

Re-Emerging Tropical Disease: Our Local Experience with Mycobacterial Ulcers in Benin City, Nigeria

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ABSTRACT

BACKGROUND

Buruli ulcer and other Mycobacteria infections especially *Mycobacterium tuberculosis*, involving the skin frequently occur in the tropics and have a lot in common in terms of their mode of presentation and extent of systemic involvements. Since the Yamoussoukro declaration, emphasis has been placed on the increasing prevalence of buruli ulcer; earning it a place among re-emerging diseases. Notwithstanding, other tropical ulcers continue to plague the region which are yet diagnosed or underdiagnosed.

In developing countries where the burden of these mycobacterial infections is enormous, the problem of diagnosis and speciating these mycobacterial organisms continues to be a daunting task due to their similar mode of presentation and lack of appropriate laboratory facilities.

A high index of suspicion based on detailed history, clinical presentations as well as therapeutic responses to treatment including anti-tuberculosis medication is time-saving and crucial in establishing a possible diagnosis in resource poor settings. This will help combat the burden of these infections and attendant complications and disfigurement associated with these tropical mycobacterial ulcers.

KEYWORDS: Cutaneous Tuberculosis infection, Buruli ulcers, Re-emerging diseases, Diagnostic challenge.

INTRODUCTION

Buruli ulcer has been described over a century ago but has recently acquired a new status of a re-emerging disease with global attempt at defining the disease burden with a view to formulating a holistic control strategy.^{1,2} Whereas the causative organism *Mycobacterium ulcerans* is well known and described in the literature, much remains unknown about the species, though it is said to be related to *Mycobacterium marinum* which evolved over many years ago;^{3,4} and the exact mode of spread in the specific individual remains conjectural.^{5,6} Both the reservoir of infection, its vector and mode of transmission is still in contention.⁵ A spectrum of cutaneous and osseous pathologies have been fairly well described with this disease.^{7,8} However several atypical Mycobacterial species produces similar pathologies which are often difficult to differentiate.⁹

The global burden of the disease is far from settled due to inadequate reporting even in countries where its presence has been established.¹⁰ Several cases of buruli ulcer has been reported in more than 33 countries since 2002. The highest incidence was 1370 cases in Africa and 291 cases from Western pacific region.¹¹ In most of the developing countries with inadequate health coverage the outlook in terms of epidemiology is gloomy.¹² Furthermore, the lack of cost effective, simple, rapid and accessible tool for screening, mycobacterial isolation and culture hampers the definitive diagnosis.^{12, 13}

Several publications have drawn attention to the challenges of diagnosis with a need for a high index of suspicion to reduce delayed diagnosis,¹⁴ especially with the possibility of a re-emergence in the face of immunity compromising pathologies.¹⁵ Whereas we were convinced based on clinical presentation, clinical course as well as response to therapeutic trial that these were manifestations of cutaneous mycobacteria infection; we could not pin the diagnosis to Buruli ulcers in the absence of specific Mycobacterium ulcerans isolation or detection of specific markers. In the ensuing years, more cases have presented and have been managed successfully at the Plastic Surgery Service of the University of Benin Teaching Hospital, Benin City, Nigeria. This paper describes our experience to create awareness and to contribute to the global discussion and action on Mycobacterial skin infections and Buruli ulcers in particular. The last case is presented as the index report and the others summarized in a flow chart.

CASE PRESENTATION

C. I. Male, 6 years, presented to us at the Plastic Surgery clinic with 4 weeks history of progressively widening non healing ulcer on the right side of the neck extending radially to the chest wall as well as across the neck) The wounds were described as ‘moderately painful’ with foul smelling sero-purulent discharge. There was no known inciting factor and the wounds were not bleeding. He had no fever, cough, night sweats or weight loss. He was the third of the parent’s four children and his conception and birth were uneventful. He was fully immunized. Developmental milestones were within expected period. He looked otherwise clinically healthy but had a slight torticollis to the side of the ulcer. He had been receiving treatment at another health facility and was referred because he showed no improvement. He had a deep oval ulcer with undermined edges and greenish yellow slough on the floor with exposure of parts of the supraspinal and neck muscles. The surrounding skin was hyperemic, indurated with clinical signs of spreading inflammation. . (Fig.1) An initial impressing was of spreading cellulitis, with a differential diagnosis of necrotizing fasciitis. His hematocrit was 7.3g/dl and white cell counts were within normal range (10, 000/uL, Neutrophils 57%, Lymphocytes 43%).The ESR was 120 mm/ hr. His Mantoux response was 7mm. He had a first debridement which at first inspection in 48hours appeared satisfactory. A week later he was taken in for a split thickness graft. At surgery, the edges of the ulcer had begun undermining with further sloughs on the posterior aspect. (fig.2) He had another debridement and split thickness grafting. Based on high suspicion he was commenced immediately post operatively on a therapeutic anti- Koch’s trial of Ethambutol, Rifampicin, isoniazid and pyrazinamide. 5 days post operatively, graft take was about 60% with circumferential loss. However his condition continued to improve with sustained

weight gain and epithelization from edges of the ulcer and the grafted skin. The histology read pathologic tissue showing extensive necrosis, mixed inflammatory cell infiltrates (predominantly lymphocytes) with areas of fibrosis. Further attempts at grafting residual ulcer was declined by the parents for financial reasons. The wound was sufficiently healed over the course of the next six weeks. (Fig. 3)

OTHER CASES IN THE SERIES

	Age	Sex	Lesion	Site	ESR	Mantoux	ZN	Response to Therapy	Remarks
1	6	F	Systemic	Chest wall, Pulmonary, Osseous	High	NA	NA	Good	Active pulmonary TB
2	11	F	Chest wall abscesses	Chest wall	16mm/hr	14mm	NA	Good	Cutaneous Mycobacterial ulcer probable.
3	17	M	Indurations, ulcers, sinuses	L forearm	NA	NA	NA	Good	Cutaneous Mycobacterial Ulcer probable.
4	17	M	Ulceration	L elbow	NA	NA	NA	Good	Cutaneous Mycobacterial ulcer probable.
5	55	F	nodulocystic lesions	Cheek	50mm/hr	NA	NA	Good	Cutaneous Mycobacterial ulcer probable.
6	27	M	L foot	Ulcer	NA	Mantoux +	ZN +	Good	Mycobacterium tuberculosis ulcer likely.

7.	57	M	Upper Back (R)	Ulcer	NA	NA	NA	NA	Had massive GI Bleed.
8		F	Face, periorbital, Nose	Ulcer	NA	Mantoux +	ZN +	Good	Mycobacterium tuberculosis ulcer likely.

NA: Not available.

DISCUSSION

The classic description of an ulcer with an undermined edge fits the clinical picture of a mycobacterial ulcer.^{16, 17} However the relative rarity of cutaneous tuberculosis, prior surgical and non-surgical treatment makes the diagnosis difficult.¹⁸⁻²⁰ In addition the absence of the classic picture of pulmonary, and/or systemic features makes the diagnosis sometimes elusive.²⁰ Inadequate clinical history furthers compounds the diagnostic challenge.^{18, 21} Overall, only 1- 2% of all tuberculous pathologies manifests cutaneous lesions.^{22, 23} The index case illustrates some of the numerous difficulties in resource poor settings. Early pointers to the diagnosis include a non-healing ulcer in spite of adequate debridement, non-response to conventional broad spectrum antibiotics (targeting the streptococcal group, Gram negative organisms and anaerobes), the undermined edge, sticky slough and the remarkably elevated erythrocyte sedimentation rate. As is usually advocated, a high index of suspicion is a sine qua non for early diagnosis and therapeutic intervention.^{21, 24}

Mycobacterial skin lesions are not always ulcerative^{24, 25} and may occur in isolation or together with involvement of other organs²⁶ as is shown in this series. Primary inoculation tuberculosis, lupus vulgaris, scrofuloderma, nodular and nodulocystic lesions have all being variously described as cutaneous manifestations of Mycobacterial disease.²⁰⁻²² Skin lesions may occur as a result of direct contact, blood dissemination, or as an immune phenomenon generated by distant infection in other organs.^{16, 17, 19} Primary inoculation tuberculosis arising from vaccination is well recognized and usually heals with scarring²⁷ either spontaneously or with isoniazid monotherapy.²⁸ BCG vaccination scar is common in both paediatric and adult population and is a reliable means of identifying those previously inoculated.²⁹ Other cutaneous forms have been well documented in the literature.

Definitive diagnosis relies on mycobacterial isolation in culture as the gold standard.^{22, 30, 31} However, this is time consuming.^{31, 32} The organisms can be obtained by obtaining multiple swabs from the active edge of ulcerative lesions, ulcer biopsy, and needle aspiration of abscesses or cystic lesions.³¹ The organism may be sparsely available in pathologic specimen and requires fastidious growth conditions and positive isolation requires up to four weeks.³³ Culture

techniques are not available in resource poor settings where the burden of disease is concentrated.^{34,35} Identification of acid and alcohol fast bacilli by the Ziehl- Neelson stain is useful when it is positive.^{30, 31} Ancillary imaging techniques provide supportive features but are usually not definitive. Haematologic parameters provide circumstantial features which can support diagnosis, particularly a relative lymphocytosis and grossly elevated erythrocyte sedimentation rate.³⁶ Superinfection with pyogenic bacteria can significantly alter this blood picture.³⁶ Histopathological features of caseation necrosis, lymphocytic cellular infiltrates and the presence of Langerhans giant cells is classic but these features may not all be present.^{8, 20} Amplification of specific Mycobacterial DNA sequence by the polymerase chain reaction provide specific diagnosis in up to 95% of cases.³⁷ However this technique is available only in few centres and specimen may have to be transported under strict conditions with attendant challenges and huge costs.³⁴ Skin sensitivity testing with the purified protein derivative is of limited value especially in the presence of low cell mediated response from malnutrition or immune depleting disease.³⁸

In our experience, high diagnostic suspicion, response to therapeutic trial of anti-tuberculous drugs remains a viable option to limit human suffering and retrospectively confirm diagnosis. This is not without challenges.^{20,34} The cost is high even though it may be available to the patients at reduced cost in view of the available sponsored tuberculosis control programs. The drug combinations have recognized side effects.³⁹ Furthermore anti-tuberculous drugs are also potent antibiotics;³⁹ indeed, many tuberculostatic drugs are rapidly bactericidal; as such clinical response to them cannot conclusively exclude pyogenic origin *ab initio*.

In 1997, the Director General of the World Health Organisation encountered the gory site and debility caused by flesh eating Mycobacteria thought to be due to *Mycobacteria ulcerans*. That encounter led to the series of event culminating in the Yamoussoukro declaration and subsequent resolution calling for increasing surveillance and control and intensification of research to develop tools for diagnosis, treatment and prevention.⁴⁰ However, whereas Buruli ulcer is specifically due to *Mycobacterium ulcerans*, both typical and atypical Mycobacteria produce cutaneous lesions which cannot be distinguished from each other except by direct culture and isolation or determination of gene variations by the polymerase chain reaction.⁴¹ Recently a chromatographic assay for mycolactone, a soluble polyketide toxin produced by *Mycobacterium ulcerans* and thought to play a significant role in pathogenicity has been developed and is being investigated as a rapid and reliable diagnostic tool.^{9, 13, 16}

CONCLUSION

In our series, we could not positively isolate Mycobacterial bacilli, neither are we able to discriminate from the various Mycobacteria, typical or atypical as the cause of the skin lesions. A review of the literature from across the West African region, and indeed other parts of Africa suggests a similar clinical scenario.^{17, 19} The question thus still needs to be resolved: are we really dealing with the classical Buruli ulcer, or simply cutaneous tuberculosis? To play safe we choose the latter in the absence of specific diagnostic tools and technologies.



Fig. 1: Ulcer on the back extending from the anterior chest and lower neck to the upper back. Edges are undermined with dirty slough at the borders.



FIG 2: Healing ulcer after first surgery.



Fig 3: Six weeks post-surgery; ulcer has almost completely healed after addition of anti – tuberculosis medication

IMAGES OF OTHER CASES IN THE SERIES



Fig 4: Extensive mycobacterial ulcer involving the eyelids and extending to the nasal bridge with undermined edges, discharging creamy purulent effluent.



Fig 5: Mycobacterial ulcer involving the right upper limb.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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