Inadequate Capacity to Diagnose Cutaneous Infections in Ghana: Extensive Skin Ulceration in a 28-Year-Old Man in the Northern Region

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CASE DESCRIPTION

A 28-year-old man presented to the accident and emergency unit of the Tamale Teaching Hospital in Ghana with an extensive left leg ulcer, vomiting, and diarrhea.

The patient described the ulcer beginning weeks earlier with a boil on the dorsum of the left foot that was lanced and managed at home through dressing every other day. The ulcer spread across much of his leg, and 2 days before hospital admission, the patient sought medical attention for new-onset gastrointestinal symptoms and generalized body pains.

At presentation, the patient was distressed but alert and oriented, with Glasgow Coma Scale score of 15. The patient described generalized body pain, chills, loss of appetite, and malaise. Vitals included a temperature of 100.3 °F, blood pressure of 97/59 mmHg, pulse of 168 beats/minute, respiration rate of 24 beats/minute, SpO2of 100%. Physical examination revealed a patient appearing chronically ill with rigor, severe dehydration, oral thrush, pale and jaundiced skin, alopecia, and digital clubbing. The left leg ulcer extended from the dorsum of the foot through the lateral aspect of the leg to the posterior aspect of the thigh, with exposed subcutaneous tissue and undermined cutaneous edges (Fig. 1). The patient reported no pain on palpation of the ulcer.

Laboratory investigations revealed leukocytosis [white blood cell count of 32.6 × 10^3/μL (ref 3.5 to 9.5 × 10^3/μL) with 90.3% neutrophils], anemia (Hb 9.7 g/dL), decreased potassium (2.9 mmol/L), and reported elevated blood urea nitrogen and creatinine (values not available). Blood glucose was reported as within reference range. Malaria smear and serological testing for hepatitis B and C viruses and HIV were negative. Chest X-ray was unremarkable.

The patient was admitted to the medical ward. To address dehydration and presumed coexisting gastritis, intravenous fluids were administered comprising 1 L of Ringer's lactate and 2 L of normal saline, intravenous metronidazole 500 mg 3 times/day, intravenous ciprofloxacin 400 mg twice daily, intravenous pethidine 100 mg twice daily, and oral paracetamol 1 g 3 times/day. The wound was dressed and the patient stabilized throughout the visit. The patient was discharged 3 days later and reassessed the following week in the surgical

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Fig. 1. Tamale Teaching Hospital in the Northern Region of Ghana. Patient presented with an ulceration extending from the dorsum of the left foot through the lateral aspect of the leg to the posterior aspect of the thigh.

ward. Nausea and vomiting had resolved, but the ulceration was unchanged. Suspicion of Buruli ulcer (BU) led to a biopsy and testing by the Zonal Public Health Laboratory. Acid-fast staining was performed on fresh tissue from the biopsy for the presence of Mycobacterium species and found to be negative. Culture for Mycobacterium species was not conducted given lack of availability of that testing. *Pseudomonas aeruginosa* was isolated from wound swab culture on blood and chocolate agar plates. The patient never returned to the surgical ward and was determined to be lost to follow-up. Antimicrobial therapies had yet to be prescribed for the ulceration.

DISCUSSION

In the past few years, there have been 15 patients from ages 19 and up presenting with cutaneous ulcerations from several districts in northern Ghana. Many cases have been advanced, with some requiring amputations. A vast majority of these cases are referrals from the district health facilities to higher tier hospitals in Tamale, the regional capital and site of the Zonal Public Health Laboratory. Although this patient's lesion fits the case definition for BU, the differential for such ulceration is wide and includes tropical phagedenic ulcer, necrotizing fasciitis, venous ulcer, diabetic ulcer, sickle cell disease–related ulcers, yaws, cutaneous tuberculosis, leprosy, cutaneous leishmaniasis, and malignant ulcer (1). In this particular case, the patient presented with what appears to be a very classic form of BU. Nonetheless, the public health laboratory is involved in confirming the wider number of cases, with the possibility of declaring an outbreak, but not all patients present with such classic lesions. However, no laboratory confirmation could be made for this patient. The leading clinical diagnosis was BU, with the conclusion that *P. aeruginosa* was either a contaminant or a secondary infection and that gastritis was unrelated to the ulceration.

BU is caused by *Mycobacterium ulcerans* and is classified by the WHO as a skin-related, neglected tropical disease, a subgroup of neglected tropical diseases resulting in varying severities of disability as well as social stigmatization and discrimination. BU can cause disfiguring contractures and lead to amputation with late presentation (2). According to the WHO, nearly 64 000 cases of BU were reported between 2002 to 2018 (3), largely from countries in Africa, Asia, and the South Pacific (4). However, a small number of countries in West Africa experience the greatest burden, accounting for 76% of reported cases globally in 2018 and where Ghana reported the greatest number of cases (630) (4). Children are commonly affected, and in a study in Ghana from 2008 to 2016, 40% were under the age of 15 years (5). Severe BU potentially leads to lifelong disability. The transmission route of BU is currently unknown, but hypotheses include transmission from environments

with stagnant water and a possible role of aquatic insects, adult mosquitoes, or other biting arthropods (6).

BU starts as a nodule, papule, plaque, or edematous lesion that progresses to an extensive, albeit often painless, cutaneous ulceration (1). The WHO classifies BU lesions into 3 categories. Category 1 includes single, small lesions (<5 cm). Category 2 includes single lesions 5–15 cm. Category III includes larger single lesions (>15 cm), multiple lesions, lesions at critical sites, and lesions involving bone and joints (1). The ulceration extends subcutaneously beyond the cutaneous border, creating the characteristic under mined edge (7). The ulceration is caused by the polyketide-derived macrolide mycolactone synthesized by the bacteria. Mycolactone is also produced by other mycobacteria and is known to be cytotoxic, immunosuppressive, and analgesic, consistent with disease signs and symptoms. This patient would be classified as category 3 because of extensive ulceration. An 8-week course of antibiotic treatment (rifampicin in combination with another antibiotic, such as oral clarithromycin or intramuscular streptomycin) is recommended for all category cases, with improved efficacy in category 1 cases, whereas excision with complete closure may be effective for smaller lesions. With the most severe cases, however, antibiotic treatment must be relied upon; in too many cases, contractures and lifelong disabilities occur (4, 8). It is for this reason that the WHO has prioritized early detection and surveillance of BU (9).

Four tests are currently available for BU: direct smear examination (DSE) with acid-fast stain microscopy, PCR, culture, and histopathology. Histopathology is particularly useful for diagnosing the differential (8). The WHO has set a target of 70% of reported cases to be confirmed by molecular assays, with specimen types including fresh tissue, swabs, paraffin blocks, or washes; preferable samples include fine-needle aspirates for nonulcerative lesions and swab samples for ulcerative lesions (10–12). Several studies have found PCR to have sensitivity >85% using a variety of laboratory reference standards [as reviewed by Eddyani et al. (13)]. However, diagnostic performance is difficult to assess because there is not a reliable gold standard. Furthermore, it is not well understood how test accuracy varies across WHO categories 1–3. A study in Benin of consecutive patients with lesions compatible with BU that used an expert panel to establish the gold standard found 47% sensitivity for DSE and 28% for culture. Specificities were all >90% (13). It should be noted, however, that DSE will not distinguish *M. ulcerans* from other Mycobacterial species. In this study, patients presented with the following distribution of disease: WHO category 1 (20%), category 2 (54%), and category 3 (26%).

In the Benin study, which is an endemic setting, clinical assessment performed very effectively (sensitivity, 92%; specificity, 91%) and, for this reason, should remain an important component of diagnosis. However, there was substantial variation in sensitivity between sites (98% at decentralized sites, 82% at central sites). In addition, 14% of study participants classified clinically as non-BU were reclassified as having BU by the expert panel (i.e., 86% negative predictive value of clinical diagnosis), and the majority of these cases (64%) missed by clinical assessment were positive by PCR (13). It was also noted that although clinical diagnosis outperformed all laboratory techniques, the gold standard was an expert panel of clinicians, which naturally included clinical diagnosis (and access to diagnostic data) and thus incorporation bias.

Early diagnosis of BU in the preulcerative stage is mostly clinical currently, and in this stage, nodules and plaques are difficult to differentiate from other potential causes like insect bites, sebaceous cysts, lipoma, cellulitis, and fungal infections (8). In practice, treatment probably does not occur until lesions evolve, delaying treatment and contributing to continued presentation of late-stage lesions

(13). It would greatly reduce BU morbidity if laboratory testing could improve early case detection. Another reason for laboratory testing is that approximately 20% of patients experience a paradoxical worsening of symptoms and even new lesions on treatment because of induced recovery of the immune system. This can look like treatment failure, reinfection, or recurrence, which might indicate a different intervention such as surgery, but could be distinguished with laboratory testing (1, 12). Consequently, novel diagnostics for BU that could be performed outside of specialized laboratories could transform how BU is identified, improve early detection, and facilitate patient management. In Africa, roughly one-third of cases are currently diagnosed in each of the 3 WHO categories, highlighting the importance of efforts to achieve early and accurate diagnosis (8).

Although laboratory-developed nucleic acid testing for BU and mycobacterial culture can be implemented in specialized molecular or biosafety level 3 laboratories, they are rarely available clinically in Ghana and in many other low- and middle-income countries. Importantly, *M. ulcerans* requires growth at lower temperatures than routine mycobacterial cultures and often takes longer (8–12 weeks or longer) (14). If laboratories are not informed of BU suspicion, then sensitivity will be compromised because culture conditions will not promote growth. Furthermore, specimen transport to these sites can delay diagnosis and lead to inappropriate treatment. The WHO has thus focused on supporting development of diagnostics for BU that can be used at lower tiers in the health system. The current target products include loop-mediated isothermal amplification of the IS2404 insertion sequence of *M. ulcerans* and antigen-based testing for mycolactone using immunoassays, although rigorous clinical studies to evaluate the accuracy of antigen-based testing are needed. These assay formats are amenable to use outside of specialized laboratories. This effort includes a wide partnership including the Foundation for Novel Diagnostics; in Ghana, it involves the Noguchi Memorial Institute for Medical Research (15).

TAKEAWAYS

- BU is a skin-related neglected tropical disease, as defined by the WHO, that causes extensive ulceration, lifelong disfiguring disability, and stigmatization.
- BU has been reported from 33 countries, although a handful of countries—particularly in West Africa—experience the majority of the burden.
- Diagnostics for BU are rarely available at lower levels of the health system, where most patients present, except for microscopy with acid-fast staining, which has been found to have very low sensitivity for detecting BU (<50% compared with an expert panel).
- If diagnosed early, oral rifampicin and clarithromycin combination therapy over 8 weeks is an effective cure.
- There is an international effort to develop novel diagnostics including nucleic acid testing and antigen-based testing that can be implemented widely in endemic low- and middle-income countries to improve early detection and management of BU.

Because of the great BU burden experienced by certain regions, the WHO has set 4 priority targets: ≥70% of cases having confirmation by molecular assays, <25% of cases having category 3 lesions, ≤60% having ulcerative lesions, and ≤15% of cases having movement limitation. Globally, reported BU cases have dropped from a peak of 5937 in 2004 to 2708 in 2018, although in Ghana, reported cases have increased each year from 2015 (275 cases) to 2018 (630 cases) (3). In addition, the WHO reports that progress made toward all 4 targets was lost by 2017, and several countries have deteriorated below levels of the initial assessment in 2012, underscoring the need for an international focus on early diagnosis and treatment of BU (10). Given the lack of capacity for

testing and the accuracy of clinical diagnosis in many cases, a "Buruli score" was developed such that only intermediate cases are referred for testing, safely reducing costs and saving resources (12, 16).

Currently, only DSE with acid-fast staining is available to the Tamale Zonal Public Health Laboratory, and to date, DSE has been negative for all suspected cases of BU. Although the index suspicion clinically is BU, without microbiological confirmation of an outbreak, the public health group is hesitant to react with an expansive educational campaign to sensitize communities to the need for early identification and reporting of cases. Furthermore, not all cases have had such a classic appearance as is seen in this patient, particularly in early stages. It would take an investment in capital and human resources to implement currently available PCR testing for BU in the Zonal Public Health Laboratory to improve this situation, but that is a possibility. The laboratory currently performs PCR for bacterial meningitis, which is a high-priority condition in the region, targeting *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Furthermore, such capacity strengthening at this highest tier would permit the Zonal Public Health Laboratory to act as lead for an integrated laboratory network for BU testing if novel diagnostics in the pipeline were realized, enabling quality-assured testing throughout the tiers of the Ghanaian health system to identify early cases of BU and prevent these catastrophic outcomes.

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