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Tuberculosis: Diagnostic imaging and treatment challenges

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Abstract

Tuberculosis is a potentially lethal disease if not diagnosed and treated early. Diagnosing Tuberculosis 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 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 Tuberculosis 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 Tuberculosis has a fatal outcome within one year.

Keywords: complications, diagnosis, human immunodeficiency virus, miliary tuberculosis, treatment

1. Introduction

In 1700, John Jacob Manget described a form of disseminated tuberculosis (Tuberculosis) and likened the tiny tubercles evident on gross pathological examination to that of innumerable milletseedsin size and appearance. He coined the term Tuberculosis (derived from the Latin word miliarius, meaning related to millet seed) to denote this fatal form of disseminated Tuberculosis. Tuberculosis results from a massive lymphohaematogeneous dissemination from a Mycobacterium tuberculosisladen focus.

Miliary Tuberculosis 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.

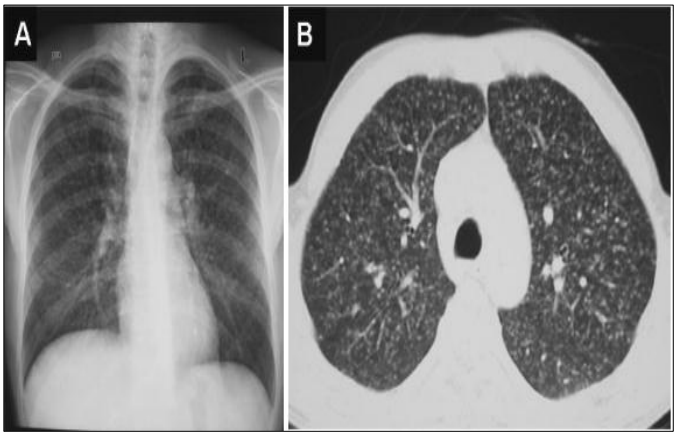

Fig 1: Chest radiograph (postero-anterior) (A) and chest CT (lung window) (B) showing classical miliary pattern.

manifestations, atypical radiographic findings and difficulties in establishing Tuberculosis as the aetiological diagnosis, among others, are challenges in diagnosis and treatment of Tuberculosis. 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 Tuberculosis and then the challengesin the diagnosis and treatment of Tuberculosis are addressed.

Mortality from this disease has remained high despite effective therapy being available. For a long time, Tuberculosis 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 Tuberculosis 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 Tuberculosis in children certain conclusions can be drawn regarding the epidemiology of Tuberculosis.

Among immune competent adults, Tuberculosis accounts for less than 2 per cent of all cases of Tuberculosis and up to 20 per cent of all extra-pulmonary Tuberculosis cases in various clinical studies. In late HIV infection, EP Tuberculosis accounts for more than 50 per cent of all cases of Tuberculosis. In autopsy studies, the corresponding figures have been higher; Tuberculosis accounts for 0.3 to 13.3 per cent of all autopsies and 11.9 to 40.5 per cent of all cases of Tuberculosis. In the

preantibiotic era, miliary Tuberculosis was predominantly a disease of infants and children.

In addition to corticosteroids, immunosuppressive and cytotoxic drugs are known to predispose to the development of miliary Tuberculosis, use of immunomodulator drugs (biologicals) has been documented to cause fatal Tuberculosis including miliary Tuberculosis in rheumatoid arthritis. These include anti-tumour necrosisfactor (TNF) agents infliximab etanercept and adalimumab.

In a recent prospective study among patients who received antiTNF therapy, EPTuberculosis constituted 62 per cent of all cases of Tuberculosis; disseminated and miliary Tuberculosis accounted for 27.5 per cent of all Tuberculosis cases, 44 per cent of extrapulmonary Tuberculosis. The rate of development of Tuberculosis was higher for adalimumab and infliximab than for etanercept. The median time to development of Tuberculosis was lowest for infliximab compared with etanercept and adalimumab.

Immunopathogenesis

The inadequacy of effector T-cell response in containment of M. tuberculosis is thought to be responsible for the development of miliary Tuberculosis. The abundance of Th1 and Th2 polarized effector T (Teff) cells in the peripheral blood and local disease site(s) among patients with miliary Tuberculosis suggest that Tuberculosis probably represents the Th end of the spectrum.

Interleukin-4 (IL-4), with its ability to down regulate 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 latentor progressive. 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. In miliary Tuberculosis, frequency of regulatory T (Treg) cells (CD4+CD25+FoxP3+) and higher levels of FoxP3 mRNA were significantly increased in local disease site specimens. Further, FoxP3+ Treg cells obtained from the bronchoalveolar lavage (BAL) fluid of patients with Tuberculosis predominantly produced interleukin-10 (IL-10) and could suppress the autologous T-cell proliferation in response to M. tuberculosis antigen. In Tuberculosis, 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.

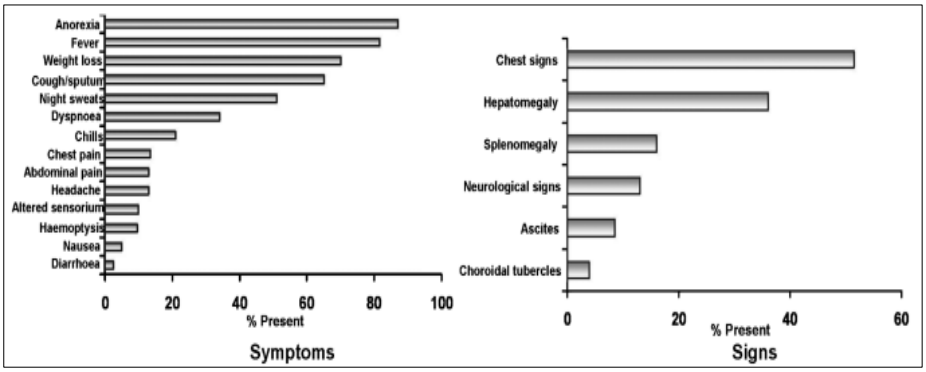

Fig 2: Median prevalence of symptoms and signs at initial presentation in patients with tuberculosis.

Observations regarding the cellular characteristics of BAL fluid in patients with miliary Tuberculosis have yielded conflicting results.

Though the diagnostic significance of these findings is not clear, these may facilitate the understanding of the pathogenesis of miliary Tuberculosis. 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.

Polyclonal hypergammaglobulinemia with increase in immunoglobulin (Ig) G, IgA, and IgM was observed in peripheral blood and BAL fluid. 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. Lymphocytic alveolitis and increased IgG and IgA levels have persisted following anti tuberculosis treatment.

Constitutional symptoms

Patients with Tuberculosis classically present with fever with evening rise of temperature of several weeks duration, anorexia, weight loss, weakness and cough. Occurrence of daily morning temperature spikes69 is reported to be characteristic of Tuberculosis. However, fever may be absent and the patients may present with progressive wasting strongly mimicking a metastatic carcinoma (cryptic Tuberculosis). Since its initial description, cryptic Tuberculosis is increasingly being reported in the elderly population.

Chills and rigors, described in patients with malaria, or, sepsis and bacteraemia, have often been described in adult patients with Tuberculosis. 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 Tuberculosis.

Since Tuberculosis can involve many organs, patients present with symptoms and signs referred to various organ systems. 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 Tuberculosis. These include erythematous macules and papules (tuberculosis miliaria cutis.

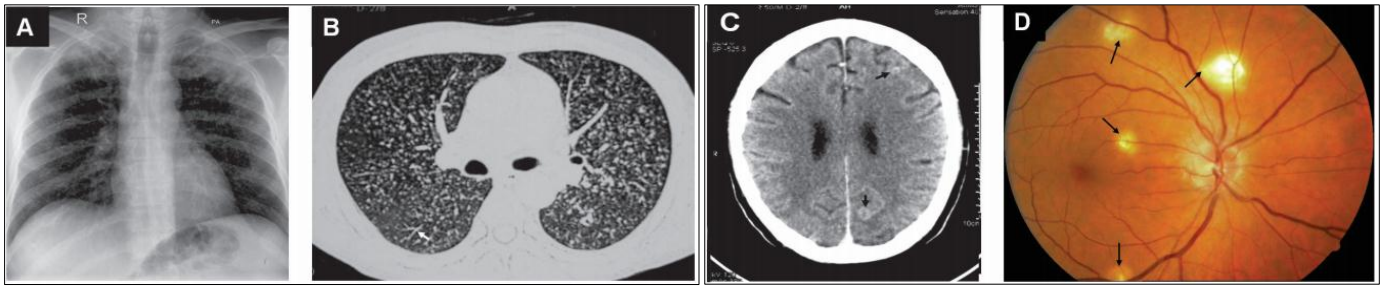

Fig 3: Chest radiograph (postero-anterior view) (A) and chest CT (lung window) (B) showing classical miliary pattern, tree-in-bud appearance (B) (arrow). The patient also had cerebral tuberculomas (arrows) and Tuberculosis meningitis (C). Choroid tubercles, located in the posterior pole of the orbit (D) (arrows) offered an early valuable clue to the diagnosis.

Diagnosis

The diagnosis of Tuberculosis can be difficult as the clinical manifestations are non-specific, the chest radiographs do not always reveal the classical 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 Tuberculosis.

Following criteria are useful for the diagnosis of Tuberculosis:

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 Tuberculosis.

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". These conditions must be differentiated from miliary Tuberculosis by detailed diagnostic work-up.

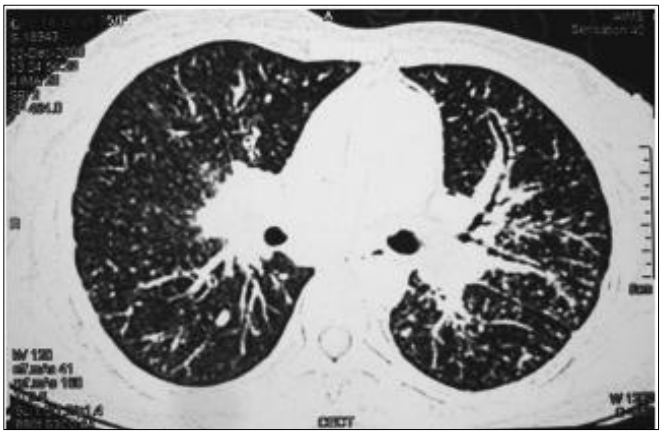

Fig 4: CT of the chest showing miliary sarcoidosis.

In some patients, predominance of lesions on one side may be evident. 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 Tuberculosis where the chest radiograph findings may be identical to that seen in ARDS due to other causes.

One of the patients seen by the authors had undergone tonsillectomy and the histopathological diagnosis was reported as Tuberculosis. 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 Tuberculosis.

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. Importantly, the HRCT may reveal classical miliary pattern even when the chest radiograph looks apparently normal and also facilitates identification of additional findings such as intrathoracic lymphadenopathy, calcification, pleural and pericardial lesions.

Air trapping has been described on HRCT both at presentation and during follow up period. 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 Tuberculosis.

The interlobular septal thickening or intralobular fine networking seen on HRCT in miliary Tuberculosis 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.

CT and MRI have been useful in identifying 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. 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 a few of which may be confluent, sometimes with irregular peripheral rim enhancement. The MRI of brain and spine is very useful in the evaluation of patients with Tuberculosis and Tuberculosis M, and spinal Tuberculosis. The MRI is particularly helpful in identification and delineating the extent of tuberculomas and cold abscesses and monitoring the response to treatment. 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.

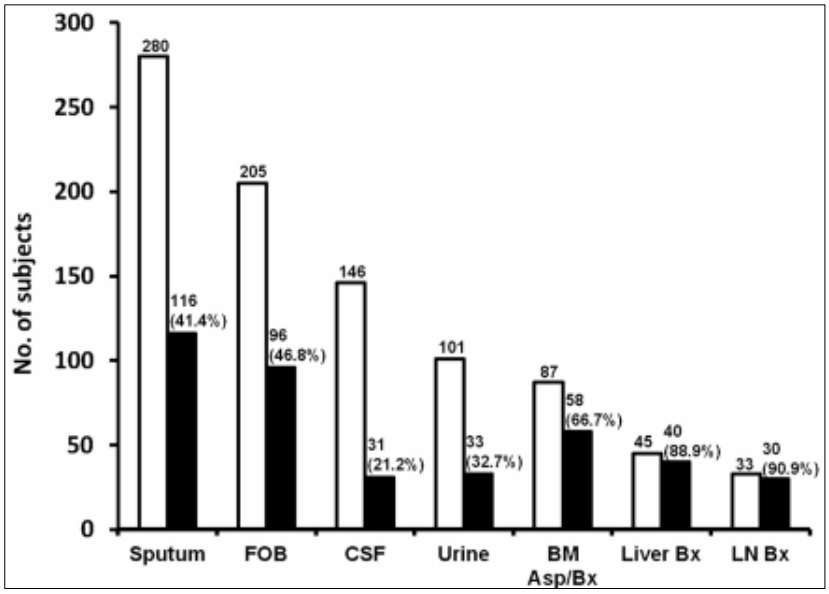

Fig 5: Cumulative diagnostic yield of various body fluids and tissues in the diagnosis of Tuberculosis

In patients with suspected Tuberculosis, 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.

The Gene Xpert M Tuberculosis /RIF assay (Cepheid, Sunnyvale, CA) that uses heminested realtime PCR assay to amplify M. tuberculosis -specific sequence of the rpoB gene which is then probed with molecular beacons for mutations within the rifampicinresistance determining region can facilitate rapid diagnosis from clinical specimens, such as, sputum in about 2 h. Line probe assays (LPAs), such as, the INNO-LiPA® Rif. Tuberculosis kit (Innogenetics NV, Gent, Belgium) and the Geno Type® M Tuberculosis DR plus assay (Hain Lifescience GmbH, Nehren, Germany) have been found to be useful for rapid screening of patients at risk for multidrug-resistant Tuberculosis (MDR-Tuberculosis).

Tuberculosis 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. Other abnormalities include, a mild reduction in flow rates suggestive of peripheral airways involvement. During the acute stage, arterial hypoxaemia due to widening of the alveolar-arterial oxygen gradient and hypocapnia due to tachypnoea are also observed. Often, the pulmonary function and gas exchange abnormalities may be of a greater magnitude than might be expected from the chest radiograph.

Abnormal cardiopulmonary exercise performance has been described in patients with Tuberculosis. The salient abnormalities included lower maximum oxygen consumption, maximal work rate, anaerobic threshold, peak minute ventilation, breathing reserve, and low maximal heart rate.

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.

Treatment

Patients with miliary Tuberculosis must be promptly treated with standard anti-tuberculosis treatment as the disease is uniformly fatal if not treated. 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.

The American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA) and National Institute for Health and Clinical Excellence (NICE) 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) advocates nine months of treatment for newly diagnosed cases of miliary Tuberculosis without meningeal involvement.

When Tuberculosis meningitis is present, it is suggested that the treatment be extended for 12 month. In several parts of the world, patients with Tuberculosis get treated under national Tuberculosis control programmes, with DOTS using short-course intermittent, thrice-weekly treatment.

In the WHO guidelines for the treatment of Tuberculosis, patients are categorized as "newpatients" or "previously treated patients". In these guidelines, miliary Tuberculosis is classified as pulmonary Tuberculosis because there are lesions in the lungs. New patients with miliary Tuberculosis 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 Tuberculosis meningitis is present given the serious risk of disability and mortality; and 9 months of treatment when bone and joint Tuberculosis 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 Tuberculosis meningitis remains undiagnosed in a patient with Tuberculosis, 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.

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