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Drug Resistant Extrapulmonary Tuberculosis: A Silent Assassin

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Abstract

Cervical-TB lymphadenitis is the most frequent extrapulmonary manifestation of tuberculosis infection. There are limited documents on multidrug-resistant cervical tubercular lymphadenitis, but there is no evidence which may occur in TB endemic regions. Multidrug-resistant tuberculosis (MDR-TB) occurs when strains of Mycobacterium are resistant to the first-line anti-tuberculosis regimen. We present the case of a 23-year-old Bangladeshi male who presented to his primary care physician complaining of a two-month history of an enlarging neck mass. Aspiration of the mass, analysis revealed granulomatous inflammation suggestive of tuberculosis. Later he was lost to follow up. Later he again presented with fever and enlarging neck mass. Biopsy of the neck node followed by histopathology, Gene X-pert TB and line probe assay revealed Mycobacterium that was resistant to first-line anti-tuberculosis medications and levofloxacin. He was labelled as Pre XDR-EPTB (extensive drug resistant extra pulmonary tuberculosis). He was subsequently placed on second line anti-tuberculosis medications under specialized center.

Keywords: extrapulmonary tuberculosis; multidrug-resistant tuberculosis; gene x-pert tb; pre xdr -eptb; line probe assay

Introduction

Tuberculosis (TB) is a deadly infection of public health significance and is one of the top ten causes of death globally. In 2016, around 10.4 million people fell ill with TB with 1.7 million TB related deaths [1]. In the United States (US), there were a total of 9272 cases (2.96 cases per 100,000) in 2016 [2]. Most cases of TB respond to first line anti-tuberculosis medications. Mycobacterium TB can, however, develop resistance to any of the first line antimicrobials used to treat the infection. Multidrug-resistant tuberculosis (MDR-TB) occurs when there is at least resistance to isoniazid and rifampin, the two most potent anti-tuberculosis medications [1]. Globally in 2016, there were 490,000 cases of MDR-TB [1]. With current advancements in therapy, extra-pulmonary forms of MDR-TB are rare and are uncommon presentations of the disease; however, they appear to be on the rise [1]. There have been few cases of MDR-TB lymphadenitis presented in the literature [3,4]. We present a case of a 23-year-old human immunodeficiency virus (HIV) negative male who presented with cervical lymphadenopathy and was diagnosed with Pre XDR-TB. Tuberculosis (TB) remains as a nightmare for the public health; TB has various forms, including the cervical tuberculosis lymphadenitis (CTL), classically known as "scrofula," which is the most common form of extrapulmonary tuberculosis that often affects children. Spreading a strain of drug-resistant tuberculosis (DR-TB) is currently witnessed all over the world that is specifically observed in TB endemic countries. While most of the clinical manifestations of tuberculosis are in the pulmonary basis, however, MTB is capable of affecting all the organs, which is termed extrapulmonary TB (EPTB). In this respect, cervical tuberculous lymphadenitis is the most common form of EPTB, accounting for 25%-30% of the cases [5]. Cervical tuberculosis lymphadenitis (CTL) typically involves the lymph nodes of the jugular, posterior triangle, and supraclavicular region, and the observed clinical manifestations of cervical tuberculosis lymphadenitis include fever weight loss, rarely coughing, night sweat, chills, malaise, suppurative lymphadenitis, granulomatous inflammation, neck mass (1-3 cm), fistula formation, and caseous necrosis [6,7]. However, cervical tuberculosis lymphadenitis can be misidentified with diseases such as malignancy, fungal infection, tularemia, actinomycosis, sarcoidosis, and non-tuberculosis mycobacteria (NTM) lymphadenitis [7,8]. There are limited reports on MDR-CTL in the world; therefore, there is restricted information about patient management, diagnostic test, and treatment of MDR-cervical lymphadenitis.[9-14] Thus, it is essential to introduce a new therapeutic regimen for the management and treatment of MDR cases of CTL patients [7,8,10,15].

Case report

Mr. Shakil, 23 years old nonalcoholic, non-smoker, Muslim student from rural Bangladesh, not known to have diabetes, hypertension or bronchial asthma presented to us with the complaints of fever for 3 months, painless neck swelling and weight loss for the same duration. Fever was initially low grade (highest recorded temperature was 100°F). Fever was neither associated with chills & rigor nor having evening peak. Fever subsided with profuse sweating after taking antipyretic. After two weeks, the pattern of fever changed to high grade, continued fever, highest being recorded as 103° F. There was history of recent travel or contact with smear positive TB case. There was also no past history of tuberculosis. He also noticed slowly growing, painless mass in right neck region without any overlying skin changes. He became lethargic and anorexic and lost about 6 kg weight in last 3 months. He denied any cough, chest pain, hemoptysis, vomiting, diarrhea, headache, altered consciousness, skin rash, joint pain, oral ulceration, hair loss, bleeding from any site of body. There was also no history of intravenous drug abuse, any previous transfusion or unprotected sexual exposure. He was vaccinated as per local vaccination schedule. On general examination, he was cachectic, with BMI 16.9 kg/m2, moderately anemic Multiple lymph nodes were enlarged involving right anterior and posterior cervical chain measuring 2.5-3.5 cm, firm in consistency, non-tender, matted, not fixed with overlying or underlying structures, there is no discharging sinus. There was no other lymphadenopathy elsewhere. Thyroid was not palpable. There was no anemia, jaundice or any other skin or nail changes. Other systemic examination including ear, nose throat examination revealed no abnormalities. Initially patient was prescribed oral Cefuroxime for one week and advised to do some routine investigations as well as FNA from cervical node. Complete blood count revealed normocytic normochromic anemia (Hb% 8.9 gm%, MCV 81.8 FL, MCH 29.9 pg.) with normal total white cell count and normal differentials and normal platelet count. ESR was raised to 79 mm in 1st hour. Liver function tests, renal function tests, LDH, ANA, Mantoux test was non-conclusive. FNAC revealed necrotic material with epithelioid cells, macrophages and lymphocytes, no definite granuloma with the possibility of tuberculosis. Patient was advised to start anti tubercular medication (rifampicin, isoniazid, pyrazinamide, ethambutol) (FDC tablets) according to body weight. He was advised for follow up but eventually he was lost to follow up. After 6 months he came to us again with recurrence of fever for 1 month & progressive cervical lymphadenopathy. On query he admitted that he completed intensive phase but continued continuation phase only for 2 weeks and then stopped it on his own due to improved wellbeing. Re-examination revealed multiple cervical nodes with characteristics as before. There was no other lymphadenopathy or hepatosplenomegaly. As patient refused to do excisional biopsy for Gene X-pert TB, again FNA from cervical gland was done which revealed 'Chronic Granulomatous lymphadenitis'. He was started retreatment with 4 first line anti tubercular drugs with Levofloxacin according to weight. With treatment, patient showed some improvement evidenced by weight gain of 5kgs and improving appetite & disappearance of cervical lymph nodes. However, his irregular fever was still persisting. During the last week of 5th month of ATC, he developed high grade fever with appearance of painless swelling in his right axilla. He was advised to admit at Dhaka Ad din Medical College Hospital to do Rt axillary lymph node biopsy for histopathology & Gene X-pert TB. He did FNAC from right axillary node rather than biopsy from outside without Gene X-pert and came with the report for follow up which again revealed Tubercular granulomatous lymphadenitis. This time he was admitted in Dhaka Ad-Din Hospital and biopsy from right axillary node was done for histopathology & Gene X-pert TB. Histopathology revealed, Multiple epithelioid granulomata containing necrosis with chronic inflammation & Langhans giant cell consistent with tuberculosis. However, Gene X-pert TB of tissue sample revealed Rifampicin resistance. So, he was labelled as Rif resistant Extra pulmonary TB (RR – TB) & referred to higher center for further management. There he was started treatment as per following regimen 208dq(6m)-Lfx-Lzd-Cfz-z (Bed aquiline, linezolid, levofloxacin, clofazimine, pyrazinamide). His first line, line probe assay (LPA) revealed sensitivity to isoniazid but second line LPA revealed resistant to fluroquinolone, so levofloxacin was withdrawn from his regimen and he was labeled as Pre XDR-EPTB. Now the patient is getting supervised treatment with 2nd line anti TB drugs (bed aquiline, pyrazinamide, dexaminid, linezolid, clofazimine and cyclomerize) with possible duration for at least 20 months.

Discussion

TB is a deadly mycobacterial infection spread via airborne droplets from infected persons; it remains a significant cause of morbidity and mortality worldwide. It afflicts a quarter of the world population as latent TB [16]. MDR-TB is an infection by a strain of mycobacteria tuberculosis resistant to at least isoniazid and rifampin; two widely used potent anti-tuberculosis medication. MDR-TB arises either as a result of direct infection from a person with a drug-resistant strain (primary resistance) or poor compliance with strict anti-tuberculosis treatment regimen (secondary or acquired resistance) [17]. In 2016, there were about 6.1 million new cases of TB worldwide with 4.1 percent due to MDR-TB [1]. Cervical tuberculosis lymphadenitis is one of the most prevalent forms of extrapulmonary TB that often occurs in immunocompromised cases [14].Although MTB often affects the lungs, in immune-compromised cases, particularly children and HIV-infected people, TB bacilli are spread through the lymphatic system due to the lack of an efficient and effective TB bacilli immune system, often occurring in the form of cervical tuberculosis lymphadenitis [9,14,18].While there have been reported cases of MDR-TB lymphadenitis in TB endemic regions of the world cases of MDR-TB lymphadenitis represent an unusual and atypical presentation of the disease in the Bangladesh [3,4]. Despite the fact that the CTL cases caused by DR-TB are very limited, but the epidemiologic importance and diagnostic difficulties of managing and treatment of these cases are quite challenging because of the lack of specific guidelines for the treatment, particularly in the immunocompromised patients, who do not usually have granulomatous inflammation due to immune dysfunction. Moreover, PPD results in these patients are negative due to a weakened immune system [9,14]. Based on the available evidence, lung CXR is usually normal in cervical tuberculosis lymphadenitis patients, merely showing the abnormalities in 24%-46% of these patients [19]. Therefore, limited cases of cervical tuberculosis lymphadenitis caused by DR-TB strains have been reported, most of which occur in the TB endemic countries. The most common clinical manifestations and symptoms of cervical tuberculosis lymphadenitis include single or multiple painless lumps, lymphadenopathy, fistula formation (in some cases), weakness, low grade of fever, coughing, and pulmonary hilar lesion (if being involved and in case of primary lung infection) the cervical tuberculosis lymphadenitis may lead to misdiagnosis in MDR-TB cases of due to treatment failure or various patients manifestation such as negative PPD, lack of lung involvement, absence of granuloma formation, and coinfection with HIV or immune disorder [19-22]. However, a review of the literatures has revealed that the mortality rate of MDR-CTL cases is low, and there is not even a relapse in the untreated CTL cases. According to the literatures, CTL diagnosis is quite challenging. The sensitivity and specificity of the diagnostic methods for detection of cervical tuberculosis lymphadenitis are in a wide range. For example, the sensitivity of acid-fast staining and culture methods for cervical tuberculosis lymphadenitis detection are estimated to be about 46%-78% and 10%-69%, respectively [20-22]. Moreover, culture also takes about 6-8 weeks due to the slow growth nature of MTB and is not quite appropriate, particularly in the MDR-TB cases [23]. Unfortunately, TB is possible to be misdiagnosed with other diseases due to treatment failure, particularly in TB endemic regions with higher number of MDR-TB cases [11-14]. We have revealed that the fine-needle aspiration is a reliable method for detection of cervical tubercular lymphadenitis. Gupta et al (1993) found that the sensitivity and specificity of FNA for diagnosis of cervical-TB lymphadenitis were 88% and 96%, respectively [24]. With the advent of increased globalization, immigration, and refugee resettlement, cases of TB and drug-resistant TB may continue to rise and represent a threat to current control programs. There may be a need to create and implement policies that intensify disease surveillance efforts, particularly in populations at increased risk. Public health systems may also need to be strengthened to ensure that patients on anti-tuberculosis medications are closely monitored to prevent the development of resistant forms of the disease, which was what may have occurred in our case.

Conclusion

In conclusion, drug-resistant tuberculosis has widespread health, social, and economic ramifications and its emergence threaten gains already made at national and global levels in TB care and control. There must be a sustained effort by healthcare professionals to work together to support the global vision of a world free of TB.

Conflict of interest

None declared.

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