CASE PRESENTATION

Scrofuloderma: A Rare presentation of drug-resistant Cutaneous Tuberculosis

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ABSTRACT

Tuberculosis is one of the leading causes of death from a single infectious agent, just after COVID-19. Extrapulmonary tuberculosis can involve any organ in the body; skin is one of these organs that can get rarely involved. Cutaneous tuberculosis has many clinical varieties depending on the route of inoculation and the bacilli load. One of the cutaneous tuberculosis is scrofuloderma. Multi-drug resistant TB (MDR-TB) remains a public health crisis and health security. Multi-drug resistant cutaneous TB is a rare clinical problem; however, it must be kept in mind. Here, we present a four-year-old male from Baghdad with axillary tuberculous lymphadenitis that has not responded to two courses of the first-line anti-TB drugs. The patient's clinical course was complicated by two skin lesions diagnosed as multidrug-resistant scrofuloderma that responded to a full new all oral anti-tuberculosis regimen according to the updated WHO recommendation.

Key words: tuberculosis, scrofuloderma, multidrug-resistant.

INTRODUCTION

Tuberculosis (TB) is an infectious disease that is considered a major cause of health illness and one of the leading causes of death worldwide. Until the pandemic of coronavirus (COVID-19), TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS. The bacillus Mycobacterium tuberculosis (Mtb) causes TB, which a sick person spreads via expelling bacteria into the air (e.g. by coughing).[1]

Tuberculosis (TB) infection is a state that is characterised by a persistent immune response to a stimulation by Mycobacterium tuberculosis (Mtb) antigens with no evidence of clinically manifest TB disease.[2] It is estimated that about a quarter of the world's population is infected with Mtb.[3] The disease typically affects the lungs (pulmonary TB) but can affect other sites.[1]

Cutaneous tuberculosis is relatively uncommon, comprising 1-1.5% of all extrapulmonary tuberculosis,[4,5] which in turn manifests only in 8.4-13.7% of all tuberculosis cases. Although the global prevalence of skin TB is rare, it is important for the clinicians to distinguish the many clinical variants of tuberculosis of the skin and to differentiate it from other skin lesions like granulomatous syphilis, discoid lupus erythematosus, psoriasis, tuberculoid leprosy, sarcoidosis, actinomycosis, mycetoma, bacterial abscesses, and other skin infections.[5]

Cutaneous tuberculosis can be caused in one of the following ways:

Direct inoculation: An exogenous infection occurs with direct inoculation of bacilli into the skin of predisposed individuals. Here the host's natural immune response is considered the pivotal factor for the clinical presentations before contact with TB bacilli. Tuberculous chancre and tuberculosis verrucosa cutis are examples of this way of transmission.[6]

Lymphatic dissemination or haematogenous dissemination of a pulmonary focus: An endogenous infection that is usually secondary to a preexisting primary focus and sometimes can result from contiguous foci like orificial tuber-

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culosis, scrofuloderma.[7,8]

The tuberculosis skin variants can also be classified into two broad categories depending on the load of the pathogens on the skin:

Multibacillary forms: when the bacilli are easily detected in cutaneous tissue. These include tuberculous chancre, scrofuloderma, orificial tuberculosis, acute miliary tuberculosis, and tuberculous gumma.

Paucibacillary forms: when the are sparse in the lesions. These include TB verrucosa cutis, tuberculoid, and lupus vulgaris.[9,10]

In most cases, cutaneous tuberculosis (TB) is caused by Mycobacterium tuberculosis and rarely by Mycobacterium bovis.[11] One of the cutaneous manifestations of tuberculosis is Scrofuloderma which usually occurs when underlying tuberculosis such as lymphadenitis directly involves the skin.[12] The diagnosis of scrofuloderma is based upon the identification of the causative organism by culture, smear, or skin biopsy.[13]

The diagnosis of cutaneous tuberculosis is challenging. The lesions are usually not pathognomic and resemble other dermatological conditions such as sarcoidosis and fungal infections, so it may take a long duration before reaching the diagnosis. In such a situation, high clinical suspicion and microbiological and histopathological examinations are necessary for early diagnosis and treatment.[14] Implementing and using new molecular diagnostic tools, treatment decision algorithms, and WHO-recommended treatment regimens are vital components of antimicrobial stewardship. Also, appropriate treatment of children with MDR/RR-TB with a WHO-recommended regimen is an important step to ensure a successful treatment outcome and prevent the acquisition of further drug resistance.[15] Drug-resistant TB treatment is based on the use of second-line TB drugs (while some first-line TB drugs can also be used sometimes), which are classified further into three groups (A, B and C) of different combinations in designing effective treatment regimens.[16]

CASE PRESENTATION

A four-year-old male was referred to the drug-resistant (DR) TB unit at the National TB institute in Baghdad with a history of treatment failure of left axillary TB adenitis. The patient was diagnosed at the age of two years with TB lymphadenitis in the left axilla, confirmed by histopathological diagnosis. He received two courses of first-line anti-TB medications. The first course lasted six months; isoniazid (INH), rifampicin, pyrazinamide, and ethambutol for the first two months, followed by INH and rifampicin for four months. Due to failure of the first course, a second one has been initiated for eight months; INH, rifampicin, pyrazinamide, ethambutol, and streptomycin for the first two months followed by INH, rifampicin, and ethambutol for five months. The patient did not get a complete improvement, and local examination still showed a remnant of the left axillary lymph node.

Two months after finishing the 2nd course of treatment, the patient developed a skin lesion on the left axilla and another skin lesion on the upper chest two months after that. The treating physician thought the patient may have a resistant TB and decided to refer him to our institute for further management.

On presentation to the DR unit at our institute, the patient was complaining of two skin lesions. The first was on the upper chest, painless, purple in colour, and about 1.5 x 1.5 cm in size. The second lesion was in the left axilla, about 3x3.5 cm in size, red-brown in colour, ulcerated with granular base and purulent discharge.

A piece of skin was taken and sent for histopathological study. A histopathologist examined the piece, and reported surface ulceration surrounded by a hyperplastic epidermis. The dermis was characterised by nodular aggregates of epithelioid cells, foamy histocytes, multinucleated giant cells, and foci of suppurative inflammation and necrosis. The conclusion was granulomatous dermatitis, most probably due to cutaneous mycobacterial infection. At the same time, a swab was taken for direct AFB examination, culture, genXpert MTB/RIF, and

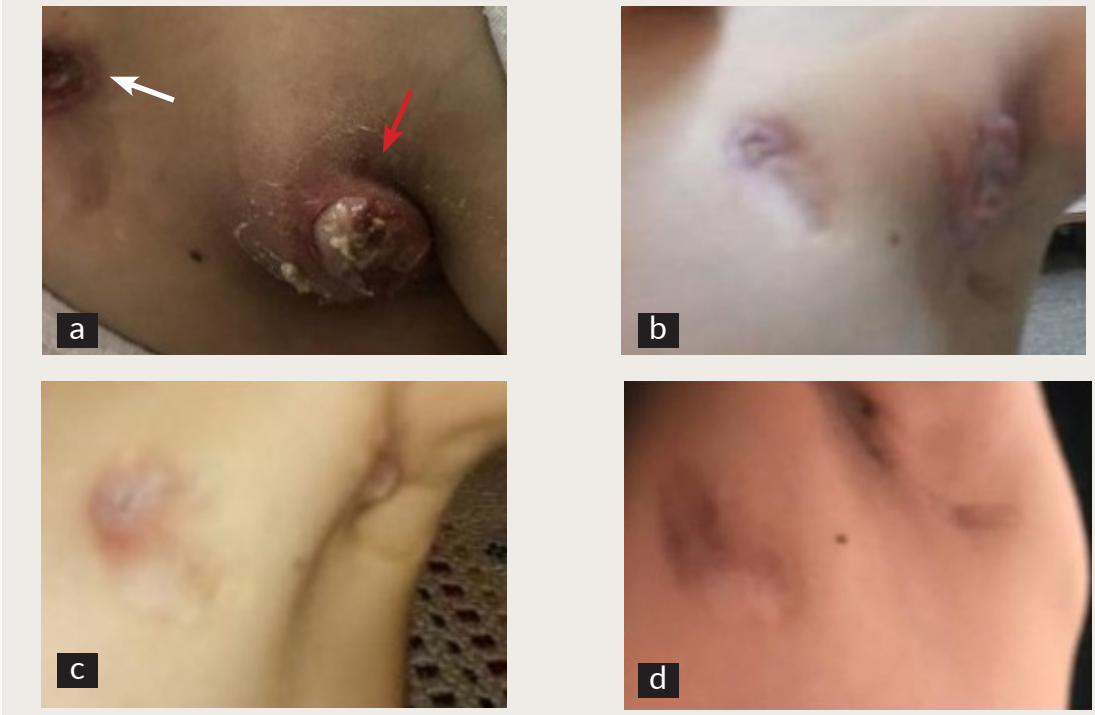

Figure 1 | **a)** Before treatment, two skin lesions; one in the upper chest (white arrow) and the second (red arrow) is ulcerated lesion in the left axilla. **b)** two months after treatment. **c)** four months after treatment, **d)** six months after treatment; the lesions are healed leaving little scar and pigmentation.

drug susceptibility test (DST) for the 1st line.

The smear for AFB and culture were positive for mycobacterium tuberculous bacilli. Genxpert detected low MTB with resistance to rifampicin, and Phenotypic DST for the 1st line of therapy revealed resistance to INH and rifampicin. Other baseline investigations like complete blood counts (CBC), renal function (RFT) and liver function tests (LFT) were within normal, and the HIV test was negative. At the same time, the chest X-ray showed upper lobe consolidation, a prominent left hilar region, and a hazy pericardial area. The right lung field was clear.

The patient was diagnosed with cutaneous multi-drug-resistant TB, and to start 2nd line anti TB regimen. Based on his body weight, which was 17.5 kg, he received amikacin 750 mg intramuscularly, levofloxacin 375 mg daily, ethionamide 250 mg twice daily, cycloserine 250 mg twice daily, pyridoxine 50 mg twice daily, and pyrazinamide 600 mg once daily. The patient received treatment for two months then he was lost to follow up.

The patient presented two months later on with worse skin lesions. A swab for AFB, culture and DST for the 2nd line therapy (line probe assay) was taken. Other baseline investigations were done, including ECG, CBC, RFT, LFT, serum electrolytes and serum albumin. We decided to use the oral regimen according to the updated WHO recommendations to safe the child the need for injections that negatively effect his compliance. Based on his body weight, 18 kg, he received delamanid 25 mg twice daily, levofloxacin 375mg once daily, clofazmine 100mg on alternate days, linezolid 300mg once daily, cyclosirine 250 mg twice daily, and pyridoxine 50 mg twice daily.

After 24 weeks, delamanide was stopped, and the result of DST 2nd line revealed that fluoroquinolone resistance was not detected. Linezolid stopped after one month, and we continued on three drugs. Progressively the patient became generally well, and the skin lesion responded to treatment within two months

and completely healed within six months. The patient completed 15 months with continuous monitoring, and the treatment course was uneventful apart from skin pigmentation due to clofazimine.

DISCUSSION

TB is a curable and preventable disease. About 85% of people who develop TB disease can be successfully treated with a 6-month drug regimen, while regimens of 1–6 months can be used to treat TB infection (latent).[1] From the mid-twentieth century onwards, there was a resurgence of the disease, with the main causes being the increased incidence of HIV-positive patients, the emergence of multidrug-resistant tuberculosis and the growing number of patients receiving immunosuppressive treatments.[7] Our patient presented as a case of axillary TB adenitis that failed with two courses of anti-TB medication and was found to be a case of multi-drug resistance. He was not receiving immunosuppressive treatments, and his HIV status was negative.

Cutaneous tuberculosis exhibits diverse clinical manifestations: inflammatory papules, verrucous plaques, suppurative nodules, chronic ulcers, and other atypical lesions.[17] Our patient complained of 2 skin lesions; one was painless and purple on the upper chest, and the second was a red-brown, ulcerated lesion in the left axilla with a granular base and purulent discharge.

Scrofuloderma, also called colliquative cutis, is a common form of cutaneous tuberculosis[5] that usually occurs in areas with underlying lymph nodes such as the neck. The underlying focus of tuberculosis in lymph nodes (lymphadenitis) sometimes extends into the overlying skin leading to scrofuloderma.[20] Our patient initially presented with axillary TB adenitis and then developed two skin lesions in the axilla near the primary LN and the upper chest. The neck, axillae, and groin are often involved, with the cervical lymph nodes as a common source of infection.[5]

Scrofuloderma is the result of cutaneous infection adjacent to a tuberculous focus. The clinical picture is characterised by the presence of subcutaneous, painless, slowly growing red-brown nodules that evolve to ulcers and fistulous tracts with drainage of serous, purulent, or caseous content. Spontaneous healing may occur, leaving keloid scars, retractions, and the atrophic sequel.[19,20] Scrofuloderma may occur at any age but most commonly in children, as in our case. It can occur in adolescents and older adult individuals.[21] Scrofuloderma is the most common form of cutaneous tuberculosis, accounting for 47% of total cases of cutaneous tuberculosis in children.[22] It is reported that extrapulmonary TB is common in young children and children and adolescents living with HIV.[23] Our patient is at the age of 4, in a competent immune state, and tested negative for HIV. However, he developed these skin lesions; one of them was ulcerated, leading to purulent discharge. These lesions improved and completely healed with treatment leaving only skin pigmentation and a small scar.

The possibility of multidrug-resistant cutaneous tuberculosis should be kept in mind when encountering a poor response to standard anti-tubercular drugs in patients where no other cause is forthcoming. Multidrug-resistant cutaneous tuberculosis is diagnosed in 1.9% of patients with cutaneous tuberculosis. Such a diagnosis was provisionally made based on failure to show response to the standard first-line anti-tubercular therapy; three or four of these drugs, rifampicin, isoniazid, pyrazinamide, and ethambutol.[24] Patients with multidrug-resistant TB (MDR-TB) should be treated using mainly ambulatory care rather than models of care based principally on hospitalisation. Access to rapid diagnostic testing, which could reliably identify resistance to fluoroquinolones, would help clinicians to decide whether the patient is eligible for the shorter MDR-TB regimen and what agents to include in a longer MDR-TB regimen. The GenoType MTB DRsl LPA may be used for this purpose.[25]

Our patient completed two courses of the standard first-line anti-TB medication; however, the results were unsuccessful. This failure raised the probability of multi-drug resistance

TB, an assumption that GenXpert and LPA confirmed.

Treatment of Multi-drug resistant scrofuloderma should follow similar recommendations to treat other forms of TB with multi-drug therapy (MDT) with adjustment based on culture and susceptibility. Surgery may rarely be required to manage extensive scrofuloderma,[22] and it was not needed in our patient. The key to success in the diagnosis of multidrug-resistant scrofuloderma in our patients lies behind raising awareness, availability of accurate diagnostic methods of resistant TB and close monitoring of the patient during the whole course of treatment.

CONCLUSION

New all oral drug resistant anti TB regimen is more tolerant by the patient than old injection included anti TB regimen. Scrofuloderma should be kept in mind as a cutaneous manifestations of tuberculosis especially when underlying tuberculosis such as lymphadenitis is present.

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Abbreviations Acid Fast Bacillus (**AFB**), Complete blood counts (**CBC**), Coronavirus Disease (**COVID-19**), Drug susceptibility test (**DST**), Drug-resistant (**DR**), Electrocardiography (**ECG**), Isoniazid (**INH**), Liver function tests (**LFT**), Multidrug-resistant TB (**MDR-TB**), Mycobacterium tuberculosis (**MTB**), Renal function test (**RFT**), Rifampicin (**RIF**), Tuberculosis (**TB**), World Health Organization (**WHO**).

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