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NODULAR LYMPHANGITIS IN HIV-INFECTED PATIENTS IN TANZANIA

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SUMMARY

Data on nodular lymphangitis among HIV-infected patients in Tanzania are scarce. Nodular lymphangitis defines a clinical presentation with erythematous subcutaneous nodules along the lymphatic channels. Early diagnosis, biopsy or culture of skin lesions and treatment are essential for improving outcomes. However, this is challenging in resource-limited settings. We present two HIV-infected patients with nodular lymphangitis treated with ketoconazole in the absence of itraconazole or amphotericin B with good initial response. At the end of treatment, patient no. 2 showed a total resolution of the lesions, but patient no. 1 died after self-withdrawing from treatment at month four.

INTRODUCTION

Nodular lymphangitis (NL) is a lymphocutaneous syndrome characterised by inflammatory nodules formed due to pathogens entering the lymphatic system either through the skin or by transmission from infected animal bite (1). Causes of NL include *Sporothrixschenckii, Norcadiabrasiliensis, Mycobacterium marinum, Leishmaniapanamensis* and *guyanensis, Francisella tularensis* and systemic mycoses. There are few cases in the literature in association with HIV infection. To our knowledge, this is the first report from Tanzania.

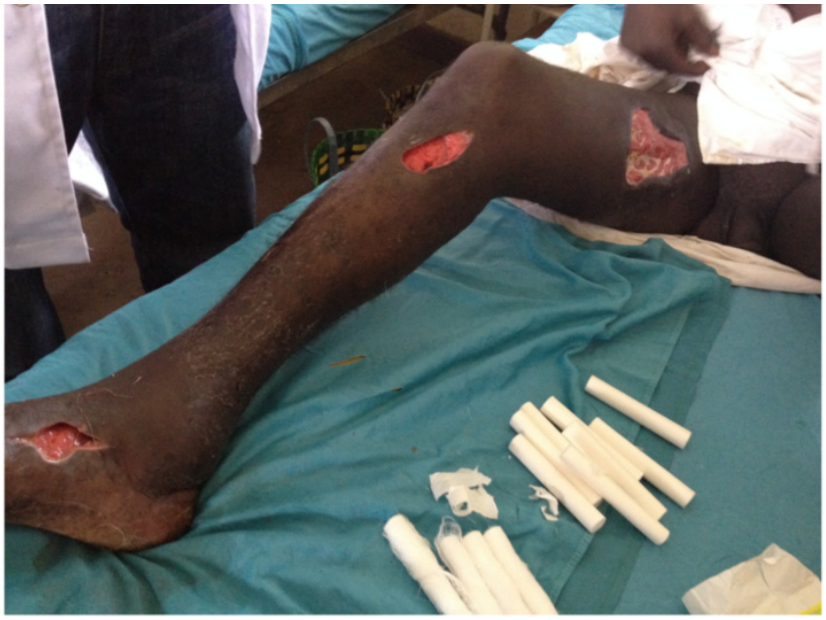
Despite the high burden of deep fungal infections among people living with HIV (PLHIV), there is a scarcity of appropriate microbiological diagnostics and available effective drugs in resource-limited health facilities such as in rural Tanzania to manage these infections. We present two cases of NL in two HIV-infected individuals who recovered from suspected *Sporothrixschenckii* infection after treatment with ketoconazole plus daily wound cleaning.

CASE PRESENTATION

CASE I

A 38 years old male HIV-positive antiretroviral therapy (ART) naïve patient was admitted at Saint Francis Referral Hospital, in southeastern Tanzania, after developing ulcers involving his right lower limb. He initially experienced a small cut wound while working in the farm. After two weeks he developed progressively ascending lesions involving the right ankle, knee and middle aspect of thigh. All lesions were painful, having started as a boil and finally erupted. On admission he had normal vital signs; on physical examination he had an ulcer of approximately 3cm × 2cm on his lateral right ankle, another 5cm × 2 cm on his right knee and approximately 4cm × 3cm around his right inguinal area with unilateral right inguinal lymphadenopathy (Figure 1). The rest of the physical examination was unremarkable.

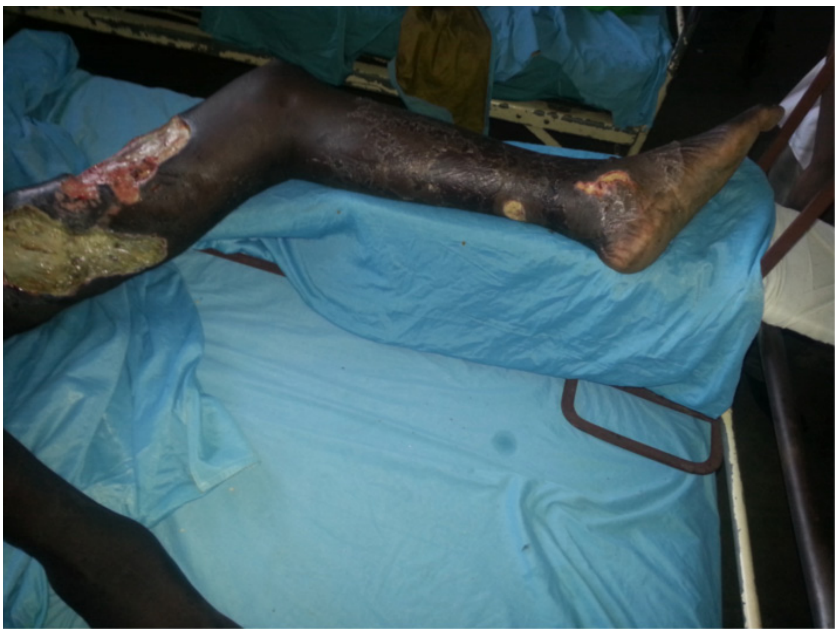
Figure 1
Picture of a case I before treatment with ketoconazole



CASE II

A 40 years old known HIV-positive male patient on ART was admitted complaining of developing ulcers on his left lower limb. He was on zidovudine/lamivudine/efavirenz regimen and cotrimoxazole 960mg once daily since three months prior to the admission with previously reported poor adherence. He had a cut wound while working in the farm, and one month later he developed local lymphadenopathy involving the left inguinal lymph nodes which ruptured after one week to form two wounds of approximately 10 cm diameter with a brownish color floor. After two weeks he developed another wound on the medial part of the left ankle joint of approximately 3 cm in diameter (Figure 2). On admission he had normal vital signs; the rest of the physical examination was unremarkable.

Figure 2
Picture of case II before treatment with ketoconazole



INVESTIGATIONS

Case I

His baseline investigations showed CD4 count of 283 cells/μL with normal full blood counts, renal and liver function tests. A chest, knee, ankle and hip joint radiography revealed no abnormalities.

Case II

His baseline investigations showed CD4 count of 388 cells/μL, with normal full blood counts, renal and liver function tests. A chest, ankle and hip joint radiography revealed no abnormalities.

Biopsy samples of the ulcers were taken from both patients and sent for histopathological analysis to the referral pathology department of the University Hospital Basel. Unfortunately this was after extensive surgical debridement, and no evidence of *Sporothrixschneckii* or other fungi was found.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of NL includes Sporothrixschenckii, Nocardiabrasiliensis, Mycobacterium marinum, Leishmania (Viannia) panamensis/guyanensis, and Francisellatularensis(2). Sporothrixschenckii is the most common cause of NL and traumatic inoculation of the fungus is most common usually occurs after exposure to wood or soil, although zoonotic transmission has been described (3). The infection usually occurs among people exposed to the organism like mine workers, farm workers, gardeners and florists.

Atypical Mycobacteria, mainly M. marinum are possible causes of NL but none of the patients had history of exposure to the marine environment. Francisellatularensis infection is confined to the Northern hemisphere. Leishmaniasis is caused by the protozoa Leishmaniae and can be found in large parts of tropical and subtropical Africa and Asia. Occasionally, it can be associated with non-tender enlargement of a solitary regional lymph node in comparison with tenderness and satellite lesions in nocardiosis. The progressive good response to initial therapy with ketoconazole made this two diagnostic less probable.

TREATMENT

Case I

He was prescribed ketoconazole 200 mg and cotrimoxazole 960 mg both once daily with daily wound cleaning and dressing. In order to avoid the possibility of Immune Reconstitution Inflammatory Syndrome (IRIS) related to sporotrichosis we were planning to start ART 12 weeks after treatment with ketoconazole but the patient was lost to follow-up before its initiation.

Case II

He was also prescribed ketoconazole 200mg, cotrimoxazole 960mg both once daily, continued with zidovudine/lamivudine/efavirenz and daily wound cleaning and dressing.

OUTCOME AND FOLLOW-UP

Case I

Eleven weeks after treatment with ketoconazole the lesions were healing. He was discharged home, came back to the clinic after one month with good resolution of the wounds (Figure 3). He was lost of follow-up, four months later we learned from the relatives he stopped taking the medications and died three months later.

Figure 3
Picture of case I after treatment with ketoconazole for eleven weeks

Case II

After three months on ketoconazole there was good epithelialisation of the wounds (Figure 4 and 5). He asked for a discharge because he could no longer afford to be admitted in the hospital and wanted to continue treatment as an outpatient at the nearby health centre just close to his place. When he was discharged all the wounds were no longer infected (Figure 4 and 5).

Figure 4
Picture of case II after treatment with ketoconazole for three months

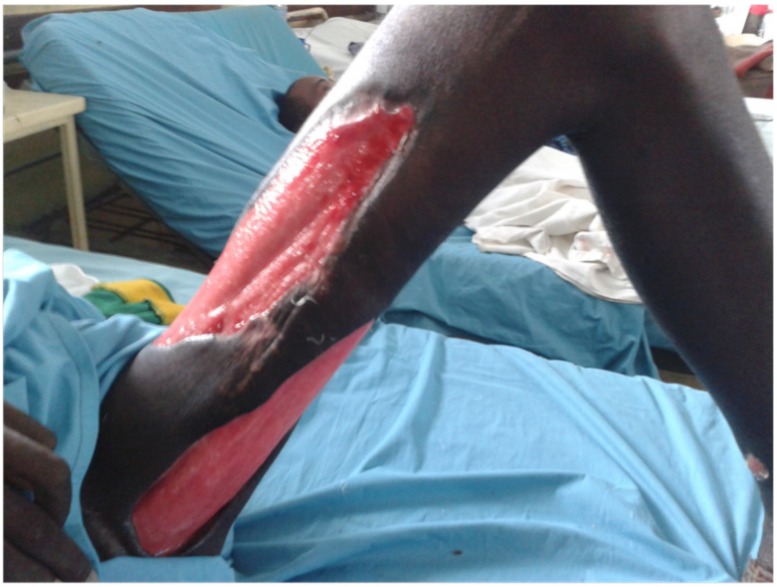
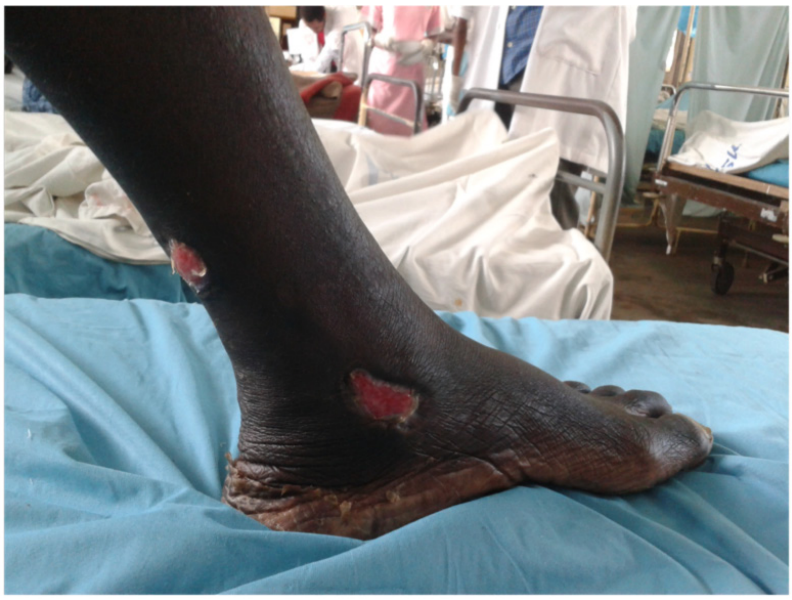


Figure 5
Picture of case II after treatment with ketoconazole for three months



DISCUSSION

Nodular lymphangitis is characterised by inflammatory skin nodules along the lymphatics following superficial inoculation with causative organism. Both patients recalled a history of trauma while working in the farm with a time span of two to four weeks preceding the presentation of ulcerated and painful lesions. Therefore, the source of infection may have been the soil or the surrounding vegetation. The etiology of NL can be accurately related to the epidemiologic context, associated

clinical circumstances, estimated incubation period and response to initial empiric treatment. Based on these features, we suspected both patients developed NL secondary to infection from *Sporothrixschenckii*.

Sporotrichosis is a subacute or chronic fungal infection caused by the fungus Sporothrixschenckii although multiple distinct Sporothrix species have been identified previously. The characteristic infection involves suppurating subcutaneous nodules that progress proximally along lymphatic channels. Two different cutaneous forms have been described for lymphocutaneous sporotrichosis; hyperkeratotic plaques without apparent lymphangitic spread and ulcerated nodules with lymphatic involvement as how the two patients presented.

Several biopsy samples from both patients were sent to the referral Pathology Department of University Hospital Basel, Switzerland. Histopathological examination with Gomori-methenamine Silver stain and culture in Sabouraud agar were done with no evidence of microbiological pathogens. Nevertheless, the biopsy specimens were undertaken after several surgical debridements of the wounds and we presupposed this could be the reason for negative results.

Treatment options for management of sporotrichosis include local measures (hyperthermia), saturated solution potassium iodide, azoles (ketoconazole and itraconazole), amphotericin B, and the allylamine, and terbinafine(4)(5). We acknowledged the potential liver toxicity of ketoconazole (6) but due to lack of availability of itraconazole and amphotericin B (drugs of choice), we decided to treat both patients with ketoconazole 200mg once daily for 3 months (7). Being aware of recent reported cases of Sporotrichosis-associated IRIS we delayed initiation of ART for the first case(8). An estimated rate of 4993 cases of fungal infections per 100, 000 person/year occurs in Tanzania (9). Political will is needed to address the challenges posed by the underestimated burden of AIDS-associated mycoses in sub-Saharan Africa. Better epidemiologic surveillance, accurate laboratory and point-of-care diagnostics, efficacious and available existing drugs, training in medical mycology and targeted funding are imperious in resource-limited settings where expertise and facilities for fungal identification are lacking (10).

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