammation and fibrosis in submucosa mimicking a neoplasm.
3. **Mixed variety** : The mucosa has a cobblestone appearance with pseudopolyp, and flaps
4. **Diffuse** : Resembling ulcerative colitis.

Granulomas in bowel and lymph node are usually caeseating.

Clinical features: Symptoms include nonspecific abdominal pain, weight loss, lassitude, distension of abdomen. ("Ball of Wind-gala"), constipation, diarrhea, occasionally bleeding. The pain in lower abdomen can be in the right, or left lower quadrant, crampy or colicky pain increases on eating and decreases by vomiting and defaecation. There is doughy feeling of the abdomen due to extensive fibrous adhesion and inflammation.

Treatment: Short Course Chemotherapy cures majority of the cases.

Complications: 1. Stricture formation with subsequent obstruction. 2. luminal narrowing due to inflammation and adenitis, colonic traction, diverticula,fixation and sinus formation. 3. fistula due to secondary bacterial infection. 4. secondary malabsorption syndrome due to decreased absorptive area, bacterial overgrowth ("Stagnant loop syndrome").

Peritoneal TB: Constitutes 4 – 10 % of extra pulmonary TB. It may be due to activation of latent focus or hematogenous spread. Ascitis occurs due to studding of parietal and visceral peritoneum by exudation or from contiguous nodes. There are three types 1) **ascitic type** or exudative type. 2) plastic or **hyperplastic** type involving the greater omentum. 3) **fibrotic** with focal and minimal fibroblastic with peritoneal adhesion.

Table 3 : Histopathological Features

Histopathological features differentiating TB and Crohns	TB	Crohn's
Granuloma surrounded by inflammation	+	----
Submucosal widening	-----	+
Transmural /follicular hyperplasia	--------	+
Epithelial regeneration	+	-------
Glandular metaplasia	+	--------

Clinical features: Common in females, insidious in onset. Symptoms include anorexia, abdominal distention, and doughy abdomen ("cotton wool sign"). Plastic form presents as a lump. Fibrotic form presents with features of obstruction.

Tabes Mesenterica

Glandular TB abdomen involving mesenteric nodes in children mimicking appendicitis. Children present with fever, intermittent abdominal pain, localized to right iliac fossa mimicking appendicitis.

Investigations: *USG Abdomen*: which may show fixed membranes, septa, floating debris or Omental cake; thickened mesentery with adherent loops, lymphadenopathy. CT scan of the abdomen may show high-density ascitis with abdominal lymphadenopathy. Paracentesis shows straw colored exudative high proteineceous fluid with lymphocytic predominance which is classical of tuberculosis. Smear is positive for AFB in 3%. Culture positive in 10-20%. Increased ADA activity in ascitic fluid is sensitive and specific for TB peritonitis. But it may be diminished in HIV. Stool examination for AFB culture can be a useful addition. Barium study of the small intestine and colon may show 1)increased transit time with hyper segmentation and flocculation of barium (earliest sign). 2) thickening of mucosal folds with scalloping speculation. 3)ulceration 4)Sterling sign : exclusion of barium from an involved segment with adjacent normal looking segments. 5) Fleishner's sign: ileocaecal valve is patulous in TB, stenotic in Crohns. (Table 3 gives the histopathological differences between TB and Crohns). Biopsy: either direct or laparscopic /USG or CT guided biopsy. Yield is nearly 60-75%.[4]

Treatment: Short course chemotherapy.

TB BRAIN

Tuberculosis of the brain occurs in 5-10% of adult cases of clinical TB and 20-60% of children dying with active TB have a brain or meningeal involvement. In India, TB meningitis constitutes nearly 50-55% of bacterial meningitis.

Bacteriology: majority of cases is due to mycobacterium tuberculosis. NTM and bovine species contribute to less than 5%.[5]

TB Meningitis (TBM)

Pathology: TBM occurs in 3 stages. 1) hematogenous seeding of the meninges "**RICH FOCUS**". 2) Quiescent phase for weeks, months. 3) releasing phase which may be triggered by immune

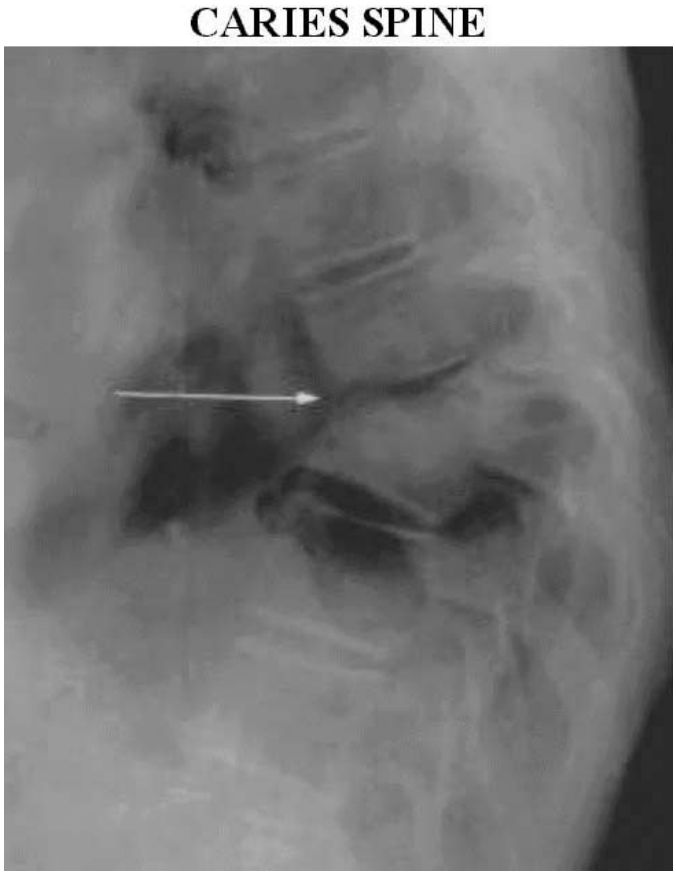

Fig. 5 : CT contrast showing typical enhancement of the Sylvian fissure

activation, coinfection, trauma which releases antigenic material into the meninges.

Progression and manifestation depends on 1) number of bacilli 2) virulence of the strain 3) immune status of the individual.

Meningeal changes: Exudation occurs between pia and arachnoid thickening the arachnoid. This is mainly composed of fibrin and inflammatory cells with neutrophils in the early period followed by lymphocytes, plasma cells, epitheloid and giant cells subsequently.

Vascular changes: All size of arteries are involved .the terminal portion of ICA and the proximal portion of MCA in the slyvian fissure are commonly affected. Vertebro-basilar vessels usually escape. (Fig. 5)

Parenchymal changes : Due to meningeal and vascular changes, there is vascular insuffiency, edema, hydrocephalus, portion of brain adjacent to meninges has "border zone reaction" of edema, perivasculitis and gliosis.

Hydrocephalus: it occurs if the patient survives for 4-6 weeks, reasons are 1.blockage of cistern with the exudates in acute phase. 2. adhesive leptomeningitis 3.due to obstruction of CSF circulation.4.blockage of aqueduct.

Clinical features : Clinical profile has changed due to 1) mass BCG vaccination 2) later onset of primary infection 3) malnutrition 4)HIV/ AIDS.

Stages: **Prodromal phase** (in *children*) of vague ill health, apathy, irritability, loss of appetite, nausea, abdominal pain,

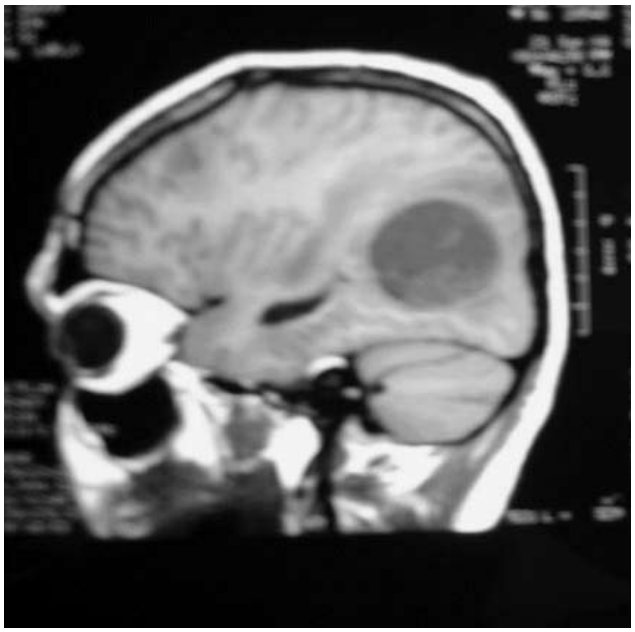

Fig. 6 : MRI showing Tuberculoma Brain

convulsions in less than 2 years and depression, behavioural changes, headache, fever, meningismus in adults.

Stages in TBM (modified by BMRC) Stage 1: nonspecific symptoms, fully conscious and alert.

Stage 2: meningismus, drowsiness, lassitude, cranial nerve palsy due to presence of thickened basilar exudates compounded by hydrocephalus. Commonest is VI nerve palsy followed by III, IV, and VII. Stage 3: Advanced stage comprising of stupor, systemic toxicity, gross paresis/paralysis, seizures, choreoathetosis, and coma. Ophthalmic signs include choroidal tubercles, papilloedema, and internuclear opthalmoplegia.

Diagnosis: chest x-ray may show active or healed lesion of pulmonary TB

CT scan of the brain may give valuable information regarding enhancing exudates.

Hydrocephalus, infarcts due to vascular obstruction, tuberculoma or miliary nodules Gadolinium enhanced MRI is more sensitive as peripheral lesions are better visualized.

Treatment: Short Course Chemotherapy (9-12 months)

Steroids are indicated in stages II and III. When there is significant cerebral edema, spinal cord disease, and drug reaction. **Surgery**: is indicated 1) in releasing hydrocephalus if ICT is life threatening.

2) Vision is compromised 3) CT shows progressive increase in size of the ventricles inspite of treatment. Prognosis depends on 1) age of onset 2) stage of the disease 3) malnutrition 4) prior BCG vaccination 5) increased ICT 6) encephalopathy 7) inadequate, improper, irregular treatment 8) drug resistance.[6]

Tuberculoma (Fig. 6)

A tuberculoma results when intracranial tubercles enlarge without rupturing into the subarachnoid space. Tuberculoma refers to aggregate of small granulomatous lesion in the parenchyma of the brain. Sometimes there is a paradoxical reaction on treatment

with ATT resulting in enlargement due to inflammatory response originating from released antigen.[6]

Types: 1) *Tuberculoma en-plaque* 2) *cystic tuberculoma* 3) *tuberculous abscess*.

They usually present with signs and symptoms of raised intracranial tension. focal signs occur in 85% of supratentorial type with seizures, focal motor deficits. Unlike meningitis, fever and systemic symptoms are not common. CT of the Brain may show a thick ring of enhancement surrounded by a punctuate central clearing representing the casesous centre of the lesion.

Treatment: Short Course Chemotherapy. Rarely surgery is required.

EXTRAPULMONARY TB IN HIV

The global prevalence of HIV is 40 million with 3 million deaths/year. In India, there are an estimated 5.1 million cases. TB enhances HIV replication by secretion of TNF alpha , destruction of CD4 cells and fastened release of virions from infected cells and increased apoptosis. HIV promotes TB by decreasing macrophage activating lymphocytes, decreasing CD4 cells and increasing tissue destruction. *Mycobacterium tuberculosis* by itself may contribute to immunosuppresion shown by Ellner et al. 1989. TB remains the most common opportunistic infection among HIV positive patients in India. The clinical and radiographic features vary with the degree of immunosuppresion.[9] There is a greater tendency for extra pulmonary forms as well as disseminated TB as immunity goes down.[10] Extrapulmonary involvement in AIDS patients may be high as 70%.[11]

The introduction of HAART has dramatically changed the survival rate in all opportunistic infections including TB. In patients with HIV and TB, Anti retroviral therapy (ART) can be instituted if CD4 is less than 50 cells and after the intensive phase if CD4 is between 50-200 cells. This is because the maximum side effects of the ATT drugs usually occur during the first 2 months. However, ART has to be modified due to the interactions between rifampicin and nevirapine and rifampicin and other protease inhibitors.

Immunoreconstitution Syndrome (IRS)

The development of a paradoxical reaction or IRS should be considered in patients with (1) emergence or worsening of the clinical manifestations of tuberculosis with or without positive acid-fast bacilli smear or culture results obtained from the involved organs; (2) exclusion of other potential causes of the symptoms and signs after an extensive diagnostic evaluation, particularly drug fever and other infections related or not with HIV; and (3) exclusion of drug-resistant tuberculosis or other causes that could explain the persistence or relapse of tuberculosis.

Often there is an aggravation of symptoms, flare up of the disease, radiological worsening on instituting ART. It usually occurs in the first 1-4 weeks after initiating ART. This kind of paradoxical reaction has been reported earlier in TB itself especially with Tuberculomas of the brain and lymph nodes. As a rule, other infections and resistance should be ruled out first. After reasonably excluding other causes, steroids can be given and gradually tapered along with ATT preferably in a tertiary care unit. Termination of ATT or HAART is rarely required.

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