Ulcerative Cutaneous Mycobacteriosis
Due to *Mycobacterium ulcerans*: Report of Two Mexican Cases

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ABSTRACT

We report two patients from Central Mexico, with ulcerated cutaneous lesions containing acid-fast bacilli (AFB) and ultimately diagnosed as *Mycobacterium ulcerans* disease. The first patient had a long history (11 years) of disease involving multiple lesions of both upper and lower extremities. Histopathological changes included necrosis of the subcutaneous tissue with large numbers of extracellular AFB. Cultures at 32°C were “positive for mycobacteria,” but were not further identified. The polymerase chain reaction for *M. ulcerans* performed on skin biopsies was positive. The lesions improved after treatment with rifampin and isoniazid (INH) for one month, followed by ethambutol and streptomycin.

The second case followed trauma to the right hand, which spread over 2 years to the right upper extremity, the back, and both legs, with a loss of digits and metacarpal bones of the right hand. The histopathological findings were similar to the first case, including presence of AFB. PCR for *M. ulcerans* on extracts of skin biopsies was positive. Rifampin, INH, pyrazinamide, and levofloxacin resulted in marked improvement of the ulcer; ethambutol and streptomycin were later used, also.

We report these cases because they are rare (approximately 6 previous cases were reported from Mexico), and both are unusually disseminated. They are significant in alerting the medical community to *M. ulcerans* infection, which is still active in Mexico, and the treatment used has not been reported previously.

RÉSUMÉ

Cet article décrit la maladie de deux patients habitant la région centrale du Mexique, qui souffraient de lésions cutanées ulcérées contenant des bacilles acido-alcool-résistants (AAR) et qui ont finalement été diagnostiqués comme souffrant de maladie causée par...
**CLINICAL CASES**

*Case 1.* A 76-year-old woman, occasional farmer, born and lived in Esperanza Tarimoro, (Guanajuato, Central Mexico), presented in 1995 with an eleven-year history of an evolving dermatosis, affecting the left forearm and elbow, index and middle fingers and back of the right hand, the left thigh on its anterior and lower sides, the knee, and posterior mid-left leg. The lesions consisted of 10 nodules between 2 to 4 cm in diameter, red-violet in color, with a hard consistency, and non-pitting edema. Some also had ulcerations and were draining bloodstained serum at the center (gummae). Seven ulcers measured 2 to 10 cm in diameter had open, undermined borders that allowed the introduction of a clamp. The underside was necrotic and partially covered with purulent secretion (Fig. 1, Case 1). At the right knee were three circular scars, 1
cm in diameter, with erythema and marked swelling.

At the onset there were small, erythematous nodules on the legs. Some of these had healed spontaneously one year earlier, and new lesions had appeared on her arms, which ulcerated after 9 mos. Previous treatments included home remedies. The initial clinical diagnosis was deep nodular tuberculous (Hutchinson type). General medical examination revealed a patient in good general condition. Laboratory analysis showed aleukocytosis with 14,900 white blood cells (83% segmented cells), an incremented globular sedimentation rate of 25 mm/hr, and normal hepatic function and chest x-rays. The skin test with 5TU purified protein derivate (PPD) was negative.

Two skin biopsies were taken, one from the border of the ulcer on the left forearm and the other from the nodule on the left thigh. Histologically, we observed large necrosis zones affecting the middle and deep dermis and hypodermis in both biopsies (Figs. 2 and 3). Fite-Faraco stains revealed large numbers of acid-fast bacilli (AFB) in necrotic areas, some in clusters and forming “globi,” (Figs. 4 to 7), similar to those described by MacCallum (15) and Connor (28).

Further analysis of an acid-fast smear of the purulent secretion from borders and bottom ulcers, using a Ziehl Neelsen stain, revealed clusters of AFB. Cultures on Lowenstein-Jensen media at 32°C were positive for mycobacteria. The cultures were damaged before further identification could be obtained from a referral center. The final diagnosis was Ulcerative Cutaneous Mycobacteriosis (UCM), species unknown.

Treatment with rifampin 600 mg/day and isoniazid 300 mg/day, and daily soaks of ul-
cers in sulfate solution (1:1000) for one month resulted in improvement. Rifampin was discontinued after the patient developed clinical hepatitis attributable to this drug. Two weeks later, after hepatic function tests returned to normal, treatment was initiated with ethambutol 600 mg/day and streptomycin 1 gm/day for 15 days, then reduced to 1 gm every three days, for a total of 30 gr. With this regimen, the ulcers healed. At this stage the patient returned to her hometown and was lost to follow-up.

**Case 2.** A 23-year-old male horse-meat merchant who lived in Chimalhuacán, Mexico (Central Mexico), presented with a 2-year evolving dermatosis, affecting the lower right arm and elbow, forearm, and dorsum of the right hand, anterior aspect of both legs, and posterior aspect of the left leg. There were four nodules of 2 cm in diameter and 10 ulcers between 1 and 5 cm in diameter with the characteristics described for the first case. Some ulcers were communicating and alternated with small areas of apparently normal skin. The largest ulcerative lesion was on the forearm, measuring 15 × 25 cm in diameter, with viscous crust, surrounded by scar tissue (Fig. 8), in the area previously grafted. Scars were present, 3 cm in diameter. We also observed absence of all of the fingers of the right hand, with exception of the thumb and the metacarpal bones.

The disease presented after trauma to the right hand from a prick with a horse bone chip; 15 days later, there was reddening and swelling of the area that quickly extended to the forearm. At the trauma site, the patient observed necrosis, which was excised, but despite this the disease continued. The patient was then sent to the Instituto Nacional de Ortopedia in Mexico City in August 1997, where the forearm lesion was excised, four fingers were amputated, and the metacarpal zone was covered with a skin graft. Results were poor and the disease continued. Two years later, the patient was sent to the Centro Dermatologico Pas- cua (CDP), where the initial clinical diagnosis was cutaneous tuberculosis. The skin test with 5TU PPD showed 5 mm of induration, and the physical examination was otherwise normal. With the history of trauma precedents, long evolution, and poor response to the prescribed treatment, we considered the possibility of a diagnosis of UCM.

Four biopsy specimens were taken from the necrotic area on the ulcers of the fore-
arm and leg nodules. Microscopic findings were similar in all specimens and identical to those previously described in Case 1, confirming the clinical diagnosis.

Bacilloscopies revealed AFB and an enzyme-linked immunosorbant assay (ELISA) was positive for *Mycobacterium* sp., but cultures for mycobacteria were negative. Routine laboratory determinations were within the normal range.

Surgical cleaning and soaks with sulfate solutions (1:1000) were carried out twice a day. Rifampin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 300 mg/day and levofloxacin 400 mg/day, were administered for two months, with great improvement of the ulcers, marked by a decrease of purulent drainage and necrosis. The nodules, however, persisted. Surgical excision of nodules was performed and microscopic analysis showed necrotic zones and numerous acid-fast bacilli. Streptomycin 1 gr intramuscularly (IM) every three days (30 gr total dose) and ethambutol 1200 mg/day were then administered. Additionally, surgical cleaning was performed once a week and topical soaks with sulfate solutions was performed daily. After streptomycin was discontinued, rifampin 600 mg/day was resumed with ethambutol 1200 mg/day again for 10 months, and the cutaneous lesions healed. (Fig. 9). At present, the patient is under periodic monitoring and shows no lesions, and a prosthesis has been fitted to the patient’s right hand.

Paraffin blocks of biopsies from both patients were sent to Dr. Francois Portaels at the Institute for Tropical Medicine, Antwerp, Belgium, for analysis by polymerase chain reaction. Specimens from both patients were found to contain DNA sequence IS2404 from *M. ulcerans*.

**DISCUSSION**

The skin ulceration caused by *Mycobacterium ulcerans* was described for the first time by MacCallum, *et al.* in Australia in 1948 (16). In 1950 in the Belgian Congo (now the Democratic Republic of Congo) the first African case was reported (29), and in the same year, Fenner (7) identified the bacillus and named it *Mycobacterium ulcerans*. Since 1959, several authors have described numerous patients with this disease in tropical and subtropical regions of Central and West Africa (13). Buruli ulcer is recognized as a public health problem, for example, in Uganda, Nigeria, Gabon, Ghana, Cameroon, Liberia, the Ivory Coast (1, 6, 17, 28, 30), Malaysia (25), New Guinea (14), Togo (15), French Guyana (5, 23), and the Republic of Benin (20). In the Americas, it is an exceptionally rare disease and only a few cases have been reported. In 1953, Lavalle, *et al.*, reported the first UCM case in Mexico (11, 13) and until 1990, only five additional cases from Guanajuato State in Central Mexico were reported (13, 14, 15).

This mycobacteriosis has been given several names according to the place where it occurs or where it has been observed. For example, it was called Bairnsdale ulcer in Australia (17), Buruli ulcer in Uganda (20), and Tora ulcer and Mexican ulcer in México (19). Nevertheless, Lavalle proposed the name of Ulcerative Cutaneous Mycobacteriosis, caused by *Mycobacterium ulcerans* (15).

*Mycobacterium ulcerans* is a slowly grow-
ing, acid-fast organism generally consi-
dered to be an environmental saprophyte. It
is usually observed in aquatic ecosystems in
marshy terrain, a soil rich in silica, and in
stagnant bodies of water or near rivers, at
temperatures ranging between 32°C and
33°C, with pH between 5.5 and 6.9 (8, 20, 21).
The bacillus grows best in Lowenstein-
Jensen culture medium at 32°C.

The disease affects both sexes and all
ages, but is more frequent in children be-
tween 5 and 14 yrs old (28). In the countries
where it is endemic, it is frequent in farmers
and may be considered an occupational dis-
ease. After tuberculosis and leprosy, M. ul-
cerans infection is considered the third
most common mycobacterial disease affect-
ing non-immunocompromised humans (20).

The exact manner of transmission of M. ul-
cerans is not known. It is assumed that a
not-yet identified environmental factor ex-
ists that is related to slowly flowing or stag-
nant water and near rivers. There are some
reports suggesting possible transmission by
mosquito or insect bites (3, 4, 24). However,
inoculation appears to occur via trauma to
skin, on uncovered, unprotected regions of
the body. Its topography in adults includes
limbs, especially near joints, predominatly
on legs (knees) and forearms (elbows) (5, 8, 19),
but in children it can be found anywhere.

M. ulcerans affects humans by producing
a heat-stable exotoxin that causes extensive,
chronic, necrotizing damage to the papil-
lary skin, subcutaneous fat and muscle (fas-
cia and bone are also sometimes affected),
resulting in deformity and disability (12).

The lesion begins as a small subcuta-
neous swelling, more palpable than visible,
that grows slowly until it develops into a
nodule that is adherent to the skin but not to
deep tissues. These nodules are soft, un-
dergo liquefaction, and finally ulcerate,
with an oily, purulent discharge. Ulcers are
often well defined and the borders are un-
dermined. The base of the pristine ulcers
contains a whitish, cotton wool-like slough
and sometimes eschars. Skin surrounding
the lesion becomes hyper-pigmented (15).

Ulcers can be small or extensive, involving
even an entire extremity or large portions of
the trunk. Microscopic alterations are usu-
ally diagnostic, including extensive necrosis
of the dermis and large numbers of extracel-
lular AFB, in clumps or clusters (2, 6, 16).

Disease evolution can vary in severity. In
some areas, ulcers heal slowly with fibrosis
and retraction, even while the disease may
progress in other areas. Secondary bacterial
infection may develop, but the patient’s gen-
eral condition is not affected. There is no re-
gional clinical lymphadenopathy nor fever.

The two cases described in this report are
particularly interesting because of the un-
usual dissemination of the disease and the
large number of nodules and ulcers. The
possible mode of transmission was not ap-
parent in the first case, whereas in the sec-
ond case, the initial lesion followed trauma
with a horse bone chip, similar to one of the
Lavalle cases (15). This information allows
us to suspect that a direct inoculation was
made in this case.

The last report of Buruli ulcer the disease
in Mexico was made several years ago, and
no reports of other cases have been made
since. This may be attributable to possible
rarity of the disease in Mexico. As Lavalle
suggests, the paucity of reports may be a re-
sult of a lack of awareness of the disease, or
to the status of the public health services in
endemic areas. Innate or acquired immunity
of the populations may also contribute to
low endemicity.

We conclude that the following features
must be considered for the diagnosis of M. ul-
cerans infection: (i) a chronic dermatosis
in a patient with good general health; (ii)
the histopathological findings of extensive
necrosis in the dermis and subcutaneous tis-
sue and the presence of numerous extracel-
lular acid-fast organisms (2, 5, 16).

Although it is difficult to culture this or-
ganism, it is now possible to identify the
agent by PCR analysis carried out on the
skin specimen (10, 20), although in our opin-
ion these studies are not necessary for the
diagnosis. In both cases presented in this re-
port, PCR analysis for M. ulcerans DNA
was performed on paraffin blocks of the
skin biopsies, and these studies were done
some years after the diagnoses were made.
The treatments were initiated on the basis
of clinical and histopathological findings,
and the patients healed. This indicates that
the molecular studies are not indispensable
if there is an adequate clinical and histolog-
ical study, but PCR contributes to support
the diagnosis by identifying the mycobacte-
rial DNA sequence IS2404.
Despite the fact that the first cases were adequately described more than 50 years ago, there remains no standard effective treatment. Surgical excision of skin lesions and, if necessary, skin graft application in the initial stages, are considered the best treatment, in addition to anti-mycobacterial agents. Hyperbaric oxygenation has been used experimentally (26). This schedule of antimicrobial treatment was applied in Case 2 as described in this report, obtaining a complete recovery after 12 months. The regimens used for treatment in both patients have not been reported previously, and they give affected patients the possibility of healing without important sequelae such as amputation. Additional preventive efforts, such as BCG vaccination (23) and wearing long pants in endemic regions to protect molecular biology (PCR) studies.

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REFERENCES


