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Mycobacterium ulcerans Infections in Leprosy Patients

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In a population of 1061 patients with leprosy and 180 patients with *Myco. ulcerans* infections, we recorded a history of both diseases in 6 individuals. There was no evidence that either infection altered the tissue response or clinical course of the other.

Introduction

Cross-sensitization and cross-resistance in man to more than one species of mycobacteria has long been a lively topic for discussion among "myco-bacteriologists" and their ilk. Opposite and extreme opinions have been recorded. Mitsuda and Ogawa (1937) reported, for instance, that tuberculosis is the most common cause of death in leprosy patients, while Chaussinand (1950) proposed that by the "phénomènes de para-allergies bactériennes" the increase of tuberculosis in Europe in the Middle Ages caused the well-known decline of leprosy. Leiker (1971), while espousing the concept of Chaussinand in citing inverse relationships between the prevalence of leprosy and tuberculosis, points out the complexities of this relationship. Discussions in this vein today often revolve around the usefulness of BCG as an anti-leprosy vaccine. We shall not debate this controversy, but we do record new data on two mycobacterial diseases occurring in the same patient.

In this communication, we present six patients with both *Mycobacterium ulcerans* infection and leprosy, treated at the Institut Médical Evangélique, Kimpese, Bas-Zaïre, Republic of Zaïre. We know of no published reports of patients with both of these diseases. Verhagen (personal communication) states that in Uganda he saw three leprosy patients among 70 patients with *Myco. ulcerans* infections.

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Brief Discussion of *Myco. ulcerans* Infection

Infection by *Myco. ulcerans* has a focal geographic distribution, therefore some readers may be unfamiliar with its clinical and pathological features. The disease prevails in large foci in Uganda (Barker, 1972) and Zaïre (Meyers *et al.*, 1974) but has also been reported from Australia, Bolivia, Cameroon, Congo (Brazzaville), Gabon, Indonesia, Malaysia, Mexico, New Guinea, Nigeria and Peru. The aetiologic agent, first isolated by MacCallum *et al.* (1948), is a mycobacterium which grows slowly at 32° C. on Löwenstein-Jensen medium but is usually inhibited at 37° C. Feldman *et al.* (1957) suggested that the tail of the mouse was particularly susceptible to experimental lesions of *Myco. ulcerans* because of its low temperature (about 25° C). This temperature growth requirement may also be an important factor in determining the nature of human infection by *Myco. ulcerans*. In man the skin and subcutaneous tissues, with temperatures below 37° C, are nearly always the sites involved; rarely other sites, notably bone, are affected. Perhaps in those instances where bone is infected, strains growing at 37° C are responsible; however, *Myco. ulcerans* has not yet been cultured from bone lesions.

Natural reservoirs and modes of transmission are not known but the disease tends to occur only in warm climates in swampy and riverine savannah. Barker *et al.* (1972) postulate that the organism is present on grasses but have not recovered

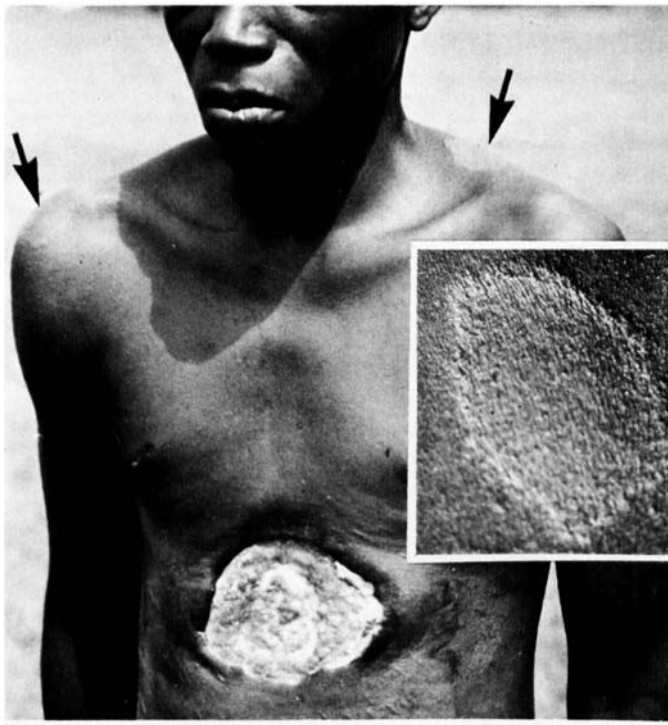

Fig. 1. Patient No. 6, showing abdominal lesion of *Mycobacterium ulcerans* and two borderline (dimorphous) (BT) lesions of leprosy (arrows). Inset is a closeup of leprosy lesion on the back of this patient.

it from this hypothetical source. Meyers *et al.* (1974*b*) observed patients who developed lesions at sites of trauma, including hypodermic injections, suggesting that the infection results from direct inoculation.

Dodge and Lunn (1962) proposed the name "Buruli ulcer" for this infection, after the geographic area where the first cluster of Ugandan patients lived. In lower-Zaïre, one indigenous term for the disease is "mputa matadi". This Kikongo expression, meaning "rock-hard sore," may refer to the nature of the early lesion which is a hard subcutaneous nodule. This expression may, alternatively, refer to the firm oedema frequently seen early in the disease. The nodule, often accompanied by itching, gradually enlarges, ulcerates, and discharges necrotic sloughs and an oily liquid. The ulcer is widely undermined, has a necrotic base, and may be surrounded by edematous skin. Ulcers are most common on the extremities, especially over major articulations, but also develop on the trunk (Fig. 1). Microscopically, the characteristic feature is a contiguous, spreading coagulation necrosis of the subcutaneous and deep dermal tissues. All tissues and structures including vessels and appendages are destroyed and this spreading necrosis is responsible for the undermining of the overlying skin, producing the distinctive contour of the ulcer margin. The necrotizing process (Fig. 2) may be caused by the toxin which Read *et al.* (1974) demonstrated in cell-free *Myco. ulcerans* culture filtrates.

Mycobacterium ulcerans infections are usually self-limiting but patients may die from complications of advanced lesions. Even self-limiting lesions often cause severe deformities from contractures, and loss of important structures (e.g. eyes and limbs). Wide surgical excision and skin grafting is the usual treatment, but locally applied heat may be a helpful adjunct (Glynn, 1972) or effective by itself (Meyers *et al.*, 1974*a*).

Description of Patients

During the period April 1960 to June 1973, 971 patients with active leprosy were registered at Kivuvu. Of this number, 770 were registered after September 1965 when diagnosis and classification became routinely based on clinical, histopathologic and bacteriologic findings and the lepromin reaction. Ninety individuals with an established history of leprosy but without currently active disease where also registered, making a total of 1061 leprosy patients in the study group. During this same interval, 180 patients with *Myco. ulcerans* infection were registered. The *Myco. ulcerans* patients all came from Songololo Territory and adjacent areas, described by Andersen (1965), Smith (1970) and Meyers *et al.* (1974). The leprosy patients came from a much larger geographic area but included the *Myco. ulcerans* endemic areas of lower-Zaïre, with about 20% of the leprosy patients coming from Songololo Territory. All patients were Bantu and approximately 95% of them were of the Bakongo tribe, with origins in either Zaïre, Angola or Congo (Brazzaville).

In the above two groups, there were six individuals with a history of both leprosy and *Myco. ulcerans* infection. Each of these patients will be described briefly:

Patient No. 1, MA (Hosp. No. 63/3501), 55 yr female, was admitted to hospital in September 1968 for a large undermined ulcer on the left knee. The lesion was excised and a biopsy specimen from the edge was typical of *Myco. ulcerans* infection. She gave a history of leprosy, treated at a nearby hospital and

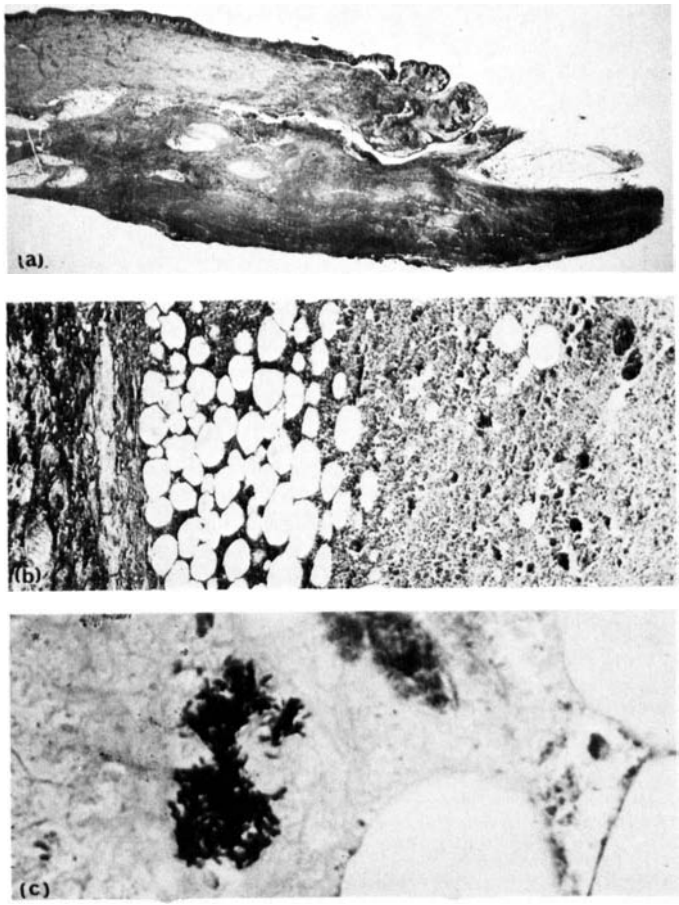

Fig. 2. Histopathologic features of *Myco. ulcerans* lesion in patient No. 6. (a) Low magnification of edge of *Myco. ulcerans* lesion. The undermining of the epidermis (top surface) and dermis, and the destruction of the subcutaneous fat are clearly demonstrated. (AFIP Neg. 74-803, Movat stain, x3.3.) (b) Higher magnification of the same lesion showing necrosis and fat cell ghosts. (AFIP Neg. 74-800, Movat stain, x90.) (c) High magnification revealing a microcolony of *Myco. ulcerans* organisms in the area of necrosis. Portions of fat cell ghosts are seen on the right. (AFIP Neg. 74-802, Ziehl-Neelsen stain, x750.)

considered inactive in 1950. We verified this history from records obtained at the hospital and our impression was that she had had borderline leprosy. There was no evidence of active leprosy on this admission. No skin tests were done. The patient died of unknown causes in December 1968.

Patient No. 2, BD (Hosp. No. 67/1398), 32 yr male, was admitted to hospital in February 1967 with a chronic undermined ulcer on the right leg. The lesion was excised and skin-grafted. A biopsy specimen was compatible with *Myco. ulcerans* infection. The patient said he had been treated for leprosy at another hospital and the records examined there confirmed a clinical diagnosis of tuberculoid leprosy. No skin tests were done. The *Myco. ulcerans* lesion healed

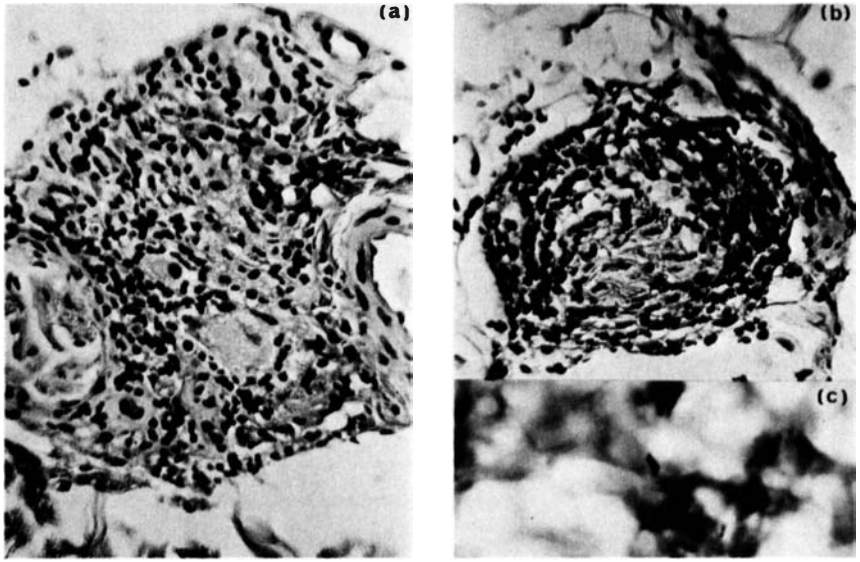

Fig. 3. Histopathologic features of leprosy lesion in patient No. 6. Biopsy specimen was from the edge of lesion on the right shoulder, shown in Fig. 1. (a) Cellular infiltration about a nerve and blood vessel in the lower dermis. Infiltration composed primarily of epithelioid cells, giant cells and lymphocytes. (Saffron trichrome stain, ×400.) (b) Infiltration and partial destruction of a small dermal nerve. (Saffron trichrome stain, ×400.) (c) Two juxtaposed acid-fast bacilli in dermal nerve shown above. (Fite-Faraco stain, ×1000.)

and he returned home in June 1967. When last seen in May 1973 he had no evidence of active leprosy or of active *Myco. ulcerans* infection.

Patient No. 3, DS (Hosp. No. 68/1223), 60 yr male, was admitted for leprosy in January 1968. His lesions began in June 1967 and a biopsy specimen revealed characteristic features of borderline (BB) leprosy. The Mitsuda reaction was 7 mm. He gave a history of *Myco. ulcerans* infection treated in 1953 at another institution. A histopathologic diagnosis was not made, but the clinical history and the appearance of the scar on the right knee were characteristic of a healed *Myco. ulcerans* infection. When last seen in May 1973 his leprosy was inactive and the *Myco. ulcerans* infection had not recurred.

Patient No. 4, MM (Hosp. No. 71/2395), 60 yr female, was admitted to hospital in March 1971 with a large undermined ulcer about the right eye and a hypopigmented, slightly infiltrated, anaesthetic skin lesion over the left elbow. Biopsy specimens confirmed *Myco. ulcerans* infection and borderline leprosy (BT) respectively, and the Mitsuda reaction was 20 mm. The *Myco. ulcerans* lesion appeared in December 1970 but the date of onset of leprosy was not known. The ulcer was successfully treated by wide excision, including enucleation of the eye, and oral rifampicin. She remains on sulphone therapy for leprosy.

Patient No. 5, ED (Hosp. No. 71/3707), 57 yr male, was admitted to hospital in June 1971 with a large widely undermined ulcer of the left leg and a second smaller ulcer on the right foot. In addition, there were numerous widely scattered, hypopigmented, slightly infiltrated, anaesthetic skin lesions, and enlarged tender ulnar nerves. The right foot was deformed. Biopsy specimens from these lesions confirmed the diagnoses of both *Myco. ulcerans* infection and borderline leprosy

(BT). Lesions of leprosy were first noted in 1969 and those of *Myco. ulcerans* in May 1971. The *Myco. ulcerans* lesions healed under rifampicin therapy and excision and grafting, and the leprosy has become inactive. The patient remains on sulphone therapy.

Patient No. 6, JA (Hosp. No. 73/2277), 20 yr male, was admitted to hospital in March 1973 with an undermined ulcer 10 x 14 cm over the upper abdomen. He also had eight widely scattered, infiltrated, hypopigmented, anaesthetic skin lesions with well defined edges (Fig. 1). The ulcer began in November 1972 and the lesions of leprosy sometime between July 1972 and February 1973. Histopathologic findings of the *Myco. ulcerans* lesion are shown in Fig. 2, and those of leprosy in Fig. 3. The latter specimen was interpreted as borderline-tuberculoid (BT) leprosy. *Mycobacterium ulcerans* was cultured from the lesion on the abdomen on Löwenstein-Jensen medium incubated at 32°C. Fernandez reaction was negative and the Mitsuda reaction was 9 mm. The ulcer was excised and grafted with a good result. He remains on sulphone therapy for leprosy.

Discussion

A direct detailed comparison of the antigenic structures of *Myco. leprae* and *Myco. ulcerans* has not been published. Stanford (1973), by immunodiffusion studies on 35 strains of *Myco. ulcerans* from various parts of the world, including 11 strains from Zaïre, found that all strains were antigenically similar. Furthermore, while possessing distinct antigenic components, *Myco. ulcerans* cross-reacted with other mycobacteria. For example, there were seven precipitins in common with *Myco. kansasii* and five with *Myco. smegmatis* and *Myco. fortuitum.* Goihman-Yahr *et al.* (1968) cited cross-reactions to lepromin in guinea pigs sensitized to *Myco. kansasii* and *Myco. smegmatis.* This indirect evidence suggests that *Myco. ulcerans* and *Myco. leprae* could possess common antigens.*

Clinically and histologically we could discern no interaction between leprosy and *Myco. ulcerans* infections. We note that all six of our patients, as well as Verhagen's three patients, had higher resistant forms of leprosy, but we are not able to attach any special significance to this fact. There is the remote theoretical possibility that the anti-mycobacterial antibodies commonly present in the serum of lepromatous patients could protect against the extracellular parasite *Myco. ulcerans* or its toxic products.

In addition, we are uncertain whether or not, in the population studied, six patients is an unusually high number with both diseases. Based on a population of 156,000 for the major area of endemicity for *Myco. ulcerans* (official Zaïre census for Songololo Territory for 1970), we estimate that 0–1 patient would have been anticipated. Extensive epidemiologic surveys for both leprosy and for *Myco. ulcerans* infection would be necessary to determine if this difference is representative of the entire population.

The low temperature growth requirement *in vitro* for *Myco. ulcerans* is well established, and there is a widely accepted belief that the clinical picture of leprosy is largely a result of the selective growth of *Myco. leprae* in the cooler parts of the human body. Thus, these six patients are especially interesting in that

* Stanford (personal communication, 1974) reports that *Myco. leprae* and *Myco. ulcerans* do share at least 5 antigens and that these are the same antigens which *Myco. ulcerans* shares with most other mycobacterial species.

they demonstrate in the same individual two mycobacterial skin diseases which are probably temperature-related, and which provoke distinctly different tissue responses.

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