CASE REPORT

Cutaneous Tuberculosis in HIV Patient: A Case Report

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Summary
Tuberculosis (TB) is a serious communicable disease of major concern in endemic regions. Cutaneous tuberculosis (CTB), which accounts for less than 1% of all cases, can cause severe infection in susceptible patients.[1] The diagnosis of CTB is challenging as it can present with a multitude of clinical presentations. The diagnosis must be supported by highly sensitive and specific investigations. This paper highlights the susceptibility of immunocompromised patients to the development of CTB and the challenges in making a diagnosis.

Key words: *Cutaneous tuberculosis, CTB, HIV, Tuberculosis-HIV, CTB-HIV, Co-infection*

Introduction
Mycobacterium tuberculosis (MTB) is the causative agent for TB. TB essentially affects the lungs and can involve extrapulmonary sites including the skin.[2] The occurrence of CTB is driven by the human immunodeficiency virus (HIV) epidemic as well as in specific settings such as healthcare facilities, prisons and homeless shelters. Increased incidence is also noted among intravenous drug users, and in those with diabetes mellitus and on immunosuppressive therapy.[3] It is estimated that one-third to one-half of people with HIV infection are also co-infected with MTB worldwide.[4]

Case report
A 46-year-old gentleman with underlying hepatitis C and HIV presented with worsening oral thrush and dysphagia. He had multiple pinhead-sized nodulo-pustular lesions initially over face (Figure 1-d), which then progressed to the ears and then the upper limbs and lower limbs over one week. Some of nodules appeared to have central necrosis. He was an intravenous heroin abuser and diagnosed with HIV in October 2009 when he presented with a prolonged headache and left sided weakness. He was treated for cerebral toxoplasmosis. His baseline viral load was more than 50,000 copies/ml, CD4/CD8 ratio was 0.01 (0.83-6.1)

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and CD4 count was 64 (355-1213). He was on Stavudine/Lamivudine/Nevirapine since June 2010. He managed to achieve a non-detectable viral load when he was compliant. This was until October 2016, after which he defaulted treatment.

General examination revealed extensive oral candidiasis. He had a residual left sided hemiparesis from previous cerebral toxoplasmosis. Sensory examination and lung findings were normal. There was no lymphadenopathy found. Clinically the differential diagnosis were atypical mycobacterial cutaneous infection and subcutaneous or deep fungal infection. Initial blood investigations showed normochromic normocytic anemia with thrombocytosis but no leucocytosis. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were significantly raised. Chest X-ray was normal initially. Tuberculin skin test reading was 0mm after 48 hours.

This patient underwent echocardiography which showed a 0.6cm to 1.5cm posterior inferior wall pericardial effusion and computed tomography of thorax, abdomen and pelvis showed a pericardial effusion on the posterior inferior wall with enhancement of the pericardial lining, multiple nodular opacities over the right lung, left lower lobe collapsed consolidation with minimal pleural effusion, necrotic mediastinal lymph nodes, hepatomegaly with minimal ascites but no evidence of focal liver lesion.

A punch biopsy of skin was done over the forehead. There was a localised ulceration with collection of neutrophils and histiocytes in the dermis forming microabscesses. However, no well-formed granuloma, obvious dysplasia or malignancy were seen. Abundant acid-fast bacilli (AFB) were demonstrated with Ziehl Neelson stain and Wide Fite stains.

Split skin smear (SSS) was positive with bacterial index 3.3 and morphological index 1.5. MTB and fungal tissue culture and sensitivity were negative. However MTB PCR (polymerase chain reaction) was positive and negative for *Mycobacterium leprae.* Based on clinical, radiological and PCR findings, the patient was treated for acute cutaneous military tuberculosis (ACTMB). He was started on intensive regimen of anti-TB drugs consisting of Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Pyridoxine. After 2 weeks, this patient had significant improvement of the skin lesions (Figure e-h).

Figure 1. (a) Localised ulceration with collection of neutrophils and histiocytes in the dermis, involving pilosebaceous units (Haematoxylin & Eosin stain (H&E), 4x); (b) The edge of the lesion is composed of histiocytes and some scattered within were epithelioid looking. No well-formed granuloma is seen (H&E, 10x); (c) Acid fast bacilli were demonstrated (Ziehl Neelson stain, 60x)

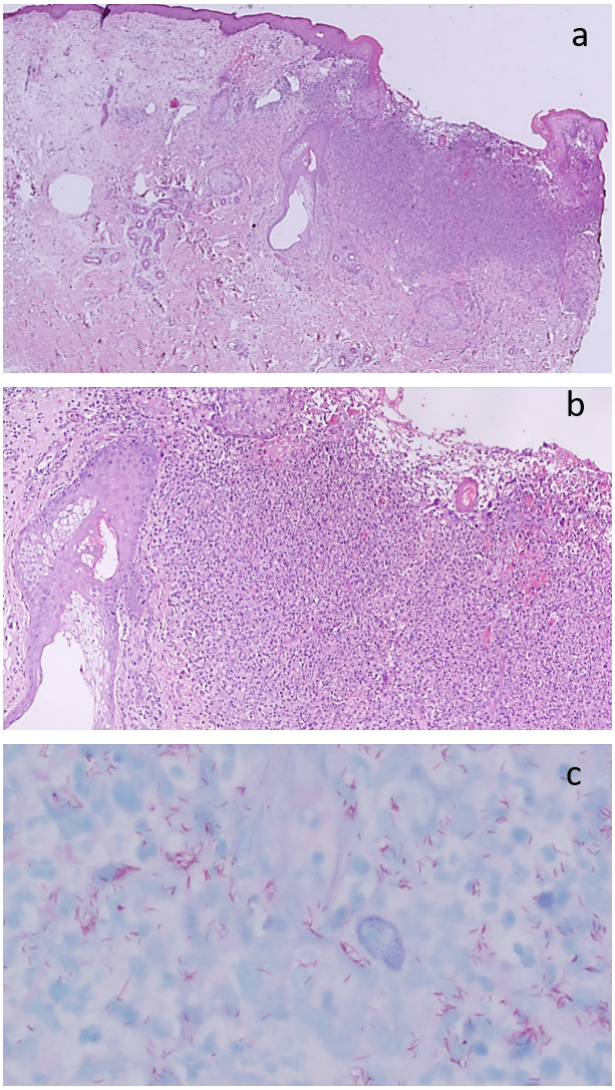
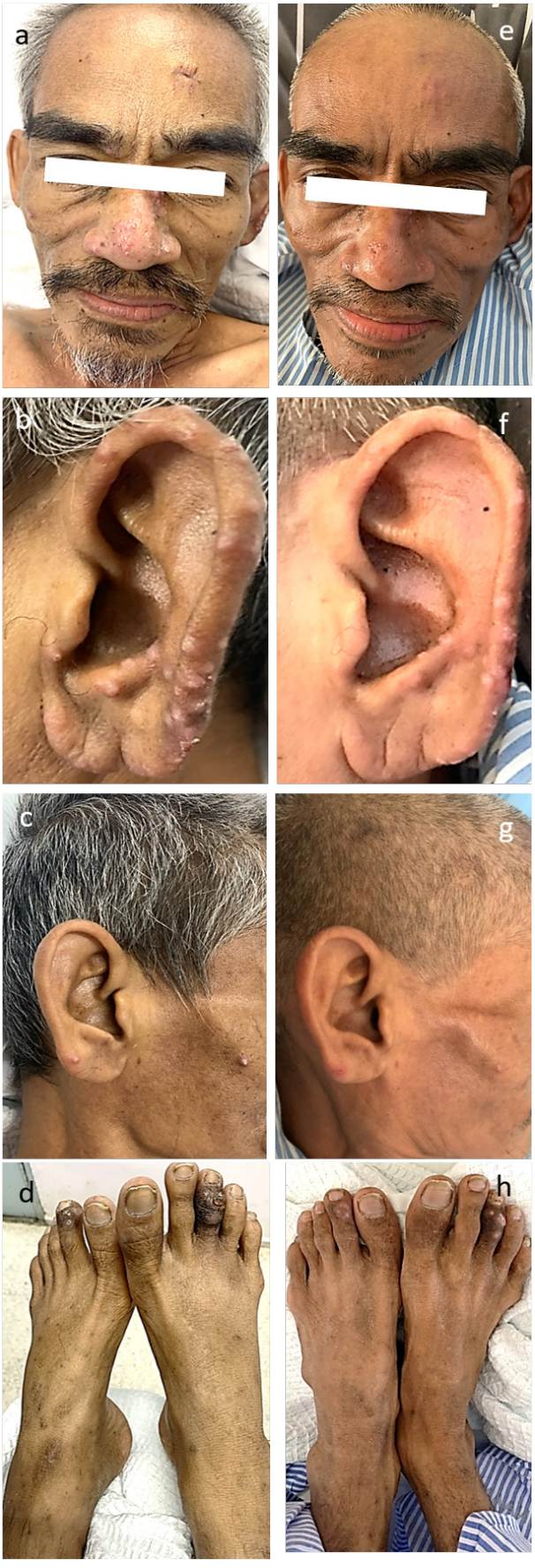


Figure 2. (a-d) Nodulo-pustular lesions over face, ear, cheek and dorsum of foot. Baseline photo prior to anti-TB. (e-h) Photo after anti-TB



Discussion

The estimated incidence for TB-HIV cases was 193000 in 2013. In general, Asian countries demonstrated a lower estimated prevalence of TB-HIV co-infection at 17.2% as compared to other regions such as Africa (31.2%), Europe (20.1%), Latin America (25.1%) and USA (14.8%).[5-6] This low number may be unreliable due to poor screening as not many countries in the Asia-Pacific region tested more than two-third of patients who had TB for HIV.[5] Many countries in Asia only demonstrated a prevalence of TB-HIV coinfection rate of less than 10% except for Thailand (15%) and Papua New Guinea (14%). This was in contrast to the African regions where the majority exceeded 50% and had the highest number of reported HIV co-infection cases.[5,7] Overall, the incidence of CTB was only 0.7% with 9.1% HIV concurrence from 2007 to 2009 in India.[8] Male patients demonstrated a higher prevalence of TB and TB-HIV co-infection in Malaysia (91.1%).[9]

The lifetime risk to develop active TB in HIV individuals is 5-15% annually as compared to immunocompetent adults which is at 5-10%. Co-infection with HIV increases the risk of reactivation of latent TB by 20. On the other hand, TB exacerbates HIV infection.[10] The depletion of CD4 T-cells due to HIV infection causes impairment of the intracellular clearance of MTB and disrupts the integrity and architecture of the granuloma which leads to TB reactivation.[11,12] It has been proposed that TB-HIV co-infection as a 'danger-couple' model in which dysfunctional HIV-infected T cells lead to loss of intracellular killing abilities of macrophages harbouring MTB, while MTB-infected macrophages containing lipoarabinomannan (LAM) produce increased levels of TNF- α, IL-1 and IL-6 leading to enhanced viral replication and persistence in the macrophages.[13]

Clinical variants of CTB mainly depends on cell-mediated immunity as the primary response to mycobacterial infection. It can be concluded that it is a direct reflection of the host's cellular

immune status. This is totally different from leprosy where the predominant response is immunological.[4] It is also important to note that the presentation of CTB depends on the bacillary load.[4]

The clinical morphology of CTB can be differentiated by the mode of infection, i.e. either through exogenous or endogenous sources. The former is significantly less common. An exogenous source infection is by primary inoculation on the traumatic skin or mucous membranes which can lead to tuberculosis verrucosa cutis (TVC) and tuberculosis chancre.[1,7] Endogenous routes may also be via hematogenous, lymphatic or contiguous spread to the skin which may lead to scrofuloderma, lupus vulgaris (LV), tuberculous gumma, orificial tuberculosis or ACTMB as clinical presentations.[1,7] As MTB can be found at the lesional sites via PCR in this case, it is defined as true CTB instead of tuberculids.[7] Tuberculids are delayed-type hypersensitivity reaction to bacterial antigens and can be manifested as papulonecrotic tuberculid, lichen scrofulosorum or erythema induratum of Bazin.[4,7]

Scrofuloderma (80%) is the most common presentation of TB-HIV cases in Brazil followed by tuberculous gumma (20%) from samples collected from 2000 to 2016.[10] In India, where there is a high incidence of TB and HIV, one study showed that 10.4% of patient with scrofuloderma, 7.5% of patient with LV, 11.7% with TVC were HIV positive. Scrofuloderma represented the most commonly seen variant in the study.[8]

ACMTB or tuberculosis cutis miliaris acuta generalisata usually occurs in immunocompromised patient such as Acquired Immunodeficiency Syndrome (AIDS) via hematogenous spread. The lesion can present with scattered erythematous macules and papules with central vesicles or pustules, characteristically from a pinhead size to 6 mm in diameter, that may rupture, and then form a crust. Ultimately, it heals with a hypopigmented scar and brownish halo.[4,14,15] Pulmonary basal involvement, hilar or mediastinal lymphadenopathy and military TB are most commonly observed.[13] Microscopic examination may demonstrate ill-formed or no granulomas, focal or extensive necrosis, microabscesses, abundant AFB and scattered non inflammatory cells.[14,15] The absence of a cell mediated response in ACMTB results in non-specific necrosis with high bacillary load and negative tuberculin test.[4] In this case, the patient demonstrated a few characteristics of ACMTB.

SSS was taken from the most representative lesion and stained by modified Ziehl Neelson (ZN) stain to demonstrate AFB.[16] ZN stain was developed to show mycobacterial genus fastness which has become the cornerstone in TB diagnosis.[17] Differentiation of MTB and *Mycobacterium leprae* by SSS alone is impossible. It was proven that PCR had higher sensitivity and specificity compared to SSS in diagnostic challenges.[18] The lack of a positive tuberculin test, granulomatous reaction and high bacillary load would make ACMTB analogous to lepromatous leprosy.[4] Even though co-infection between tuberculosis and leprosy has occurred since the thirteenth century, the probability is estimated at 0.0006 cases per 100000 population in Malaysia.[19]

Routine sputum microscopy is inadequate to rule out TB and is not an optimal screening tool since 24-61% of TB-HIV patients presents with sputum-negative disease.[5] WHO has endorsed the Xpert MTB/RIF assay (PCR) as the primary TB diagnostic test for symptomatic people living with HIV as it is associated with 35-45% improvement in the diagnostic sensitivity. Urine LAM assay can be added to rule out active TB in severely immunocompromised patients (CD4 count less than 100) to achieve diagnostic certainty.[5]

One in four deaths among HIV patients is attributed to TB even though significant reduction of TB-related deaths among HIV patients was seen in Asia Pacific region.[5,6] The outcome for ACMTB is grave. Seventy five

percent of cases had multidrug resistance to at least Rifampicin and Isoniazid and these cases eventually succumbed.[4]

Female patients showed a higher tendency for treatment success according to *Jalal et al*. This study also significantly supports that a positive tuberculin test leads to a higher chance of treatment success and was assumed to be due to development of immune response to the MTB.[9] However, this patient demonstrates a good response to treatment despite being a male and showing no reaction on tuberculin test.

Conclusion

CTB is a rare entity and the outcome is rarely reported. This case posed its own diagnostic challenges and high level of suspicion is needed due to the variable clinical manifestations. Early and specific diagnostic screening may improve patient's prognosis.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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