Extrapulmonary Tuberculosis: a Diagnosis Challenge

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis*. It most commonly affects the lungs, but it can affect otherorgans. A case with TB outside thelungs is considered an extrapulmonary TB (EPTB) case. Tuberculosis (TB) is a disease that affects many people around the world. The prevalence of tuberculosis in Indonesia in 2012 is 297(144-506)/100.000 people. The incidence of tuberculosis in Indonesia is about 185(153-220)/100.000 people. The mortality cases from tuberculosis are 69.100 cases, and there are 15.697 cases of extrapulmonary tuberculosis from 331.424 new case findings in Indonesia. Extrapulmonary tuberculosis (EPT) represents between 20 and 25% of all TB cases.

Although there are many sites that can affected by EPT, the lymph nodes are affected most of all, followed by the pleura, bones and joint, genitourinary tract, disseminated miliary tuberculosis, meninges, and gastrointestinal. Extrapulmonary TB can affect any part of the body, and due to the heterogeneity in clinical manifestations, the diagnosis is especially challenging. Symptoms may be diffuse and mimic other pathologies. Diagnosis requires a high index of suspicion. Symptoms and signs can be relatively vague and sometimes occur in normal chest radiograph and smear-negative patients, therefore hampering the consideration of the disease in the initial approach and difficulty in establishing a definitive diagnosis.

According to International Standards for Tuberculosis Care (ISTC) standard 4,for all patients, including children, suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microbiological and histological examination. An Xpert MTB/RIF test on cerebrospinal fluid is recommended as the preferred initial microbiological test in persons suspected of having tuberculous meningitis because of the need for a rapid diagnosis.

A definitive diagnosis of TB can only be made by culturing *Mycobacterium tuberculosis* organisms from a specimen obtained from the patient. However, diagnosing EPTB remains challenging because clinical samples obtained from relatively inaccessible sites may be paucibacillary, decreasing the sensitivity of diagnostic tests. Since the conventional smear microscopy Acid Fast Bacil (AFB) has a low sensitivity with a range of 0%–40%, negative results cannot exclude the presence of TB.As a result, the diagnosis of EPTB mostly depends on histological evidence. For histopathological diagnosis, presence of granulomas, caseation, and demonstration of AFB have been commonly used to define a positive test. However, loss of host immune function can result in histopathologic findings demonstrating greater suppurative response and less well-formed granulomas. Additionally, the granulomas can be seen also in nontuberculous mycobacteria disease, fungal infections, brucellosis, or syphilis.So that cautious interpretation is required. Histopathologic examination requires the specimen to be placed in formalin, which destroys the mycobacteria and prevents further culture confirmation. Therefore, biopsy material for mycobacterial culture should be submitted fresh or saved in a small amount of sterile saline.

Because EPT shows complex clinical pattern, and the histological diagnosis is not easy, effort must be applied in various direction to provide the diagnosis. Imaging can play an important role in

the diagnosis of EPTB. It is often necessary to resort to invasive diagnostic testing such as ultrasound-guided FNAB (Fine Needle Asoiration Biopsy), used to collect biological samples for diagnosis. The major advantage of Nucleic Acid Amplification Test (NAAT), such as PCR (Polymerase chain reaction), is rapid diagnosis. The greatest promise is the early diagnosis of life-threatening disease such as TB meningitis. Because EPTB is a paucibacillary disease, the sensitivity could be improved by PCR, as it can detect as few as 10 mycobacteria. Tuberculin skin test (TST) and IFN-γ releasing assay (IGRA) may be the supportive method for diagnosing EPTB, but it has a limited diagnostic value. Some factors such as HIV infection, poor nutritional status, recent viral or bacterial infections, or live vaccines can reduce response to the TST. IFN-γ releasing assay cannot distinguish between latent infection and active pulmonary TB or EPTB, and negative results cannot entirely exclude the disease. Despite the growing use of an advances in recent years of molecular methods for early detection of mycobacteria DNA, cultures still becomegold standard that enables a firm microbiological diagnosis to be made.

Diagnosis of EPTB poses challenges due to the diversity of symptoms with which EPTB may present, the low level of suspicion among clinicians, and the difficulty in obtaining an adequate sample for confirmation. Raising awareness among physicians about EPTB and guidelines for diagnosis and treatment of EPTB may result in more timely and adequate diagnosis

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