

# **MILIARY TUBERCULOSIS**

# DEFINITION

- Disseminated Tuberculosis refers to concurrent involvement of at least two non contiguous organ sites of the body or involvement of the blood or bone marrow by tuberculosis process. One form of disseminated tuberculosis is Miliary T. B.
- Miliary tuberculosis results from massive hematogenous dissemination of tubercle bacilli which results in tiny discrete foci usually the size of millet seeds (1-2 mm) more or less uniformly distributed in the lungs and the other viscera.
- Miliary pattern on chest x-ray is a hallmark of MTB.

# EPIDEMIOLOGY

- Data from CDC (Centers for Disease Control) remarkably consistent 1.3% of reported cases of T.B. were classified as miliary.
- In urban areas incidence of Miliary T.B. is now increasing because of Joint emergence of HIV and Multidrug resistant strains of Myc T.B.
- Males are more often affected than women in most series.
- CDC in (1969-1973) found that disseminated disease comprise 2.9% of all cases of T. B. reported for blacks, while 1.2% was seen reported for whites.
- (it was found that HLA Phenotype (BW15) appeared to be a marker for advanced tuberculosis disease (disseminated disease in blacks).

# EPIDEMIOLOGY...

- In preantibiotic era children (<3 yrs were most affected, in post isoniazid era it became common in elderly, now with increase HIV risk it is more prevalent in relatively young adults.
- Prevalence of military T. B. is become biphasic with peaks in early adult hold and later in life.

# PATHOGENESIS

- Unchecked dissemination can occur during primary infection or after reactivation of latent focus.
- During primary infection small number of tubercle bacilli usually gain access to circulation via lymphatics with predilection for most vascular and most oxygenated organs like liver, spleen, marrow and brain.
- Reactivation later in life may lead to localised extra pulmonary T.B.
- This occurs due to impaired cellular immunity, that usually occurs within 6 months of primary infection.
- Less commonly caseous necrosis of mediastinal lymphnode with drainage into Thoracic duct, caseation into pulmonary vein or caseation of extrapulmonary focus drained by portal circulation (Spleen, mesenteric nodes) leads to miliary T. B.

# PATHOGENESIS...

- A complex set of interactions between T lymphocytes, macrophages and organisms modulated by exogenous factors (coinfection, nutrition medications, toxic exposure) and genetic factors seem to determine likelihood of military dissemination
- Prior to onset of specific cell mediated immunity defective Tcell independent macrophage microbicidal function and antigen presentation can lead to uncontrolled bacillary growth and primary dissemination.
- In human 1, 25-hydroxy vitamin D<sub>3</sub> enhance macrophage microbicidal activity. Lack of sunlight and hence vitamin D<sub>3</sub> predisposes to disease and perhaps dissemination in susceptible individual.

# PATHOGENESIS...

- Monocytes from black donors will more permissive for intracellular growth of MTB and are less sensitive to 1, 25- hydroxy Vit D<sub>3</sub>.
- Disseminated T. B. has been associated with impaired expansion of Gamma delta T cells.
- In our study 9 of 12 black patients with pulmonary T.B. and the HLAB<sub>w</sub> 15 allele also had evidence of dissemination
- Failure to generate cell mediated immune CD<sub>4</sub> lymphocytes by generating activated blood born macrophages via IFN- $\gamma$ , IL-2 and other lymphokine appear to play a central role in rapid spread of infection at distant sites.
- Disseminated infection and impaired tuberculin reactivity are commonly associated with advanced HIV infection, as CD<sub>4</sub> count falls

# PATHOGENESIS...

- Viral infection – Measles, pertussis may predispose to disseminated T B. in early childhood.
- Certain aspects of normal cell mediated immune response may facilitate dissemination clonal expansion of CD<sub>8</sub> cytolytic T cell are able to lyse target cells presenting Myc antigen and MHC class I proteins is known to occur in course of tuberculosis infection.
- Overxuberant lysis of target cell Macrophages, by released of intracellular proteases, oxidents and viable organisms could contribute to tissue necrosis and facilitate extra cellular spread of organism.
- Virulance factors for M.T.B. remains poorly characterized
- Some isoniazid resistant strains lacking catalase activity are less likely to disseminante and there resistant strains that possess catalase activity are as virulent or slightly more virulent than sensitive strains.



# PATHOGENESIS...

- Iatrogenic disseminated T.B. the direct result of medical procedure, occurs rarely but has been reported to occur with extracorporeal shock wave lithotripsy, renal allograft placement ureteric catheterization and cardiac valve homograft placement.
- Disseminated BCG infection has occurred after intravascular BCG installation as chemotherapy for bladder cancer.

# CLINICAL MANIFESTATIONS

Clinical manifestations ranges from ARDS (Adult respiratory distress syndrome) shock, and multi-system organ failure to dysfunction of one or two organ systems to fever unknown origin to failure to thrive without fever may all be associated with Miliary T.B.

## **Pre disposing conditions found in patients with Miliary T.B.**

- History of alcohol
- History of steroid Rx
- Chronic renal failure
- Connective tissue disease
- Hematological disorder
- Immunosppressive R<sub>x</sub>
- Diabetes melitus

# CLINICAL MANIFESTATIONS...

## Symptoms in Patient with Miliary T. B.

- Anorexia
- Fever
- Weight loss
- Weakness
- Night sweats
- Cough
- Dyspnea
- Pleurisy
- Abdominal pain
- Headache
- Hemoptysis
- Nausea

# CLINICAL MANIFESTATIONS...

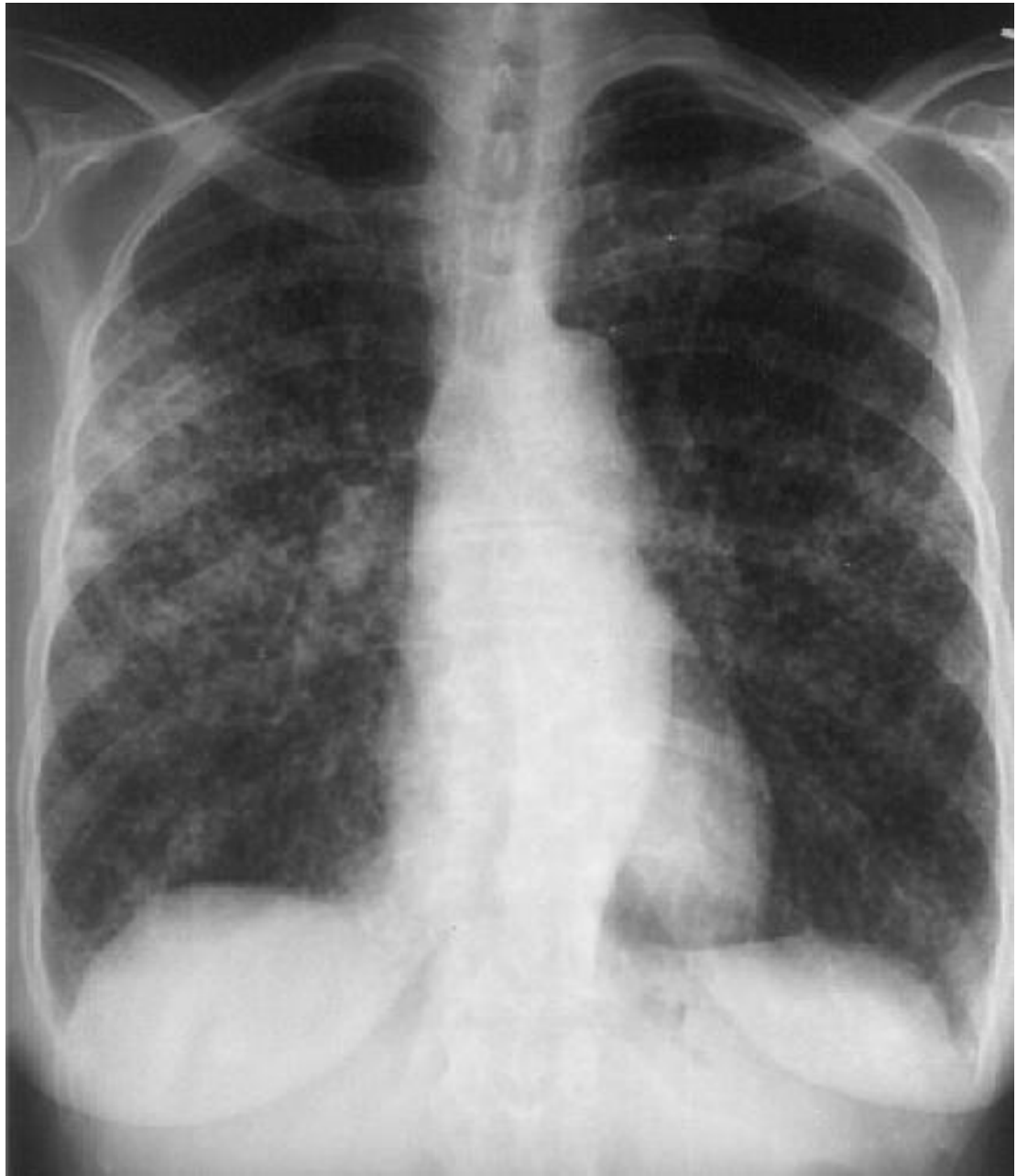
## Physical finding in patient with Miliary T.V.

- Fever
- Rales
- Hepatomegaly
- Lymphadenopathy
- Altered MS
- Splenomegaly
- Meningismus
- Jaundice
- Skin lesion
- Ascitis
- Choroidal tuberculosis

# LABORATORY FINDINGS

## IMAGING

- Miliary radiological pattern consist of multiple 1-3mm. well defined nodules which are distributed uniformly thought all lung fields.
- The radiological findings of disseminated T.B. associated with HIV infection are similar to those seen in HIV seronegative patients.
- Lymphadenopathy, lower lobe infiltrates or clear lung field are more common in advanced HIV co-infection.



# HRCT

- Innumerable 1-3mm nodules, both sharply and poorly defined are seen uniformly distributed in lung fields. Diffuse or localized septal thickening accompanies nodule HRCT finding do not discriminate miliary T. B. from other miliary lung diseases.
- HRCT appears to be useful in demonstrating miliary pattern when C<sub>x</sub>ray appears atypical (i.e. predominantly linear opacities) or even normal.





# DIFFERENTIAL DIAGNOSIS

(Miliary infiltrates with fever)

- **Infectious Diseases**

- Mycobacterial
  - M. tuberculosis
  - Atypical mycobacterial in immuno compromised hosts
- Fungal
  - Histoplasmosis
  - Coccidiomycosis
  - Blastomycosis
  - Cryptococcosis
- Viral
  - Varicella
  - Influenza
  - Measles
  - Cytomegalo virus infection
- Bacterial
  - Myplasma infection
  - Nocardiosis
  - Legionella infection
  - Brucellosis

- Staphylococcus aureus
- Melioidosis
- Psittacosis
- Tularemia

- Parasitic

- Schistosomiasis
- Toxoplasmosis
- Strongyloidiasis

- **Neoplastic Diseases**

- Lymphoma

- **Inflammatory diseases**

- Hypersensitivity Pneumonitis
- Sarcoidosis
- Good Pastures Syndrome
- Other alveolar Hemorrhage syndromes

## **GALLIUM SCAN**

- Gallium is concentrated by it shows diffuse pulmonary and extra pulmonary uptake in miliary disease, but it is not specific.
- USG of liver can show a bright echogenic pattern.

## **BLOOD ABNORMALITIES**

- CBC reveals a mild normochromic normocytic anemia in half of patient's
- A normal WBC is a rule neutrophilia may be seen more common than lymphocytosis or monocytosis left shift with increase number of band forms may be present.
- DIC occurs in over whelming and usually fatal disease. ``

- ESR is usually elevated acute phase reactants such as c-reactive protein, intercellular adhesion molecule and polyclonal gamma globulin increases.
- Hyponatremia present.
- Hypocalcemia may present but rare.
- Widened alveolar arterial (A-a) gradient and a mild respiratory alkalosis.
- Alkaline phosphatase is often elevated transaminase are usually normal or mildly elevated.

## **OTHER LABORATORY ABNORMALITIES**

- PFT can reveal a mild restrictive defect.
- BAL fluid reveals predominant lymphocytosis with depressed CD<sub>4</sub> sub population in untreated patient after t/t it shows predominance of CD<sub>4</sub> lymphocytes.
- Pulmonary artery pressure were usually normal.

# DIAGNOSIS

- A diagnosis of miliary T. B. should be thought in any patient with unexplained fever or wasting history of T.B. or exposure should be sought evidence of HIV infection should also be looked for.
- All accessible secretions and body fluids should be examined microscopically and cultured once the diagnosis is suspected.
- Acid fast strains of sputum are positive with frequency similar in HIV infected patients and non HIV infected patients (25% in one series)
- Culture of urine, blood, CSF is typically of higher yield in HIV seropositive than in HIV seronegative with Miliary T.B.

# DIAGNOSIS...

- Tuberculin skin test reported in older studies to be positive in 60 to 73% of patients. It was more often negative in more recent series.
- Histopathologic demonstration of granulomas in tissue continues to play central role in rapid diagnosis of miliary T. B. and fast stains of tissue are neither sensitive nor in HIV infected patients specific. Lung liver and bone marrow all through in which granulomas are most likely to be found. Presence of liver granulomas is not specific for disseminated T. B. it is also noted that majority of hepatic granulomas are due to *M. avium* intracellular.
- Fiberoptic bronchoscopy with bronchial brushing and transbronchial biopsy in smear negative miliary T.B.
- Immediate diagnosis (the smear or histopathology) was made in 65% of patient culture results raised the overall diagnostic yield to 79%
- In series of HIV infected patients with all forms of T. B. the bronchoscopic yield was lower or equivalent to that in HIV seronegative patients.

# DIAGNOSIS...

- PCR is a rapid diagnostic test the detection of MTB specific DNA in sputum and other clinical sample using PCR is of utility in Pulm T. B. and T. B meningitis. Using PCR and insertion element IS6110 as a probe found test sensitivity for sputum sample from non military patient to be greater than that of careful examination of fluorochrome stained smears (83 versus us 66% specificity (99 versus 73%).
- In smear negative T. B. sensitivity was 57% PCR analysis of sputum cannot yet replace mycobacterial culture.
- Sociological diagnosis of military T. B. by ELISA using antibodies directed against purified secreted antigens or cell wall components continues to evolve.
- There role in diagnosis remains to be defined.

# THERAPY

- Therapeutic recommendations for disseminated T.B. are same as for pulmonary T.B. four drug regimen is given isoniazid, rifampicin, pyrazinamide and ethambutol should be given for 2 months and then isoniazid and rifampicin continued for a total 6 month.
- If drug resistance is suspected regimens need to be changed according to susceptibility pattern after culture conversion.
- Dissemination with bone or joint involvement or extensive lymphadenitis may require longer therapy.
- Role of fluoroquinolones which demonstrate excellent penetration of all tissue including meninges remains to be defined in miliary T.B.

# ROLE OF CORTICOSTEROIDS

- Adjunctive use of corticosteroids to modulate deleterious effects of inflammatory response has not been prospectively investigated in disseminated T.B.
- Evidence exists that steroids are of benefit in selected patients with menigeal, or pericardial inflammation or when rare and clearly aberrant immunological phenomenon appear (eq. immune complex nephritis).
- When deterioration of organ function despite adequate ATT therapy some clinicians add steroids, although the prevalence of MDR strain now complicates this decision.
- Also in severely immunocompromised patients, opportunistic infection may coexist, it may progress during steroid therapy.
- Replacement dose of steroid should be given if adrenal insufficiency is suspected.



# ROLE OF CORTICOSTEROIDS...

- A retrospective evaluation of steroid in military T.B. found no difference in mortality in children given steroids as compared to those not given steroids.
- Another retrospective study suggested a reduction in mortality and faster subjective improvement in steroid treated cohort.

- Reported complication arising during therapy of miliary T.B.
- Perforation of structure at the site of granulomatous involvement. Pneumothorax, small bowel or mycotic aortic aneurysm. Expansion of intracranial tuberculosis, hydrocephalus, cutaneous abscesses and tenosynovitis.
- Response to therapy by recovery of appetite and sense of well being which usually becomes apparent in 7 to 14 days after therapy is initiated but may be delayed by weeks. Mean time of radiologic clearing ranges from 10-19 weeks in most series time of radiologic clearance was inversely correlated with degree of BAL fluid lymphocytosis, particularly number of CD8 lymphocyte in one series.
- Old reports of residual miliary calcifications had poor documentations of mycobacterial infection and probably represented healed viral (Varicella) or fungal lesions.

# PREVENTION

- Miliary disease can be prevented by application of isoniazid prophylaxis to infected persons at greatest risk for disease.
- HIV seropositive patients, should be screened for infection, preventive therapy should be given to HIV infected persons at high risk for exposure to T.B. even if PPD negative.
- BCG vaccine appears to reduce the incidence of miliary spread, particularly in children.
- Three case control studies demonstrated a combined 78% protective effect against disseminated disease the duration of protective effect could not be assessed.
- Vaccine should not be given to immuno compromised hosts because of risk of disseminated BCG infection.

# PROGNOSIS

- Prognosis is related to comorbidity (age, underlying chronic organ dysfunction) and to those factors contributing to delay in diagnosis (lack of fever, lack of respiratory symptoms, negative PPD test result etc.)
- Presence of HIV infection, multidrug resistance and adverse drug reactions (rash, hepatitis, thrombocytopenia) with miliary T.B. contributes to morbidity and mortality.
- The overall mortality rate stands to approximately 20% has not changed for 25 years.

**All the best..**