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Case Report

Tuberculosis verrucosa cutis that mimics atypical mycobacterium cutaneous infection

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Abstract Tuberculosis verrucosa cutis (TBVC) is a rare diagnosis, which often underdiagnosed and was delayed for treatment. We present a case of TBVC of a twenty-eight-year-old man with complain of a painless verrucous nodule coaslesced from tiny nodules, that sometimes bleed. The patient had history of pulmonary TB contact from his friend, but symptoms, laboratory tests (complete blood count, erythrocyte sedimentation rate, transaminase, urea, and creatinine), and lung radiograph were unremarkable. The patient had no history of chronic illness, vaccination history was completed. histopathology result showed small foci containing epithelioid cells that surrounded granuloma with suggestive caseous necrosis with no sign of malignancy and positive acid fast bacilli in paraffin section. The patient was treated with first line antituberculous drugs regimen, that includes isoniazid, rifampicin, ethambutol, and pirazinamid. After 6 months, the lesion improved significantly and the patient did not feel any pain or bleed in the lesion. There was no recurrence on follow up 5 months post therapy. The major risk factors for development of cutaneous TB are increased exposure to the source of infection. Diagnosis of TBVC lies in identifying the presence of etiology either by histopathology, PCR, or other methods with various sensitivity and specificity. Cutaneous infection of TB might present in various manifestation with multiple differentials and multiple diagnostic modalities that vary in diagnostic accuracy. The trial of TB therapy may be justified and diagnosed based on the improvement after therapy.

Key words
Cutaneous tuberculosis; Tuberculosis verrucosa cutis; Mycobacteria.

Introduction

Tuberculosis is a communicable disease that is caused by acid-fast bacilli *Mycobacterium tuberculosis*.[1] The disease mostly affects the lung causing pulmonary TB, but it can affect extrapulmonary sites, such as skin, central nervous system, gastrointestinal tract, urogenital tract, and bone. According to Global Tuberculosis Report 2020, it is estimated there are 10 million people that have tuberculosis worldwide.[2] This burden is complicated by the emergence of Multidrug-resistant TB (MDR-TB) and *human immunodeficiency virus* (HIV)/*acquired human immunodeficiency virus* (AIDS).[3] According to World Health Organization (WHO), in 2020, tuberculosis (TB) remains the 13th leading cause of death and the second leading infectious killer.[4] TB can occur in all age groups, including adults in their productive years, especially in developing countries. Here we present a cutaneous tuberculosis (CTB) case, that consist only 1-1.5% of all extrapulmonary TB, which occurrence is only 8.4-13.7% of all TB cases.[5]

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Figure 1 Pre-treatment lesion.

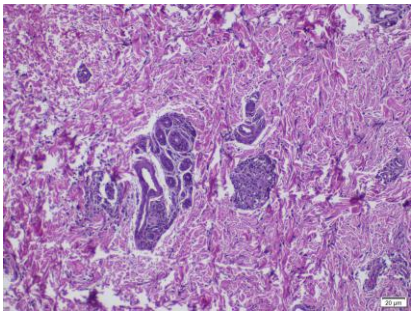

Figure 2 Tissue section of skin lesions with hematoxylin-eosin staining (10X magnification).

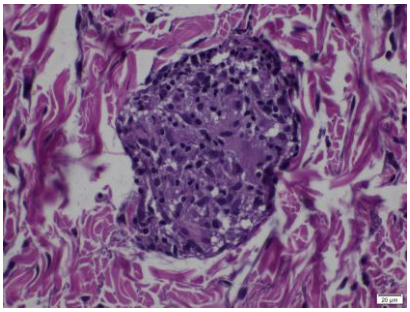

Figure 3 Tubercle containing caseous necrosis with hematoxylin-eosin staining (40X magnification).

Case report

A twenty-eight-year-old man came to the hospital complaining about a lump on the base of the third phalanx of his right hand. The lesion has been there for about 18 months which started as small as the size of a pea, without tenderness or itchiness but sometimes bled. Around 17 months ago, after the first lesion appeared, several tiny lumps emerged in the surroundings and coalesced into bigger lumps. The patient went to a doctor and was given antibiotics and painkillers, but the lesion did not improve. He denied having a chronic cough, night sweating, and low-grade fever. Three months before the patient noticed the lesion for the first time his colleague, whom the patient often contacted, had been diagnosed with pulmonary TB and treated with anti-tuberculous therapy. The patient denied a history of soil contact. The patient cleared his fish tank regularly without any protective equipment, years before the patient has the lesion. The patient frequently went to the seashore for recreational fishing several years before. He worked in a vegetable oil factory as a forklift operator, product checker and helped to oversee the manufacturing process. The patient's vaccination status was complete and he has no history of chronic illness.

In the physical examination, there was an erythematous plaque on the dorsal aspect of the right metacarpophalangeal III with defined-margin, oval-shaped with petaloid margin and the size of 2.5 cm x 1.5 cm. The surface was verrucous with fissures, scales, and dark-red crust (**Figure 1**). There were several differentials based on clinical findings, included tuberculosis verrucosa cutis (TBVC), atypical mycobacteria infection, verruca vulgaris, coccidioidomycosis, and histoplasmosis. We decided to perform a biopsy of the lesion and ordered lab testing for complete blood count (CBC), erythrocyte sedimentation rate (ESR), transaminase (AST and ALT), urea, and creatinine, which all but biopsy were found to be normal. The patient routinely underwent medical check-up from his company, including a thorax x-ray, which was found normal.

The histopathology result showed small foci containing epithelioid cells that surrounded granuloma with suggestive caseous necrosis (**Figure 2,3**). The stroma was compact and hyperemic with perivascular and periadnexal chronic inflammatory infiltrates. Modified Acid Fast staining for paraffin section showed Acid Fast Bacilli (AFB) (**Figure 4**). These findings suggested chronic granulomatous inflammation possibly caused by *Mycobacterium tuberculosis* or atypical mycobacteria, and there was no sign of malignancy. Profunda fungal infection diagnosis such as coccidioidomycosis and histoplasmosis were excluded. A week after the first visit, the patient was treated as tuberculosis

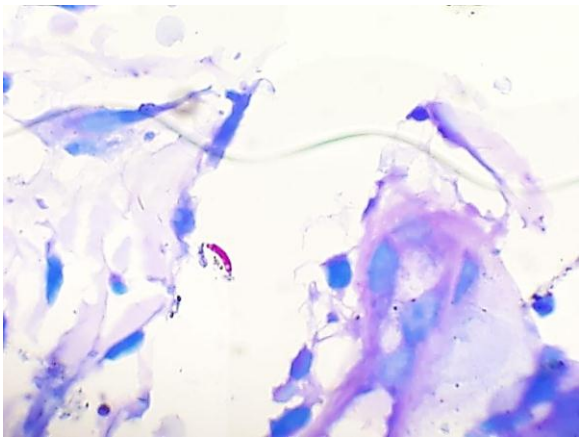

Figure 4 Acid-fast staining showed the presence of acid-fast bacilli (100X magnification).

verrucosa cutis and prescribed anti-tuberculous medication that consisted of Isoniazid 300 mg, Rifampicin 600 mg, Pirazinamid 1500 mg (@tab 500 mg), Ethambutol 750 mg (@tab 250 mg), and Pyridoxine (Vitamin B6) 10 mg once a day. He was treated for 2 months and then continued for another 4 months with Isoniazid, Rifampicin, and Pyridoxine. The symptoms improved in the fifth month of treament. In the final month of treatment, the patient did not feel any pain and bleed in the lesion. The patient's lesion improved significantly. In the physical examination, we found an oval-shaped hyperpigmented macule with an ill-defined margin and smooth surface with the size as same as before, there was no excoriation (**Figure 5**). There was no recurrence on follow up 5 months post therapy.

Discussion

TB mostly affects the lungs causing pulmonary TB. Unlike pulmonary TB, CTB is considered rare.[6] CTB is an uncommon form of extrapulmonary tuberculosis that is caused by *Mycobacterium tuberculosis* infection, and less commonly by *Mycobacterium bovis* and bacille Calmette-Guerin (BCG) vaccine. Invasion of *M. tuberculosis* in the skin can be exogenous or endogenous.[7] Endogenous invasion is caused by hematogenous or lymphatic dissemination, usually from pulmonary infection. Endogenous invasion includes scrofuloderma, some cases of lupus vulgaris, orificial tuberculosis, tuberculosis gumma, and acute miliary tuberculosis. While exogenous invasion is caused by direct inoculation of bacteria into the skin. Exogenous invasion includes tuberculous chancre and TBVC.[7,8]

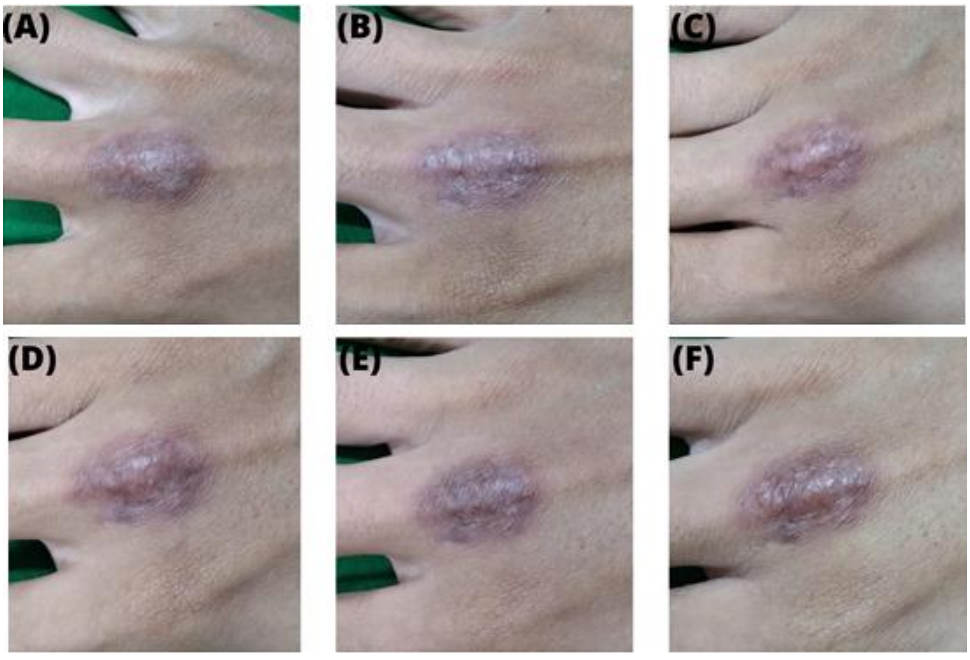

Figure 5 Lesion appearance after the first to sixth month of anti-tuberculous therapy. (A to F). (A) 1st month, (B) 2nd month, (C) 3rd month, (D) 4th month, (E) 5th month, (F) 6th month.

The major risk factors for development of cutaneous TB are increased exposure to the source of infection.[9] The host factors also influence the risk for specific cutaneous manifestation of TB infection including ages, sex, and immunological status.[10,11] In pediatric population, the most common cutaneous manifestations are primary inoculation TB, scrofuloderma, and lichen scrofulosorum.[10] Female was more frequently affected by lupus vulgaris and erythema induratum of Bazin. Individual with high immunity, TBVC, lupus vulgaris, and tuberculides are more common, while in immunocompromised individuals, TB cutis orificialis, metastatic tuberculous abscess are most frequently found.[12,13] TBVC, or also known as warty tuberculosis, prosector's warts, or anatomist's warts itself is the third most common manifestation of cutaneous tuberculosis. TBVC is caused by exogenous paucibacilar invasion of *M. tuberculosis* that activates an immunologic reaction on the skin, or re-infection from individuals who have been sensitized to *M. tuberculosis.*[14,15] High risk groups of population for TBVC include doctors, pathologists, laboratory workers, farmers, butchers and veterinarians with the prevalence of male is higher than women.[16] History of trauma is also a significant risk factor.[17] In our case, the patient was male with history of frequent fish tank cleaning, which might posed the patient into repeated trauma to the hand unknown to the patient.

TBVC has a typical appearance, starting as an asymptomatic, small, warty papule or nodule that progresses over time becomes a well-defined verrucous plaque.[6,7,18] Sometimes purulent discharge and crusting can also be found. Lesion of TBVC is painless and usually located on the extremities or areas which are exposed to trauma and infected sputum, or other tubercular materials. In this case, the patient complained about a non-tenderness lesion that appeared on the exposed area, which is the base of the third phalanx of the right hand.

Diagnosing TBVC often becomes a challenge for clinicians as the clinical features resemble warts.[18] The clinical features is often atypical making the diagnosis difficult and need more diagnostic modalities. Histopathologies may show pseudoepitheliomatous hyperplasia of the epidermis and dermis with inflammatory infiltrates including neutrophils, lymphocytes and plasma cells on early lesions.[9] Over time, the neutrophils can be replaced by chronic inflammatory cells and granulomatous inflammation, with variable caseation necrosis. Acid-fast staining test also often shows negative results, especially in patients with high immune status and once granulomas develop. Acid-fast staining test also often shows negative results, especially in patients with high immune status.[6,7,16] Histopathology findings often vary in mycobacterial infection, depending on the severity of the CTB and immunological reactions. In this case, the histopathology examination reveals the presence of epithelioid cells that surround well-formed granuloma with suggestive caseous necrosis and positive AFB, which increase the suspicion for TBVC.

Positive Mantoux test also provides a high diagnostic value, although a negative result cannot rule out the possibility of CTB.[9] There are also tests which are not routinely performed but have a definite role in diagnosing CTB, such as interferon-Gamma Release Assays (IGRA), Xpert MTB/RIF®, enzyme-linked immunosorbent assay (ELISA) serology, cytology, and PCR, with various sensitivity and specificity.[19-22] In TBVC, culture sensitivity is relatively low because of its state of paucibacillary types.[6] Due to limitation in our institution, all of those tests could not be conducted. Patients with CTB should also be screened with chest x-ray and sputum smear to

rule out pulmonary TB, while in this case, the patient's chest x-ray was normal and he did not have any symptom of cough or sputum production.

The treatment of TBVC is multidrug regimen, which is the same as the treatment for the other organs, with regimen category 1 serves as the first-line therapy, including Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide.[23] The treatment of TB consist of two stages, the initial (or intensive) and maintenance stage. In the initial phase, the patient was given Rifampicin 600 mg, Isoniazid 300 mg, Pyrazinamide 1500 mg, and Ethambutol 750 mg for the first two months followed by maintenance stage with only rifampicin and isoniazid with the same dosage. The use of Isoniazid was accompanied by pyridoxine 10 mg, due to the neurotoxic nature of Isoniazid. It competes with pyridoxine or vitamin B6 in its action as a cofactor in the synthesis of synaptic neurotransmitter.[24] Isoniazid toxicity can manifest as peripheral neuropathy, ataxia, and paresthesia, particularly in older adults, pregnant women, children or individuals with comorbidities.

Other conditions with verrucous lesions such as hypertrophic lichen planus, verrucous carcinoma, verruca vulgaris, keratoacanthoma centrifugum may mimic TBVC. Infectious skin diseases such as leishmaniasis, sporotrichosis, chromomycosis. and atypical mycobacteriosis (AM) should also be considered when diagnosing TBVC.[25] One of atypical mycobacteriosis that may be a concern in this case is an infection caused by *Mycobacterium marinum. M. marinum* infection leads to a condition called fish-tank granuloma. This condition usually develops on the fingers after exposure to contaminated aquariums. In this case, the patient regularly cleared his fish tank.[26] *M. Marinum* infection can frequently develop into nodular lymphangitis in sporotrichoid pattern on hand or arm, but can also present as pustules, ulceration, abcess, or verrucous plaques which can undergo spontaneous resolution in months or progressing into deep infection that leads to tenosynovitis ('fish-tank finger').[27,28] The most common reported symptoms in *M. marinum* infection were pain with tenderness, swelling, drainage and pruritus. The histopathological findings in atypical mycobacteria infections can present in many forms, including tuberculoid, palisading or sarcoidal granulomas, poorly-formed granulomas, spindle cell pseudotumours, rheumatoid-like nodules, or nonspecific chronic inflammations with non-caseating granuloma, and the AFB stains usualy show low positivity regardles of the staining method.[26,27,29] Poorly formed granulomas with chronic inflammation increase the suspicion for atypical mycobacteria infection.[27] Clinically, atypical mycobacteria infections should be suspected in any patient with negative culture and failed typical antibiotic therapy, particularly lesions occuring at the location of prior trauma or procedures.[30] In this case, the patient's histopathology findings suggested chronic granulomatous inflammation with modified Acid Fast staining for paraffin section showed Acid Fast Bacilli that lead to *Mycobaterium tuberculosis* or atypical mycobacteria. Its still difficult to differentiate between TBVC and other atypical mycobacteria infection. The culture is usually needed to find the causative organism, however, due to limitation in our institution, atypical mycobacteria culture could not be conducted.[14] Considering high endemicity of TB Indonesia and high suspicion of TB due to clinical manifestation and histopathology findings, the patient was treated as tuberculosis verrucosa cutis. The lesion improved 5 months after the patient received anti-tuberculous medications, supporting the diagnosis of tuberculosis verrucosa cutis.

Conclusion

Cutaneous infection of TB might present in various manifestation with multiple differentials and multiple diagnostic modalities that vary in diagnostic accuracy. The trial of TB therapy may be justified and diagnosed based on the improvement after therapy.

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