Buruli Ulcer: A Systemic Disease

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We studied a 4-year-old boy from Angola who presented with 2 cutaneous ulcerations of the right hip and osteomyelitis of the left knee and right ankle. *Mycobacterium ulcerans* disease was confirmed by direct smear examination and by polymerase chain reaction. The patient was treated with antimycobacterial drugs, repeated surgical debridement, skin grafting, and daily hyperbaric oxygenation. Despite significant improvement of the local lesions in response to hyperbaric oxygenation, swelling of the right knee, without associated skin lesions, was noted. Radiological evaluation and open biopsy revealed extensive metaphyseal osteomyelitis of the right distal femur. A technetium bone scan revealed an additional focus in the diaphysis of the left humerus, without soft-tissue involvement. This case documents, for the first time (to our knowledge), the systemic spread of *M. ulcerans*, with subsequent multifocal osteomyelitis and secondary involvement of soft tissues and supports the hypothesis that low tissue oxygen levels promote hematogenous spread of *M. ulcerans*. Sickle cell anemia, with associated microthrombosis and microinfarction, may have contributed to tissue hypoxia.

Buruli ulcer (BU) is an infectious tropical disease of skin and subcutaneous tissue caused by *Mycobacterium ulcerans*. After tuberculosis and leprosy, BU is the third most common mycobacterial disease in Africa [1].

BU is primarily a disease of the skin. Two major active forms of BU are recognized: nonulcerative (papules, nodules, plaques, and edematous forms) and ulcerative disease. Laboratory diagnosis includes direct smear examination by Ziehl-Neelsen stain, culture, PCR, and histopathologic examination [2]. *M. ulcerans* grows preferentially at 30°C–33°C and in an atmosphere of reduced O2 concentration (2%–5%) [3]. Usually there is neither clinical regional lymphadenopathy nor systemic manifestations. There is speculation that very large and disseminated lesions may cause systemic toxic effects [4].

Standard treatment is en bloc surgical excision of early lesions, followed by primary skin closure, primary or secondary skin grafting, or open-wound treatment with healing by secondary intention [1, 5]. Chemotherapy alone has been unsuccessful in most clinical trials. However, *M. ulcerans* is susceptible in vitro to several antimycobacterial drugs, such as rifampin, clarithromycin, dapsone, and streptomycin [6]. Hyperbaric oxygenation (HBO) has also been proposed because of its efficacy in experimental infection in mice [7].

Systemic spread of *M. ulcerans* resulting in osteomyelitis was first reported in 1993 in a patient who had been bitten by a snake [8]. Osteomyelitis may lead to amputation and other crippling disabilities. In some areas where *M. ulcerans* is endemic, such as Benin, up to 10% of patients have severe osteomyelitis, sometimes necessitating amputation [9].

We document here the hematogenous spread of *M. ulcerans* with subsequent multifocal osteomyelitis in an Angolan boy. In this patient, HBO effectively promoted healing of surgically treated lesions, especially of the deep ulcerations associated with osteomyelitis.

**Case report.** The patient, a 4-year-old Angolan boy, was admitted on 6 December 1998 to the University Clinic Ulm (Abteilung für Unfallchirurgie, Hand und Wiederherstellungschirurgie, Ulm, Germany). The clinical features are summarized in table 1. On admission to the hospital, the boy had 1 nodule on the left cheek, ulceration of the right hip, ulceration and focal osteitis in the left knee, and osteomyelitis of the proximal metaphysis of the tibia. There were 2 superficial ulcerations on the right hip and deep ulcerations of the right ankle, with osteomyelitis of the distal metaphysis of the tibia, talus, and calcaneus (figure 1), and osteoarthritis of the tarsal and ankle joints. Two scars, on the left shoulder and the left hip, were interpreted as sequelae of previous lesions of *M. ulcerans* disease. The patient was febrile, with spiking morning temperatures of up to 39°C. No concomitant viral infection was found. He had tertian malaria (caused by *Plasmodium vivax*) and was heterozygous for sickle cell trait (20.6% hemoglobin S). No
Table 1. Chronologic observation of the clinical features of a patient with Buruli ulcer and multifocal osteomyelitis, December 1998 through June 1999.

<table>
<thead>
<tr>
<th>Month</th>
<th>Event</th>
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<tbody>
<tr>
<td>December 1998</td>
<td>Admission to the hospital; Nodule on left cheek and ulcer on right hip</td>
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<td></td>
<td>Multifocal osteomyelitis of left knee, left tibia, right tibia, calcaneus, and talus (figure 1)</td>
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<td></td>
<td>Scars (left shoulder and left hip)</td>
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<tr>
<td>February 1999</td>
<td>Enlargement of lesions on left knee and right ankle</td>
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<tr>
<td>April 1999</td>
<td>Destructive osteomyelitis in right ankle</td>
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<tr>
<td>May 1999</td>
<td>Relapse ulcer on left knee after skin grafting; New lesion: swelling of the left hand (osteomyelitis of os hamatum; figure 2)</td>
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<td>Fistula on right ankle</td>
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<td>June 1999</td>
<td>Whole-body scan (99technetium; figure 3)</td>
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<td></td>
<td>New lesions: osteomyelitis of right femoral metaphysis and left humerus diaphysis and metaphysis (without soft-tissue component; figure 4)</td>
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<td>Returned to Angola on 15 June; no follow-up information available</td>
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abnormalities were observed with regard to immunological parameters for T cell phenotypes and quantitative immunoglobulins.

Laboratory findings were negative for hepatitis A, B, and C and HIV but revealed earlier infection with cytomegalovirus and Epstein-Barr virus. The patient’s C-reactive protein level was initially elevated and remained at 90 mg/L. He had hypochromic anemia (hemoglobin concentration, 8.4 g/dL; hematocrit, 28%; mean corpuscular hemoglobin, 15.0 pg; mean corpuscular volume, 76.2 fl; and mean corpuscular hemoglobin concentration, 32.8%). Hematological findings also included leukocytosis (16.6 × 10^3 leukocytes/mm^3) and thrombocytosis (576 × 10^4 thrombocytes/mm^3). Ultrasound examination of the abdomen revealed relative hepatomegaly (liver size, 10 × 10 cm; height of the patient, 91 cm) but no other abnormalities.

The results of acid-fast bacilli (AFB) testing of initial smears from all open wounds (left knee, right hip, and right ankle) were strongly positive. Surgical treatment was followed with repeated debridement, curettage of bones, and antimicrobial therapy with clarithromycin (125 mg po b.i.d.), rifabutin (75 mg po b.i.d.), and prothionamide (125 mg po b.i.d.). In February 1999, healthy granulation was observed on the right hip, and a split-skin mesh graft was placed. Lesions on the left knee and the right ankle were characterized by enlargement of wounds, and debridement and curettage were again performed.

Trimethoprim-sulfamethoxazole (240 mg b.i.d.) was added to the therapeutic regimen, and prothionamide treatment was discontinued. Ciprofloxacin (165 mg po b.i.d.), amikacin (165 mg iv q.d.), imipenem/cilastin (180 mg po t.i.d.), and amoxicillin (250 mg t.i.d.) were included as indicated by culture and antibiogram results. With a combination of these medications and excision, suturing, and grafting, the 2 superficial ulcerations at the right hip were effectively treated. In contrast, the deep ulcerations affecting the bone persisted, despite repeated extensive debridement after bone surgery.

Antimicrobial therapy was based on clarithromycin and rifabutin; however, during the third and fourth months of therapy, clarithromycin treatment was discontinued because of continuing advancing disease. Five weeks after modification of the chemotherapy regimen, K-wire arthrodesis of the right ankle was performed. Perioperative fistulography of the right ankle showed enhancement of contrast medium in regional blood vessels, which suggested hematogenous spread of M. ulcerans to the right extremity. This procedure may have enhanced systemic spread of M. ulcerans. Shortly after the intervention, the left hand became swollen, although no other skin lesion was visible (figure 2). A white gelatinous substance was drained from the lesion and was found to be smear-positive for AFB, but cultures were negative for mycobacteria. Further surgical investigations revealed involvement of the os hamatum, in addition to the subcutaneous lesion. Because a new metastatic lesion caused by M. ulcerans was suspected, the os hamatum was removed, and the antimicrobial therapy regimen was changed to clarithromycin (125 mg po b.i.d.) and rifabutin (75 mg po b.i.d.).

After 5 months of unsuccessful surgical and antimicrobial treatment and relapses of ulcers and other lesions, we attempted therapy by HBO. Initial success was observed after 27 sessions of HBO within a period of 33 days. When HBO therapy was

![Figure 1. Radiograph of the right ankle showing osteomyelitis of the right distal tibia, talus, and calcaneus (arrows).](https://academic.oup.com/cid/article-abstract/37/6/w78/300951)
combined with excision and skin grafting, the ulcers healed very rapidly. Complete closure of the ulcers at the left knee was obtained in 3 weeks. Rapid granulation was seen after open-wound treatment of the left hand. Four weeks after arthrodesis, the K-wires were removed. The ulcer at the right ankle initially healed, but a fistula in the calcaneus area persisted. All lesions closed after 6 weeks of HBO combined with surgical wound care, blood transfusions, and chemotherapy.

In May 1999, after all open wounds had closed, a painful swelling of the left knee recurred. The skin was intact. Radiological investigation revealed osteomyelitis in the metaphysis of the left distal femur, with increased radiodensity of the surrounding dorsomedial soft tissue. Surgery revealed a large intramedullary lesion containing white gelatinous necrotic material. The lesion eroded the dorsal cortex and spread into the surrounding soft tissue. An intramedullar biopsy specimen was tested for AFB, with strongly positive results. The identification of M. ulcerans was confirmed by PCR. After this relapse, ethambutol (300 mg q.d.) and clofazimine (50 mg q.d.) were added to the regimen.

In June, a whole-body scan revealed a focus of infection in the distal part of the left humerus (figure 3). This focus was not clinically conspicuous but was already apparent in a previous technetium scan. Imaging studies identified intramedullary osteomyelitis of the diaphysis and metaphysis of the left humerus with a periosteal reaction but without any soft-tissue component. This was confirmed by MRI (figure 4).

The patient was discharged from the hospital but received extended antimicrobial therapy and returned to Angola on 15 June 1999. No follow-up information is available.

**Discussion.** Systemic dissemination of BU is reported with increasing frequency. In Benin, for example, of the 1167 patients with BU seen between 1989 and 1997, only 4.5% had severe osteomyelitis [1]; in 1998, however, 14.5% of the 357 patients had osteomyelitis [9]. Hematogenous spread of M. ulcerans has often been suspected but not confirmed [6].

Our case supports the concept of hematogenous dissemination of M. ulcerans to metaphyseal regions of long bones with subsequent osteomyelitis. The fact that all lesions in our patient were located in the metaphyseal areas of long bones, with or without soft-tissue involvement, makes direct lymphatic spread unlikely and hematogenous dissemination most probable. Spread of M. ulcerans from the skin lesion may, however, have been initiated by lymphatic invasion, because local and regional lymph nodes may be invaded by the etiologic agent [2]. M. ulcerans was detected by PCR in specimens obtained from all osseous lesions by bone biopsy. The pattern of hematogenous spread was, thus, carefully observed and documented. However, we did not attempt to identify M. ulcerans in blood by culture or by PCR.

Assuming that M. ulcerans is spread by the hematogenous route, effective antimicrobial chemotherapy could be highly efficacious in controlling the disease. Therapy with rifampin, clarithromycin, and ethambutol was proposed to control dissemination [6]. In our case, such a regimen had little healing effect on the ulcers; nevertheless, recurrence of disease after clarithromycin therapy was discontinued strongly suggests that this drug prevented hematogenous dissemination. Failure of antibiotic regimens to control local progress has been attributed to poor penetration of antibiotic agents into necrotic tissue. Nevertheless, patients should receive adequate empirical antimycobacterial therapy before surgery and for several weeks af-
Figure 3. Whole-body scan (99technetium) showing new metastatic lesion in the left humerus (circle) in addition to the previously established lesions of bone.

Figure 4. MRI of left humerus showing osteomyelitis (arrow) without soft-tissue changes.

In our patient, clarithromycin and/or amikacin may have prevented dissemination; we observed a relapse (in May 1999) after use of these drugs was discontinued.

In vitro and in vivo studies have shown that M. ulcerans is susceptible to clarithromycin and to the combination of rifabutin and amikacin [6, 10, 11]. On the other hand, it was demonstrated that the combination of rifabutin and clarithromycin substantially reduced clarithromycin serum levels [12]. However, in our patient, clarithromycin and/or amikacin may have prevented dissemination; we observed a relapse (in May 1999) after use of these drugs was discontinued.

In spite of earlier research showing that temperatures ≥37°C and high oxygen levels limit the survival of M. ulcerans [2], in our own laboratory investigations (Microbiology Unit, University Clinic Ulm), cultures were positive for M. ulcerans in BACTEC 12-B medium (Becton Dickinson Diagnostic Instrument Systems), even at 36°C. This may help explain survival of M. ulcerans at body temperature, hematogenous spread, and the development of osteomyelitis caused by M. ulcerans. Recent in vitro studies performed on Löwenstein-Jensen medium have demonstrated that after 10 days at 37°C, most M. ulcerans strains were inactive [13, 14]. Meyers et al. [15] have, however, found that some strains are able to multiply at 37°C.

The survival of M. ulcerans in blood, where normally the oxygen tension is high, may be explained by the hypochromic anemia in our patient, which could have resulted in reduced blood oxygen levels. This chronic anemia could have been related to several factors: chronic infection (main cause of anemia), intraoperative blood loss, and heterozygous sickle cell anemia. To our knowledge, only 1 case of association between BU and sickle cell anemia has been described [16]. In a recently initiated prospective study in Benin, we have found several cases of osteomyelitis due to M. ulcerans associated with sickle cell anemia (F. Portaels, C. Zinsou, J. Aguiar, M. Debacker, E. de Biurrun, A. Guédénon, R. Josse, V. Lagarrigue, M. T. Silva, C. Steunou, and W. M. Meyers, unpublished data). The relation-
ship between sickle cell anemia and the severity of clinical presentation of BU needs further study.

It was recently reported that HIV infection could favor dissemination of *M. ulcerans* [17]. Our patient was HIV negative, and cellular and humoral immunological parameters were normal. Immunosuppression could have resulted from the combined effect of severe illness and the specific systemic action of the toxin of *M. ulcerans*, enhancing dissemination and spread of *M. ulcerans* [18].

This case shows that, even under optimal conditions in a university hospital, treatment of BU associated with disseminated osteomyelitis remains very difficult. The probable systemic spread of BU must receive serious consideration in developing therapeutic approaches. Effective treatment should be multimodal and should include en bloc surgical excision, amputation of extremities when necessary, adequate antimicrobial chemotherapy, and supportive therapy of concurrent diseases, such as anemia. In our patient, supportive therapy with HBO promoted healing after surgical excision of the deep ulcers with osteitis. Further clinical studies should be done to attempt to increase the efficacy of antimicrobial therapy in preventing dissemination.

It has been observed that 70% of osteomyelitic lesions caused by *M. ulcerans* are located in extremities close to joints. This supports the hypothesis that the metaphysis could be the primary target of hematogenous spread in *M. ulcerans* infection, with resulting secondary local soft-tissue damage and ulceration. *M. ulcerans* is a necrotizing microaerophilic organism [2, 3]. The ideal environment for proliferation is, therefore, necrotic subcutaneous tissue. The high blood perfusion in the metaphysis of bones promotes the hematogenous spread to this area. The survival of these necrotizing bacteria in the highly vascularized metaphyseal bone may be related to other factors, such as anemia.

Our observations support the hypothesis that anemia, low tissue oxygen levels, and, possibly, unspecified immunomodulation caused by other diseases (e.g., malaria and sickle cell anemia) are important promoters of osteomyelitis in patients with *M. ulcerans* infection and of its possible subsequent hematogenous spread.

**Acknowledgments**

We thank Prof. R. Marre and Dr. A. Essig (Abteilung für Mikrobiologie und Hygiene, Universitätshospital Ulm, Ulm, Germany) and Dr. G. Luyckx (Institute of Tropical Medicine, Mycobacteriology Unit, Antwerp, Belgium).

References


