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Laboratory, Radiological, And Anesthetic Considerations In The Management Of Miliary Tuberculosis With Respiratory Compromise-An Updated Review

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Abstract:

Background: Miliary tuberculosis (TB) is a severe disseminated form of Mycobacterium tuberculosis infection characterized by hematogenous spread and multisystem involvement. Its nonspecific presentation often delays diagnosis and increases morbidity and mortality.
Aim: To provide an updated review of the laboratory, radiological, anesthetic, and clinical considerations in diagnosing and managing miliary TB, particularly in patients presenting with respiratory compromise.
Methods: This review synthesizes current evidence on epidemiology, pathophysiology, clinical manifestations, diagnostic modalities, and management strategies, drawing from microbiological, immunological, histopathological, and imaging-based investigations.
Results: Miliary TB exhibits protean manifestations involving pulmonary and extrapulmonary organs, often requiring combined laboratory abnormalities, characteristic imaging, and molecular confirmation for diagnosis. Standard antitubercular therapy remains the cornerstone of treatment, with extended regimens recommended for CNS, skeletal, and immunocompromised cases. Complications include ARDS, MODS, and neurological involvement, all associated with increased mortality. Early diagnosis, multidisciplinary management, and vigilant monitoring significantly improve outcomes.
Conclusion: Miliary TB demands high clinical suspicion and integrated diagnostic approaches. Early initiation of therapy, tailored management in organ-specific involvement, and multidisciplinary care are essential to reducing mortality and enhancing patient outcomes.

Keywords: Miliary tuberculosis, disseminated TB, diagnosis, imaging, antitubercular therapy, immunology, complications, respiratory compromise.

Introduction:

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (MTB), a slow-growing, obligate aerobic bacterium. Transmission primarily occurs via inhalation of aerosolized droplet nuclei expelled by individuals with active pulmonary TB. Activities such as coughing, sneezing, or even speaking can release these droplets into the air, where they may remain suspended for hours before being inhaled by susceptible hosts. Other routes of MTB transmission, including ingestion or contact with contaminated surfaces, contribute negligibly to the spread of the disease. Although TB predominantly affects the lungs, up to one-third of cases involve extrapulmonary sites, reflecting the pathogen's capacity for systemic dissemination. MTB preferentially infects regions of high oxygen tension, which explains its predilection for the upper lobes and superior aspects of the lower lobes adjacent to the pleura. The alveolus represents the lung's primary functional unit, where gas exchange occurs across a highly specialized blood-air barrier. This barrier consists of alveolar epithelium, basement membrane, and capillary endothelium, collectively facilitating oxygen and carbon dioxide diffusion while maintaining separation between air and blood. Alveolar macrophages, derived from circulating monocytes, patrol the alveolar space, engulfing pathogens and debris. These phagocytic cells are central to the innate immune defense but paradoxically provide a niche for MTB survival and replication, contributing to disease pathophysiology. Structural features such as the pores of Kohn, small inter-alveolar openings, allow the passage of exudates and microorganisms between adjacent alveoli, promoting intra-pulmonary spread of the infection [1][2].

The pulmonary vasculature and lymphatic system are integral to both normal lung function and the dissemination of TB. Pulmonary arteries, branching from the pulmonary trunk, deliver deoxygenated blood to the lungs, while pulmonary veins return oxygenated blood to the left heart. The bronchial arteries, arising from the thoracic aorta and intercostal arteries, supply oxygenated blood to the lung root and visceral pleura, with corresponding bronchial veins draining into the azygos and hemiazygos systems. Lymphatic drainage involves superficial subpleural plexuses that empty into hilar lymph nodes and deep bronchopulmonary plexuses draining into intrinsic pulmonary nodes. From these, the tracheobronchial lymph nodes channel lymph toward the right lymphatic and thoracic ducts. Parietal pleural lymphatics drain toward the thoracic wall and axillary nodes. In immunocompromised patients, the failure to contain MTB locally allows hematogenous spread, resulting in disseminated disease involving multiple non-contiguous organs or the blood, bone marrow, and liver. Miliary tuberculosis represents a severe, potentially fatal form of disseminated TB. It arises when tubercle bacilli enter the bloodstream and distribute widely across pulmonary and extrapulmonary sites, leading to the formation of numerous millet-seed-sized (1–2 mm) granulomatous foci. The term "miliary tuberculosis" was introduced by John Jacobus Manget in 1700 to describe the gross pathological appearance of these tiny, millet-like tubercles. Its etymology derives from the Latin word miliarius, meaning "millet seed." Radiologically, miliary TB is often identified by diffuse, fine nodular opacities across the lung fields, commonly referred to as miliary mottling, which remains a diagnostic hallmark. The disease bridges pulmonary and extrapulmonary TB classifications, reflecting its systemic nature and potential for multi-organ involvement.

Immunological failure plays a critical role in miliary TB development. In healthy individuals, alveolar macrophages and other innate immune mechanisms often contain the infection within granulomas. In contrast, immunocompromised patients, including those with HIV, malnutrition, or other systemic conditions, lack the ability to effectively restrict bacterial proliferation. This enables hematogenous dissemination to organs such as the liver, spleen, bone marrow, and central nervous system. Clinically, miliary TB presents with non-specific systemic symptoms, including prolonged fever, weight loss, night sweats, and generalized malaise, complicating early recognition. Laboratory findings may reveal cytopenias, elevated liver enzymes, and positive MTB cultures or molecular assays. Radiologically, chest X-rays and high-resolution CT scans demonstrate diffuse nodular patterns consistent with millet-sized lesions throughout the lung parenchyma [1][2]. The pathophysiology of miliary TB underscores the interaction between bacterial virulence, host immunity, and organ-specific susceptibility. Hematogenous dissemination occurs when MTB breaches the alveolar-capillary interface, evades macrophage killing, and enters the systemic circulation. Once in the bloodstream, bacilli lodge in highly vascularized organs, leading to the formation of small granulomas. These granulomatous foci can coalesce, resulting in organ dysfunction and systemic inflammatory responses. Understanding these

mechanisms is crucial for early diagnosis, risk stratification, and management, particularly in patients undergoing immunosuppressive therapy or presenting with atypical clinical features. In summary, TB remains a global health challenge due to its complex transmission, variable clinical presentations, and potential for systemic spread. Miliary TB represents the severe end of this spectrum, characterized by hematogenous dissemination, millet-seed granulomas, and multi-organ involvement. Diagnosis relies on the integration of clinical suspicion, laboratory testing, and radiological imaging. A comprehensive understanding of lung anatomy, alveolar immune defense, vascular and lymphatic pathways, and host-pathogen interactions is essential for effective recognition and management of this life-threatening condition [1][2].

Etiology

Mycobacterium tuberculosis (MTB) remains the principal causative agent of tuberculosis in regions where bovine TB has been successfully eradicated, with humans serving as the primary reservoir for infection. The bacterium is a non-motile, non-spore-forming, obligate aerobic organism that exhibits facultative intracellular survival within host phagocytic cells. It lacks catalase activity and demonstrates unique structural and staining characteristics that facilitate its identification. MTB is considered gram-neutral and is typically visualized using Ziehl–Neelsen (ZN) staining, which exploits the presence of mycolic acids in the cell wall. These long-chain fatty acids confer acid-fast properties, enabling the bacilli to resist decolorization by acid-alcohol solutions, a defining feature that has led to the alternative designation of the pathogen as acid-alcohol-fast bacillus (AAFB). The acid-fast characteristic not only aids in laboratory detection but also contributes to the organism's resilience within hostile intracellular environments, allowing persistent infection. Other members of the genus Mycobacterium that do not cause classical tuberculosis are collectively referred to as nontuberculous or atypical mycobacteria, which exhibit variable pathogenicity and differing clinical implications compared to MTB [3]. The unique etiology of TB underscores the interplay between pathogen biology, host susceptibility, and epidemiological factors, forming the basis for diagnostic, therapeutic, and preventive strategies.

Epidemiology

Tuberculosis (TB) continues to pose a significant global health burden, with the World Health Organization (WHO) estimating approximately 10 million incident cases and 1.3 million deaths worldwide in 2017 [4]. The highest incidence is observed in developing regions, reflecting disparities in healthcare access, socioeconomic conditions, and public health infrastructure. Miliary tuberculosis, a severe disseminated form of the disease, exhibits dynamic epidemiological patterns influenced by several contemporary factors. The increased use of immunosuppressive therapies, including corticosteroids and biologic agents, has heightened susceptibility to hematogenous dissemination of Mycobacterium tuberculosis. Global migration from regions with high TB prevalence introduces additional risk, while the concurrent rise in HIV infection further amplifies vulnerability to miliary disease. Chronic conditions that impair immune competence, such as diabetes mellitus and chronic kidney disease, alongside lifestyle factors like alcoholism, contribute to altered disease patterns and clinical outcomes. In the United States, the Centers for Disease Control and Prevention reported 8,920 newly diagnosed TB cases in 2019, highlighting that miliary TB represents approximately 1% to 2% of all TB cases and up to 20% of extrapulmonary manifestations in immunocompetent individuals [5]. Historically, miliary TB predominantly affected infants and young children prior to the widespread availability of effective antibiotics. Current epidemiological data demonstrate a bimodal age distribution, with peaks among adolescents and young adults, as well as older adults, suggesting both primary exposure in early life and reactivation in later years. Additionally, the disease shows a slight male predominance, reflecting subtle sex-based differences in susceptibility and disease progression [6]. Understanding these epidemiological trends is critical for targeted public health interventions, early detection strategies, and the prioritization of high-risk populations for preventive and therapeutic measures.

Pathophysiology

The pathophysiology of tuberculosis (TB) begins with the interaction between Mycobacterium tuberculosis (MTB) and alveolar macrophages lining the lung epithelium. Upon inhalation, the bacilli are phagocytosed by these macrophages, where they initially replicate without significant restriction.

The host's adaptive immune system, particularly T-helper lymphocytes, subsequently activates macrophages to limit bacterial proliferation through cell-mediated immune mechanisms. In individuals with intact immunity, this response often contains the infection within granulomatous structures, preventing widespread dissemination. However, in immunocompromised hosts, including those with HIV infection, malnutrition, or chronic disease, the failure of cell-mediated immunity permits bacilli to escape local containment. The organisms gain access to pulmonary lymphatic channels and are transported to the thoracic duct, ultimately draining into the right side of the heart and pulmonary arteries, allowing hematogenous dissemination. Systemic spread occurs when infected foci in the lungs seed the pulmonary venous circulation, facilitating arterial distribution to multiple organs [7]. The immunopathogenic processes driving miliary TB are complex and remain incompletely defined. Effective containment by effector T-cells is often compromised, and the precise roles of cytokines, chemokines, and other immune-regulatory factors in host-pathogen interactions have not been fully elucidated. What is established is that miliary TB arises from lymphohematogenous dissemination of MTB, originating either from a primary pulmonary lesion or reactivation of a latent focus. In endemic regions, reinfection may precipitate miliary TB, while in certain cases, concurrent reactivation of dormant bacilli in multiple organs can lead to widespread disease. The resultant pathology involves the formation of numerous millet-seed-sized granulomatous lesions in the lungs and other organs, reflecting the systemic nature of the infection and underscoring the critical role of host immune competence in disease progression [7].

Histopathology

Miliary tuberculosis (TB) exhibits distinct gross and microscopic pathological features that reflect its systemic dissemination. Gross examination reveals numerous small, punctate lesions distributed throughout the lungs and extrapulmonary organs. These lesions are typically rounded, measuring approximately 1 to 2 millimeters in diameter, and present with a gray to reddish-brown coloration, demonstrating remarkable uniformity in size. Such lesions correspond to hematogenously seeded tubercular foci resulting from widespread Mycobacterium tuberculosis dissemination. Microscopically, in immunocompetent individuals, each lesion represents a fully formed granuloma or tubercle. The center of the tubercle exhibits caseation necrosis, which is a hallmark of TB, and contains viable and degenerating bacilli. Surrounding the necrotic core are immune effector cells, including Langhans-type multinucleated giant cells, epithelioid macrophages, lymphocytes, and fibrocytes. These organized cellular structures indicate an effective host immune response, reflecting the ability to contain bacterial replication while maintaining localized inflammation. The granulomatous architecture is critical in limiting systemic spread and providing a controlled environment for immune-mediated bacterial clearance. In contrast, in immunocompromised patients, the histopathology differs significantly. The lesions often display extensive caseation necrosis but lack the classic granulomatous organization. Tubercle bacilli are present in large numbers without surrounding Langhans giant cells or epithelioid cells, and lymphocytic infiltration is minimal. This pattern is referred to as nonreactive or poorly organized miliary TB and indicates a failure of the host's cell-mediated immunity to mount an effective granulomatous response [8][9]. The absence of structured granulomas in these individuals correlates with a higher risk of rapid disease progression, systemic involvement, and increased mortality, highlighting the interplay between immune status and histopathological manifestations of miliary tuberculosis.

History and Physical

Miliary tuberculosis (TB) presents a wide spectrum of clinical manifestations that depend on the organs predominantly involved and frequently remain indiscernible until advanced stages of the disease. Initial symptoms are typically gradual in onset and nonspecific, often manifesting as constitutional signs including persistent fever, generalized fatigue, anorexia, weight loss, and malaise. Respiratory symptoms, including productive cough, dyspnea, chest discomfort, and occasional hemoptysis, may also appear early, reflecting pulmonary involvement. Gastrointestinal manifestations, such as nausea, vomiting, abdominal pain, and discomfort, are common and can complicate the initial clinical picture. Extrapulmonary involvement is frequent, with the lymphatic system, skeletal structures, liver, central nervous system (CNS), and adrenal glands representing the most commonly affected sites. Nevertheless, any organ system can be implicated, and symptoms specific to the affected organ typically

emerge as the disease progresses. Miliary TB can be categorized into two clinical variants: classical acute and cryptic forms, each displaying distinct demographic patterns and clinical presentations that necessitate heightened clinical suspicion for timely recognition and management. Acute miliary TB predominantly affects individuals younger than 40 years, often presenting with subacute or chronic constitutional symptoms. Fever is typically episodic, occurring in the evening with night sweats, although early morning temperature spikes may also be observed. Nonproductive cough and dyspnea are common initial respiratory signs, and hemoptysis can occasionally be noted. In rare cases, acute respiratory distress syndrome (ARDS) may occur as a severe, life-threatening complication [10][11]. Hematogenous dissemination to the abdominal viscera can result in hepatic, intestinal, or peritoneal involvement. Hepatic TB manifests with right upper quadrant pain, fatigue, nausea, vomiting, fever, jaundice, and hepatosplenomegaly [12][13][14]. Intestinal TB may present with fever, malnutrition, altered bowel habits, and subacute or acute intestinal obstruction, particularly in pediatric patients, who often demonstrate failure to thrive. TB peritonitis may mimic acute abdomen clinically, and surgical exploration frequently reveals miliary tubercles on the omentum and peritoneal surfaces, with biopsy confirming tuberculous foci.

Adrenal involvement may present as Addison disease, either at initial presentation or during anti-tubercular therapy. Clinical manifestations include hyperpigmentation, hypotension, hypoglycemia, and electrolyte imbalances [15]. Ophthalmological examination may reveal choroid tubercles, which are pathognomonic of miliary TB, particularly in pediatric populations. These lesions are typically bilateral, pale to gray-white or yellow, small in size relative to the optic disc, and located within 2 cm of the optic nerve [16]. Musculoskeletal involvement accounts for approximately 10% of extrapulmonary TB. The spine is the most frequently affected site, manifesting as Pott's disease with insidious back pain, tenderness, fever, and weight loss. Progressive deformities, including kyphosis or scoliosis, and neurological deficits such as paraplegia or paraparesis may develop in advanced disease. Tuberculous arthritis, osteomyelitis, tenosynovitis, bursitis, and pyomyositis are additional musculoskeletal manifestations [17]. Neurological involvement may present as tubercular meningitis, characterized by headache, nuchal rigidity, and potential tuberculoma formation. Thoracic spinal cord involvement may lead to sensorimotor deficits [18][19]. Cutaneous involvement, termed tuberculosis miliaria cutis, manifests as erythematous macules and papules resulting from lymphohematogenous spread. Cardiac and renal involvement are rare but may include myocarditis, congestive heart failure, endocarditis, mycotic aneurysms, and acute kidney injury as part of multiorgan dysfunction syndrome (MODS) [20]. Clinical presentation differs between adults and children. Pediatric patients are less likely to present with chills, night sweats, hemoptysis, and productive cough but more frequently exhibit hepatosplenomegaly and peripheral lymphadenopathy. TB meningitis occurs in 20% to 40% of pediatric cases compared with 15% to 30% in adults. BCG vaccination confers partial protection, reducing the incidence of miliary TB in children. HIV-infected individuals display disease manifestations correlated with CD4+ counts. Patients with counts above 200 cells/mm^3 exhibit a presentation similar to immunocompetent hosts, whereas those with profound immunosuppression often manifest atypical features including cutaneous lesions, intrathoracic lymphadenopathy, and tuberculin anergy [21][22].

Cryptic miliary TB predominantly affects individuals over 60 years. This variant frequently presents as fever of unknown origin or mimics metastatic malignancy, characterized by progressive weight loss, generalized debility, and minimal organ-specific findings. Mild hepatosplenomegaly may occasionally be noted. Normal chest radiographs and negative tuberculin skin tests often delay diagnosis [23][24]. Uncommon presentations, including ARDS, pneumothorax, cytopenias, septic shock, glomerulonephritis, endocarditis, mycotic aortic aneurysms, cholestatic jaundice, and hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion, further complicate clinical recognition. Overall, the clinical history and physical findings in miliary TB are highly variable, influenced by host immunity, age, underlying comorbidities, and the extent of organ involvement. Awareness of these diverse manifestations is critical for early recognition, prompt diagnosis, and initiation of appropriate anti-tubercular therapy, particularly in immunocompromised individuals and in cases presenting with atypical or cryptic features.

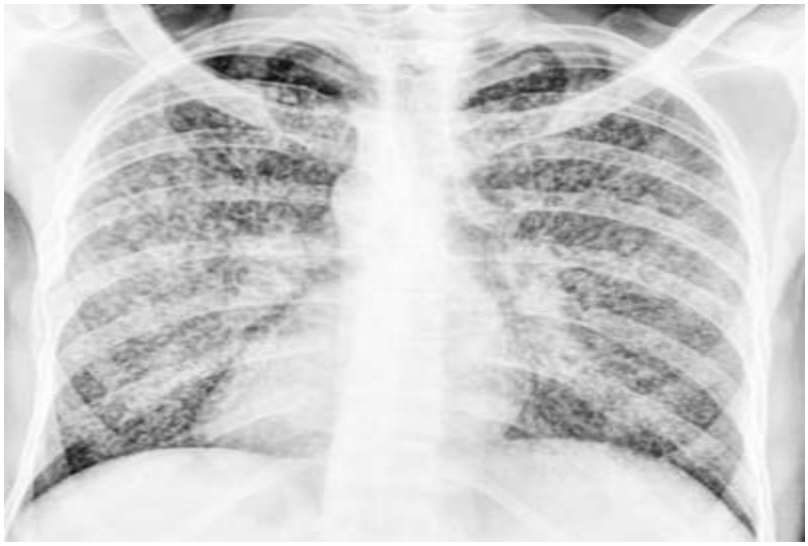
Evaluation

The diagnosis of miliary tuberculosis (TB) requires a high index of clinical suspicion due to its protean manifestations and potential for rapid progression. A systematic, multi-faceted approach is essential, integrating detailed patient history, comprehensive physical examination, and targeted laboratory and radiological investigations. Early recognition is critical to prevent severe complications and improve treatment outcomes, particularly in immunocompromised patients or those presenting with atypical clinical features. Laboratory evaluation in miliary TB often reveals nonspecific hematological abnormalities. Anemia of chronic disease is the most frequently encountered finding, reflecting prolonged systemic inflammation. Other reported abnormalities include pancytopenia, leukopenia, leukocytosis with lymphocytic predominance, thrombocytopenia, and thrombocytosis. Occasionally, miliary TB can present with a leukaemoid reaction, mimicking hematologic malignancies and complicating the diagnostic process. In severe systemic involvement, particularly in the context of acute respiratory distress syndrome (ARDS) or multiorgan dysfunction syndrome (MODS), disseminated intravascular coagulation may occur, although this is rare [25][26]. Biochemical analyses may be normal or demonstrate subtle perturbations depending on the extent of organ involvement. Hyponatremia is frequently observed and is often attributable to central nervous system involvement or dysregulated antidiuretic hormone secretion, serving as an early indicator of neurological compromise. Liver function tests may reveal hyperbilirubinemia and hypoalbuminemia, while elevated alkaline phosphatase levels indicate hepatic or bone involvement. Rarely, hypercalcemia may occur, reflecting granulomatous activity and dysregulated vitamin D metabolism [27][28]. Overall, laboratory evaluation in miliary TB provides supportive, though often nonspecific, evidence of systemic infection. Combining hematological and biochemical findings with clinical assessment and adjunctive imaging studies enhances diagnostic accuracy, facilitating timely initiation of anti-tubercular therapy and reducing morbidity and mortality. Clinicians must maintain vigilance for subtle laboratory deviations that may precede overt organ dysfunction in this disseminated form of TB.

Imaging Studies

The diagnosis of miliary tuberculosis (TB) relies on a combination of clinical, laboratory, and imaging criteria, as no single standardized guideline exists. Suggested diagnostic criteria include a clinical presentation indicative of TB, such as prolonged fever with evening spikes, night sweats, anorexia, weight loss, and tachycardia, persisting for more than six weeks and showing improvement with antitubercular therapy. Imaging plays a pivotal role, particularly in detecting characteristic pulmonary and extrapulmonary lesions, and in guiding invasive diagnostic procedures. Chest radiography remains a fundamental tool in identifying miliary TB. The hallmark radiographic feature is miliary mottling, characterized by numerous, discrete, homogenously distributed lesions of uniform size, approximately 1 to 2 millimeters in diameter, resembling millet seeds. These lesions are typically present throughout all lung zones and represent hematogenous dissemination of Mycobacterium tuberculosis within the pulmonary parenchyma. However, these classical findings may be absent in early or cryptic miliary TB, necessitating more sensitive imaging techniques. High-resolution computed tomography (HRCT) enhances detection of parenchymal nodules that may be subtle or obscured on plain radiographs, while contrast-enhanced CT (CECT) provides superior visualization of lymphadenopathy, calcifications, and pleural pathology [29][30]. Extrapulmonary involvement, which is common in miliary TB, requires additional imaging modalities. Ultrasonography, CECT, and magnetic resonance imaging (MRI) are frequently employed to assess the extent of organ involvement, including the liver, spleen, kidneys, and central nervous system. Positron emission tomography (PET)-CT has emerged as a valuable tool for evaluating suspected TB foci and differentiating active lesions from fibrotic or necrotic tissue [31][32][33][34]. In cases where noninvasive imaging is insufficient, invasive procedures provide diagnostic confirmation. Sampling of cerebrospinal fluid, pleural or ascitic fluid, gastric aspirates, urine, and pus from cold abscesses offers valuable microbiological and cytopathological information. Tissue biopsies of bone marrow and liver, often guided by ultrasound, CT, or MRI, allow histopathological and culture-based confirmation of TB [35][36]. These imaging strategies, in conjunction with laboratory and clinical evaluation, are essential for accurate diagnosis, assessment of disease severity, and formulation of effective management plans for patients with miliary TB.

Fig. 1: Miliary Tuberculosis Radiology.



Immunology-Based Methods

Immunological techniques play a complementary role in the evaluation of miliary tuberculosis (TB), particularly in cases where conventional diagnostic modalities are inconclusive. Tuberculin skin testing (TST) frequently demonstrates anergy in patients with miliary TB, a phenomenon more common than in localized pulmonary TB (PTB). This anergic response reflects impaired cell-mediated immunity due to the widespread dissemination of Mycobacterium tuberculosis (MTB). Interestingly, TST may convert to a positive result during the course of antitubercular therapy, highlighting the dynamic interplay between host immune recovery and mycobacterial containment [37]. Interferon-gamma (IFN-γ) release assays provide evidence of infection but cannot differentiate latent from active disease. Consequently, their diagnostic utility is limited in endemic regions where latent infection is highly prevalent. Serological tests for TB are generally not recommended due to low sensitivity and specificity. Nevertheless, adenosine deaminase (ADA) and IFN-γ measurements in body fluids can serve as adjunctive tools for detecting TB in pleural, pericardial, and ascitic effusions. ADA activity is particularly valuable in diagnosing TB meningitis (TBM) and extrapulmonary TB. The established cutoff values for ADA are 40 U/L in pleural and pericardial effusions, 39 U/L in tuberculous ascites, and 10 U/L in cerebrospinal fluid (CSF). Clinicians must interpret these results cautiously, as ADA may be falsely elevated in other conditions including empyema, parapneumonic effusions, malignancies, collagen vascular disorders, cerebral malaria, brucellosis, neurosarcoidosis, pyogenic meningitis, and immunocompromised states such as AIDS [38][39][40][41][42][43][44][45][46]. Molecular diagnostics have revolutionized early TB detection. Polymerase chain reaction (PCR), Gene Xpert MTB/RIF, and line probe assays allow rapid identification of MTB and determination of drug resistance profiles. These methods can be applied to various tissue specimens, yielding results within hours and significantly expediting the initiation of targeted therapy [47][48][49][50].

Definitive diagnosis relies on isolating mycobacteria from clinical specimens, including sputum, body fluids, tissue, or biopsy samples. Specimens are cultured on solid media, such as Lowenstein-Jensen (LJ), or in liquid media with fluorescence-based detection systems. Acid-fast bacilli (AFB) visualization is achieved via Ziehl-Neelsen staining or the more sensitive auramine-rhodamine fluorochrome technique. Liquid culture media reduce detection time to 1–3 weeks compared to 6–8 weeks on solid media and facilitate earlier drug susceptibility testing [51][52][53]. Although blood cultures are rarely positive, they may yield MTB in immunocompromised individuals with hematogenous dissemination [54]. Differentiation of MTB from nontuberculous mycobacteria is achieved through nucleic acid probe hybridization, biochemical tests, or advanced techniques such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) [55]. Histopathological examination of biopsy specimens remains an essential adjunct, typically demonstrating granulomatous

inflammation with central caseation. While identification of a granuloma is suggestive of TB, definitive confirmation requires demonstration of tubercle bacilli through staining or culture [56]. In summary, immunology-based methods, molecular diagnostics, and definitive microbiological and histopathological testing collectively enable accurate detection and characterization of miliary TB. These techniques complement clinical assessment and imaging studies, providing a comprehensive framework for timely diagnosis, appropriate management, and improved patient outcomes.

Treatment / Management

Miliary tuberculosis (TB) requires prompt and systematic management due to its disseminated nature and potential for rapid progression. The cornerstone of therapy is pharmacological, using standard antitubercular regimens similar to those employed for pulmonary TB (PTB). According to World Health Organization (WHO) recommendations, the standard regimen consists of a six-month course, beginning with a two-month intensive phase comprising isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a four-month continuation phase with isoniazid and rifampicin. The intensive phase targets active mycobacterial replication, while the continuation phase eradicates residual organisms to prevent relapse. Treatment duration, however, may be individualized depending on the patient's age, immune status, and primary site of disease involvement [57][58][59]. Extended therapy is generally recommended for children, immunocompromised individuals, patients exhibiting slow clinical response, and those with extrapulmonary manifestations such as skeletal TB, tuberculous meningitis (TBM), or lymphadenitis. The minimum suggested duration for skeletal TB is nine months, while TBM typically requires at least twelve months of therapy. For abdominal TB, conventional practice favored nine months of treatment, but recent multicenter randomized trials indicate that a six-month regimen is equally effective, allowing for flexibility in duration without compromising outcomes [60]. Neurological involvement must be actively assessed in all cases of miliary TB, as CNS involvement necessitates prolonged therapy and often concomitant corticosteroid administration to mitigate inflammatory complications [61].

Drug susceptibility testing (DST) is essential for previously treated patients. WHO guidelines recommend obtaining culture specimens and performing DST for at least isoniazid and rifampicin at the start of therapy. Where rapid molecular DST is available, the results should guide regimen selection, enabling tailored therapy that addresses potential drug resistance. Treatment duration may also be adjusted according to the patient's clinical status, disease severity, and response to therapy. Screening for comorbid conditions such as HIV and diabetes mellitus is imperative before initiating therapy, as these factors significantly influence both clinical outcomes and pharmacological considerations [62][63]. Patients with HIV are particularly vulnerable to immune reconstitution inflammatory syndrome (IRIS), which can occur during or after the initiation of antitubercular therapy. ART initiation must be carefully timed to reduce IRIS risk: it should be deferred for at least eight weeks after starting TB therapy, except in patients with profound immunosuppression (CD4+ counts <50 cells/mm^3), where ART may be initiated after two weeks under close monitoring [62][63]. Supportive medical and surgical interventions are occasionally required. Mechanical ventilation may be necessary in acute respiratory distress syndrome (ARDS) secondary to miliary TB. Abdominal surgery may be indicated in cases of small bowel perforation, and neurosurgical interventions, such as ventriculoperitoneal shunt placement, are sometimes performed to manage TBM complications. These interventions are adjunctive and aim to reduce morbidity associated with organ-specific TB manifestations.

Corticosteroid therapy, although not universally indicated, has demonstrated clinical benefit in specific scenarios. These include TBM, large pericardial or pleural effusions, adrenal insufficiency, IRIS, ARDS, immune-complex nephritis, and secondary hemophagocytic syndrome. The rationale for steroid use is to suppress excessive inflammatory responses that contribute to tissue damage while antitubercular therapy addresses the underlying infection [64][65]. Monitoring treatment-related adverse effects is critical. Liver function tests (LFTs) should be obtained prior to and periodically during antitubercular therapy to identify hepatotoxicity early. Criteria for ATT-induced hepatitis include transaminase elevation up to five times the upper limit of normal in asymptomatic patients, or three times in symptomatic patients, or a doubling of bilirubin levels after ruling out other causes of hepatic injury. In cases of hepatotoxicity, all potentially hepatotoxic drugs—isoniazid, rifampicin, and pyrazinamide—should be temporarily discontinued. Once LFTs normalize, a cautious reintroduction of ATT is advised, either in incrementally increasing doses or full doses, based on patient tolerance and

clinical judgment, following guidance from the British and American Thoracic Societies [66][67]. In conclusion, management of miliary TB requires an integrated approach combining standard antitubercular pharmacotherapy, individualized therapy duration for extrapulmonary or high-risk cases, early recognition and management of comorbidities, careful monitoring for drug-related toxicities, and selective use of adjunctive therapies such as corticosteroids. Early diagnosis, adherence to therapy, and close follow-up are crucial to prevent disease progression, minimize complications, and achieve favorable outcomes in this disseminated and potentially fatal form of tuberculosis.

Differential Diagnosis

The clinical presentation of miliary tuberculosis (TB) is notably protean and nonspecific, often leading to a wide range of differential diagnoses. Patients frequently present with constitutional symptoms such as fever, chills, night sweats, anorexia, weight loss, and profound fatigue. These symptoms are not exclusive to miliary TB and can be observed in a variety of infectious, autoimmune, and neoplastic conditions. Neurological complaints, including headache, seizures, and altered sensorium, along with respiratory manifestations such as cough, chest pain, and hemoptysis, add to the diagnostic complexity. Gastrointestinal involvement can produce abdominal pain, nausea, and vomiting, while lymphatic and hepatosplenic involvement may lead to palpable lymphadenopathy and organomegaly. Musculoskeletal complaints, including back pain, may signify skeletal TB but are also common to other pathologies. Collectively, the gradual onset and nonspecific nature of these manifestations can result in delayed recognition and treatment, particularly in populations with atypical clinical features or immunocompromised states. Radiologically, miliary TB can produce a characteristic miliary pattern on chest imaging, but similar patterns may be generated by a variety of other diseases. Differential considerations for diffuse micronodular lung involvement include fungal infections such as histoplasmosis, blastomycosis, and coccidioidomycosis, which can present with systemic symptoms and pulmonary nodules. Nocardiosis may mimic TB in immunocompromised individuals. Non-infectious etiologies, including sarcoidosis, pulmonary hemosiderosis, and hypersensitivity pneumonitis, can also exhibit diffuse micronodular radiographic patterns. Malignant conditions, such as primary lung carcinoma with lymphangitic spread or metastatic disease, can produce similar radiographic appearances and systemic manifestations. Additionally, pyogenic infections originating from remote sites can disseminate hematogenously and simulate miliary patterns. Thorough evaluation, including microbiological, histopathological, and molecular investigations, is therefore essential to distinguish miliary TB from these diverse conditions and establish an accurate diagnosis [68].

Prognosis

Miliary TB carries a significant risk of morbidity and mortality, particularly in patients in whom diagnosis and treatment are delayed. Mortality is influenced by host factors such as age, immune status, and the presence of comorbid conditions, as well as by disease-related factors including organ involvement and disease severity. Reported mortality rates range from approximately 15% to 20% in pediatric populations and 25% to 30% in adults, reflecting the critical impact of timely intervention [69][70][71]. Early recognition and initiation of antitubercular therapy (ATT) are therefore paramount for improving survival outcomes. In patients who develop acute respiratory distress syndrome (ARDS) as a complication of miliary TB, mortality can be predicted using the Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system. Scores greater than 18 are associated with high mortality, while patients with scores of 18 or lower who also present with hyponatremia and a PaO_2/FiO_2 ratio of 108.5 or less are similarly at elevated risk [72]. These predictors underscore the importance of close monitoring and early supportive intervention in critically ill patients. Prognostic outcomes are influenced not only by the timeliness of treatment but also by the extent of organ involvement. Patients with multiorgan dissemination or central nervous system involvement, such as tuberculous meningitis, typically experience a more guarded prognosis. Conversely, early diagnosis in immunocompetent individuals with limited organ involvement is associated with favorable recovery. Prognostic improvement relies on a combination of prompt diagnostic evaluation, initiation of appropriate therapy, and multidisciplinary supportive care tailored to the individual's clinical status.

Complications

Miliary TB may give rise to a spectrum of serious and potentially life-threatening complications, particularly in the context of delayed diagnosis or profound immunosuppression. Pulmonary complications include ARDS, which can rapidly progress to respiratory failure requiring mechanical ventilation. Multiorgan dysfunction syndrome (MODS) is another severe consequence of widespread hematogenous dissemination. Pulmonary air leak syndromes, including pneumothorax and pneumomediastinum, can occur secondary to necrotizing lung lesions. Tubercular pericardial involvement may manifest as effusion or pericarditis, potentially leading to cardiac tamponade. Extrapulmonary complications are equally diverse. Immune reconstitution inflammatory syndrome (IRIS) may develop in HIV-positive patients following initiation of antiretroviral therapy, producing paradoxical clinical deterioration. Cardiac involvement can include myocarditis, endocarditis affecting native or prosthetic valves, and intracardiac masses. Vascular complications such as mycotic aneurysm formation in the aorta are rare but catastrophic. Neurological sequelae, including tuberculous meningitis with focal deficits, occur in a significant subset of patients and can lead to long-term morbidity. Renal and hematologic complications include immune complex glomerulonephritis, bone marrow suppression, and, rarely, disseminated intravascular coagulation. Systemic amyloidosis has also been reported in prolonged untreated disease. Risk factors for these complications include HIV infection with low CD4+ counts, chronic immunosuppressant use, advanced age, and congenital or acquired immune deficiencies. The potential for rapid deterioration in these vulnerable populations highlights the need for early recognition, aggressive treatment, and vigilant monitoring to prevent progression and reduce mortality [71][72].

Patient Education

Patient education constitutes a critical component of miliary TB management and overall public health strategy. Educating patients and at-risk populations can reduce transmission, enhance early detection, and improve adherence to antitubercular therapy. Individuals diagnosed with TB must understand the disease process, the rationale for ATT, the importance of completing therapy, and the potential consequences of nonadherence, including drug resistance. Counseling should also address monitoring for signs of drug toxicity, including hepatotoxicity, hypersensitivity reactions, and hematologic abnormalities. Education should extend to preventive measures aimed at limiting Mycobacterium tuberculosis (MTB) transmission within households and communities. Patients must be counseled on respiratory hygiene, isolation precautions when necessary, and the importance of prompt reporting of symptoms in close contacts. Healthcare providers play a central role in reinforcing adherence, adjusting therapy according to tolerance and response, and providing support for follow-up visits. Comprehensive patient education programs are particularly important in high-risk groups such as immunocompromised individuals, children, and elderly patients. Community health initiatives, such as the Directly Observed Treatment, Short-Course (DOTS) strategy recommended by the WHO, rely heavily on patient education and engagement. Through structured support, patients are more likely to complete therapy, achieve microbiological cure, and prevent the spread of infection. Effective patient counseling and education, therefore, serve as a cornerstone of miliary TB management, complementing pharmacological and clinical interventions to optimize outcomes and reduce disease burden [72].

Other Issues

Miliary TB represents a severe and potentially fatal form of disseminated tuberculosis, distinguished by the formation of millet-seed-like granulomas across multiple organs. The condition typically arises from a primary pulmonary focus that spreads hematogenously, although extrapulmonary primary sites may also precipitate dissemination. Clinical presentations are diverse, often starting with nonspecific constitutional symptoms such as fever, fatigue, weight loss, and respiratory complaints, which complicates early diagnosis. Immunocompromised individuals, including those with HIV/AIDS, older adults, and patients receiving immunosuppressive therapy, are particularly susceptible to miliary TB. Imaging modalities, including chest x-rays and computed tomography scans, frequently reveal characteristic diffuse micronodular patterns, though these may be absent in early or cryptic disease. Central nervous system involvement, particularly tuberculous meningitis, represents a critical and life-threatening complication. Definitive diagnosis requires a combination of clinical assessment, imaging studies, and laboratory confirmation via microbiological culture, molecular assays such as Gene Xpert MTB/RIF, or histopathological examination of tissue specimens. The WHO-recommended

antitubercular regimen forms the mainstay of therapy, with duration extended in cases of skeletal or neurological involvement. Adherence to therapy is paramount to prevent drug resistance, and prognosis is influenced by the extent of organ involvement, timeliness of diagnosis, and treatment efficacy. Preventive strategies include BCG vaccination and early identification and treatment of active TB cases. Miliary TB necessitates a high level of clinical vigilance, prompt intervention, and coordinated diagnostic and therapeutic management to achieve optimal patient outcomes [72].

Enhancing Healthcare Team Outcomes

Management of miliary TB benefits significantly from an interprofessional team approach that integrates expertise across multiple disciplines. Physicians provide diagnostic acumen and treatment planning, while nurses ensure bedside care, adherence monitoring, and patient education. Laboratory personnel perform essential microbiological, molecular, and immunological analyses that guide therapy. Pharmacists are vital in monitoring drug interactions, dosing, and potential adverse reactions. Nutritionists contribute to optimizing the patient's dietary intake to support recovery, and physical and occupational therapists assist in maintaining functional independence during convalescence. Specialist involvement is often required, including pulmonologists, intensivists, infectious disease experts, neurologists, gastroenterologists, endocrinologists, cardiologists, surgeons, and radiologists, depending on organ-specific involvement. Implementation of the WHO DOTS strategy at the community level ensures adherence to therapy and limits disease transmission. Collaboration, communication, and shared decision-making within the healthcare team are essential for comprehensive care. A coordinated approach allows for timely intervention, minimizes complications, and enhances patient outcomes, reinforcing the need for a structured, evidence-based care pathway in managing miliary TB [72].

Conclusion:

Miliary tuberculosis remains a life-threatening manifestation of Mycobacterium tuberculosis due to its widespread hematogenous dissemination and highly variable clinical presentation. The disease demonstrates significant diagnostic challenges, often mimicking other systemic conditions, especially in immunocompromised or elderly patients. Early recognition is critical, as delays substantially increase the risk of complications such as ARDS, MODS, CNS involvement, and multiorgan failure. Effective management requires a comprehensive approach integrating clinical evaluation with laboratory, imaging, molecular diagnostics, and histopathology. Standard antitubercular therapy is effective for most patients; however, extended treatment durations are necessary for neurological and skeletal involvement or when host immune competence is impaired. Multidisciplinary collaboration—encompassing infectious disease specialists, radiologists, intensivists, and laboratory teams—plays a pivotal role in optimizing care. Ultimately, timely diagnosis, vigilant monitoring for complications, adherence to therapy, and patient education remain the cornerstone strategies to improve survival and reduce disease burden.

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