Review Article

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Challenges in the diagnosis & treatment of miliary tuberculosis

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Miliary tuberculosis (TB) is a potentially lethal disease if not diagnosed and treated early. Diagnosing miliary TB can be a challenge that can perplex even the most experienced clinicians. Clinical manifestations are nonspecific, typical chest radiograph findings may not be evident till late in the disease, high resolution computed tomography (HRCT) shows randomly distributed miliary nodules and is relatively more sensitive. Ultrasonography, CT and magnetic resonance imaging (MRI) are useful in discerning the extent of organ involvement by lesions of miliary TB in extra-pulmonary locations. Fundus examination for choroid tubercles, histopathological examination of tissue biopsy specimens, conventional and rapid culture methods for isolation of *Mycobacterium tuberculosis,* drug-susceptibility testing, along with use of molecular biology tools in sputum, body fluids, other body tissues are useful in confirming the diagnosis. Although several prognostic markers have been described which predict mortality, yet untreated miliary TB has a fatal outcome within one year. A high index of clinical suspicion and early diagnosis and timely institution of anti-tuberculosis treatment can be life-saving. Response to first-line anti-tuberculosis drugs is good but drug-induced hepatotoxicity and drug-drug interactions in human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) patients pose significant problems during treatment. However, sparse data are available from randomized controlled trials to define the optimum regimen and duration of treatment in patients with drug-sensitive as well as drug-resistant miliary TB, including those with HIV/AIDS.

Key words Complications - diagnosis - human immunodeficiency virus - miliary tuberculosis - treatment

Introduction

In 1700, John Jacob Manget[1] described a form of disseminated tuberculosis (TB) and likened the tiny tubercles evident on gross pathological examination to that of innumerable millet seeds in size and appearance. He coined the term miliary TB (derived from the Latin word *miliarius*, meaning related to millet seed) to denote this fatal form of disseminated TB. Miliary TB results from a massive lymphohaematogeneous dissemination from a *Mycobacterium tuberculosis*-laden focus[2-4] (Fig. 1).

Miliary TB still remains a perplexing disease that continues to elude the most erudite and experienced clinicians and is a diagnostic and therapeutic challenge. Mortality from this disease has remained high despite effective therapy being available. The myriad clinical

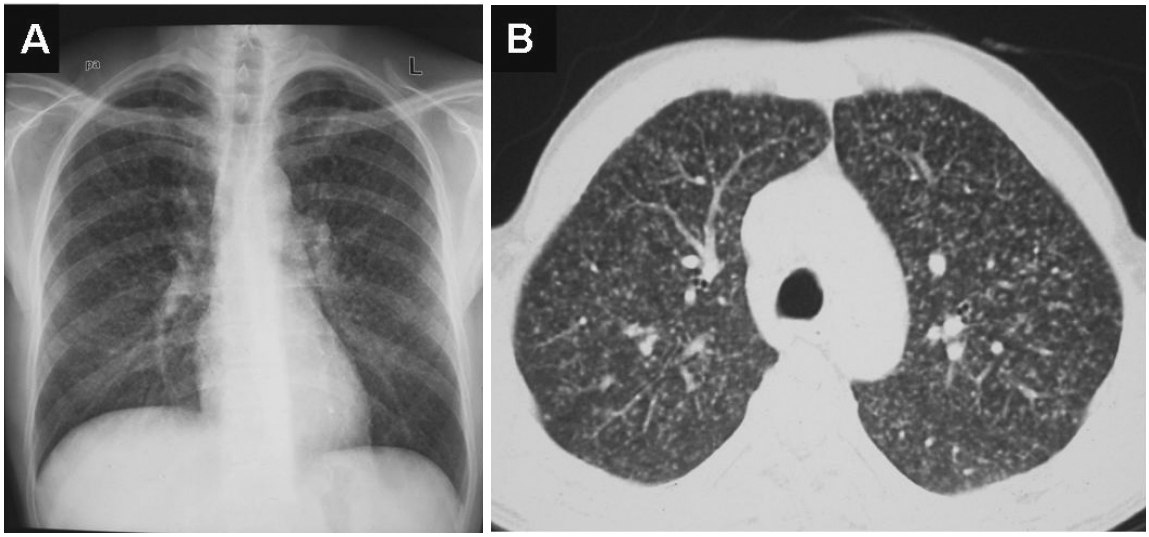

Fig. 1. Chest radiograph (postero-anterior view) **(A)** and chest CT (lung window) **(B)** showing classical miliary pattern.

manifestations, atypical radiographic findings and difficulties in establishing TB as the aetiological diagnosis, among others, are challenges in diagnosis and treatment of miliary TB (Table I).

In this review, we first provide an overview regarding the epidemiology, current understanding of key pathogenetic mechanisms, molecular basis of dissemination, predisposing and associated conditions, the varied clinical manifestations that have been documented in miliary TB, and then the challenges in the diagnosis and treatment of miliary TB are addressed.

Burden of the problem

Mortality from this disease has remained high despite effective therapy being available. For a long time, miliary TB has been considered to be a childhood disease. However, during the last three decades, it is increasingly being recognized in adults as well. Several reasons are thought to be responsible for this changing epidemiological trend. These include: human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), ever increasing list of causes of immunosuppression, such as use of biologicals and immunosuppressive drugs for treatment of various medical disorders, increasing occurrence of organ transplantation, chronic haemodialysis programme, among others.

Interpretation of published epidemiological data on miliary TB is hampered by certain methodological issues. Even after giving allowance for non-availability of community based data on the prevalence, different denominators used, lack of a "gold standard" for the diagnosis and variation in the nature of invasive methods used for securing tissue to confirm the diagnosis, sparse autopsy data regarding miliary TB in children certain conclusions can be drawn regarding the epidemiology of miliary TB. Among immunocompetent adults, miliary TB accounts for less than 2 per cent of all cases of TB and up to 20 per cent of all extra-pulmonary TB (EPTB) cases in various clinical studies[5-12]. In late HIV infection, EPTB accounts for more than 50 per cent of all cases of TB[4]. In autopsy studies[13-19], the corresponding figures have been higher; miliary TB accounts for 0.3 to 13.3 per cent of all autopsies and 11.9 to 40.5 per cent of all cases of TB. In the pre-antibiotic era, miliary TB was predominantly a disease of infants and children[20,21]. Currently, two peaks are evident- one involving adolescents and young adults and another later in life among elderly persons[4,9,11,22-44]. Males seem to be more frequently affected by miliary TB in paediatric as well as adult series[4,9,11,22-44]. A few recent adult series on miliary TB[9,19,29,33] describe a female preponderance probably reflecting increased awareness and utilization of health services by women. In USA, a higher incidence of miliary TB has been described in African Americans in some of the earlier publications though such a trend is not evident from recent data[4,24,34].

Predisposing, associated conditions

Several predisposing or associated conditions have been described in patients with miliary TB. These

Table I. Why miliary TB is a challenge for diagnosis and treatment?

- Clinicians may not be familiar with the atypical presentation(s), such as, presentation with normal chest radiograph, abnormal behaviour in TB meningitis, hyponatraemia, ARDS, and skin manifestations, *etc*.
- Fundus examination following mydriatic administration may not be a routine practice in health care facilities.
- Patients may be too sick to undergo various investigations.
- Patients genuinely are not able to produce sputum, body fluids may be absent, may not have meningitis; sometimes, sputum specimen may be negative, body fluids, tissue specimens may be difficult to procure; state of-the-art facilities and expertise may not be available except in tertiary care centers.
- Quality assured, periodically accredited laboratory infrastructure may not be available for carrying out mycoabcterial culture and drug-susceptibility testing and molecular diagnosis.
- Even when appropriate specimens are submitted, especially in HIV-negative miliary TB, these specimens may yield genuinely negative results because EPTB is a paucibacillary disease.
- Treatment: choosing the right anti-tuberculosis drug regimen, addition of steroids, duration of anti-tuberculosis treatment, lack of laboratory monitoring facilities, difficulties in the management of complications (especially in peripheral centres due to lack of expertise) are all therapeutic challenges. Not assessing the extent of organ system involvement initially (e.g., TB meningitis) may result in sub-optimal duration of therapy.
- While treating TB, drugs should be genuine with good bioavailability which may not be the case in resource-constrained nations where the disease is most prevalent.
- In some situations, especially in HIV co-infected patients, despite regular anti-tuberculosis drug intake, adequate plasma levels may not be achieved due to malabsorption problems.
- ART and ATT: several issues that are still not clear, like adequate staff training for recognition of adverse effects and close monitoring of co-drug toxicities, scarcity of quality assured laboratory facilities where the disease is common, IRIS diagnosis (adequate education of the patients for recognition of drug toxicities, drug adherence issues).

TB, tuberculosis; HIV, human immunodeficiency virus; EPTB, extra-pulmonary tuberculosis; ART, anti-retroviral treatment; ATT, anti-tuberculosis treatment; IRIS, immune reconstitution inflammatory syndrome

include childhood infections, malnutrition, HIV/AIDS, alcoholism, diabetes mellitus, chronic kidney disease, dialysis, post-gastrectomy, organ transplantation, connective tissue disorders, pregnancy, postpartum, presence of an underlying malignancy, and silicosis[4]. However, their pathogenetic significance is not clear.

In addition to corticosteroids, immunosuppressive and cytotoxic drugs are known to predispose to the development of miliary TB, use of immunomodulator drugs (biologicals) has been documented to cause fatal TB including miliary TB in rheumatoid arthritis[45-48]. These include anti-tumour necrosis factor (TNF) agents infliximab[48], etanercept[47], and adalimumab[46]. In a recent prospective study among patients who received anti-TNF therapy[45], EPTB constituted 62 per cent of all cases of TB; disseminated and miliary TB accounted for 27.5 per cent of all TB cases, 44 per cent of extra-pulmonary TB. The rate of development of TB was higher for adalimumab and infliximab than for etanercept. The median time to development of TB was lowest for infliximab compared with etanercept and adalimumab (Table II). Patients with non-white ethnicity had a 6-fold higher risk of TB compared with white patients[45].

Several procedures and interventions have been implicated in the causation of miliary TB. These include ureteral catheterization, extracorporeal shockwave lithotripsy, laser lithotripsy, cardiac valve homograft replacement, intravesical bacille Calmette-Guerin (BCG) therapy for urinary bladder carcinoma[49-53].

Table II. Risk of developing miliary TB with the use of anti-TNF agents in patients with rheumatoid arthritis

Variable	Infliximab	Adalimumab	Etanercept
Rate of development of miliary TB (events/100,000 person-years)	136	144	39
Median time to development of TB (months)	5.5	18.5	13.4

TB, tuberculosis; TNF, tumour necrosis factor

Data from reference 45

Immunopathogenesis

The inadequacy of effector T-cell response in containment of *M. tuberculosis* is thought to be responsible for the development of miliary TB[54-57]. The abundance of Th1 and Th2 polarized effector T (Teff) cells in the peripheral blood and local disease site(s) among patients with miliary TB suggest that miliary TB probably represents the Th2 end of the spectrum[56,57]. Interleukin-4 (IL-4), with its ability to downregulate inducible nitric oxide synthase (iNOS), toll-like receptor 2 (TLR2) and macrophage activation, may play an important role in the events that determine whether the infection becomes latent or progressive[4,54,55]. *M. tuberculosis* can either fail to evoke the protective response or can drive the protective mechanisms and then deliberately 'sabotage' them leading to progressive disease[55-57]. In miliary TB, frequency of regulatory T (Treg) cells (CD4+CD25+FoxP3+) and higher levels of FoxP3 mRNA were significantly increased in local disease site specimens[57]. Further, FoxP3+ Treg cells obtained from the bronchoalveolar lavage (BAL) fluid of patients with miliary TB predominantly produced interleukin-10 (IL-10) and could suppress the autologous T-cell proliferation in response to *M. tuberculosis* antigen[56]. In miliary TB, the attempt by the host to selectively recruit the Teff cells at the pathologic site, however, fails to provide an adequate level of effector immunity at the disease site due to efficient and comparable homing of Treg cells (FoxP3+), which inhibit the function of the Teff cells that have infiltrated the disease site. It has been postulated that when the balance of homing of Treg and Teff cells shifts toward the former, there is a state of local immunosuppression leading to disease dissemination[4,56,57].

Observations regarding the cellular characteristics of BAL fluid in patients with miliary TB have yielded conflicting results[58-60]. Though the diagnostic significance of these findings is not clear, these may facilitate the understanding of the pathogenesis of miliary TB. The proportion and absolute number of lymphocytes are substantially increased in BAL fluid. A raised CD4+/CD8+ T-lymphocyte ratio and B-lymphocytes as well as a decrease in CD4+/CD8+ T-lymphocyte ratio have earlier been reported in BAL fluid[61,62]. Polyclonal hypergammaglobulinaemia with increase in immunoglobulin (Ig) G, IgA, and IgM was observed in peripheral blood and BAL fluid[61]. These findings probably result from increased local synthesis by activated B-lymphocytes. Increased BAL fluid fibronectin and serum C3 levels reflect an acute phase response to ongoing inflammation[61,62]. Lymphocytic alveolitis and increased IgG and IgA levels have persisted following antituberculosis treatment[61].

Molecular basis of dissemination

Several molecular mechanisms have been implicated in the development of miliary TB. These include impaired expansion of γ/δ T-cells[63], failure to generate adequate cell-mediated immunity[64], presence of HLA-Bw15[65], HLA-DRB1*15/16, DRB1*13, and DQB1*0602[66], absence of HLA-Cw6, HLA-DRB1*10, and DQB1*0501[66], impaired MHC class II restricted target cell lysis, and over-exuberant lysis of target cell macrophages[67] and LTA+368 G/A polymorphisms[68].

Clinical manifestations

The clinical manifestations of miliary TB in adults are protean, non-specific and can be obscure till late in the disease (Fig. 2).

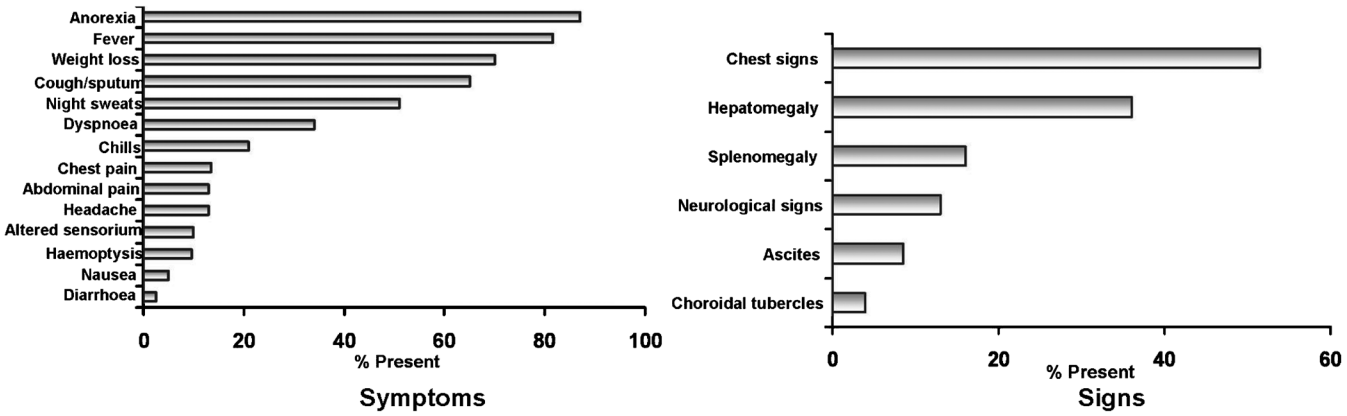

Fig. 2. Median prevalence of symptoms and signs at initial presentation in adult patients with miliary tuberculosis. Data from references 9,18,24-27,29,31-34,36,37,39-42,44.

Constitutional symptoms: Patients with miliary TB classically present with fever with evening rise of temperature of several weeks duration, anorexia, weight loss, weakness and cough[3,4]. Occurrence of daily morning temperature spikes[69] is reported to be characteristic of miliary TB. However, fever may be absent and the patients may present with progressive wasting strongly mimicking a metastatic carcinoma (cryptic miliary TB)[70]. Since its initial description, cryptic miliary TB is increasingly being reported in the elderly population[20,21].

Chills and rigors, described in patients with malaria, or, sepsis and bacteraemia, have often been described in adult patients with miliary TB[3,4]. Night sweats are common. A "damp shadow" sign (where sweat engraved the patient's silhouette on the bed, closely resembling a body's shadow) has also been described in miliary TB[71].

Systemic involvement: Since miliary TB can involve many organs, patients present with symptoms and signs referred to various organ systems (Fig. 2). Dry cough and dyspnoea are often present. Sputum may be scanty. Haemoptysis can occur rarely. Cutaneous lesions may offer a valuable clue to the diagnosis of miliary TB (Fig. 3). These include erythematous macules and papules (*tuberculosis miliaria cutis*)[4].

Choroidal tubercles when present in an appropriate clinical setting, provide a valuable clue to the diagnosis of miliary TB. The presence of choroidal tubercles is considered to be pathognomonic of miliary TB[3,4,39]. Choroidal tubercles are bilateral, pale, gray-white or yellowish lesions usually less than one quarter of the size of the optic disc and are located within 2 cm of the optic nerve. These are more commonly seen in children. Therefore, a systematic ophthalmoscopic examination is recommended after mydriatric administration in all patients with suspected miliary TB (Fig. 4).

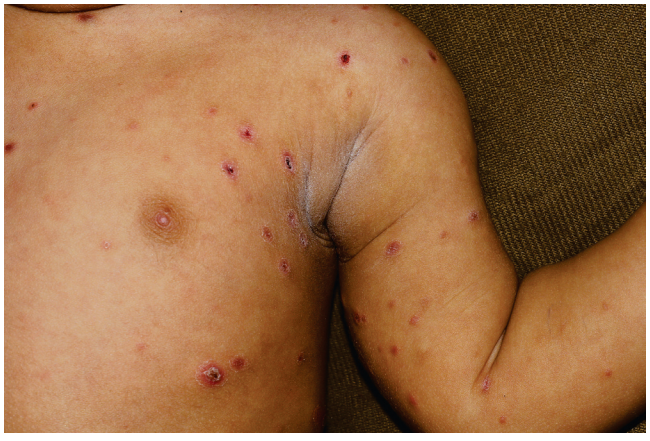

Fig. 3. Clinical photograph of a child showing cutaneous lesions of miliary tuberculosis (*Kind courtesy*: Dr M. Ramam, Department of Dermatology, All India Institute of Medical Sciences, New Delhi, India).

TB meningitis (TBM) has been described in 10 to 30 per cent adult patients with miliary TB[9,18,22-27,29,30,32-39,41,42]; conversely, about one-third of patients presenting with TB meningitis have underlying miliary TB[72]. In a recently published study[73], the spectrum of neurological involvement in adult patients with miliary TB included TB meningitis with and without tuberculoma; and thoracic transverse myelopathy.

Before the advent of modern imaging modalities, such as CT, MRI and echocardiography, clinically evident cardiac or renal involvement was seldom documented in patients with miliary TB. Overt adrenal insufficiency manifesting as Addison's disease at initial presentation, or during anti-tuberculosis treatment has also been described in miliary TB[74,75].

Children

There are only a few published series on childhood miliary TB[6-8,22-38]. Miliary TB develops less often in children who have received the BCG vaccination[4]. Compared with adults, chills and night sweats, haemoptysis, productive cough are less common; peripheral lymphadenopathy and hepatosplenomegaly are more frequent in children with miliary TB. A larger proportion of children with miliary TB (20-40%) suffer from TBM[6-8,22-38] compared to adults (15-30%)[9,18,22-27, 29,31-34,36-42,44].

Miliary tuberculosis in immunosuppressed individuals

The prevalence of miliary TB in persons with early HIV infection (CD4+ cell counts >200 cells/mm^3) is similar to that observed in immunocompetent individuals. With progression of immunosuppression, in late, advanced stage of HIV infection (CD4+ cell counts <200 cells/mm^3), miliary TB is seen more often[4,58,76]. Table III shows a comparison of various aspects of miliary TB in late advanced stage of HIV infection and in immunocompetent individuals, early HIV infection[4,41,58,76-82]. Cutaneous involvement, a rare clinical manifestation in HIV-seronegative patients with miliary TB, is more commonly seen in late HIV infection with severe immunosuppression[4,58,76-82]. The skin manifestations include tiny papules or vesiculopapules,

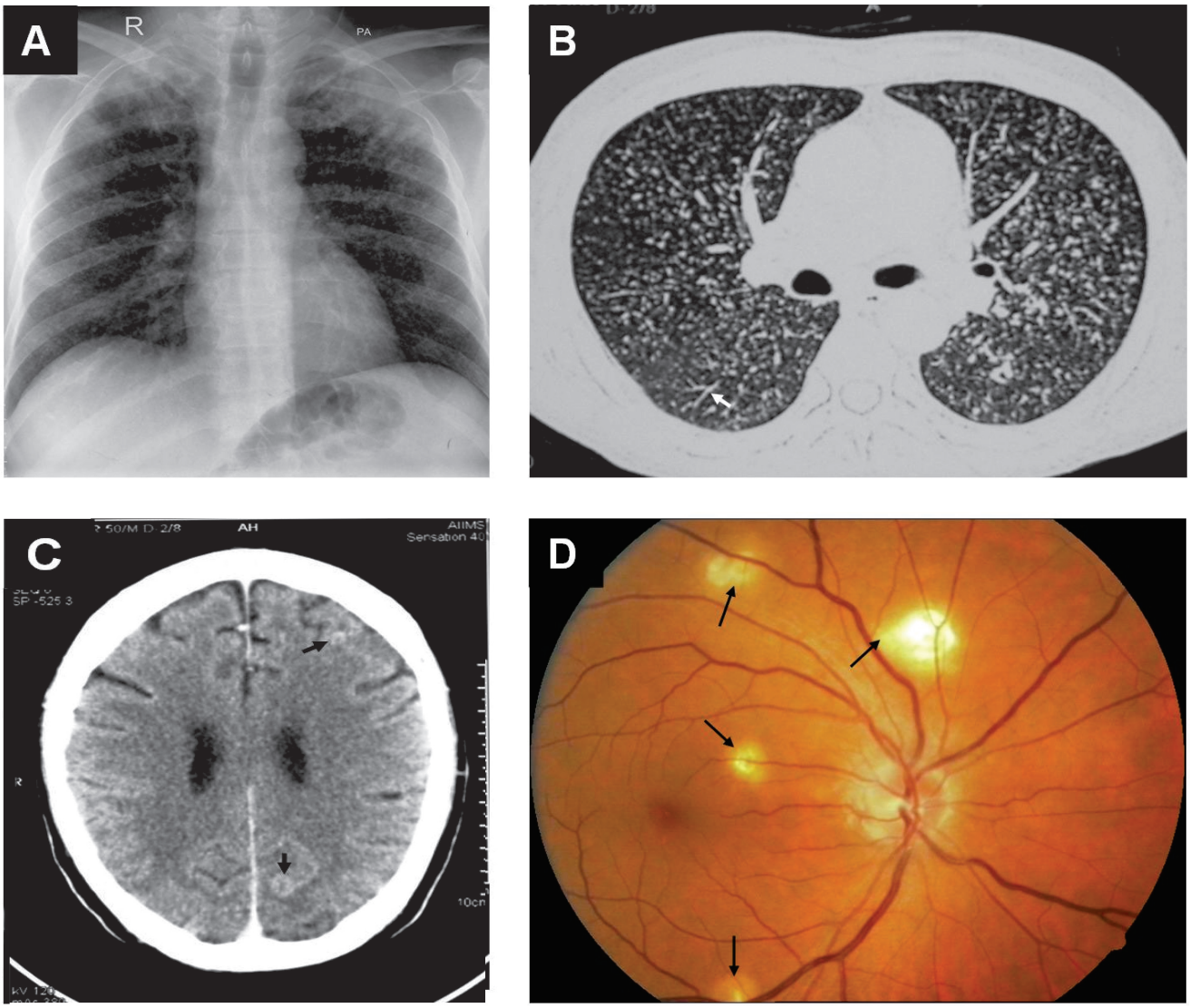

Fig. 4. Chest radiograph (postero-anterior view) **(A)** and chest CT (lung window) **(B)** showing classical miliary pattern, *tree-in-bud appearance* **(B)** (arrow). The patient also had cerebral tuberculomas (arrows) and TB meningitis **(C)**. Choroid tubercles, located in the posterior pole of the orbit **(D)** (arrows) offered an early valuable clue to the diagnosis. The present case illustrates the importance of documenting the presence of neurological involvement, particularly, TB meningitis in patients with miliary TB and thereby ensuring adequate duration of anti-tuberculosis treatment and need for corticosteroid treatment.

(*tuberculosis cutis miliaris disseminata*, *tuberculosis cutis acuta generalisita)*, and disseminated tuberculosis of the skin (Fig. 3). Sometimes, macular, pustular, or purpuric lesions, indurated ulcerating plaques, and subcutaneous abscesses have been reported[83].

In miliary TB patients co-infected with HIV, especially in those with profound immunosuppression, intrathoracic lymphadenopathy and tuberculin anergy are more common; sputum smears are seldom positive and blood culture may grow *M. tuberculosis*[4,58,76-82] (Table III). These observations seem to be applicable to other causes of immunosuppression as well[84].

Uncommon clinical manifestations and complications

Several uncommon clinical manifestations and complications have been observed in patients with miliary TB (Table IV). In some patients, complications like ARDS or myocarditis may in fact be the initial

Table III. Clinical presentation of miliary TB in adult patients with and without HIV co-infection

Variable	Miliary TB in HIV-seronegative persons	Miliary TB in late HIV infection*
Epidemiology	Accounts for 20% of all EPTB cases in clinical studies	Accounts for 50% of all EPTB cases in clinical studies
Clinical manifestations		
Cutaneous lesions	Rare	More common
Peripheral lymphadenopathy	May be present	Often present
Choroid tubercles	May be present	Often present and may be the initial clue
Atypical clinical presentation (*e.g.*, Cryptic miliary TB, ARDS, AKI, *etc*.,)	Rare	Common ARDS may be difficult to differentiate from ARDS due to *Pneumocystis jiroveci* and bacterial infections
Imaging findings		
Intrathoracic, intraabdominal lymphadenopathy	Rare	Common
Extra-thoracic organ-system involvement	Common	More common (hepatic, spleenic and prostatic abscesses, rarely cardiac involvement can occur)
Diagnosis		
Sputum smear positivity	Less common	Common
Diagnosis of EPTB	Difficult due to paucibacillary state	Bacillaemia frequent and bacilli at EPTB sites readily demonstrable
Tuberculin anergy	Rare	Common
Clinical and laboratory monitoring on follow-up	Relatively easy. May require liver functions, serum uric acid and ocular monitoring	Complex and expensive. In addition to liver functions, serum uric acid and ocular monitoring, CD4 + T-lymphocyte count, plasma HIV viral load, drug toxicities, drug-drug interactions need to be monitored
Treatment	Anti-TB treatment + corticosteroids in some patients	Anti-tuberculosis treatment + antiretroviral drugs + co-trimoxazole prophylaxis
IRIS	Rare	Common. Might require expert opinion for diagnosis. Imaging guided procedures may be required frequently for drainage of abscesses. Essential to rule out drug-resistant TB and new infection
Drug-drug interactions	Rare	Common Interactions between antiretroviral drugs and anti-TB treatment may require frequent treatment interruptions. Periodic , close laboratory monitoring is required
Adverse drug reactions	Rare	Common
Frequency of radiographic monitoring	Less frequently required	More frequently required
Mortality	Less	Higher
Relapse after treatment	Rare	Common

*CD4+ T-lymphocyte count < 200/mm^3. In early HIV infection, the clinical presentation of TB is similar to that observed in HIV-seronegative individuals

TB, tuberculosis; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; EPTB, extra-pulmonary tuberculosis; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury

Source: Refs 4,41,58,80-82

Table IV. Uncommon clinical manifestations and complications in miliary tuberculosis

Systemic manifestations
Cryptic miliary tuberculosis
Pyrexia of unknown origin
Shock, multiorgan dysfunction
Incidental diagnosis on investigation for some other reason
Pulmonary
Acute respiratory distress syndrome
"Air leak" syndrome (pneumothorax, pneumomediastinum)
Acute empyema
Haematological
Myelopthisic anaemia
Immune haemolytic anaemia
Endocrinological
Thyrotoxicosis
Renal
Overt renal failure due to granulomatous destruction of the interstitium
Immune complex glomerulonephritis
Cardiovascular
Pericarditis with or without pericardial effusion
Sudden cardiac death
Mycotic aneurysm of aorta
Native valve, prosthetic valve endocarditis
Hepatic
Cholestatic jaundice
Others
Presentation as focal extra-pulmonary tuberculosis

Source: Refs 2-4,39,58,85-89,91-97,112,114

presentation. Atypical clinical presentation often delays the diagnosis and treatment and miliary TB is often a "missed diagnosis".

Acute respiratory distress syndrome

Although ARDS may develop anytime during the course of miliary TB, it is usually seen at the time of initial presentation (Fig. 5); ARDS may develop as a component of the multiorgan dysfunction syndrome (MODS) due to TB or as a manifestation of immune reconstitution inflammatory syndrome (IRIS)[85-89]. In a study from two large teaching hospitals at New Delhi and Tirupati in India[89], among patients with TB, prolonged illness, miliary TB, absolute lymphocytopaenia and elevated alanine aminotransferase (ALT) were found to be independently associated with the development of ARDS. In another study[90] from Korea, higher C-reactive protein levels and an increasing nutritional risk score were found to be independent risk factors for the development of ARDS in patients with miliary TB.

Air-leak syndromes

Pneumothorax, which may sometimes be bilateral, may be the presenting feature or may sometimes develop while the patient is receiving anti-tuberculosis treatment[3,4,91,92]. Classical miliary shadows may not be discernible initially and may become apparent once lung expands. Intrapulmonary rupture of alveoli and consequent air-leak that traverses into the mediastinum after spreading along the vascular sheath can result in pneumomediastinum with subcutaneous emphysema which may be fatal[93]. Rarely, pneumothorax may develop as a complication in TB-ARDS patients receiving mechanical ventilation (Fig. 5E).

Acute kidney injury

In addition to being a part of MODS, acute kidney injury (AKI) may occur due to direct renal parenchymal involvement in patients with miliary TB[4,94]. In HIV co-infected patients with miliary TB, AKI can also develop as a manifestation of IRIS[95]. Uncommonly, renal failure can develop as a consequence of obstructive uropathy caused by the disease process[58].

Hepatic and gastrointestinal manifestations

Fulminant hepatic failure may rarely be the presenting manifestation in miliary TB. In some of these patients the characteristic pulmonary lesions that constitute the hall mark of miliary TB are absent[96,97]. This could probably be the result of extrapulmonary focus discharging the tubercle bacilli into the portal circulation, resulting in hepatic miliary TB. Peritoneal involvement may be evident by the presence of ascites. Some patients may manifest diarrhoea or altered bowel habit suggestive of intestinal involvement. Small intestinal perforations at the site of granulomatous involvement have been described in some patients while on treatment[98].

Lesions located elsewhere in the body

Thoracic and abdominal lymphadenopathy: Patients with miliary TB, especially those co-infected with HIV manifest associated intrathoracic

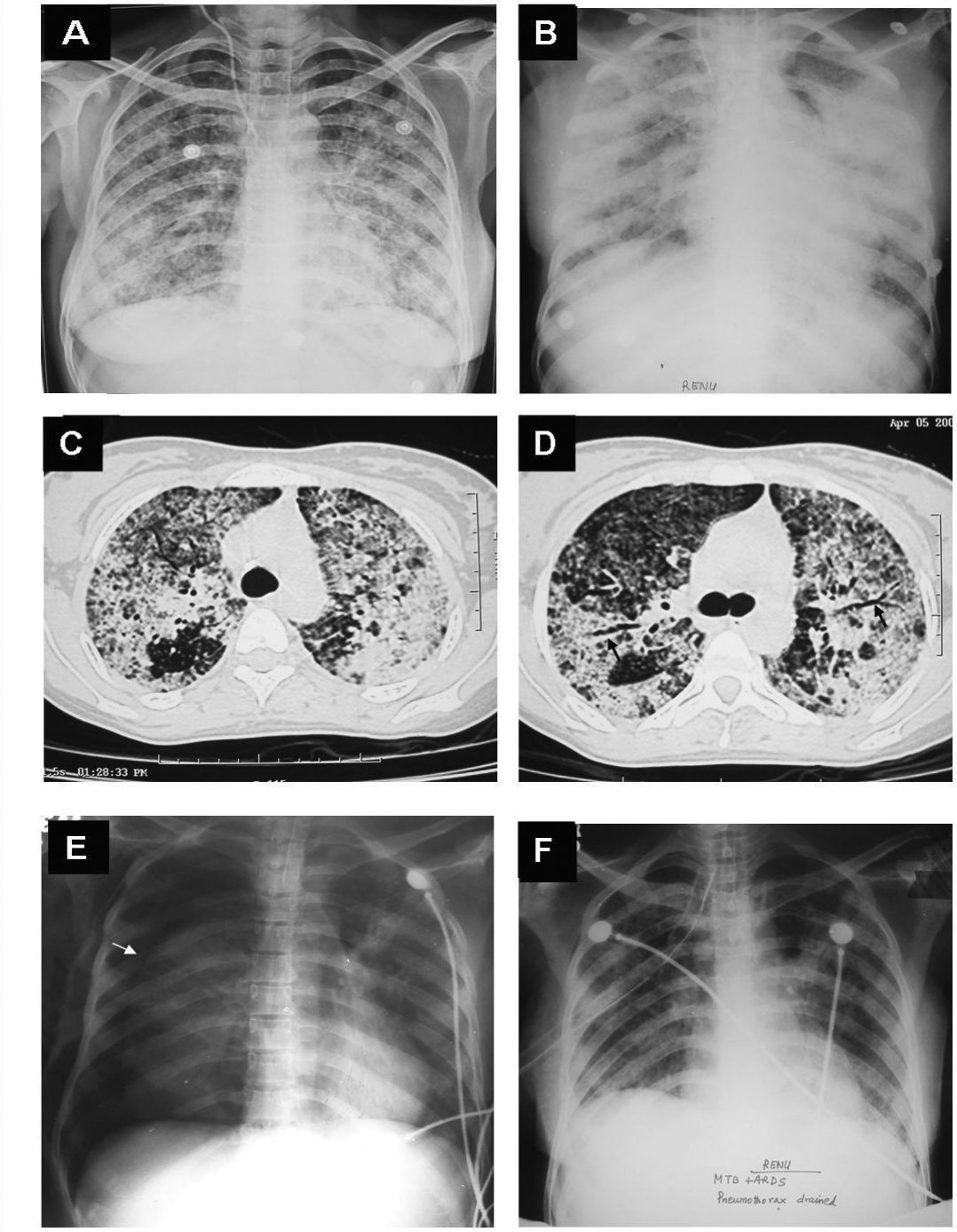

Fig. 5. Chest radiograph (postero-anterior view) of a pregnant woman who presented with prolonged pyrexia showing a classical miliary pattern **(A)**. Fundus examination following mydriatic administration in both the eyes revealed choroid tubercles and had raised the suspicion of miliary TB. The patient developed ARDS during the course of her illness. Chest radiograph (antero-posterior view), obtained with a portable X-ray machine, bed-side showing bilateral frontal opacities suggestive of ARDS **(B)**. CT chest obtained at the same time reveals air-space consolidation **(C and D)**; air-bronchogram (arrow) **(D)**. While assisted ventilation was being administered, the patient developed pneumothorax (asterisk) on the right side; collapsed lung border is also evident (arrow) **(E)**. The patient required tube thoracostomy and underwater seal drainage. Eventually the patient was weaned off the ventilator and the intercostal tube was removed following resolution of the pneumothorax. The chest radiograph obtained thereafter shows significant improvement in the lesions **(F)**. The patient survived the turbulent in-hospital course, went on to complete full-term of pregnancy and was successfully delivered a live baby. ARDS, acute respiratory distress syndrome; CT, computed tomography; TB, tuberculosis.

lymphadenopathy. Sometimes, intra-abdominal lymphadenopathy involving portahepatis, pre- and para-aortic and mesenteric lymph nodes; retroperitoneal lymphadenopathy may be present.

Pott's spine: Pott's spine with or without myelopathy may also be present in patients with miliary TB.

Cold abscesses: Cold abscesses in association with peripheral lymphadenopathy in the cervical or axillary regions, Pott's spine with paraspinal cold abscess may also be evident in patients with miliary TB.

Genitourinary lesions: Women with miliary TB can manifest pelvic ascites, tubo-ovarian masses, pyosalpinx and should be carefully evaluated for the same.

Cardiovascular manifestations

In patients with miliary TB, life-threatening complications such as myocarditis[99], congestive heart failure[99], native[100-102] and prosthetic valve[103] endocarditis, pericarditis, intracardiac mass[99], mycotic aneurysm[104], infection of a pacemaker pulse-generator pocket[105], infection of ventriculoatrial shunt causing miliary TB[106] and sudden cardiac death[107-109] have been described.

Immune reconstitution inflammatory syndrome (IRIS)

The IRIS, occasionally described in HIV-negative individuals with TB, has been reported to occur in about one-third of patients co-infected with HIV and TB within days to weeks of the initiation of highly active antiretroviral therapy (HAART)[110,111]. The IRIS can be brief or prolonged with multiple recurrences. Manifestations of IRIS range from isolated instances of fever to increased or initial appearance of lymphadenopathy, new or worsening pulmonary infiltrates, serositis, cutaneous lesions, and new or expanding central nervous system mass lesions[76,110,111]; AKI[95,112] or ARDS[85] can develop during the course of IRIS.

Differential diagnosis

Radiologically, the miliary pattern has been defined as "a collection of tiny discrete pulmonary opacities that are generally uniform in size and widespread in distribution, each of which measures 2 mm or less in diameter"[113]. Many conditions can present with a miliary pattern on the chest radiograph or CT (Fig. 6) and are listed in Table V. These conditions must be differentiated from miliary TB by detailed diagnostic work-up.

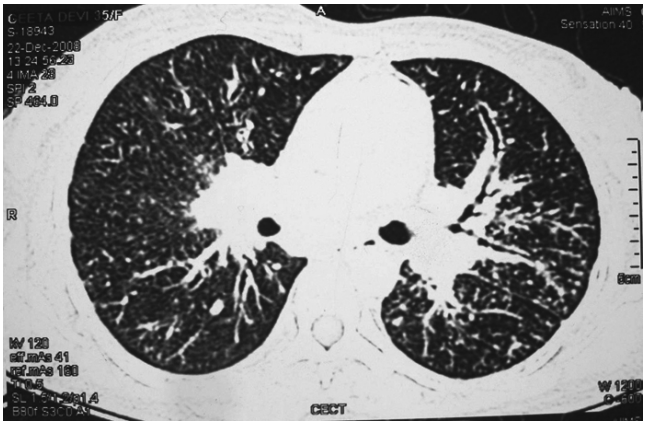

Fig. 6. CT of the chest showing miliary sarcoidosis. While the lesions of miliary TB (Fig. 1B) are randomly distributed, the lesions of miliary sarcoidosis are distributed along the bronchovascular bundle (lymphangitic distribution). Thus transbronchial lung biopsy gives a higher diagnostic yield in miliary sarcoidosis.

Diagnosis

The diagnosis of miliary TB can be difficult as the clinical manifestations are non-specific, the chest radiographs do not always reveal the classical miliary changes and patients may present with complications thus distracting the clinicians. Therefore, a high index of clinical suspicion and a systematic approach to diagnostic testing is required to establish the diagnosis of miliary TB.

Following criteria are useful for the diagnosis of miliary TB: *(i)* clinical presentation consistent with a diagnosis of tuberculosis such as, pyrexia with evening rise of temperature, weight loss, anorexia, tachycardia and night sweats of greater than six weeks duration responding to antituberculosis treatment; *(ii)* classical miliary pattern on chest radiograph; *(iii)* bilateral diffuse reticulonodular lung lesions on a background of miliary shadows demonstrable either on plain chest radiograph or HRCT; and *(iv)* microbiological and/or histopathological evidence of TB[39]. The diagnostic approach to a patient with suspected miliary TB is shown in Fig. 7.

Tuberculin skin test

Tuberculin anergy is more common in miliary TB than in pulmonary and EPTB; tuberculin skin test (TST) conversion may occur following successful treatment. In various published paediatric[6-8,22,38] and adult series[24-27,31,32-34,36,37,114] tuberculin anergy has ranged from 35 to 74 per cent and 20 to 70 per cent, respectively. However, a positive TST only indicates

Table V. Some conditions presenting with a miliary pattern on the chest radiograph

Common causes
Infections[*]
Tuberculosis
Histoplasmosis
Blastomycosis
Coccidioidomycosis
Mycoplasma pneumonia
Nocardiosis
Immunoinflammatory disorders[*]
Sarcoidosis
Malignant
Bronchoalveolar carcinoma
Carcinoma lung with lymphangitis carcinomatosa
Metastatic carcinoma
Tropical pulmonary eosinophilia
Haemosiderosis in long standing rheumatic heart disease, mitral stenosis
Hypersensitivity pneumonitis
Drug-induced interstitial lung disease (*e.g.*, methotrexate, chrysotherapy, cyclophosphamide, nitrofurantoin, antidepressants)
Uncommon causes
Infections
Cryptococcosis
Legionellosis
Melioidosis
Tularaemia
Psittacosis
Brucellosis
Staphylococcus aureus bacteraemia
Toxoplasmosis
Schistosomiasis
Strongyloides stercoralis hyperinfection
Malignant
Bronchial carcinoid
Lymphoma
Lymphomatoid granulomatosis
Occupational lung diseases

[*]Fever commonly present

infection with *M. tuberculosis* and does not always indicate active disease. A positive reaction with necrosis often (but not always) indicates active disease.

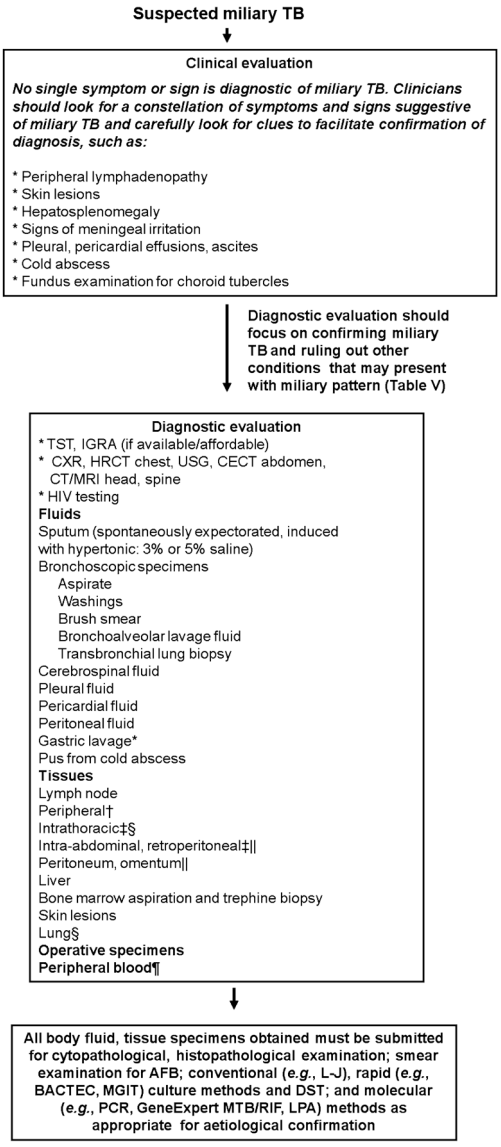

Fig. 7. Algorithm for the diagnostic work-up of a patient with suspected miliary TB. The clinical and imaging diagnostic work-up should also aim at accurately assessing the extent of extrapulmonary involvement to facilitate monitoring and ensure adequate duration of treatment. All laboratory testing, especially, antituberculosis drug-susceptibility testing must be carried out in quality assured, periodically accredited laboratories. *Often used in children; †FNAC/excision biopsy; ‡ Radiologically guided FNAC/biopsy; §Mediastinoscopic/video-assisted thoracoscopic surgery, biopsy; ||Laparoscopic biopsy; ¶Useful in advanced HIV infection. TB, tuberculosis; TST, tuberculin skin test; IGRA, interferon-γ release assays; HRCT, high resolution computed tomography; CECT, contrast enhanced computed tomography; MRI, magnetic resonance imaging; FNAC, fine needle aspiration cytology; HIV, human immunodeficiency virus; AFB, acid-fast bacilli; L-J, Lowenstein-Jensen medium; DST, drug-susceptibility testing; MGIT, mycobacterial growth inhibitor tube; BACTEC, radiometric culture method; PCR, polymerase chain reaction; GeneExpert MTB/RIF, GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA); LPA, line probe assay.

Interferon-gamma release assays

Newer *in vitro* T-cell based interferon-gamma release assays (IGRAs) available in the enzyme linked immunosorbent assay (ELISA) and enzyme linked immunospot (ELISPOT) formats appear to be promising in detecting latent TB infection (LTBI) and have several advantages over the TST. These tests may be particularly useful in children, BCG vaccinated individuals and in HIV infection and AIDS[115,116]. As with TST, a positive IGRA test result, however, does not distinguish between LTBI and active disease, but a negative IGRA result may be helpful in ruling-out a diagnosis of TB[116]. These tests are costly and on the basis of available evidence their routine use is not indicated.

Haematological and biochemical abnormalities

A number of haematological and biochemical abnormalities are known to occur in miliary TB (Table VI)[6-9,18,22,23,24-27,29,31,32-36,36-42,44] but their significance is controversial. Disseminated intravascular coagulation (DIC)[86,89] has been described in patients with miliary TB in the setting of ARDS and MODS and is associated with a high mortality. Immune mechanisms have been implicated to cause bone marrow suppression and miliary TB has also been implicated as a cause of pancytopenia, hypoplastic anaemia[4,117]. Hypercalcaemia has been documented in miliary TB, but is uncommon[118].

Table VI. Laboratory abnormalities in miliary TB

Haematological
Anaemia
Leucocytosis
Neutrophilia
Lymphocytosis
Monocytosis
Thrombocytosis
Leucopenia
Lymphopenia
Thrombocytopenia
Leukaemoid reaction
Haemophagocytosis
Elevated ESR, CRP levels
Biochemical
Hyponatraemia
Hypoalbuminaemia
Hypercalcaemia
Hypophosphatemia
Hyperbilirubinaemia
Elevated serum transaminases
Elevated serum alkaline phosphatase
Elevated serum ferritin levels

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein
Source: Refs 2-4,39,114

Hyponatraemia in miliary TB can occur due to an acquired disturbance of neurohypophyseal function resulting in unregulated antidiuretic hormone (ADH) release; an antidiuretic principle in the lung tissue affected by TB that may either produce ADH or absorb an inappropriately released hormone from the posterior pituitary[119-121]. Hyponatraemia may indicate the presence of TB meningitis[34] and may also be a predictor of mortality[39] in patients with miliary TB. Rifampicin-induced adrenal crisis in a patient with miliary TB and Addison's disease who developed generalized malaise and hyponatraemia while initiated on antituberculosis treatment has also been described[75].

Imaging studies

Miliary pattern on the chest radiograph is often the first clue suggestive of miliary TB. Several other imaging modalities, such as, ultrasonography, CT, MRI, positron emission tomography (PET) help to assess the extent of organ involvement and are also useful in evaluating response to treatment (Figs. 8 and 9).

Chest radiograph: The chest radiographic abnormalities in miliary TB are depicted in Table VII[4,114]. Miliary pattern on chest radiograph[3,4,113] is the hall mark of miliary TB and is evident in a majority of patients**.** Classically, subtle miliary lesions are best delineated in slightly underpenetrated films especially when the diamond shaped areas of the lung in between the ribs are carefully scrutinized using bright light[122,123]. However, in 10 per cent of the cases, the nodules may be greater than 3 mm in diameter[124]. Before the advent of CT, it was observed that classical miliary pattern would not be evident in the chest radiograph in up to 50 per cent of the patients and would be detected only at the time of autopsy[14,17,18,24,34,124].

When caseous material, collagen or both are present in the tubercles, these became visible on the chest radiograph[122]. Classical miliary pattern on the chest radiograph represents summation of densities of the tubercles that are perfectly aligned and imperfectly aligned tubercles result in curvilinear densities and a reticulonodular pattern[125]. Rarely, lymphatic obstruction or infiltration can result in ground glass

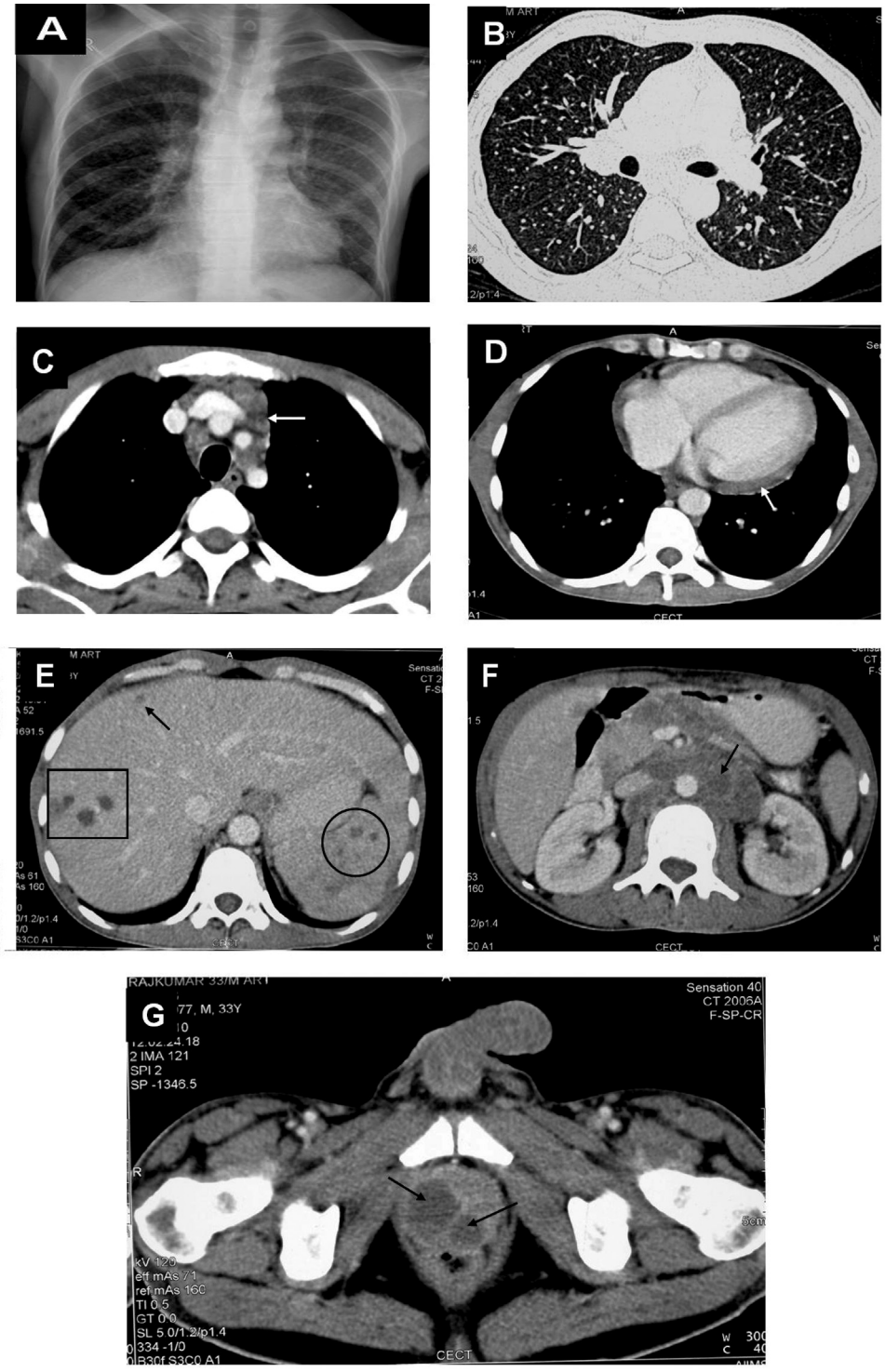

Fig. 8. Chest radiograph in a patient with HIV/AIDS (postero-anterior view) **(A)** and chest CT (lung window) **(B)** showing classical miliary pattern. The CECT chest (mediastinal window) also reveals intrathoracic lymphadenopathy (arrow) **(C)** and pericardial thickening and effusion **(D)**. The CECT of the abdomen of the same patient reveals focal miliary lesions in the liver (square, arrow) and spleen (circle) **(E)** and retroperitoneal lymphadenopathy (arrow) **(F)**; pelvic CECT shows a prostatic abscess (arrows) **(G)**. Ultrasound guided trans-rectal prostatic aspirate smear and culture examination confirmed the diagnosis of miliary TB. The diagnostic evaluation of this patient illustrates the judicious use of imaging modalities to define the extent of organ system involvement and procuring tissue for diagnostic confirmation. Such extensive involvement usually occurs in HIV/AIDS with miliary TB. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CT, computed tomography; CECT, contrast enhanced computed tomography; TB, tuberculosis.

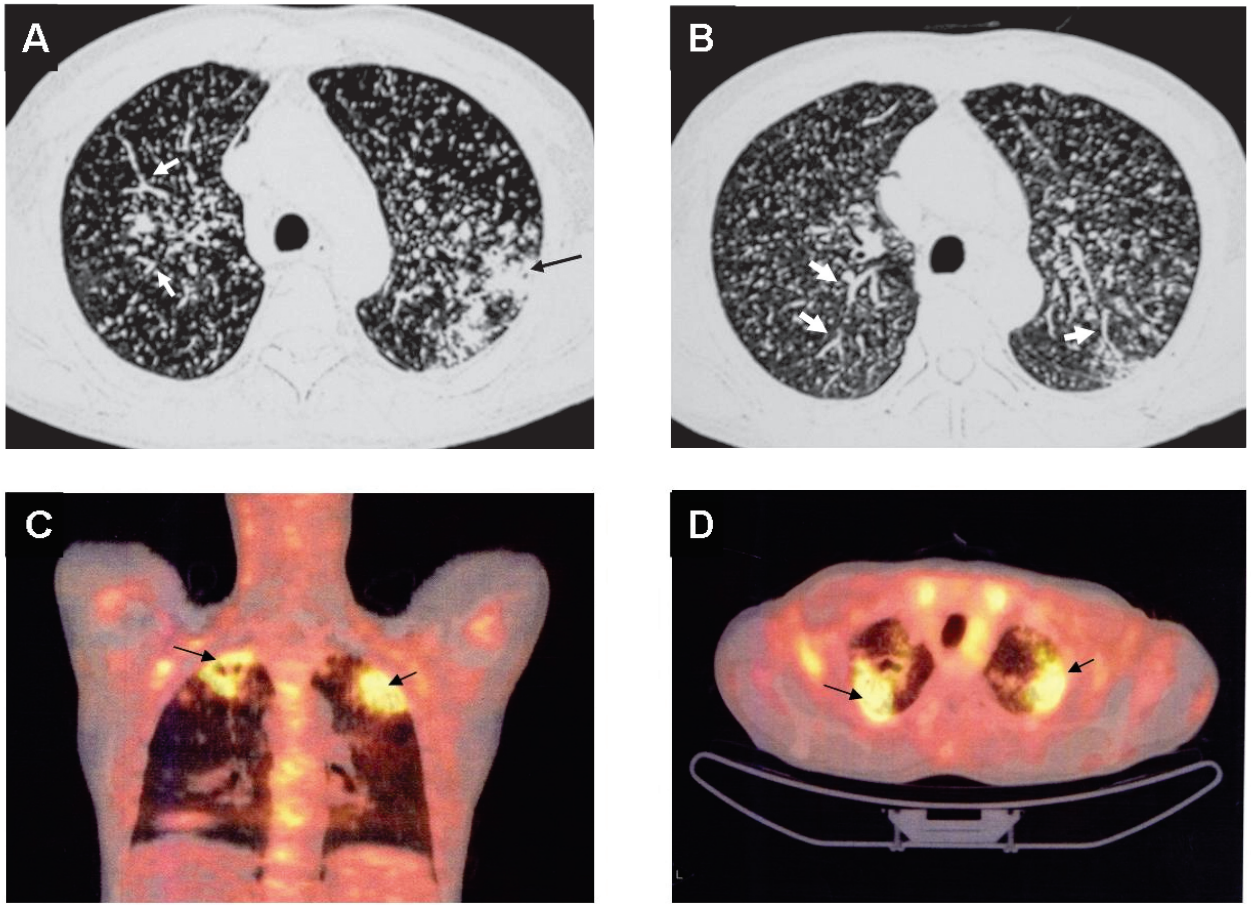

Fig. 9. Chest CT (lung window) of the same patient as in Fig. 4 showing pulmonary parenchymal lesions (black arrow) **(A)**. In addition to the miliary pattern, well-defined, linear, branching opacities (*tree-in-bud appearance*) (thick white arrows) **(A and B)** are also seen. This pattern is evident when centrilobular bronchioles are dilated, or, are filled with mucus, fluid or, pus and represents endobronchial spreading of infection. ^{18}FDG-PET CT of the same patient showing increased activity in the pulmonary parenchymal lesions (arrows) but not in the miliary lesions **(C and D)**. The ^{18}FDG-PET has potential to further understanding the clinico-radiographic-functional correlation in miliary tuberculosis and merits further study. However, it may not be useful in intracranial TB. CT, computed tomography; ^{18}FDG-PET CT, ^{18}F labelled 2-deoxy-D-glucose positron emission tomography-computed tomography; TB, tuberculosis.

appearance[126]. In some patients, predominance of lesions on one side may be evident (Fig. 10). Some patients may have normal chest radiographs initially and the typical miliary pattern may evolve over the course of disease. This is particularly evident in ARDS due to miliary TB where the chest radiograph findings may be identical to that seen in ARDS due to other causes[86,89]. One of the patients seen by the authors[39] had undergone tonsillectomy and the histopathological diagnosis was reported as miliary TB. On further diagnostic testing, a repeat chest radiograph revealed classical miliary pattern that was not discernible in the earlier chest radiographs, thus, emphasizing the importance of periodic repeat chest radiographic examination in patients with suspected miliary TB[4,39].

Ultrasonography: Ultrasonography helps in detecting ascites which may sometimes be loculated, focal hepatic and splenic lesions and cold abscesses, intra-abdominal lymphadenopathy, involvement of other abdominal organs and pleural effusion(s). Ultrasonography guidance also facilitates diagnostic thoracic or abdominal paracentesis to procure pleural or peritoneal fluid for diagnostic testing especially if the fluid is loculated.

Computed tomography (CT) and magnetic resonance imaging (MRI): In comparison with pre-CT era, high resolution CT (HRCT), thin-section multidetector row CT (MDCT) have facilitated the antemortem diagnosis of miliary TB. With the availability of these imaging modalities, cryptic miliary TB, that could previously

Table VII. Chest radiographic abnormalities in miliary TB

Classical presentation (50%)	Non-miliary pulmonary manifestations (10-30%)	Other associated findings (<5%)
Miliary pattern	Asymmetrical nodular pattern	*Pulmonary*
	Coalescence of nodules	Parenchymal lesions and cavitation
	Mottled appearance	Segmental consolidation
		Thickening of interlobular septae
	"Snow storm" appearance	*Pleural*
	Air-space consolidation	Pleural effusion
		Empyema
		Pneumothroax
		Pneumomediastinum
		Others
		Intrathoracic lymphadenopathy
		Pericardial effusion

Source: Refs 3,4,114,122,123

be diagnosed only at autopsy, can now be diagnosed antemortem[4,40].

The HRCT reveals a mixture of both sharply and poorly defined, less than 2 mm nodules that are widely disseminated throughout the lungs associated with diffuse reticulation[127,128]. Importantly, the HRCT may reveal classical miliary pattern even when the chest radiograph looks apparently normal[4,39] and also facilitates identification of additional findings such as intrathoracic lymphadenopathy, calcification, pleural and pericardial lesions (Fig. 8D)[129].

Air trapping has been described on HRCT both at presentation and during follow up period[128]. The clinical significance of these findings is unclear. Rupture of these areas of air trapping may perhaps be responsible for the development of air-leak syndromes in miliary TB. The interlobular septal thickening or intralobular fine networking seen on HRCT in miliary TB seems to be caused by the caseation necrosis in the alveolar walls and interlobular septa. Sometimes, in subjects with active post-primary disease, centrilobular nodules and branching linear structures giving a "tree-in-bud appearance" may be evident[127,128]. A higher prevalence

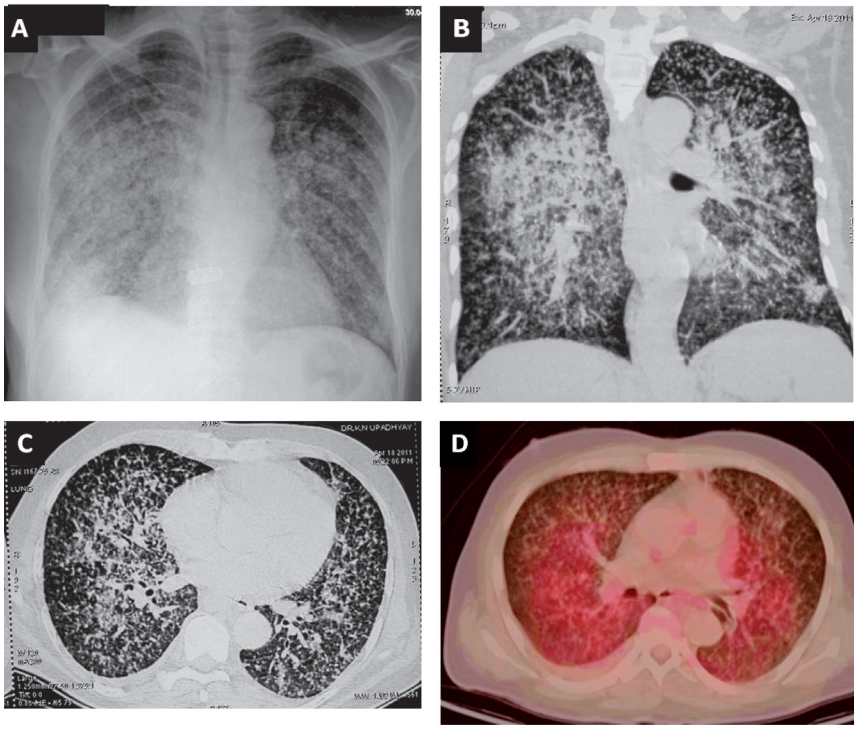

Fig. 10. Chest radiograph (poster-anterior view) **(A)** and chest CT (lung window) **(B and C)** showing predominance of miliary lesions on the right side. ^{18}FDG-PET CT of the same patient **(D)** showing increased activity in the coalesced pulmonary lesions, which is evident more prominently on the right side. CT, computed tomography; ^{18}FDG-PET CT, ^{18}F labelled 2-deoxy-D-glucose positron emission tomography-computed tomography.

of interlobular septal thickening, necrotic lymph nodes and extrathoracic involvement has been observed in HIV-seropositive patients with miliary TB[80].

CT and MRI have been useful in identifying miliary lesions at extra-pulmonary sites. Abdominal CT has been useful in identifying lesions in the liver, spleen, intestine, mesentery, peritoneum, adrenals and lymph nodes, and also detects cold abscesses[4]. Unlike the CT of the chest where the classical less than 2 mm nodular lesions are evident, miliary lesions in the liver and spleen may appear as discrete hypodense lesions (Fig. 8E) a few of which may be confluent, sometimes with irregular peripheral rim enhancement[130].

The MRI of brain and spine is very useful in the evaluation of patients with miliary TB and TBM, and spinal TB. The MRI is particularly helpful in identification and delineating the extent of tuberculomas and cold abscesses and monitoring the response to treatment[4].

Pelvic evaluation with all imaging modalities should be routinely done in all female patients for defining the extent of involvement. Tubo-ovarian masses, hydro- and pyosalpinx, fluid collection in the pouch of Douglas may become obvious. Image guided radiological procedures such as fine needle aspiration for cytological examination (FNAC) and biopsy under CT or MRI guidance are useful for procuring tissue/ body fluids for diagnostic testing.

Sputum examination

Though not all patients with miliary TB manifest productive cough, when available, sputum must be subjected to smear and mycobacterial culture examination. Sputum smear microscopy using Ziehl-Neelsen stain is useful in detecting acid-fast bacilli (AFB). Fluorescent staining may also facilitate rapid diagnosis. Sputum mycobacterial culture and drug susceptibility testing carried out in an accredited laboratory with external quality assurance can facilitate identification and appropriate management of drug-resistant TB.

Bronchoscopy

Fibreoptic bronchoscopy, BAL, bronchoscopic aspirate, brushings, washings, and transbronchial lung biopsy (TBLB) are useful in confirming the diagnosis of miliary TB. The cumulative diagnostic yield for various bronchoscopic specimens by smear and culture methods in published studies has been found to be 46.8 per cent[23,31,32,37,39,131]. In patients with dry cough BAL fluid obtained through fiberoptic bronchoscopy should be submitted for mycobacterial smear, culture and molecular methods (if facilities exist).

Laparascopy

Laparascopy provides an opportunity to visualise the lesions, facilitates biopsy from the liver, spleen, peritoneum, omentum, mesenteric lymph nodes for diagnostic confirmation[132]. When associated abdominal involvement is present, laparascopy should be considered for procuring tissue for diagnostic testing.

Body fluids and tissue examination

In patients with suspected miliary TB, depending on the extent of organ system involvement, appropriate tissue and body fluid samples must be obtained to confirm histopathological microbiological diagnosis. Elevated serum alkaline phosphatase levels indicate diffuse liver involvement; needle biopsy of the liver can be useful in confirming the diagnosis. Bone marrow aspiration and needle biopsy have also been found to be useful for the diagnosis of miliary TB. Pleural fluid, pericardial fluid, ascitic fluid, CSF, urine, bronchoscopic secretions, blood and tissue biopsy specimens have all been employed to confirm the diagnosis of disseminated and miliary TB. The diagnostic yield of various tissue and body fluid specimens has been variable[6-9,18,22-27,29,31-34,36-41,42,44] (Fig. 11).

When imaging studies reveal focal lesions in organs (*e.g.*, liver, spleen prostate), intrathoracic or intra-abdominal lymphadenopathy or cold abscess, image-guided FNAC or tru-cut biopsy can be carried out and subjected to histopathological and microbiological evaluation to confirm the aetiological diagnosis.

Mycobacterial culture and drug-susceptibility testing (DST)

Mycobacterial culture and drug susceptibility testing of sputum, body fluids and tissue specimens carried out in an accredited laboratory with external quality assurance can facilitate identification and appropriate management of drug-resistant TB. Rapid culture methods such as the BACTEC-460 radiometric method, mycobacterial growth indicator tube (MGIT), and molecular methods may be useful for rapid drug-susceptibility testing[4].

Serodiagnostic methods

The recently published World Health Organization (WHO) policy statement on the use of serodiagnostic

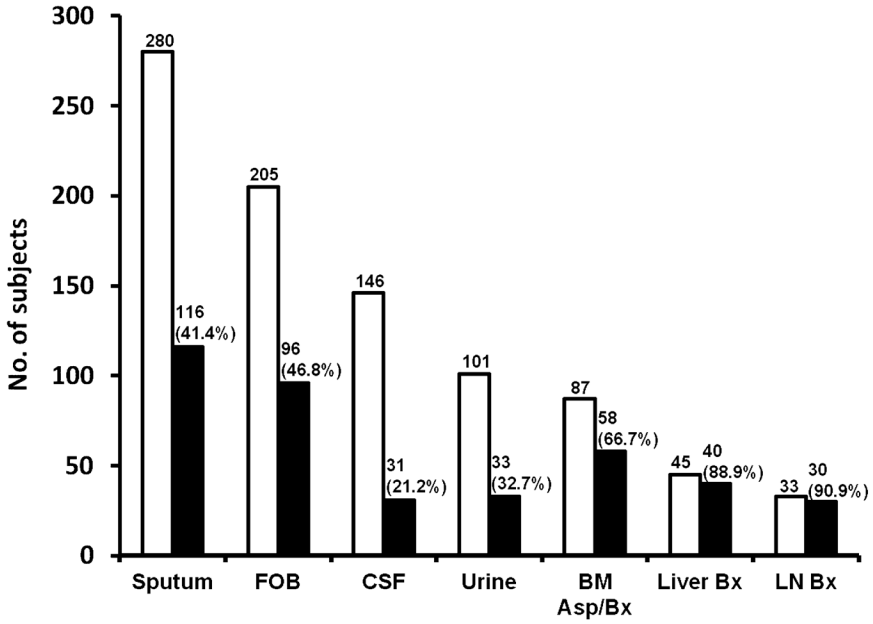

Fig. 11. Cumulative diagnostic yield of various body fluids and tissues in the diagnosis of miliary TB. Cumulative diagnostic yield is expressed as percentage. The data are pooled for various specimen categories and may not be comparable across various series because different criteria were employed; however, these can be appropriately used in the individual patient to ascertain the diagnosis of miliary TB. FOB, fibreoptic bronchoscopy; CSF, cerebrospinal fluid; LN, lymph node; BM, bone marrow; Bx, biopsy.
Source: Refs 9,18,24-27,29,31-34,36,37,39-42,44

tests strongly recommends that the currently available commercial serodiagnostic tests should not be used for the diagnosis of active pulmonary and extra-pulmonary TB disease including miliary TB[133].

Adenosine deaminase

Adenosine deaminase (ADA) and interferon-gamma level estimation in ascitic fluid, pleural fluid can be helpful in the diagnosis of miliary TB[134-139]. A recent study[139] has shown that that CSF-ADA is a more sensitive indicator than PCR for the diagnosis in patients with TB meningitis. However, another recent systematic review and meta-analysis[140] has shown that CSF-ADA cannot distinguish between TB meningitis and bacterial meningitis. Since ADA estimation is a cheap, cost-effective test, utility of CSF-ADA estimation in the diagnosis of TB meningitis merits further study.

Molecular methods

Polymerase chain reaction (PCR) of CSF, tissue biopsy specimens and blood (especially in HIV-infected patients), may be useful for confirmation of diagnosis[58]. The PCR has been found to be most useful when applied to clean specimens such as CSF where its sensitivity and specificity have been reported to be 0.5 to 0.9 and 1.0, respectively[71].

In patients with suspected miliary TB, wherever possible, automated molecular tests for *M. tuberculosis* detection and drug-resistance testing may be used for early confirmation of diagnosis. Based on currently available evidence and expert opinion, molecular assays to detect gene mutations that signal drug resistance have been endorsed by the WHO as being most suited for rapid diagnosis[141]. The GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA) that uses heminested real-time PCR assay to amplify *M. tuberculosis* -specific sequence of the *rpoB* gene which is then probed with molecular beacons for mutations within the rifampicin-resistance determining region can facilitate rapid diagnosis from clinical specimens, such as, sputum in about 2 h[142,143]. Line probe assays (LPAs), such as, the INNO-LiPA® Rif. TB kit (Innogenetics NV, Gent, Belgium) and the GenoType® MTBDR*plus* assay (Hain Lifescience GmbH, Nehren, Germany) have been found to be useful for rapid screening of patients at risk for multidrug-resistant TB (MDR-TB)[144].

Positron emission tomography

Positron emission tomography CT (PET-CT) using the radiopharmaceutical ^{18}F labelled 2-deoxy-D-glucose (FDG) is useful to assess activity of various infectious lesions including TB (Fig. 9)[145,146]. The PET-CT is ideally suited to define the extent of disease at

the time of initial presentation. The utility of PET-CT in assessing the activity of lesions that might persist following antituberculosis treatment in miliary TB also merits further study.

Pulmonary function, gas exchange abnormalities and cardiopulmonary exercise testing

Miliary TB is associated with abnormalities of pulmonary function typical of interstitial lung disease. Impairment of diffusion is the most common abnormality and may sometimes be severe[59,147]. Other abnormalities include, a mild reduction in flow rates suggestive of peripheral airways involvement[59]. During the acute stage, arterial hypoxaemia due to widening of the alveolar-arterial oxygen gradient and hypocapnia due to tachypnoea are also observed[148]. Often, the pulmonary function and gas exchange abnormalities may be of a greater magnitude than might be expected from the chest radiograph[61,148-150].

Abnormal cardiopulmonary exercise performance has been described in patients with miliary TB. The salient abnormalities included lower maximum oxygen consumption, maximal work rate, anaerobic threshold, peak minute ventilation, breathing reserve, and low maximal heart rate[4,114,148,150]. Other abnormalities included higher respiratory frequency, peak minute ventilation at submaximal work, and high physiological dead space/tidal volume. A demonstrable fall in oxygen saturation (to 4% or more) with exercise was observed. Following successful anti-tuberculosis treatment, these abnormalities reversed in a majority of the patients[148,150].

Treatment

Patients with miliary TB must be promptly treated with standard anti-tuberculosis treatment as the disease is uniformly fatal if not treated[3,4]. However, there is no consensus regarding the optimum duration of treatment. There are no published randomized controlled trials assessing the efficacy of the standard WHO treatment regimens that have been widely used in national tuberculosis control programmes worldwide[151].

The American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA)[152] and National Institute for Health and Clinical Excellence (NICE)[153] guidelines from UK state that six months of treatment (2-month intensive phase with isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin, followed by a 4-month continuation phase with isoniazid and rifampicin) , whereas the American Academy of Pediatrics (AAP)[154] advocates nine months of treatment for newly diagnosed cases of miliary TB without meningeal involvement. When TB meningitis is present, it is suggested that the treatment be extended for 12 months[136-138]. In several parts of the world, patients with miliary TB get treated under national TB control programmes, with DOTS using short-course intermittent, thrice-weekly treatment[151].

In the WHO guidelines for the treatment of TB[155], patients are categorized as "new patients" or "previously treated patients". In these guidelines, miliary TB is classified as pulmonary TB because there are lesions in the lungs. New patients with miliary TB receive 6 months of daily or intermittent treatment as described above. The guidelines mention that some experts recommend 9 to 12 months of treatment when TB meningitis is present given the serious risk of disability and mortality; and 9 months of treatment when bone and joint TB is also present.

For previously treated patients, the guidelines advocate that specimens for culture and DST should be obtained at or before the start of treatment. The DST should be performed for at least isoniazid and rifampicin and in settings where rapid molecular-based DST results are available, the results should guide the choice of regimen.

These observations highlight the importance of accurately assessing the extent of involvement clinically and radiologically. Thus, if underlying TB meningitis remains undiagnosed in a patient with miliary TB, such a patient has a risk of receiving anti-tuberculosis treatment only for 6 months which may be sub-optimal. Therefore, though the standard duration of treatment may be sufficient for many, each patient needs to be assessed individually, and wherever indicated, treatment duration may have to be extended.

Other issues such as quality of anti-tuberculosis drugs and their bio-availability are important in resource-poor nations. Especially in HIV-seropositive patients, consideration must also be given to inadequate plasma levels of anti-tuberculosis drugs in spite of regular intake in adequate dosage due to malabsorption problem.

Monitoring for adverse drug reactions

Patients with miliary TB receiving anti-tuberculosis treatment should be carefully monitored for adverse

drug reactions, especially, anti-tuberculosis drug-induced hepatotoxicity (DIH). Asymptomatic rise in hepatic transaminases is common in patients with miliary TB and unless definitive evidence of DIH is present[156-159], anti-tuberculosis treatment should not be withheld on this evidence alone. In this scenario, liver functions should be periodically monitored. In tropical countries, acute viral hepatitis must be ruled out in patients who develop antituberculosis DIH[160,161].

When patients with miliary TB develop anti-tuberculosis DIH, the potentially hepatotoxic drugs (rifampicin, isoniazid and pyrazinamide) should be stopped[158]. These patients should be treated with non-hepatotoxic anti-tuberculosis drugs, such as ethambutol, streptomycin and a fluoroquinolone, till the liver functions normalize. In patients who have developed anti-tuberculosis DIH, it is usually possible to reintroduce the same hepatotoxic drugs that have been implicated in the causation of DIH once the liver functions normalize. However, till recently, there has been a lack of consensus regarding the optimal sequence and dosage schedule for reintroduction. A recently published prospective randomized controlled study[162], provides useful data on this topic. In this study from India, 175 patients with a diagnosis of antituberculosis DIH were randomized to receive one of three different pre-defined reintroduction regimens of anti-tuberculosis drugs and were evaluated prospectively. The recurrence rate of DIH was not significantly different between the groups receiving isoniazid, rifampicin, and pyrazinamide administered simultaneously at full dosage from day 1; and the groups receiving reintroduction regimens based on the ATS[158] and British Thoracic Society guidelines[163]. Further studies are required to clarify the issue.

Corticosteroids

Only limited published data are available specifically evaluating the role of adjunct corticosteroid treatment in patients with miliary TB and the results have been conflicting. While a beneficial response was observed in some studies[164], such a benefit could not be observed in others[165]. Associated adrenal insufficiency is an absolute indication for the administration of adjunctive corticosteroid treatment. However, in patients with miliary TB, adjunctive corticosteroid treatment is considered to be beneficial with TB meningitis, large pericardial effusion, IRIS, ARDS, immune complex nephritis, and histiocyticphagocytosis syndrome[4,85,166].

Antiretroviral drugs

The efficacy of standard anti-tuberculosis treatment regimens in the treatment of HIV, miliary TB co-infection has not been studied in detail in the field setting under programme conditions. Treatment of miliary TB in patients co-infected with HIV requires careful consideration of drug-drug interactions between anti-tuberculois and anti-retroviral drugs[167,168]. Co-administration of rifampicin, by inducing the hepatic cytochrome P450 pathway, may result in dangerously low levels of anti-retroviral agents. Rifabutin is preferred over rifampicin especially when protease inhibitors are used but is costly. Efavirenz is preferred over nevirapine but should be avoided during pregnancy. Pregnancy test needs to be done while female patients are on efavirenz. A close monitoring of laboratory parameters is required to detect drug-drug interaction when patients are receiving both treatments. Recently, there has been a change in the WHO revised recommendations[167] based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[169] regarding the time of starting anti-retroviral drugs, the choice of drugs and the time of initiation in relation to institution of anti-tuberculosis treatment. The algorithm for treatment and monitoring of patients with miliary TB is shown in Figs. 12A and B.

In peripheral hospitals in endemic areas where HIV and TB are common, quality assured laboratory facilities for HIV ELISA, CD4+ T-lymphocyte counts and plasma HIV viral load estimation may not be available. Timing of initiation and antiretroviral treatment (ART), choice of ART and antituberculosis treatment regimens, drug-drug interactions, all require careful consideration. A high degree of suspicion and appropriate training of the staff is required to identify IRIS, recognize adverse drug reactions and drug toxicities, drug adherence issues.

Mechanical ventilation

Intensive care, assisted mechanical ventilation and other interventions may be required for the management of patients with miliary TB-ARDS[86,89]. Patients with miliary TB receiving assisted mechanical ventilation should be carefully watched for complications such as pneumothorax (Fig. 5F).

Interventional radiology

Image-guided pigtail catheter drainage for draining psoas abscess, coil or gel foam embolization for treating

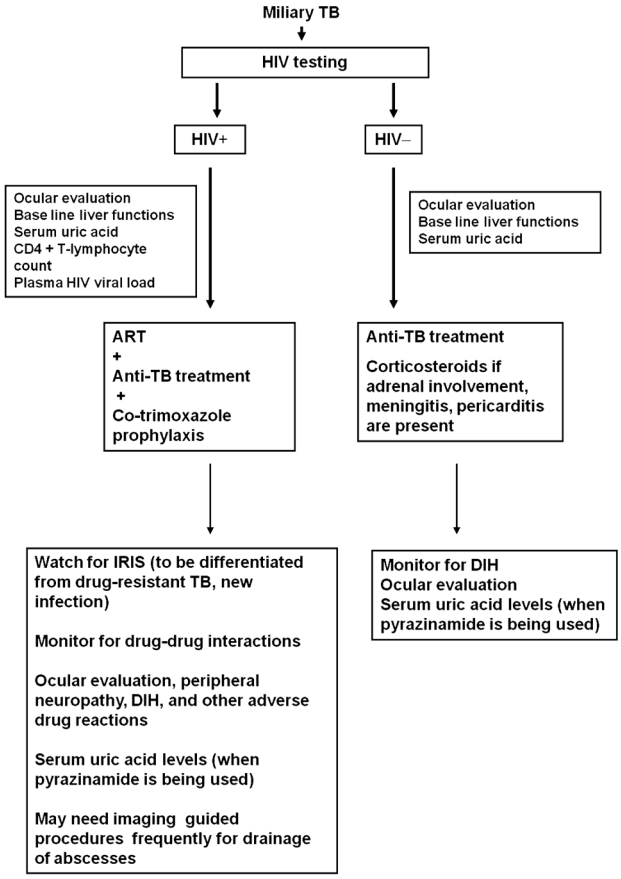

Fig. 12A. Algorithm for treatment of miliary TB patients with and without HIV co-infection.TB, tuberculosis; HIV, human immunodeficiency virus; +, seropositive; –, seronegative; ART, anti-retroviral treatment; IRIS, immune reconstitution inflammatory syndrome; DIH, anti-tuberculosis drug induced hepatotoxicity.

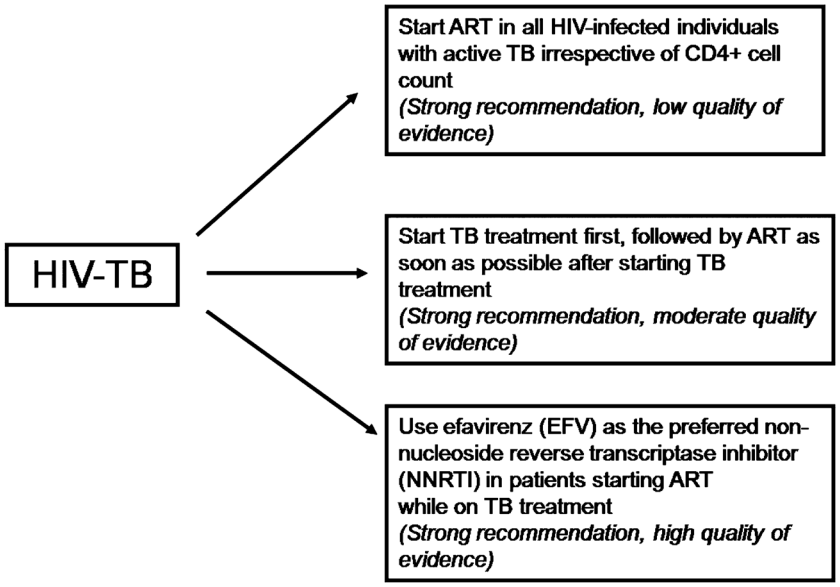

Fig. 12B. Guidelines on timing of antiretroviral treatment in patients with HIV-tuberculosis co-infection. HIV, human immunodeficiency virus; TB, tuberculosis; ART, antiretroviral therapy.
Source: Ref. 167

haemoptysis, among others are useful adjuncts for the management of complications in patients with miliary TB.

Surgery

Surgery is often required to procure specimens for diagnostic testing and to ameliorate complications, such as small bowel perforation where it may be lifesaving. Surgery may be indicated when patients fail to respond to chemotherapy with evidence of ongoing infection and for relief of spinal cord compression with persistence or recurrence of neurological deficits, or instability of the spine.

Mortality

The mortality related to miliary TB is about 15 to 20 per cent in children and is slightly higher in adults (25 to 30%)[24-27,31-34,36,37]. Delay in diagnosis and consequently, delayed initiation of specific anti-tuberculosis treatment appears to be the most important factor responsible for mortality in miliary TB.

Prognostic factors

Several factors have been identified as predictors of poor outcome in patients with miliary TB (Table VIII). In patients with miliary TB-ARDS[89], acute physiological and chronic health evaluation (APACHE II) score >18; APACHE II score ≤18 in the presence of hyponatraemia and arterial oxygen tension to fraction of inspired oxygen (PaO_2/FIO_2) ratio ≤108.5 have been identified to be predictors of death. Identification of these factors can alert the clinicians managing patients with miliary TB.

Table VIII. Predictors of poor outcome in patients with miliary TB

Variables	Predictors of poor outcome
Demographic parameters	Increasing age, female gender, male gender
Co-morbid conditions	Presence of any underlying co-morbid disease, cirrhosis of liver, Presence of one or more predisposing conditions
Symptoms	History of cough, night sweats, dyspnoea, chills
Signs	Altered mental status, meningismus, temperature >39.3 °C, icterus, hepatomegaly
Laboratory abnormalities	Hyponatraemia, hypoalbuminaemia elevated transaminase levels, elevated serum alkaline phosphatase
	Leucopenia, leucocytosis, Lymphopenia, Thrombocytopenia
Others	Presence of atypical chest radiographic patterns, treatment delay, high nutritional risk score*

*a four-point nutritional risk score was defined according to the presence of four nutritional factors: low body mass index (<18.5 kg/m^2), hypoalbuminaemia (serum albumin <30 g/l), hypocholesterolaemia (serum cholesterol <2.33 mmol/l) and severe lymphocytopenia (<7 × 10^5 cells/l). Each risk factor was assigned a value of 1 if present or 0 if absent. Patients with three or four points were classified as having a high nutritional risk score[90]

TB, tuberculosis

Source: Refs 9,18,24-27,29,31-34,36-42,44,90

Prevention

The BCG vaccination is effective in reducing the incidence of miliary TB, especially in children[170]. However, it is not effective in individuals who have latent TB infection and should not be administered to immunosuppressed hosts, such as, HIV infected infants. Targeted tuberculin testing is practised in countries with low prevalence of TB such as the USA[152,171], but anti-TB drug-induced hepatotoxicity is a potential risk with this intervention. Ongoing research[172,173] is likely to provide a more effective vaccine than BCG.

Lessons learnt

Miliary TB remains an elusive diagnosis even in areas where TB is highly endemic. The key practical issues in the diagnosis and management of miliary TB are listed in Table IX. As the clinical symptomatology and physical signs are non-specific, clinicians should have a low threshold for suspecting miliary TB. Careful physical examination for diagnostic clues such as peripheral lymphadenopathy, cold abscess, pleural effusion, ascites, among others will help in procuring tissue and body fluids for confirming the diagnosis. Fundus examination for detecting choroid tubercles must be done in all patients with suspected miliary TB as their presence is pathognomonic of miliary TB. Specific efforts should also be directed at documenting the presence of TB meningitis as this has therapeutic significance.

Imaging modalities such as CT and MRI are useful to establish the miliary pattern. In conjunction

Table IX. Key practical issues in the diagnosis and management of miliary TB

Importance of establishing the diagnosis early	
(i)	No single symptom or sign is pathognomonic for miliary TB. Clinicians should have a high index of suspicion and carefully look for a constellation of signs, symptoms suggestive of miliary TB.
(ii)	Physical examination should focus on valuable clues, such as choroid tubercles, skin lesions, palpable peripheral lymph nodes, evidence of meningitis, pleural effusion, pericardial effusion, ascites, cold abscess etc. In women, carrying out pelvic examination can prove to be valuable.
Diagnostic work-up	
Diagnostic work-up should include sputum smear examination for acid-fast bacilli, and mycobacterial culture and sensitivity testing; bone marrow biopsy, biopsy of skin lesions, peripheral lymph nodes, liver biopsy (especially if serum alkaline phosphatase levels are elevated), testing of urine and body fluids (if present at accessible sites); cerebrospinal fluid examination; smear and culture examination of material aspirated from cold abscess. All mycobacterial culture and sensitivity testing must be carried out in an accredited laboratory.	
Imaging	
Imaging modalities, such as MDCT, MRI, abdominal ultrasonogrpahy are useful in documenting the miliary pattern and localizing the lesions. The PET-CT is helpful in defining the extent of disease at presentation and at the time of stopping treatment.	
Clinical monitoring	
(i)	Patients with miliary TB should preferably be hospitalized for a complete and thorough diagnostic work-up.
(ii)	Dyspnoeic patients should be carefully monitored and if pulse oximetry reveals desaturation, gas-exchange data must be obtained (if available). These patients should be watched for the development of ARDS and may require assisted mechanical ventilation and administration of corticosteroids.
(iii)	Clinical examination and echocardiography should be carried out to look for pericardial effusion as pericardial tamponade can develop in these patients.
(iv)	The incidence of TB meningitis in patients with miliary TB is very high. Clinicians should have a low threshold for performing lumbar puncture and carrying out CSF analysis to document TB meningitis.
(v)	The MRI is the preferred modality of investigation for patients with CNS and spinal lesions, expecially because, frequent imaging will be required during follow-up and multiple CTs will result in an enormous degree of radiation exposure.
(vi)	The number, size and location of tuberculomas should be carefully counted as an increase in their number and/or size during follow-up indicates either IRIS or treatment failure, drug-resistance or re-infection.
(vii)	It is well known that early institution of appropriate specific anti-TB treatment results in a favourable outcome in patients with miilary TB. Establishing the diagnosis early will facilitate early institution of specific treatment. Clinicians should have a low threshold to initiate specific anti-TB treatment in patients with miliary TB as this can be life saving.

MDCT, multidetector row computed tomography; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging; IRIS, immune reconstitution inflammatory syndrome; CNS, central nervous system; CSF, cerebrospinal fluid

with ultrasonography, CT, MRI and PET can help in establishing the extent of organ system involvement in miliary TB. Image guided FNAC or biopsy from various organ sites, needle biopsy of the liver, bone marrow aspiration and biopsy, sputum smear and culture examination, including drug-susceptibility testing (if access to an accredited laboratory is available) must be carried out in all patients.

Treatment of miliary TB should be started at the earliest as per the standard WHO guidelines. Adjunct corticosteroid treatment is helpful when there is adrenal insufficiency, with TB meningitis, large pericardial or pleural effusion, dyspnoea and/or disabling chest pain, IRIS, ARDS, immune complex nephritis, and histiocyticphagocytosis syndrome. In patients co-infected with HIV, careful consideration must be given for drug-drug interactions between anti-tuberculosis and anti-retroviral drugs. Patients receiving anti-tuberculosis drugs must be carefully monitored for adverse drug reactions, especially DIH and other complications of miliary TB. In new patients with miliary TB without TB meningitis, nine months of anti-tuberculosis treatment should be adequate. When TB meningitis is present, 12 months of antituberculosis treatment may be required. However, the duration of treatment may have to be prolonged based on individual requirements.

In light of the continuing HIV/AIDS epidemic and increasing use of immunosuppressive and cytotoxic drugs, the burden of miliary TB will continue to rise. The utility of newer diagnostic methods such as IGRAs needs to be clarified. Even though clinical trials of a few new anti-tuberculosis drugs are ongoing, no other new anti-tuberculosis drugs appear to be on the threshold of being introduced into practice. Therefore, judicious use of available drugs to ensure regular, complete and adequate treatment is imperative. The role of adjunctive corticosteroid therapy needs to be elucidated in future studies. The scope and utility of PET-CT in assessing the activity of lesions that might persist following anti-tuberculosis treatment in miliary TB needs to be studied further. The quest for a better vaccine than BCG is still on and more data on the candidate vaccines that are currently being evaluated is likely to emerge.

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