EMJ THE EWHA MEDICAL JOURNAL

Letter to the Editor

Ewha Med J 2021;44(4):148-149
https://doi.org/10.12771/emj.2021.44.4.148
eISSN 2234-2591

Is Multidrug-resistant Extrapulmonary Tuberculosis Important? If So, What Is Our Strategy?

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I read the manuscript entitled "Differentiating between intestinal tuberculosis and Crohn's disease may be complicated by multidrug-resistant *Mycobacterium tuberculosis*" with great interest [1]. The manuscript reported a case of multidrug-resistant (MDR) tuberculosis (TB) of the colon, which was difficult to differentiate from Crohn's disease (CD). The authors concluded that although it was more difficult to differentiate CD from MDR intestinal TB (ITB) than ITB, routine mycobacterial culture of the biopsy specimens may allow an accurate diagnosis.

In the current paper, I summarize the literature on the prevalence of and diagnostic strategies for extrapulmonary MDR TB, including ITB.

M. tuberculosis can spread through the lymphatic or hematogenous systems to virtually any organ in the body to cause extrapulmonary TB. The most common sites of extrapulmonary TB include the peripheral lymph nodes, pleura, genitourinary system, bones, joints, abdomen (peritoneum and gastrointestinal tract), and the central nervous system. Extrapulmonary TB is generally less contagious than pulmonary TB; therefore, it receives less attention than pulmonary TB. However, according to the World Health Organization global TB report, extrapulmonary TB accounted for 16% of all forms of TB [2,3]. In Korea, extrapulmonary TB accounts for about 11% to 17% of all TB cases and its incidence has been increasing since 2001. Compared to pulmonary TB, extrapulmonary TB is more difficult to diagnose and has a lower reporting rate; therefore, the actual incidence of extrapulmonary TB may be higher [4].

MDR TB is diagnosed on the basis of resistance to both rifampin and isoniazid [5]. According to the World Health Organization global TB report, about 2.7% of all TB infections are caused by MDR TB [2]. As drug resistance is a 'man-made' problem, MDR TB is also not unrelated to the issues of *M. tuberculosis* treatment and patient management [6]. In India, a country with a high disease burden, 2% to 3% and 10% to 15% of pulmonary TB infections are caused by MDR and isoniazid-resistant TB, respectively. Extrapulmonary TB is caused by single drug-resistant and MDR TB in 27% and 19% of the cases, respectively [7]. Although reliable data on the incidence and prevalence of extrapulmonary MDR TB are scarce, the proportion of MDR TB among all cases of extrapulmonary TB is probably not lower than that among pulmonary TB [3]. Therefore, extrapulmonary MDR TB poses a major diagnostic and therapeutic challenge to the elimination of TB.

The most common sites for extrapulmonary MDR TB are the lymph nodes, followed by bones. Although MDR ITB is rare, it occurs more commonly than has been previously assumed. A Korean retrospective study of 400 ITB patients reported a sensitivity of 44.1% for mycobacterial culture of colonoscopic biopsy samples. The prevalence of MDR and single drug-resistance ITB were 2.7% and 17.6%, respectively [8]. In India, where ITB is endemic, 13.9% of patients had MDR ITB and required second-line anti-TB therapy on the basis of the drug sensitivity pattern. Resistance to at least one first-line

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anti-TB drug was found in 23.2% of ITB patients. Resistance to isoniazid was the most common, followed by rifampin [7].

Although mycobacterial culture is the gold standard diagnostic test for ITB, its yield for *M. tuberculosis* complex is only 25% to 50% for biopsy tissue specimens. Therefore, the diagnosis of ITB is based on the clinical, laboratory, and colonoscopy findings, as well as on the accompanying pulmonary lesion. Since several clinical and colonoscopic findings are similar for ITB and CD, differentiating between them is challenging [9-11]. A diagnostic prediction model of endoscopic findings, interferon gamma release assay, and new technologies, such as endoscopic molecular imaging [12], have been used to differentiate between ITB and CD; however, there are still limitations to overcome the diagnostic yields.

In areas where the prevalence of TB is still high, and the prevalence of CD is also on the rise, such as Korea, misdiagnosis of the two diseases can often occur, and the resulting incorrect treatment can lead to a problem that delays the recovery of the patient's true disease. A trial of anti-TB treatment is recommended to differentiate between TB and CD when the diagnosis is not clear [9]. However, the problem with this differentiation method is that if empirical first-line anti-tubercular therapy fails, the conversion to CD treatment is made without much thought, but the actual patient could be MDR ITB.

No diagnostic method can rapidly and accurately identify extrapulmonary MDR TB, including MDR ITB, at the early disease stage. Therefore, mycobacterial culture should be performed at the time of diagnosis of TB to exclude MDR TB, especially in Korea, where the prevalence of TB is higher than that in the West. According to the Korean TB practice guidelines published in 2020, culture of the initial tissue biopsy sample should be performed to increase the diagnostic yield and determine the presence of MDR TB. If the culture is positive for TB, a drug susceptibility test should be performed [5].

Although TB has been studied extensively, there is still much to learn about it. The importance of extrapulmonary MDR TB has been overlooked and data on extrapulmonary MDR TB are sparse. However, the elimination of TB requires overcoming the challenge of extrapulmonary MDR TB. Despite the limitations, diagnostic tests for MDR TB, including TB culture and drug susceptibility testing, should be routinely performed. Additionally, patients with TB should be treated with the appropriate drugs for an adequate duration.

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