EDITORIAL

Hurdles in Management of Extra pulmonary Tuberculosis

Tuberculosis is an ancient disease. It was thought that the mystery of tuberculosis had been solved to a great extent with the discovery of the Mycobacterium and anti-TB drugs. But the fact is that still it is a threatening public health concern for the 21st century. In 2014, 9.6 million people were diagnosed as new cases of tuberculosis and 380,000 patients died of tuberculosis.[1] Many mysteries of tuberculosis are being unfolded day by day. Pulmonary tuberculosis has been in the focus of attention for last three centuries because of its overwhelming symptoms, complications, transmissibility and mortality. Tuberculosis can involve almost every organ of the body. Extra pulmonary Tuberculosis (EPTB) occurs alone or along with a pulmonary tuberculosis or patients with disseminated tuberculosis. EPTB constitutes about 20 per cent of all cases of tuberculosis in immunocompetent patients. Disease patterns have changed, with a higher incidence of disseminated and extra pulmonary disease.

The risk of extra pulmonary tuberculosis increases with advancing immunosuppression.[2] Extra pulmonary involvement can be seen in more than 50 percent of patients with concurrent AIDS and tuberculosis.[3,4]

Extra-pulmonary TB (EPTB) makes up over 40% cases in Australia and more than half when EPTB definitions include concurrent PTB co-infection. This proportion has been reportedly increasing in Australia and many low prevalence countries.[5] In Turkey the most commonly seen two types of EPTB were genitourinary TB (27.2%) and meningeal TB (19.4%).[6] So it is evident that there is a wide variation of prevalence of extra pulmonary TB from region to region and society to society.

The reason for the increase in EPTB remains unclear. Increased prevalence of conditions that results in immunosuppression like HIV infection, diabetes, increased aging population, substance abuse and use of immunosuppresive agents like chemotheraputic and biological DMARDS and prolong use of corticosteroids may contribute to this. If we consider delay and difficulty of diagnostic difficulty of EPTB and missed cases, it is likely that actual proportion of EPTB will be much higher than estimated.

Lymph nodes are the most common site of involvement. Neurological, pleural, pericardial, abdominal and Skeletal involvement are also common and may cause catastrophic complication. Tuberculosis of chronic ulcers and sinuses anywhere in the body specially of perianal regions, anal tags are not uncommon. Other less common sites includes splenic tuberculosis, genitourinary tuberculosis, breast, scars including that of laparoscopic ports, etc.

Atypical presentations of extra pulmonary tuberculosis are elusive and is the main cause of diagnostic difficulty. Atypical organ and tissue involvement is another cause of delay in diagnosis. Constitutional symptoms and pyrexia of unknown origin (PUO) and this may be the only diagnostic clue in many cases. Furthermore EPTB has diverse manifestations which may mimic other diseases making it more diagnostically challenging, more frequently associated with diagnostic delay, The diagnosis of extra pulmonary tuberculosis needs a high index of suspicion from varied clinical presentations. Physicians should obtain a thorough history regarding common immunosuppressive conditions focusing on risk behaviors for human immunodeficiency virus (HIV) infection. [7]

There is Difficulty in Diagnosis in many aspects .Definitive diagnosis of tuberculosis involves demonstration of *M. tuberculosis* by microbiological, cytopathological or histopathological methods. Tissue/ relevant body fluids must be obtained for diagnostic testing for histopathological, cytopathological and micrbiological diagnosis. It's a challenge to find representative tissue/body fluid. Samples obtained from relatively inaccessible sites are paucibacillary, decreasing the sensitivity of diagnostic tests. Since the conventional smear microscopy has a low sensitivity with a range of 0%–40%, negative results cannot exclude the presence of TB. The reported yields of mycobacterial culture vary from 30% up to 80%. It usually takes 2–8 weeks to receive the results, which is too slow to help treatment decisions. Sometimes histopathology reports are inconclusive leaving the physicians in a dilemma. It remains a daunting task to differentiate tuberculosis with other granulomatous diseases with these sorts of reports. In that case clinicians have to rely on the supporting clinical, radiological and endoscopic evidences. A negative smear for acid-fast bacillus, a lack of granulomas on histopathology, and failure to

culture *Mycobacterium tuberculosis* do not exclude the diagnosis. It is the time for using PCR, as it can detect as few as 10 mycobacteria and Rapid NAAT based tests like Gene Xpert MTB/RIF. Gene Xpert was highly sensitive for TB detection in lymph node samples and moderately sensitive for the detection of TB meningitis (80.5% and 83.1%, respectively), lower sensitivity was shown (46.4%) for testing pleural fluid. Serological tests are available but mostly confined for research.[8]

The Management of EPTB remains a very difficult for the physicians even at this day of nanotechnology. There is no consensus regarding the management. Large-scale studies are not available on the treatment of extra pulmonary TB especially in relation to the duration of treatment and use of corticosteroids. Modification and extended duration are necessary for extra pulmonary tuberculosis. A nine month regimen is recommended, apart from meningitis, other central nervous system (CNS) involvement, miliary disease, and bone and joint TB, for which a one-year regimen is recommended instead. Some authorities may further prolong treatment for CNS tuberculoma and stage III meningitis. On pharmacokinetic consideration in relation to cerebrospinal fluid penetration, there may also be a role of giving pyrazinamide for more than 3 months. Duration of Anti Tb regimen are 6(2+4) months in most guideline, 12(2+10) months recommended by American Thoracic Society, Infectious disease society of America, CDC etc.[9], We practice extending the regimen for 2 years in case of Tubercular meningitis and Skeletal TB. Pyrazinamide must be present in the regimens.

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