Case Report
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Differential diagnosis of ulcerative cutaneous lesions: the emergence of buruli ulcer in western European countries

Abstract

The Buruli ulcer (BU), secondary to the infection by Mycobacterium ulcerans, is considered by the World Health Organization (WHO) to be a neglected tropical disease. Despite being the third most common mycobacteriosis, reported in more than 30 countries, it is the one that raises the most epidemiological doubts. Clinically, it manifests itself as a painless and necrotizing lesion of the skin, subcutaneous tissue and bone. Typically, it occurs on lower limbs, having several possible clinical manifestations (nodules, papules, plaques, edema and/or ulcers). Fibrosis and contractures resulting from the healing process are the factors responsible for stigmatization and morbidity associated to BU. The WHO recommends treatment with double antibiotic therapy for a period of eight weeks, even in the presence of a suspected case without laboratorial confirmation. Despite the vast knowledge about the Buruli ulcer in endemic countries, in Western European countries such as Portugal this diagnosis may be overlooked. We present a clinical case to illustrate the importance of the diagnostic suspicion and timely treatment in the prognosis of BU patients.

Keywords: buruli ulcer, mycobacterium ulcerans, infection, emerging diseases

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Introduction

Buruli ulcer (BU), described for the first time in 1948 in Australia by MacCallum et al.,[1] was thus named in 1960 following a description of a series of cases in the Buruli county in Uganda.[2] Reported in more than 30 countries, mostly in tropical and subtropical regions, it is in Africa that the majority of cases are recorded.[3] BU is caused by Mycobacterium ulcerans, and it constitutes the third most common mycobacteriosis, after tuberculosis and leprosy. It is a chronic and debilitating infection of the skin and soft tissues which, due to the permanent scarring and functional incapacity it may cause, presents itself as an emerging health problem.[4] This is why BU was classified as a neglected infectious tropical disease, for which the Global Buruli Initiative was promoted by the World Health Organization (WHO) in 1998.[3–6] Several studies have revealed the existence of risk factors for infection, namely environmental (altitude and proximity to stagnant waters, namely rivers, lakes and swamps), genetic, and behavioural (deficient hygiene and use of unprotected water in household activities).[7] However, the exact transmission mechanism remains unknown, and even the hypothesis of vector insects has been considered. Skin contamination appears to be facilitated by various types of trauma, which appears to be independent of the trauma intensity.[8]

All ages and sexes are affected, but almost half of the cases is less than 15years old.[2] Incubation period varies between two to three months.[3] The disease initially manifests as a painless nodule or an area of oedema, with the lower limbs being twice more likely to be affected than the upper limbs, and the face and the torso less than 10% of the reported cases. Early lesions usually progress without pain or fever due to the immuno suppressing capacities of mycolactone (an exotoxin produced by the mycobacteria responsible for the development and progression of lesions).[3] After a period of four weeks, lesions typically evolve into a characteristic ulcer with deep and badly defined edges.[7] Subsequently, the ulcer may heal, particularly if antibiotic therapy is initiated, or it may evolve into a disseminated disease, often reaching the bone, causing severe anatomical and functional deformities.[9] In 70% of the cases, the diagnosis is made during the ulcerative stage.[7] The disease may be classified according to:

a. Clinical form (localized or disseminated);

b. Type of lesion (ulcerative or non-ulcerative); and

c. Severity

   i. Category I-lesion less than five cm in diameter;

   ii. Category II-lesion with a diameter between five and fifteen cm; and

Category III-lesion with a diameter greater than fifteen cm, multiple lesions, atypical localization or disseminated disease).[3,4]

Currently, four methods of diagnosis are available for laboratorial confirmation:

i. Direct observation with the acid-fast bacilli (AFB) Ziehl-Neelsen staining method, in which the positivity varies according to the clinical form

ii. Culture test, which takes from two to eight weeks and has a low sensitivity due to the great growth difficulty of mycobacteria in culture media

iii. Histopathological examination, which requires biopsies of the tissues but is useful in differential diagnosis

iv. Polymerase chain reaction (PCR), in which the IS2404 sequence is identified, which is the quickest and most sensitive method, with results in 48hours.[4]

In places where laboratorial research means are unavailable, the diagnosis is clinical, based on epidemiological characteristics and

on lesions history and evolution.[3] WHO recommends treatment with double antibiotic therapy for a minimum period of eight weeks: rifampicin (10mg/Kg/day of 24/24h) associated to streptomycin (15mg/Kg/day of 24/24h) or clarithromycin (75mg/Kg/dose of 12/12h).[3,4] WHO also recommends symptomatic measures: 1) Manipulation and treatment of lesions, especially in terms of asepsis and healing care, in order to avoid the need of surgical debridement; 2) Application of skin grafts, reserved for the severest cases.[3] With this case report we intend to alert to the importance of BU diagnostic suspicion in non-endemic countries especially in patients with limb ulcers and a compatible anamnesis. In fact, it is fundamental to include BU in the differential diagnosis since early and adequate treatment seems to be the only effective means of reducing complications and disability.

Case presentation

We report a previously healthy sixteen-year-old adolescent black male, born in a swampy and eminently agricultural area in the city of Bissau, Guinea. While visiting Portugal, he was admitted to the emergency room (ER) of a general hospital, due to painful ulcerations in the right lower limb with three months of evolution. He reported the initial onset of two ulcerative lesions in the right lower limb, immediately above the external malleolus, thought to be secondary to a traumatic cause, due to daily and shoeless football matches. These ulcers presented dark, poorly defined edges and, although initially painless, gradually became painful to palpation and mobilization of the limb. He consulted a local doctor and prescription creams were applied without improvement. After two months, the initial lesions progressively grew, having reached two cm in diameter, and two new lesions emerged, proximal and larger. Given the persistence of the ulcers, the subject resorted to our ER for treatment and etiological research. He denied previous history of diabetes mellitus, hypertension, tuberculosis and leishmaniosis. He denied smoking, alcoholism and illicit drug use. There was no relevant family history. On physical examination, he presented multiple lateral-cervical and bilateral inguinal adenopathies under one cm in diameter, painless and of hard consistency. Palpable liver one cm below the rib cage on the medium clavicular line. No palpable masses. A total of four ulcerative and painful lesions at the right lower limb, ranging from one to five cm in size, with undermined edges and necrotic areas associated with seropurulent drainage without granulation tissue (Figure 1). The remaining observation was normal. The patient was admitted into the inpatient Pediatrics service. The initial laboratory workout revealed no abnormal values (Table 1). Immunity and autoimmunity screening was negative. No changes were found in the urinary sediment and in the coproparasitological exams. The thorax and lower limbs x-rays were normal. Blood cultures for pyogenic bacteria's, mycobacteria's and fungi were negative. Lesions drainage came positive for Staphylococcus aureus and group A Streptococcus pyogenes and antibiotic therapy was initiated with intravenous flucloxacillin at 100mg/kg/day.

Since after antibiotic treatment the lesions persisted in number and features, ulcerative, undermining and painful, we decided to precede the etiological investigation. Thoracic-abdominal-pelvic CT did not reveal any change. Tuberculin skin test revealed a 20mm in duration at 72h, painful and persistent until hospital discharge. IGRA was positive. Skin lesions biopsies were performed (two specimens per lesion) and the results revealed: positive (2+) acid-fast stain; negative PCR (multiple tests) for Mycobacterium tuberculosis and Mycobacterium leprae; inconclusive PCR (multiple tests) for Mycobacterium ulcerans; negative culture for fungi and mycobacteria; final histopathological examination was reported as possibly consistent with BU. Taking into account the clinical, epidemiological and analytical data, the case was discussed with a group of experts. It was decided to start oral therapy during eight weeks with rifampicin 10mg/kg/day and clarithromycin 15mg/kg/day. The adolescent evolved with clinical improvement of the cutaneous lesions and presented complete regression after the end of treatment (Figure 2). In the specimens collected from the control biopsy after eight weeks of therapy, all results came negative. Half a year after the end of the treatment the patient was clinically asymptomatic, without recurrence of the lesions.

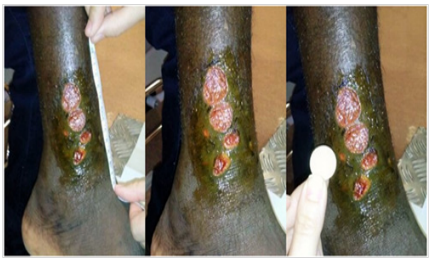

Figure 1 Initial aspect of the ulcerative lesions.

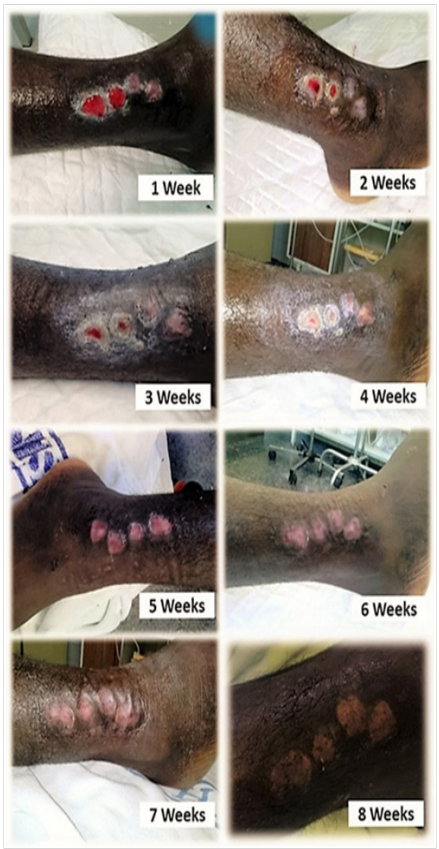

Figure 2 N=57; Epidemiological distribution of the pathological fractures, traumatic fractures, and nonunion.

ALT, alanine transaminase; AST, Aspartate transaminase; CRP, C-reactive protein; Anti-HCV, anti-hepatitis c virus; Anti-HAV, anti-hepatitis A virus; Ig, Immunoglobulin; AgHBs, hepatitis B surface antigen; HIV, human immunodeficiency virus; VDRL, venereal disease research laboratory

ALT, alanine transaminase; AST, Aspartate transaminase; CRP, C-reactive protein; Anti-HCV, anti-hepatitis c virus; Anti-HAV, anti-hepatitis A virus; Ig, Immunoglobulin; AgHBs, hepatitis B surface antigen; HIV, human immunodeficiency virus; VDRL, venereal disease research laboratory

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Table 1 Summary of laboratory results

Parameter	Amount
Haemoglobin	13.4g/dl
Haematocrit	40.70%
White blood cells	6.90x109/L
Differential leucocyte count	No changes
Platelets	254x109/L
Total bilirubin	0.5mg/dl
ALT/AST	21/22IU/L
Alkaline phosphatase	220IU/L
CRP	3.6mg/L
Anti-HCV (IgG)	Negative
Anti-HAV (IgM)	Negative
AgHBs	Negative
HIV I and II	Negative
VDRL	Not reactive

Discussion

BU, a necrotizing disease of the skin and subcutaneous tissue, globally represents the third most common mycobacterium infection. BU may manifest as nodules, oedema and patchy lesions, but most frequently as limbs ulcers, which may extend, causing disfiguration and disability. Although BU was described in 1948, many doubts persist about its transmission, prophylaxis and treatment.[1–8] That is the reason why early detection and treatment remains the cornerstone of BU control strategy. In this case, the clinical and laboratorial aspects allowed us to consider the diagnostic hypothesis of BU. Even though it is not specific, the described history resembles the one of BU, especially the fact that 1) the place of origin was a swampy and farmland area which neighbours high-endemicity countries and 2) physical trauma was previous/concomitant to the lesions appearance.

In terms of lab analysis and results, there were collected two specimens per lesion biopsy; to maximize sensitivity (can reach as high as 90%). Despite the inconclusive PCR results for M. ulcerans and the absence of isolation in culture, positive acid-fast stain in the lesions biopsies with negative PCR for other mycobacteria and the compatible histopathology (with a sensitivity of up to 90%), reinforced the diagnostic hypothesis. In fact, it is known that transporting the sample in suboptimal conditions may lead to inconclusive results in the PCR (in the present case, the sample was transported for processing in other, distant, units, and no specific reagents or transportation buffer solutions were used).[10] Additionally, the growth in culture is very difficult, with a sensitivity of 20-60%.[11] In terms of the lesions response to treatment, healing and negativity in all the biopsy tests carried out at eight weeks reaffirmed the presumptive diagnosis.

Nevertheless, it is important to highlight the differential diagnosis, given that other pathologies are concomitant with ulcerations and share some of the characteristics described in the present case. The history of trauma prior to the ulceration, for example, could raise the hypothesis of sporotrichosis and pyoderma gangrenosum.[12,13] However, considering the aspect and the evolution of the ulcerated lesions in the pyoderma gangrenosum, the typical ulcer would be preceded by papules, pustules or vesicles, it would be very painful and rapidly progressive, which differentiates it from the described case.[12,13] With the type and evolution of lesions still in mind, we could consider the hypothesis of cutaneous leishmaniosis, in which the primary lesion is generally singular and painless, with raised and hardened edges and a "bottom" with granulation tissue, prominently localized in uncovered body parts and in endemic areas. We cannot leave out of the differential diagnosis the tropical phagedenic ulcers, and bearing in mind the localization in the lower limb, vascular disease or diabetes mellitus should also be considered, in spite of the age of the patient. Frequently, in the nodular stage, the primary lesion may be mistaken for furuncles, lepidomas, lymph node tuberculosis, onchocerciasis or other fungal infections, which should all be part of the differential diagnosis. To sum up, in areas where the BU is non-endemic it remains forgotten and, consequently, under diagnosed. It is for that reason essential to direct and raise awareness among health care professionals about this pathology, whose early diagnosis, specific treatment and incapacity prevention care constitute a guarantee of a good prognosis.

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Conflict of interest

The author declares no conflict of interest.

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