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CASE STUDY

Management of Buruli Ulcer/HIV co-infection in a resource-limited setting: A case report

Brian K Ngwatu[1], Jonathan V Nunes[2], Alren O Vandy[3]

1. Paediatric Infectious Diseases, Ola During Children's Hospital/SOLTHIS, Freetown, Sierra Leone.
2. Surgery/Medical Research Unit, Masanga District Hospital, Tonkolili, Sierra Leone
3. Infectious Diseases, Connaught Hospital, Freetown, Sierra Leone

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Corresponding Author:
Brian K Ngwatu
N°1 The Maze, Off King Street, Wilberforce
Freetown, Sierra Leone
ngwatub@gmail.com

SUMMARY
We present a case of a clinically diagnosed WHO Category II Buruli ulcer of left lower limb in an otherwise virologically suppressed 36-year-old person living with HIV (PLHIV), who had completed three years of adherent antiretroviral treatment (ART) in the urban setting of Freetown, Sierra Leone. Clinical diagnosis was made following unavailability of recommended polymerase chain reaction (PCR) and non-revelatory laboratory results at microscopy and histopathology. Treatment was provided of recommended locally available antimicrobial regimens and surgery by skin grafting with full recovery of the patient with no relapse.

Key Words
Buruli; Mycobacteriosis; PLHIV; Resource Limited Setting

ABSTRACT

Buruli ulcer (BU), a mycobacteriosis of the cutaneous and subcutaneous tissues caused by *Mycobacterium ulcerans (M. ulcerans)*, mainly affects impoverished communities of West and Central Africa. It's endemic in countries with HIV prevalence between 1 per cent to 5 per cent. HIV infection increases the risk and severity of BU disease and may alter the course of treatment. Rapid diagnosis is crucial to reduce delays in effective treatment. We present a peculiar case of World Health Organization (WHO) Category II BU—a 36-year-old, healthy individual on antiretroviral treatment in Sierra Leone—that highlights the impediments to timely diagnosis and management of BU in resource-limited settings (RLS).

BACKGROUND

Dermatoses are common in HIV infection, taking advantage of a weakened immune system, with atypical to more aggressive clinical presentations in PLHIV compared to the non-HIV infected. The manifestation of these dermatoses where there is HIV co-infection can therefore cause delay and confusion in diagnosis and timely treatment. Caused by *Mycobacterium ulcerans*, Buruli ulcer is a non-contagious neglected tropical disease mainly prevalent in Africa, Asia, and South America. There is a dearth of evidence regarding reservoirs and mode of transmission of *M. ulcerans*, but the most plausible route of transmission is via skin contamination through puncture, including insect bites. Skin temperature of less than 30^0C has been suggested to correlate with the topography of lesions.[1,2]

Buruli ulcer commonly affects the extremities, with variable natural history. Early lesions are usually papular, nodular, or oedematous progressing with rolled borders, spreading laterally. Fifty-five per cent of lesions occur on

the lower extremities and severity varies from a single small lesion below 5cm in cross-sectional diameter (WHO Category I), to non-ulcerative and ulcerative plaque and oedematous forms 5 and 15cm in diameter (WHO Category II), to disseminated and mixed forms in the most extreme with osteomyelitis and joint involvement, or involving other sites such as the genitals (WHO Category III).[3,4]

The slow progress from small lesion to otherwise painless ulcer is enabled by local immunosuppressive properties of a mycolactone toxin that destroys skin and soft tissue, inhibiting characteristic inflammatory symptoms of pain and fever (otherwise diminished in the immune suppressed; eg, in HIV), which contributes to delayed hospital attendance by patients in some cases. A necrotizing cutaneous infection, early diagnosis is crucial to prevent morbid effects and misuse of an already limited option of drugs for treatment (usually parenteral Streptomycin–Rifampicin, the expensive oral Clarithromycin, or Fluoroquinolone combined with Rifampicin). Early laboratory confirmation in particular is recommended to reduce delays in effective treatment.[3]

Rapid diagnostic techniques include detection of mycolactone or microscopy (the latter less sensitive). If available, polymerase chain reaction (PCR) is the technique of choice because of its high sensitivity, but it is expensive; cost is therefore a factor for delayed diagnosis, more so for the disproportionately poor in whom BU is more prevalent. These diagnostic tests are not widely available especially in low-middle-income countries (LMICs) where diagnosis is therefore predominantly clinical, with a reliance on health worker experience and training. Treatment by chemotherapy can be effective, and alone was successful in achieving a cure rate of 47 per cent of patients and was effective against ulcers <5cm in diameter in a large study in Benin; however, HIV testing was not performed.[5]

BU is regarded as the third most common mycobacterial infection in immunocompetent patients. Amongst the immune suppressed, the correlation between BU and HIV is particularly poorly understood. However, HIV positivity in BU cases was between 2.6 per cent in Benin and 8 per cent in Ghana, respectively, where studies reported a significant effect of HIV infection on severity of *M. ulcerans* infections and higher HIV incidence in patients with BU compared to the general population.[6–8]

Sierra Leone has an estimated HIV prevalence of 1.5 per cent, in a generalised epidemic in which women are disproportionally affected (adult prevalence in women of 1.7 per cent, 1.2 per cent in men).[9] Stigma and discrimination related to HIV is high: only 6.6 per cent of the population expresses an "attitude of acceptance" with regard to PLHIV. These factors therefore hinder attendance to health centres for testing and treatment of HIV, let alone HIV-related opportunistic infections.[10] Tuberculosis (TB) is the most prevalent mycobacteriosis in Sierra Leone with estimated incidence of 304/100,000. Fourteen per cent of TB patients with known HIV status are HIV positive. A BU reporting country, surveillance in Sierra Leone suggests BU is not endemic in the country at present.[11]

METHOD

A 36-year-old woman presented to an infectious diseases clinic in Freetown, Sierra Leone, in June 2017, with a history of a chronic, painless skin ulcer of her left foot and ankle area that formed from a papular swelling 2 years before following the bite of an insect. Increasingly, she had associated swelling and reduced mobility of the ankle joint. Local examination revealed a single dry, left pedal ulcer, 14cm x 6cm bx 0.2cm in size.

Her baseline CD4 unknown, she had received antiretroviral treatment and cotrimoxazole prophylaxis for three years and had completed six months of Isoniazid (INH) TB preventive therapy as per the Sierra Leone national guidelines for the care and treatment of PLHIV. An HIV viral load test was conducted revealing "undetectable HIV viral load" (HIV RNA < 20 copies/ml). She had no history of tuberculosis, or any other significant clinical history.

Laboratory referral to the country national referral hospital followed: microscopy with Ziehl-Nielsen was not available at the hospital laboratory, and PCR testing was not available at the in-country central public health laboratory. Incisional biopsy was conducted, with no evidence of granuloma, vasculitis, or malignancy. Plain x-ray of the left foot and tibia/fibula was normal.

A clinical diagnosis of Buruli Ulcer WHO Category II was made off clinical features.

RESULTS

The patient was enrolled on combination antimicrobial therapy of oral Rifampicin (only available in public sector facilities in fixed dose combination with Isoniazid (RH) as routine supply from the National Tuberculosis/Leprosy Programme) and intravenous Streptomycin with intention to treat for eight weeks. Streptomycin was replaced with Clarithromycin after one week following adverse event of heaviness of tongue and face in the patient. The prohibitive cost of Clarithromycin was an impediment to continuity of treatment; the patient was switched to Doxycycline/Rifampicin combination completing six weeks of adherent therapy. A CD4 count conducted four months after completion of the antibiotics (January 2018) was 1708 cells/ul.

The patient was then referred for skin grafting to a district-based teaching hospital to benefit from a surgical training program, which was conducted six months later (June 2018), with full recovery and no relapse of BU (Figure 1).

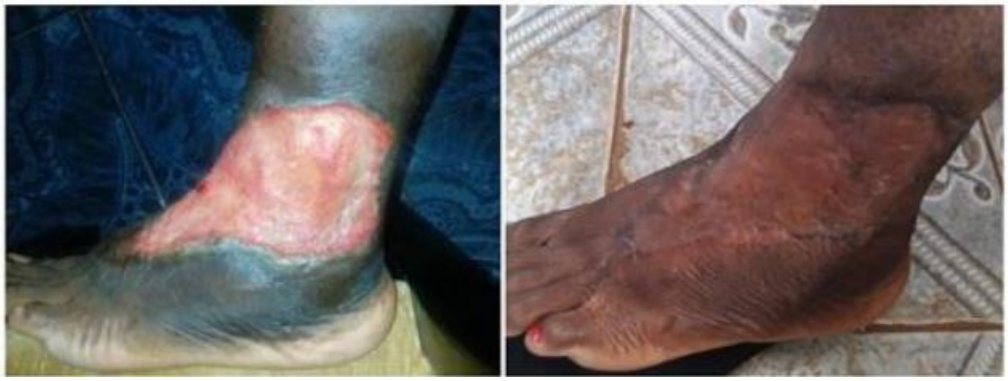

Figure 1: BU June 2017 (L) versus post-surgery - June 2018 (R)

DISCUSSION

Co-infection of HIV and tropical infectious dermatoses is common, and is a major challenge in terms of diagnosis, treatment options, and clinical courses. Despite the lack of information on the prevalence of BU-HIV co-infection, countries where BU is endemic also seem to have a high HIV prevalence. The likelihood of HIV infection in BU

patients compared to the BU-free in Benin and Ghana was eight and four times higher, respectively.[11]

HIV infection can influence BU clinical presentation; PLHIV with WHO Category II and III BU disease are likely to be significantly immune suppressed—the lesion size is significantly increased with decreasing CD4 count and lesions are more likely to be multiple, larger, and ulcerated.[6,7] For control of Buruli ulcer in HIV-positive patients, anti-microbial treatment with Rifampin/Streptomycin should be initiated (and antiretroviral therapy initiated if ART-naïve or continued).

Thirty-two per cent of hospital-identified cases of BU in Africa cases are identified as early Category I lesions. Between 25 and 72 per cent of cases require a combination of antimicrobial and surgical management, with lesion size a major factor.[12] Where antibiotic therapy and surgery are both employed, the extent of surgery and the risk of contractures and other physical impediments that may follow infection are also reduced.[13]

Diagnosis of BU can be laboratory based or clinical, the latter highly contingent on the experience and expertise of attending health worker(s). In resource-poor settings such as Sierra Leone, public sector polymerase chain reaction and microscopy for definitive laboratory diagnosis for BU may be unavailable and/or too expensive. Also, microscopy may not be sensitive as is likely in immune suppression with HIV. Treatment can also be expensive, unavailable, or cause adverse/severe side effects. Our patient lacked the resources to access these diagnostics, experienced adverse side effects from the preferred antibiotic (Streptomycin), and battled untold stigma that led to late presentation and delayed treatment to cure the BU.

CONCLUSION

The case report highlights the peculiar incidence, and complexities of diagnosis, care, and treatment of BU in HIV/BU co-infection in an otherwise healthy immune stable HIV patient, in a resource-limited setting. In our case, the patient's sustained HIV viral load suppression (HIV RNA < 1,000 copies/ml) was potentially the most crucial contributor to her relatively non-severe clinical symptoms, and positive post-treatment outcomes. The collaboration between health workers who provided her care at the different facilities was also crucial, although there was delayed decision making due to a shortage of in-country expertise and unclear management protocols. Short turnaround to design treatment plan and actions, however, would have lessened the patient's wait to final diagnosis and treatment decisions. Simple, patient-centred algorithms on the management of such cases of BU, and all cases of BU/HIV co-infection, are warranted for resource-limited settings where many gaps exist in diagnostic and treatment options.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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