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Buruli Ulcer (Acha-ere): Pathogenesis and Manifestation

Elendu C. Onwuchekwa[1*], Uzochukwu G. Ekeleme[2], Oliver Onu-Osi[1] and Okonudo P. Osezele[3]

[1]Department of Microbiology, Faculty of Biological and Physical Sciences, Abia State University, Uturu, P.M.B 2000, Uturu, Abia State, Nigeria.
[2]Department of Microbiology, College of Natural and Applied Sciences, Gregory University, Uturu, P.M.B 1012, Uturu, Abia State, Nigeria.
[3]Department of Physiology, College of Basic and Medical Sciences, Gregory University, Uturu, P.M.B 1012, Uturu, Abia State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author ECO conceived the idea of the study. Author UGE designed the work. Author OOO sourced for the literature materials used in the study and author OPO articulated the write up. All authors read and approved the final manuscript.

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ABSTRACT

Infection of subcutaneous tissue with *Mycobacterium ulcerans* can lead to chronic skin ulceration known as Buruli ulcer. It has been reported in over 33 countries around the world, the greatest burden of disease is in the tropical regions of West and Central Africa, Australia, and Japan. It primarily affects children aged 5-15 years. Buruli ulcers generally begin as a painless dermal papule or subcutaneous edematous nodule, which over a period of weeks to months, breaks down to form an extensive necrotic ulcer with undermined edges. The pathogenesis of this neglected tropical

E-mail: drelenduco@gmail.com, gregoryuniversityuturu.uzo@gmail.com;

disease is dependent on a lipidlike toxin, mycolactone, which diffuses through tissue away from the infecting organisms and elucidate its cytotoxic and immunosuppressive properties. The underlying molecular targets for mycolactone are: First, it can target scaffolding proteins (such as Wiskott Aldrich Syndrome Protein), which control actin dynamics in adherent cells and therefore lead to detachment and cell death. Second, it prevents the co-translational translocation (and therefore production) of many proteins that pass through the endoplasmic reticulum for secretion or placement in cell membranes. Treatment includes a prolonged course of antibiotics and surgical debridement. Early identification and treatment are key, as lesions heal with scarring that can be a significant source of morbidity.

Keywords: Buruli ulcer; acha-ere; mycolactone; Mycobacterium ulcerans; manifestation.

1. INTRODUCTION

Buruli ulcer (BU) is caused by *Mycobacterium ulcerans* (MU), a chronic, indolent, necrotizing disease of the skin and soft tissue with high prevalence in rural West Africa [1,2]. However, it is the third mainly widespread virulent mycobacteria disease of the immunocompetent host, after tuberculosis and leprosy. It may be noticeable initially as a pre-ulcerative nodule, plaque or a rapidly progressing oedematous lesion. Over a few weeks, these lesions break down to form characteristic ulcers with undermined edges, which are associated with extensive necrosis alongside minimal inflammatory response [3]. In contrast, other pathogenic mycobacteria are facultative intracellular pathogens of macrophages, MU is seen as extracellular clusters of bacilli lying within areas of coagulative necrosis that extend some distance from the site of bacterial colonisation [4].

Buruli ulcer been among the neglected tropical diseases (NTDs) is a serious public health concern because, it typically affects impoverished populations in the developing world. Unsafe water, lack of access to health services, malnutrition and poor sanitation all increase vulnerability to infection. NTDs are neglected because they affect the countries' most vulnerable segment of the population - women, children, uneducated and the poor. They are often underreported or unnoticed because the sufferers lack political voice to make their concerns known and insufficient government budgetary allocations to the health sector. This review is focused on the pathogenesis and manifestation of Buruli ulcer.

2. TRANSMISSION AND PATHOGENESIS OF BURULI ULCER

The exceedingly slow growth rate of *M. ulcerans*, the incubation period of BU is very long. In the Kinyara refugee camp, the period between short stays of visitors and the development of BU was estimated to be 4–10 weeks. In a more recent study from Australia, the mean incubation period of BU patients who reported a single visit to the Victorian BU endemic area was 4.5 months. The shortest period recorded was 32 days and the longest was 254 days [5]. The discrepancy between the two studies may possibly be related to differences in the mode of transmission and the inoculation dose of *M. ulcerans* which may be higher in the African setting [5]. Sero-epidemiological studies in Ghana and Cameroon have shown that children are much earlier exposed to malaria parasites than to *M. ulcerans*, indicating that an involvement of insect vectors commonly found close to the households is highly unlikely [5]. Results of other studies have been compiled in a conceptual model, where *M. ulcerans*, present in the aquatic environment such as in detritus, mud, or plant biofilms, is concentrated by water-filtering organisms and subsequently passed on to predatory aquatic vertebrates and invertebrates feeding on this prey. Infection from potential environmental reservoirs may take place via puncture wounds or lacerations after contact with concentrated *M. ulcerans* sources or via invertebrate vectors, such as aquatic insects [5, 6].

Once inoculated into the subcutaneous tissue, the organism proliferates and elaborates a toxin that has affinity for fat cells. The toxin called Mycolactone which cause local immunosuppression in infected tissue. The mycolactone functions as immune suppressant, necrotising agent and activator of cellular death [7]. Healing may occur spontaneously but more often the disease is slowly progressive with further ulceration, scarring, and contractures. Secondary infection may occur with other nodules developing and infection may occur in bone. Although seldom fatal, the disease results in considerable morbidity and deformity [3]. The

most affected are children under the age of 15 years, mortality is low but disability is high (66%) affected region mostly the upper extremities. The resulting necrosis then provides a favorable milieu for further proliferation of the organisms.

3. MOLECULAR TARGETS OF MYCOLACTONE

3.1 Wiskott–Aldrich Syndrome Protein Hyperactivation

Mycolactone targets scaffolding proteins, such as the Wiskott-Aldrich syndrome protein (WASP), which controls actin dynamics and leads to a loss of cellular detachments and cell death [8,9].

3.2 Inhibition of Co-translational Translocation Via Sec61

Mycolactone also inhibits the function of the Sec61 translocation, which is responsible for protein translocation into the endoplasmic reticulum (ER) [10,11]. This affects 30-50% of mammalian proteins, including circulating inflammatory mediators and proteins involved in lipid metabolism, coagulation, and tissue remodeling [9]. Therefore, patients with *M ulcerans* infection have global and chronic defects in protein metabolism. This is evident by reduced levels of total serum proteins and blood urea nitrogen, without the presence of malnutrition, kidney impairment, or liver impairment [11].

4. CLINICAL FEATURES OF BURULI ULCER

The pre-ulcer stage is presented as a nodule, plaque, oedema and papule. All these forms, except papules are common in Africa [3]. When pre-ulcer conditions are left untreated, they progress to ulcers which may enlarge, destroy wide areas of the skin, and infect the bone (osteomyelitis) and cause contractures and disabilities [12, 13]. Ulcers are usually painless unless infected by secondary bacteria. Small ulcers are also known to heal spontaneously without treatment if not infected [3].

I. **Nodule stage:** This is usually painless, palpable, firm lesion 1-2 cm in diameter, situated in the subcutaneous tissue and typically attached to the skin.

II. **Plaque stage**: This usually painless, well-demarcated, elevated, indurated lesion, more than 2cm in diameter.

III. **Oedema stage:** This diffuse, extensive, usually non-pitting swelling. The affected area has ill-defined margins, is firm and painless and involves part or all of a limb or other part of the body. There may be colour changes over the affected area and the disease may be accompanied by fever.

IV. **Ulcerative stage:** A typical BU is defined as a skin ulcer characterized by necrotic slough and undermined edges. In the absence of secondary bacterial infection, the ulcer is usually painless.

When the ulcers are left untreated, they progress to enlarge and destroy wide areas of the skin which may infect the bones (osteomyelitis).

5. DIAGNOSIS OF BU

Early nodular lesions are occasionally confused with boils, lymphomas, ganglions, lymph node tuberculosis, onchocerciasis nodules or other subcutaneous infections such as fungal infection.

HIV infection is not a risk factor, but in co-endemic countries, HIV infection complicates the management of the patient. The weakened immune system makes the clinical progression of *Buruli ulcer* more aggressive, and as a result the treatment outcomes are poor [12].

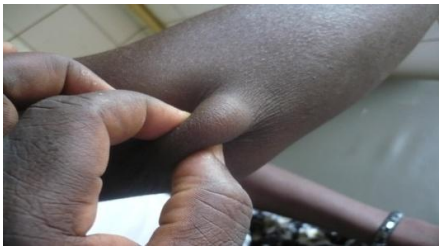

Fig. 1. Skin showing nodule stage of BU [3]

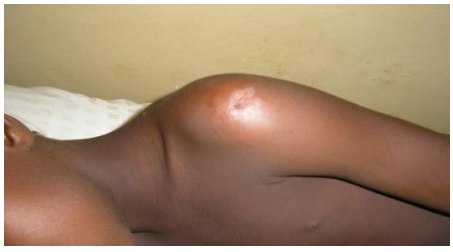

Fig. 2. Skin showing plaque stage of BU [3]

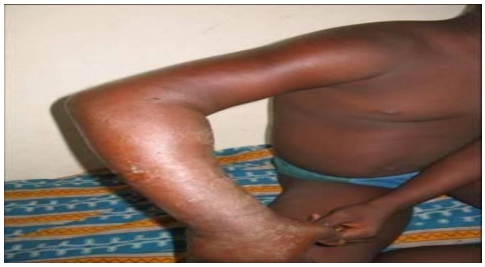

Fig. 3. Skin showing oedema stage of BU

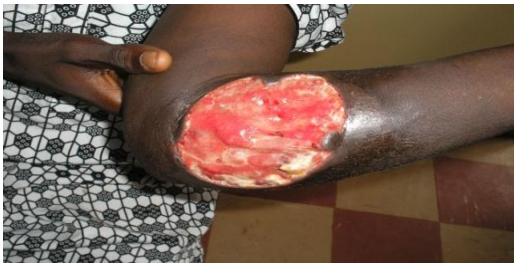

Fig. 4. Skin showing ulcerative stage of BU

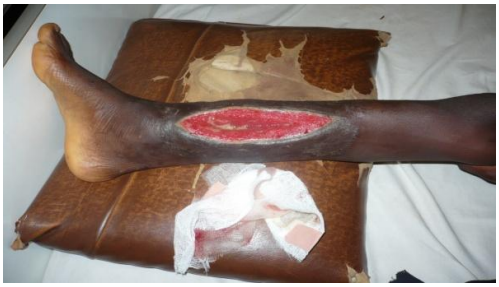

Fig. 5. Osteomylitis caused by BU [9]

Fig. 6. Osteomylitis caused by BU [9]

The four standard laboratory methods can be used to confirm *Buruli* ulcer are IS2404 polymerase chain reaction (PCR), direct microscopy, histopathology and culture [12]. PCR been the most recently used method is not easily accessible in Eastern Nigeria.

6. TREATMENT OF BU

Several antimicrobial agents have *in vitro* activity, but no single agent has been proven to regularly useful in treatment of BU. The agents used include Rifampicin, Rifabutin, Clarithromycin, Azithromycin, Streptomycin, and Amikacin. Combination therapy are mostly used. However, WHO [14,15] recommended that: All patients with BU lesions should be treated with streptomycin 15mg/ Body kg + Rifampicin 10mg/ Body kg for 8 weeks. Surgery reserved as adjuvant therapy, wound care and prevention of disability.

7. CONCLUSION

One of the main tasks for BU control will thus be to maintain public awareness of this rare, but highly debilitating disease and to sustain expertise to diagnose and treat it among local health staff. There is great need for a robust integrated diagnostic and therapeutic approach for the management of skin lesions at primary health care facilities of the resource poor African BU endemic countries. BU control and research activities should therefore be more efficiently integrated into combined programs with other skin diseases.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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