Miliary tuberculosis (TB) is the widespread dissemination of *Mycobacterium tuberculosis* via hematogenous spread. Classic miliary TB is defined as milletlike (mean, 2 mm; range, 1-5 mm) seeding of TB bacilli in the lung, as evidenced on chest radiography. This pattern is seen in 1-3% of all TB cases.\(^1\,^2\,^3\,^4\,^5\)

Miliary TB may occur in an individual organ (very rare, < 5%), in several organs, or throughout the entire body (>90%), including the brain. The infection is characterized by a large amount of TB bacilli, although it may easily be missed and is fatal if left untreated.

Up to 25% of patients with miliary TB may have meningeal involvement. In addition, miliary TB may mimic many diseases. In some case series, up to 50% of cases are undiagnosed antemortem. Therefore, a high index of clinical suspicion is important to obtain an early diagnosis and to ensure improved clinical outcomes.

Early empirical treatment for possible but not yet definitive miliary TB increases the likelihood of survival and should never be withheld while test results are pending. On autopsy, multiple TB lesions are detected throughout the body in organs such as the lungs, liver, spleen, brain, and others.

### Pathophysiology of Miliary TB
Following exposure and inhalation of TB bacilli in the lung, a primary pulmonary complex is established, followed by development of pulmonary lymphangitis and hilar lymphadenopathy. Mycobacteremia and hematogenous seeding occur after the primary infection. After initial inhalation of TB bacilli, miliary tuberculosis may occur as primary TB or may develop years after the initial infection. The disseminated nodules consist of central caseating necrosis and peripheral epithelioid and fibrous tissue. Radiographically, they are not calcified (as opposed to the initial Ghon focus, which is often visible on chest radiographs as a small calcified nodule).
Etiology of Miliary TB
Risk factors for miliary tuberculosis involve immunosuppression and include, but are not limited to, the following:

- Cancer
- Transplantation
- HIV infection
- Malnutrition
- Diabetes
- Silicosis
- End-stage renal disease
- Major surgical procedures - Occasionally may trigger dissemination

Epidemiology of Miliary TB
Of all patients with TB, 1.5% are estimated to have miliary tuberculosis. The World Health Organization reports that 2-3 million patients die with or from all forms of TB each year.

The incidence of miliary TB may be higher in African Americans in the United States because of socioeconomic risk factors and may be more common in men than in women because of socioeconomic and medical risk factors. No genetic predisposition has been identified.

Miliary disease is more difficult to detect in patients who are very young or very old. Children younger than 5 years who acquire miliary TB are more likely to develop life-threatening miliary and/or meningeal TB. The disease usually follows primary infection, with no or only a short latency period. Adults older than 65 years have a higher risk of miliary TB. Clinically, it may be subacute or may masquerade as a malignancy. If undiagnosed, the disease is detected at autopsy.

Clinical Manifestations of Miliary TB
Patients with miliary tuberculosis may experience progressive symptoms over days to weeks or occasionally over several months. Symptoms include the following:

- Weakness, fatigue (90%)
- Weight loss (80%)
- Headache (10%)

Signs of miliary TB include the following:

- Subtle signs, such as low-grade fever (20%)
- Fever (80%)
- Cough (60%)
- Generalized lymphadenopathy (40%)
- Hepatomegaly (40%)
- Splenomegaly (15%)
- Pancreatitis (< 5%)
- Multiorgan dysfunction, adrenal insufficiency

Differential Diagnosis of Miliary TB
The differential diagnosis of miliary tuberculosis includes the following:

- Acute respiratory distress syndrome
- Addison disease
- Ascites
- Blastomycosis
- Cardiac tamponade
- Disseminated intravascular coagulation
- Epididymal tuberculosis
- Hypersensitivity pneumonitis
- Pneumocystis carinii pneumonia
- Bacterial pneumonia
Community-acquired pneumonia
Fungal pneumonia
Viral pneumonia

Other problems to be considered include the following:

- Fungal infection
- Histiocytosis X (Langerhans cell histiocytosis)
- HIV-related pulmonary opportunistic infections
- Lymphangitic spread of cancer (eg, thyroid carcinoma, malignant melanoma)
- Measles
- Pancreatic abscess
- Pulmonary alveolar microlithiasis
- Talc granulomatosis

**Laboratory Studies for Miliary TB**

**Chemistry**

A decrease in sodium levels may correlate with disease severity, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or hypoadrenalism may complicate tuberculosis (TB). In approximately 30% of cases, alkaline phosphatase levels are elevated.

Elevated levels of transaminases suggest liver involvement or, if treatment has been initiated, drug toxicity.

**Complete blood count**

Leukopenia/leukocytosis may be present in miliary tuberculosis. Leukemoid reactions may occur; patients may have anemia; and thrombocytopenia or, rarely, thrombocytosis may be present.

**Erythrocyte sedimentation rate**

The erythrocyte sedimentation rate is elevated in approximately 50% of patients.

**Cultures for mycobacteria**

Cultures, as available, may include those of the sputum, blood, urine, or cerebral spinal fluid. Sensitivity testing is essential for all positive isolates, and consider investigation for multidrug-resistant TB (MDR-TB) in all cases. Negative sputum smear results (even 3 negatives) do not exclude the possibility of TB.

For mycobacterial blood cultures, findings are positive in approximately 5% of patients who do not have HIV infection. Findings are positive in many patients who have HIV infection. One study yielded an 85% positivity rate.

**Lumbar puncture** should be strongly considered, even with normal brain MRI findings, and may reveal any of the following:

- Leukocytes: Approximately 65% of patients have WBC counts with 100-500 mononuclear cells/μL.
- Lymphocytic predominance (70%)
- CSF lactic acid levels are mildly elevated.
- Elevated protein levels (90%)
- Low glucose levels (90%)
- RBCs are common
- Acid-fast bacilli (≥40% with serial spinal taps)

**Coagulation studies**

Measure the prothrombin time/activated partial thromboplastin time (PT/aPTT) prior to biopsy.

**Tuberculin skin test**

The tuberculin skin test with purified protein derivative (PPD) often yields negative results in patients with miliary TB. This may be explained by the large number of TB antigens throughout the body. Negative tuberculosis skin testing results do not exclude the possibility of TB.
Nucleic acid probes

Specificity for smear-negative and culture-negative specimens is lower than 100% (false-negative results). False-positive TB cultures are of concern, and the rate is estimated to be approximately 5%. This may be due to laboratory contamination.

Polymerase chain reaction testing of the blood may yield positive results in most cases of HIV-related disseminated TB; the yield is low in non-HIV miliary TB.

Imaging Studies for Miliary TB

Chest radiography

Findings are typical in 50% of cases. A bright spotlight helps to reveal miliary nodules. Bilateral pleural effusions indicate dissemination versus localized and unilateral pleural TB. This may be a useful clinical clue. Nodules characteristic of miliary TB may be better visualized on lateral chest radiography (especially in the retrocardiac space).

Chest CT scanning

Chest CT scanning has higher sensitivity and specificity than chest radiography in displaying well-defined randomly distributed nodules. High-resolution CT scanning with 1-mm cuts may be even better. It is useful in the presence of suggestive and inconclusive chest radiography findings.

Ultrasonography

Ultrasonography may reveal diffuse liver disease, hepatomegaly, splenomegaly, or para-aortic lymph nodes.

Head CT scanning with contrast and/or MRI of the brain

Use this to assess for suspected TB lesions. Hydrocephalus or a cerebral mass lesion (tuberculoma) may increase the risk of herniation if lumbar puncture is performed.

Abdominal CT scanning

Abdominal CT scanning may reveal para-aortic lymph nodes, hepatosplenomegaly, or tuberculous abscess.

Echocardiography

Echocardiography is the most sensitive test for pericardial effusion.

Additional Tests and Procedures for Miliary TB

Additional tests and procedures for miliary tuberculosis include the following:

- Funduscopic may reveal retinal tubercles
- Electrocardiography helps evaluate for pericardial effusion; right ventricular hypertrophy may indicate pulmonary hypertension prior to lung biopsy
- Miliary TB in a child indicates recent transmission, and contact investigation could identify the source case and associated susceptibilities; contact investigation of child index cases should be conducted quickly, and thoroughly evaluate household contacts by means of tuberculin skin testing and, if the test results are positive, chest radiography
- Sputum induction has low sensitivity, and findings are smear-negative and culture-negative in 80% of patients because of hematogenous spread
- Fiberoptic bronchoscopy is the most effective procedure for obtaining cultures (bronchoalveolar lavage)
- The culture yield for transbronchial biopsies is 90%.
- Bone marrow biopsy yield is approximately 50%, without serious adverse effect
- In liver biopsy, liver bleeding is a serious and potentially life-threatening complication estimated to occur in approximately 10% of cases
- For abdominal involvement, laparoscopy is useful to obtain tissue and material for culture.

Histologic Findings of Miliary TB
Necrotizing granulomas are the hallmark of TB, and staining for acid-fast bacilli reveals rodlike structures in approximately 80% of specimens (see the image below). The disseminated nodules consist of central caseating necrosis and peripheral epithelioid and fibrous tissue. Radiographically, the nodules are not calcified.

Acid-fast bacillus smear showing characteristic cording in Mycobacterium tuberculosis.

Treatment Overview for Miliary TB

Miliary TB with meningeal involvement may require prolonged treatment (up to 12 mo). Early treatment of patients with suspected miliary tuberculosis decreases the likelihood of mortality and improves outcome. Surgical treatment is rarely necessary. Occasionally, a ventriculoatrial shunt is indicated for hydrocephalus. Consultations may include the following:

- Pulmonary and critical care specialists
- Infectious disease specialist
- Neurologist - Steroids for meningitis or paradoxically increasing tuberculomas
- TB expert
- Health department notification
- Appropriate infection control measures
- Failure to involve a TB specialist may lead to acquired resistant TB.

Adequate attention to nutrition is important. Many patients with miliary TB are debilitated by the disease, and malnutrition can contribute to a weakened immune system.

Once the patient receives several weeks of effective therapy, experiences significant clinical improvement, and has negative sputum acid-fast bacillus smears, restrictions are minimal. However, one must be certain that the patient truly is no longer contagious. The absence of sputum positivity does not guarantee others protection against exposure. Directly observed therapy is optimal for assuring compliance and preventing relapse.

Paradoxical enlargement of the lymph nodes or intracerebral tuberculomas during adequate treatment may require steroids. Hydrocephalus may require neurosurgical decompression.

Pharmacological Therapy for Miliary TB

Early empirical therapy for suspected miliary tuberculosis is prudent. A delay of even 1-8 days contributes to a high mortality rate. Steroids are warranted for hypotension due to presumed adrenal insufficiency after an adrenocorticotropic hormone (ACTH) stimulation test.

For susceptible organisms, the treatment period is 6-9 months. For meningitis, it is 9-12 months. For miliary TB with meningeal involvement, daily medications for the entire length of therapy are recommended.

Three basic rules apply in the prevention of entirely "doctor-made" resistant TB:

1. **Rifampin** is the drug of choice for treatment; in most cases, the treatment duration is at least 18 months without rifampin
2. **Ethambutol** (EMB) is used to prevent rifampin resistance if the organism is resistant to isoniazid (INH); EMB can be discontinued as soon as the organism is found to be susceptible to rifampin and INH
3. **Pyrazinamide** is used for the first 2 months of treatment to decrease the treatment duration from 9 months to 6 months if the organism is susceptible to rifampin and INH
For MDR-TB, use a minimum of 1 susceptible injectable and at least 3 additional susceptible drugs to prevent the development of additional resistance. Treat MDR-TB with the consultation of an expert in the care of TB.

Intermittent-type therapies have not been established. If MDR-TB test results are pending, increasing the number of drugs is reasonable. For example, use 6 or 7 initial drugs, including an injectable.

Further Inpatient Care for Miliary TB
If the infected patient lives in a home with immunocompromised persons (eg, with HIV infection) or with children younger than 5 years, or if the patient lives in a communal residence type of facility (eg, homeless shelter, senior citizen facility, jail, prison), keep him or her hospitalized until sputum stain results are negative and significant clinical improvement is shown.

Evaluate all close contacts who might have been infected prior to initiation of effective therapy for evidence of tuberculosis (TB). Contagiousness is low because miliary TB spreads hematogenously, not via the endobronchial system. Cavitary lesions are highly unlikely.

Further Outpatient Care for Miliary TB
Patients may start and continue treatment in an outpatient setting if no children or immunocompromised persons are in the home or if the patient is not in a communal residence facility.

Each patient should be offered directly observed therapy in the clinic, home, or workplace.

Miliary TB and Pregnancy
Miliary tuberculosis during pregnancy can be treated safely with RIE (ie, rifampin, INH, vitamin B-6 [25 mg/d] and ethambutol [EMB] [15 mg/kg/d]), but miliary TB in a newborn of a mother with TB is difficult to diagnose.

Placenta examination by the pathologist is imperative. In a newborn, 3 gastric aspirates of the newborn are helpful, but tuberculin skin testing of the newborn during the first 6 months is rarely helpful because of the limited immune response of the newborn. Lumbar puncture is indicated if the newborn does not thrive. Bacille Calmette-Guérin vaccine clouds the interpretation of a positive tuberculin skin test result after age 6 months.

Transfer of Patients with Miliary TB
The patient is usually removed from isolation when 3 consecutive sputum smear results are negative and clinical improvement is shown. The patient must not be confined with immunosuppressed patients prior to the establishment of negative sputum cultures. Place the patient in a negative pressure room or in adequate respiratory isolation.

Patients who discontinue medication may be subject to public health laws. Patients may be remanded to custody and ordered to continue therapy if judged to be a public health hazard.

When ordered compliance is not successful, the health department may obtain an order of detention.

Prognosis of Miliary TB
If left untreated, the mortality associated with miliary tuberculosis is assumed to be close to 100%. With early and appropriate treatment, however, mortality is reduced to less than 10%. The earlier the diagnosis, the better the likelihood of a positive outcome. Early treatment for suspected TB has been shown to improve outcome.

Most deaths occur within the first 2 weeks of admission to the hospital. This may be related to delayed onset of treatment. Up to 50% of all cases of disseminated TB detected at autopsy were missed antemortem in reported case series.

The relapse rate is 0-4% with adequate therapy and directly observed therapy, although results from studies vary. Most relapses occur during the first 24 months after completion of therapy.

Patient Education
Educate the patient and contacts about the mode of transmission.

For patient education information, see Bacterial and Viral Infections Center, as well as Tuberculosis.
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