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A Case report of Multidrug-resistant Extrapulmonary Tuberculosis presenting as Cervical Lymphadenitis in HIV seronegative patient

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Abstract
Multidrug-resistant tuberculosis (MDR-TB) occurs when the strains of Mycobacterium are resistant to the first-line anti-tuberculosis regimen. Extra pulmonary presentations with multidrug-resistant (MDR) tuberculosis (TB) are uncommon forms of the disease, which warrant high degree of suspicion and strong laboratory back up. We report a case of 10 years old female child who presented with persistent glandular swelling over left side of neck even after 9 months of completion of anti-tubercular therapy. Aspiration of pus from the swelling , then analysis of multidrug resistance done by CBNAAT(Cartridge based nucleic acid amplification testing) based on the Xpert MTB/RIF assay technology.

Key Words: *Multidrug- resistant tuberculosis, Cartridge based nucleic acid amplification testing, Human Immunodeficiency virus ,Extensive drug resistant tuberculosis.*

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I. Introduction

Tuberculosis (TB) is a deadly infection of public health significance and is one of the top ten causes of death globally. In 2019, around 10 million people fell ill with TB with 1.4 million TB related deaths [1,2]. Most cases of TB respond to the 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 2019, there were 0.2 million cases of MDR-TB[1].

Multidrug-resistant extrapulmonary tuberculosis is an uncommon form of the disease, but it seems that by increasing the number of the drug resistant tuberculosis around the world, the number of cases of multidrug resistant tuberculosis with extrapulmonary presentation also going to rise. Diagnosis is difficult often requiring biopsy several times. Treatment monitoring is more complex due to peculiar behavior of TB lymph nodes.

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]. We present a case of a 10-year-old Human immunodeficiency virus (HIV) negative female who presented with cervical lymphadenopathy and sinus discharge at the site of the involved lymph nodes and was diagnosed with MDR-TB.

II. Case Presentation

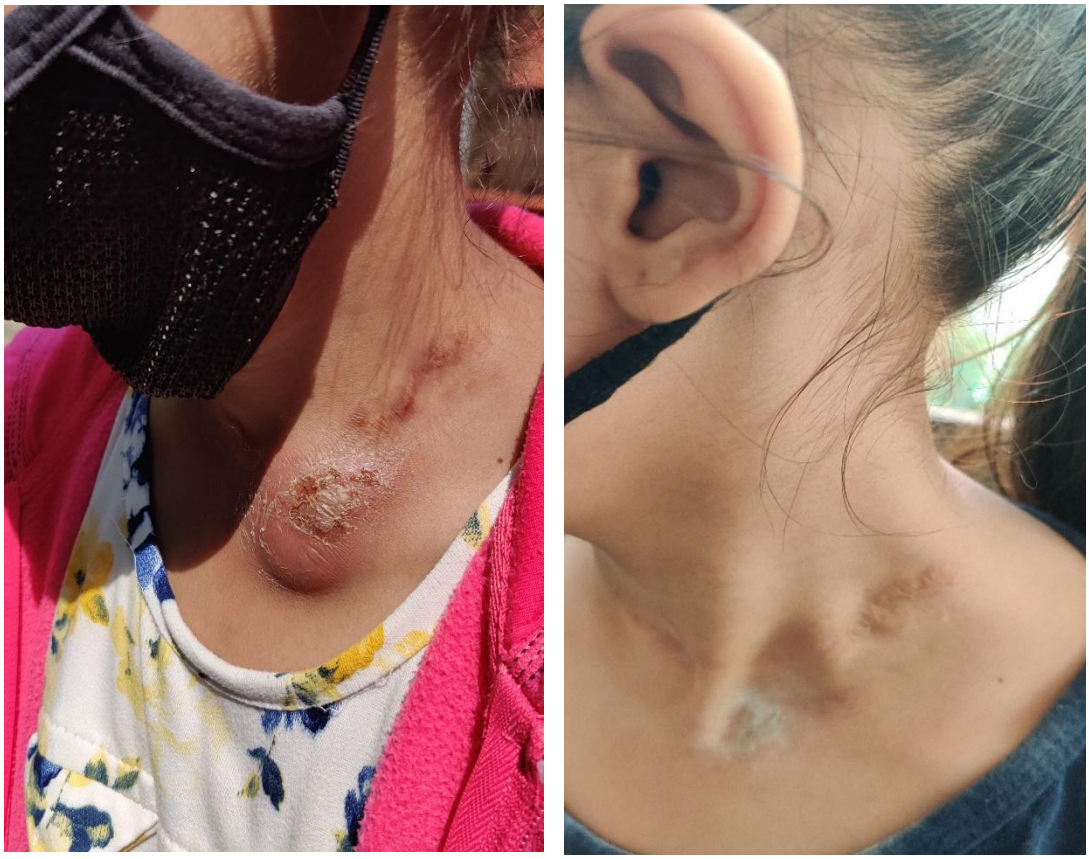
A 10-year-old female student patient presented with slow growing glandular swelling over left side of neck of ten months duration. There was no history of fever, cough, night sweats, fatigue, or weight loss. The patient was on first line anti-tubercular therapy for tubercular cervical lymphadenitis for 9 months duration with glandular swelling initially decreases with treatment, then remains the same.

Now patient presents with the persistence of glandular swelling even after treatment. The patient had no history of medical or surgical problems; she could independently perform activities of daily living. The blood pressure was 110/70 mm Hg, the pulse was 78 beats per minute, oxygen saturation was 98%.On examination, she had a 4.5x 5 cm soft tissue neck mass that was non-mobile, soft, and tender. There were no palpable enlarged lymph node groups in the neck or any other part of the body. Systemic examination of the body was essentially normal.

Laboratory examination revealed hemoglobin of 12.6 g/dl, lymphocyte count of 8.2 x10e3/ul, random blood glucose of 90 mg/dl, BUN of 21 mg/dl and creatinine of 0.44 mg/dl. All other laboratory parameters were within normal limits. Mantoux test was negative and HIV was negative for both HIV 1 and 2.

Chest Xray showed Hilar prominence on right side of chest. Aspiration of purulent fluid from the neck swelling wasdone; sent for fluid analysis (culture, gram stain, acid fast bacilli(AFB) stain, and Xpert

MTB/RIF).AFB culture for mycobacterium tuberculosis bacilli of the aspirate was positive, and Xpert MTB/RIF detects DNA sequences specific for Mycobacterium tuberculosis in fluid aspiration and shows resistance for Rifampicin. She was diagnosed with MDR-TB lymphadenitis and was started on Kanamycin, Moxifloxacin, Isoniazid, Ethambutol, Pyrazinamide, Clofazimine, Ethionamide and the glandular swelling relieved after the treatment.



(a) (b)

Figure 1 : Neck swelling before(a) and after(b) treatment with anti-tubercular drug treatment.

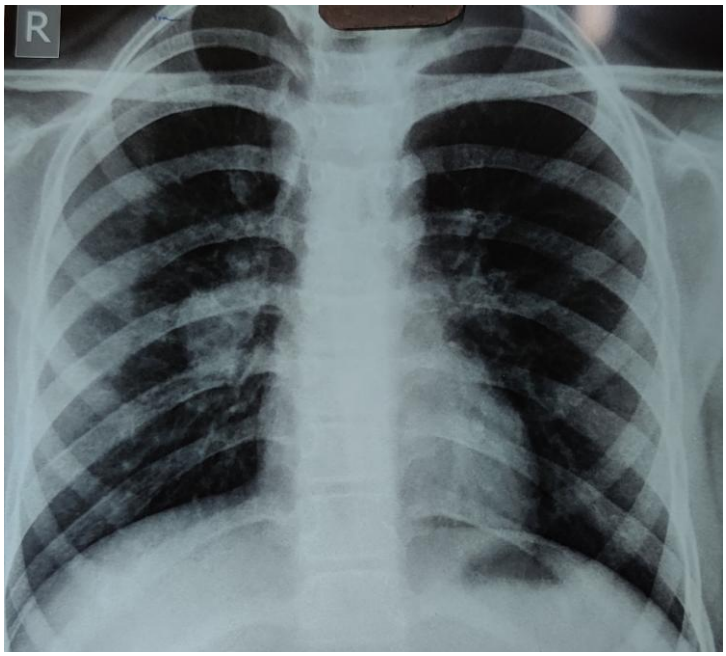


Figure 2 : CXR showing right hilar enlargement.

III. 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[4].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)[3].

In 2019, an estimated 10 million people fell ill with tuberculosis(TB) worldwide. Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. A global total of 206 030 people with multidrug- or rifampicin-resistant TB (MDR/RR-TB) were detected and notified in 2019, a 10% increase from 186 883 in 2018[1].

Tuberculosis (TB) is an infectious disease with varied clinical presentations, extra-pulmonary forms being more common in HIV patients[5].High mortality rates have been reported for patients co-infected with extensively drug-resistant tuberculosis (XDR-TB) and HIV, but treatment outcomes have not been reported. Without adequate second-line TB and HIV treatment, reported mortality rates for persons co-infected with XDR TB and HIV approach 100%[6].Data regarding treatment of extrapulmonary drug-resistant TB are limited. A few cases are described within larger series of MDR-TB cases. Patients with extrapulmonary TB are at risk of treatment failure due to poor drug penetration to the affected tissue and the lack of accessibility of tissue for serial cultures. Surgical resection (scrofula) and drainage (empyema, abscesses, and arthritis) may decrease bacterial burden and improve outcome. Full medical treatment is still indicated. Drug-resistant TB meningitis is challenging to treat due to the incomplete CSF penetration of many second-line drugs. Intrathecal administration of medications and the use of newer fluoroquinolones may improve outcome and should be evaluated prospectively Among XDR TB patients who survive to initiation of second-line TB therapy, early treatment outcomes reported describe low rates of sputum culture conversion, major adverse events, and a substantial number of early deaths [7].Tubercular lymphadenitis involving cervical region is the most common form. The diagnosis is difficult requiring high index of suspicion. Definitive diagnosis is made by demonstration of *Mycobacterium tuberculosis* in tissues or fluids. There is scanty information regarding extra-pulmonary primary drug resistant TB in the literature [8].

Cervical lymphadenopathy refers to a frequently observed clinical presentation in numerous pathological conditions. A wide spectrum of diseases can cause cervical lymphadenopathy, irrespective of the facts that the patients are infected with HIV or not.The most common presentation of tubercular lymphadenitis is an isolated, chronic non-tender lymphadenopathy in the anterior or posterior cervical triangles, that can be present for up-to 12 months before diagnosis and can be complicated by ulceration, fistula or abscess formation. Systemic symptoms are not common.

The four different categories of drug resistant TB are monoresistance, poly-resistance, multidrug-resistance TB (MDR-TB) and extensive drug-resistance TB (XDR-TB). MDR-TB is defined as resistance to at least rifampicin and isoniazid and XDR-TB is defined as MDR-TB plus resistance to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin). Extra-pulmonary TB among the immunocompetent individuals constitutes about 15% to 20% of all cases of TB, and in HIV patients it accounts for more than 50% [9]. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis are generally thought to have high mortality rates. As, drug resistance is a man -made problem, its emergence and spread can be prevented by prompt diagnosis and effective treatment of all drug susceptible and resistant cases[10].However, many cases can be treated with the right combination and rational use of available antitubercular drugs. The recommended regimen is the combination of at least four drugs to which the *Mycobacterium tuberculosis* isolate is likely to be susceptible. Drugs are chosen with a stepwise selection process through five groups on the basis of efficacy, safety, and cost. Among the first group (the oral first-line drugs) high-dose isoniazid, pyrazinamide, and ethambutol are thought of as an adjunct for the treatment of MDR and XDR tuberculosis. The second group is the fluoroquinolones, of which the first choice is high-dose levofloxacin. The third group are the injectable drugs, which should be used in the following order: capreomycin, kanamycin, then amikacin. The fourth group are called the second-line drugs and should be used in the following order: thioamides, cycloserine, then aminosalicylic acid. The fifth group includes drugs that are not very effective or for which there are sparse clinical data. Drugs in group five should be used in the following order: clofazimine, amoxicillin with clavulanate, linezolid, carbapenems, thioacetazone, then clarithromycin [11].Without adequate second-line TB and HIV treatment, reported mortality rates for persons co-infected with extensive XDR TB and HIV approach 100% [7]. Extrapulmonary MDR-TB is treated with the same strategy involving the same regimen and duration as pulmonary MDR-TB. The second-line drugs are generally widely distributed in most body fluids and tissues [12]. Penetration into cerebrospinal fluid is good with pyrazinamide, ethionamide, prothionamide, cycloserine and newer generations of fluoroquinolones. Aminoglycosides have good penetration in the presence of the meningeal inflammation [12].

IV. Conclusion

Multidrug resistant tuberculosis has emerged as a significant global health concern. Patients of extrapulmonary tuberculosis should be closely monitored to prevent the development of resistant form of the disease. Possibility of Multidrug-resistant TB should be kept if the patient did not respond to the first line anti-tubercular drugs, even in immunocompetent cases as seen in the present case of cervical lymphadenopathy.

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