Clinical Features and Treatment of Pre-Ulcerative Buruli Lesions (*Mycobacterium Ulcerans* Infection)

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Summary: At Kinyara, and in other areas of Uganda, 250 patients with pre-ulcerative Buruli lesions (*Myco. ulcerans* infection, have been seen over the past three years. The clinical feature of the pre-ulcerative stage of the disease are painless nodules, usually occurring singly on the legs or forearms. As the nodule can grow rapidly to become an extensive fulminating lesion, early recognition of the nodule and an appreciation of its significance by both doctor and patient are essential. Excision of the nodule is simple and usually curative, thus preventing ulcers developing and requiring prolonged hospital treatment.

Introduction

Chronic necrotizing skin ulcers due to *Mycobacterium ulcerans* were first described by MacCallum *et al.*, (1948) in six patients in Australia. In Uganda similar chronic skin ulcers with undermined edges resistant to usual treatment were first noticed in 1958 near the Nile in Buruli County—hence the name Buruli ulcer (Clancey *et al.*, 1961). These lesions have now been reported from other parts of Uganda and many parts of the world (for references see Lunn *et al.*, 1965; Connor and Lunn, 1966; Pettit *et al.*, 1966). In some areas in Uganda they constitute a major public health problem (Lunn *et al.*, 1965; Uganda Buruli Group, 1969).

Previously, clinical attention has been concentrated on the ulcerative stage of the disease (Fig. 1), though pre-ulcerative stages have been described (Connor and Lunn, 1965). The early pre-ulcerative stage is painless, causes no trouble, and may be overlooked by the patient. It is only in communities that are aware of the significance of these early lesions that patients will seek advice in the pre-ulcerative stage. One such community is the Kinyara Refugee Settlement, where we have been working since May 1966 (Uganda Buruli Group, 1969). During the past three years many patients have been seen during this pre-ulcerative phase, so that the term Buruli ulcer is a misnomer in many patients which have a *Myco. ulcerans* infection. The present paper describes the clinicopathological features, diagnosis and treatment of these lesions, and is based on our experience of more than 250 patients with pre-ulcerative nodules seen at Kinyara and in other areas of Uganda.

Case 1

A 13-year-old boy presented with a small painless nodule on the left anterior upper arm noticed 12 days previously. There was a barely visible, firm subcutaneous swelling about 6 mm. in diameter attached to the skin but mobile over the deeper structures. (The lesion was too small to photograph.) The lesion was widely (about 2·5 by 1·5 cm. ellipse) excised under local anaesthesia and the wound sutured. It healed by primary intention and when the patient was last seen, seven months later, there was no evidence of recurrence.

*Members of the group set up by the Uganda Ministry of Health and Makerere Medical School: Dr. D. J. Bradley, Professor M. S. R. Hutt, Mr. J. W. M. Kiryabwire, Mr. A. Kisuule, Dr. A. Lloyd, Mr. J. Mafigiri, Dr. R. H. Morrow, Professor W. Parson, Dr. I. Phillips, Dr. M. C. Pike, Dr. P. A. Pike, and Dr. W. D. L. Revill.

This report was written by Dr. Revill, Professor Hutt, and Mr. Kiryabwire. Requests for reprints should be addressed to Mr. Kiryabwire, Makerere University College, Medical School, P.O. Box 7072, Kampala, Uganda.

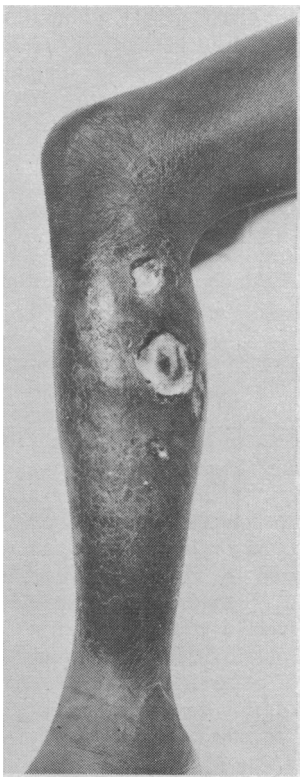

FIG. 1.—Typical ulcerated lesion.

Histological Examination.—In the central part of the excised skin there is a small localized area of bland necrosis involving the subcutaneous tissues and the lower part of the dermis. In this area all structures are necrotic. The necrosis affects the fat cells, connective tissues, nerves, and blood vessels, and merges almost imperceptibly into the normal tissues. At this junctional zone very few inflammatory cells are present except where the necrosis extends into the the dermis. Large numbers of acid-fast bacilli are seen in the centre of the lesion; they are present mainly in the connective-tissue septa, and in the deep fascia (Fig. 2). A detailed description of the histopathology of these lesions will be published elsewhere.

Case 2

A 9-year-old girl presented with a painless, slowly enlarging swelling of the left forearm which she had first noticed four months previously (Fig. 3). There was a firm, discrete subcutaneous swelling 1·5 cm. in diameter attached to the skin but mobile over the deeper structures. The overlying skin was shiny, slightly paler in the centre, and surrounded by a ring of superficial desquamation. The lesion, including a margin of normal fat, was totally excised under local anaesthesia. The lesion involved the deep fascia, but this separated easily from muscle sheath. The centre of the bisected nodule was structureless, pale yellow, and surrounded by a greyish zone where the interlobular septa and the fascia were thickened. The wound was sutured and healed by primary intention.

Histological Examination.—There is extensive necrosis of the subcutaneous tissue which has a wider lateral extent in the deeper fat. All structures in this area are necrotic and there is a minimal inflammatory response at the edges. Occasional groups of

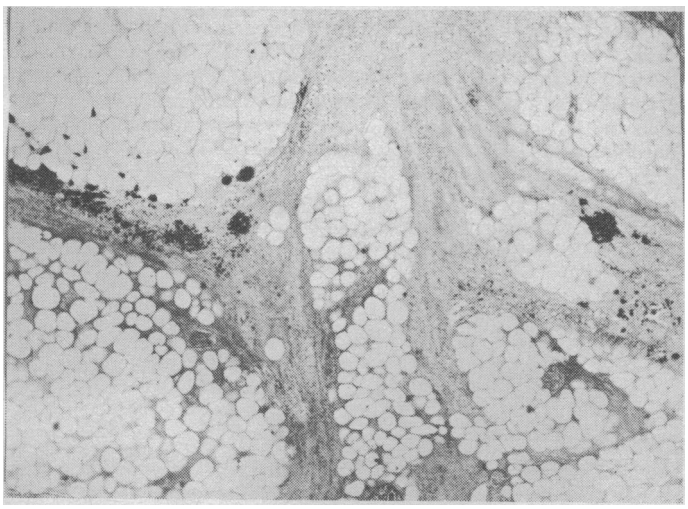

FIG. 2.—Case 1. Biopsy. Complete necrosis of subcutaneous tissue with clumps of acid-fast bacilli (black) in connective-tissue septa. (Ziehl-Neelsen × 6·5.)

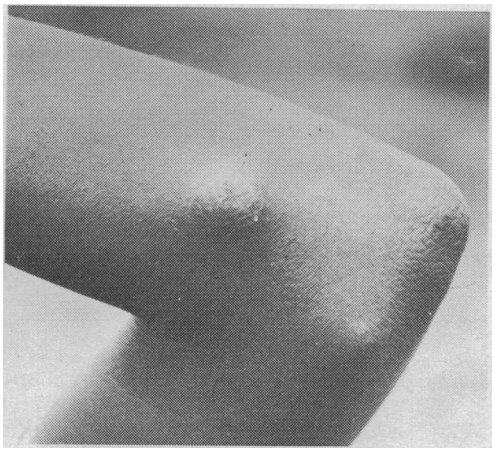

FIG. 3.—Case 2. Pre-ulcerative nodule on left forearm.

polymorphs are seen in one part of the necrotic tissue, and there is a non-specific chronic inflammatory cell reaction in the upper dermis. In the centre of the lesion the necrosis extends into the dermis, but does not involve the epithelium, which shows only reactive acanthosis. Acid-fast bacilli are present in the necrotic connective-tissue septa.

Case 3

A 15-year-old boy presented with a swelling above the left buttock which had been noticed one week previously because of pruritus. An area of subcutaneous induration about 5 cm. in diameter was attached to the skin and fixed deeply. The edges were indistinct. There was a pale area in the centre about 1 cm. in diameter.

Five weeks later (Fig. 4) the lesion had enlarged, had become painful, and was still pruritic. The pale area had extended to 4 cm. in diameter, but the lesion had not ulcerated. The induration was about 12 by 8 cm. but the edges were difficult to define. There was slight oedema at the edges. The lesion was excised under general anaesthesia. It extended more widely in the deep fascia than was expected (16 by 11 cm.). In the centre the muscle sheath was involved and so was the dense fibrous tissue over the sacrum. The subcutaneous tissue in the centre appeared pale and structureless. This was surrounded by a pink zone with thickened interlobular septa. At the margins the deep fascia was thickened with oedematous but otherwise normal-looking fat overlying it.

Histological Examination.—There is extensive bland necrosis which extends laterally from one end of the section to the other in the deep subcutaneous tissues (Fig. 5). The necrosis also involves the dermis, almost reaching the epidermis—which is affected only in the central part of the section—and all the structures in the area. For the most part the necrosis merges imperceptibly with the normal tissue, with no zone of inflammatory cell response. Nevertheless, focal collections of polymorphs are seen in some areas, particularly where the necrosis approaches the epidermis. Acid-fast organisms, which are present in very large numbers both in large clumps and in small groups, are most numerous in the necrotic area of the lower dermis. They are also found in the connective-tissue septa of the subcutaneous tissues.

Two further excisions were performed at weekly intervals until the area was covered with a thin layer of healthy red granulations. Grafting was performed successfully at the end of the third week. When last seen, four months after discharge, the patient had a healthy scar with good quality skin.

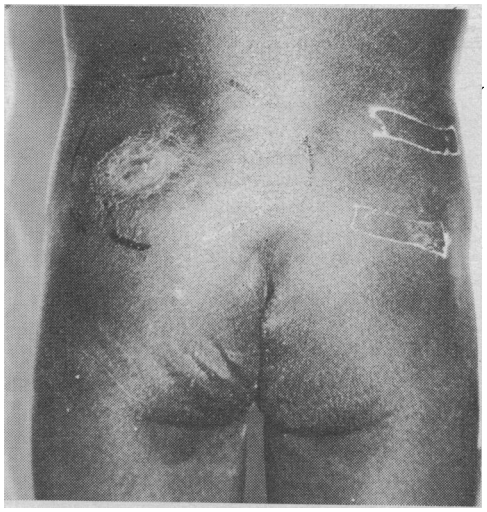

FIG. 4.—Case 3. Pre-ulcerative lesion on left buttock with skin changes but no ulceration.

FIG. 5.—Case 3. Biopsy. Necrosis of subcutaneous tissue extending into dermis. (H. and E. × 6·5.)

Case 4

An 11-year-old boy presented with an extensively swollen right leg (Fig. 6). Three weeks previously a swelling about 5 cm. in diameter had been noticed on the lateral aspect of the thigh. The swelling steadily increased in size and became pruritic. There was no history of trauma. The induration extended about 19 cm. above the knee and involved the lateral half of the thigh. Its extent in the lateral aspect of the leg was difficult to define. Superficial desquamation was present over part of the induration and pitting oedema of the leg down to the ankle—but not of the dorsum of the foot. The leg was not tender, though the patient could not fully extend the knee, and movements were painful.

Deep multiple incisions were made under general anaesthesia to

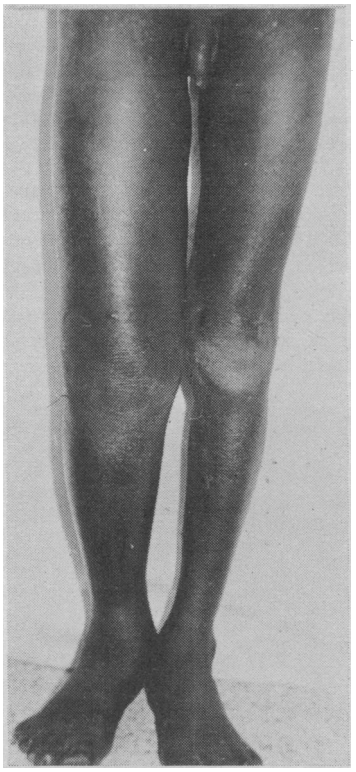

FIG. 6.—Case 4. Extensive swelling with induration of right leg.

relieve the tension. Oedema fluid welled out of these incisions. A week later the oedema was less pronounced and an extensive excision about 35 cm. long was carried out. An attempt to preserve skin was made by cutting skin flaps. These partly necrosed and the surviving flaps remained undermined. Further operations were carried out at weekly intervals to remove necrotic material from under the skin flaps and from around the tendon of biceps femoris. The area was not ready for grafting until the fifth week. Almost all the graft took except for some areas at the margins. In these areas, and extending laterally beneath the skin, a thick, pale oedematous tissue developed. This was easily removed by curettage but tended to recur, and several curettages were necessary. Eventually the patient was discharged after four months in hospital with a healed and healthy scar and knee mobility from full extension to 90° of flexion.

Histological Examination.—Extensive necrosis of subcutaneous tissue extends into the dermis in the centre of the section but does not involve the epidermis. At one end of the section the junctional zone shows a pronounced acute inflammatory reaction with many polymorphs in the tissues. A non-specific chronic inflammatory cell reaction is present in the upper dermis and there is acanthosis of the overlying epithelium. Acid-fast organisms are present in large numbers in the fibrous tissue septa of the deep subcutaneous tissue.

Case 5

An 8-year-old girl was seen at Kinyara camp with a small indurated nodule on the right forearm which had been present for about four months. The skin over the nodule was slightly raised and discoloured. The whole lesion was excised with a zone of normal skin and fat.

Histological Examination.—There is a circumscribed nodule in the upper part of the subcutaneous tissue which just involves the deep dermis. The nodule is composed of a central core of necrosis which is surrounded by epithelioid cells, fibroblasts, and lymphocytes (Fig. 7). In places the epithelioid cells are palisaded and form small granulomas. Outside this zone there is fibrosis with focal collections of lymphocytes. The dermis and subcutaneous tissues adjacent to the lesion are normal.

No acid-fast bacilli were seen in this case but the sections stained for organisms did not include the necrotic area. In contrast to the other four cases this patient showed a dominantly granulomatous lesion; such lesions are usually found in patients who are or have become hypersensitive to tuberculin (Uganda Buruli Group, 1969).

FIG. 7.—Case 5. Biopsy. Nodule in subcutaneous tissue with normal overlying skin. (H. and E. × 6·5.)

Clinical Features

Children aged 5 to 14 years are most commonly affected, but the disease can occur at any age (Uganda Buruli Group, 1969). Lesions are almost always single. In adults the most common sites are the legs and forearms, but in children they may occur almost anywhere. The only sites where we have not seen lesions originating are the scalp, the palms, and the soles. The patients are otherwise healthy and, even with an extensive lesion, show little systemic disturbance.

When a nodule is first noticed it is usually symptomless and often discovered accidentally by the patient (or mother) while washing. The nodule is occasionally pruritic, but pain is rarely a feature. Only those patients who appreciate the significance of the painless nodule seek advice before ulceration occurs. At first examination pre-ulcerative lesions can be divided into three types: (1) nodules (Cases 1 and 2), (2) an intermediate group (Case 3), and (3) extensive or "fulminating" lesions (Case 4).

The Nodule

The lesion starts as a small subcutaneous swelling which is barely palpable but not visible. It gradually increases in size until the skin is slightly raised. The nodule is firm with a regular margin and is attached to skin but is not attached to the deep fascia. As the lesion enlarges it involves the deep fascia and then extends in this layer (Fig. 8). At this stage the edges are less distinct owing to an intervening layer of normal tissue. The skin overlying the lesion tends to desquamate, leaving a shiny surface which often appears darker than normal. Later the skin over the centre of the lesion loses its pigmentation, becomes necrotic, and eventually ulcerates. In some lesions a small central vesicle develops, which may be broken to exude a small amount of clear fluid. The burst vesicle may progress to an ulcer or it may heal.

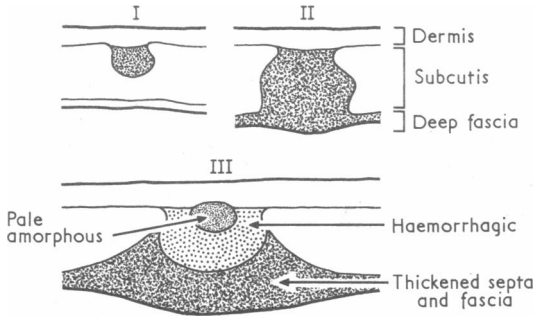

FIG. 8.—Diagrammatic representation of lesion. Stages in development of pre-ulcerative lesion.

The rate of growth of lesions varies considerably. One patient (Case 2) had a small nodule for several months. One of the Kinyara patients had a Buruli nodule for a year. Most lesions, however, as in Case 3, progress more rapidly. Certain features, in particular pruritus, oedema, and indistinct margins, are associated with rapid progression in a lesion. No Buruli nodule can be ignored, however, because occasionally a small nodule may, after several months, start growing rapidly. In some cases, as in Case 4, the history may be very short and the patient presents with an extensive fulminating pre-ulcerative lesion.

Fulminating Lesion

In some patients with a fulminating lesion there is no history of a preceding nodule, though we believe that these lesions do in fact start as nodules. The lesion rapidly increases in size and may involve a large part of the limb or trunk. Characteristically the swollen area is neither hot nor tender, and the patient does not show signs of systemic disturbance. Most of the affected area is tense and shiny owing to the massive oedema which becomes softer towards the edges. These edges are difficult to define. The skin over the centre of the lesion may have "orange peel" thickening. At a later stage the peripheral oedema subsides and definition of the hard induration becomes easier. Superficial desquamation occurs—and in some cases superficial bullae. As necrosis proceeds the skin becomes depigmented and eventually ulcerates. Secondary pyogenic infection may occur (even before ulceration) and the appropriate symptoms and signs develop.

Differential Diagnosis

In areas where Buruli lesions are endemic any small subcutaneous swelling should be suspected of being a *Myco. ulcerans* infection even though the pre-ulcerative lesion has distinctive features for both history-taking and at clinical examination. Other subcutaneous swellings from which it should be differentiated are: (1) foreign body granuloma, a history of trauma will usually point to the diagnosis and on excision the foreign body itself may be evident; (2) Nodular fasciitis, fibroma, or low-grade fibrosarcoma, these lesions are usually deep seated and only occasionally attached to the skin; (3) Phycomycosis, the definitive diagnosis can only be made histologically; (4) Injection abscess, these lesions are usually very painful and deeply seated; (5) Boil or panniculitis, the diagnostic confusion with Buruli lesions arises only if they have been inadequately treated with antibiotics masking the acute inflammation; it should be noted that Buruli lesions sometimes present as small subcutaneous abscesses; and (6) Sebaceous cyst or skin accessory tumours, these common lesions may be confused with a pre-ulcerative Buruli lesion, especially if the punctum is not present.

The fulminating lesion should be differentiated from subacute and acute cellulitis. In contrast to *Myco. ulcerans* infection a patient with cellulitis is always ill with fever and malaise, and the lesion is tender with signs of inflammation. The diagnosis can usually be made with certainty on clinical grounds, but histological confirmation is essential and excised tissues should always be sent for pathological confirmation.

Treatment

At present we treat Buruli lesions by excision. The small pre-ulcerative lesion can be excised completely under local anaesthesia as an outpatient procedure. The wound is sutured and usually heals by primary intention. We emphasize the ease with which this procedure can be carried out, and its value as a "preventive" measure. Larger lesions are, if possible, totally excised and grafted; they are usually larger than the preoperative assessment of induration (Case 3).

Often grafting can be done successfully at the initial operation. With very extensive lesions, however, it is not usually feasible to carry out a total excision. In these cases the object of the initial operation is to excise the non-viable skin and to cut skin flaps to gain access to the diseased fascia and fat. Though this conservative approach to skin excision has advantages, it is usually not possible to remove all the diseased tissue initially, and repeated operations with prolonged stay in hospital may be required.

If a wound does not show healthy granulations and the skin flaps do not stick down (and this should occur one to two weeks after operation), the disease is still present. If further operation is delayed the discharge and organization of necrotic material take months to occur, and is accompanied by considerable fibrosis, which will limit the final result. We therefore carry out frequent excisions (if necessary) and early grafting.

Though several drugs are effective in vitro against *Myco. ulcerans* (Clancey, 1964), in our experience chemotherapy has been generally disappointing. We do use antimycobacterial drugs for hospital patients, but it seems that the most important factor in healing is surgical technique. Lunn and Rees (1964) reported that a riminophenazine derivative (Geigy B663) helped limit the spread of the disease and the extent of the operation required. We are at present carrying out a controlled clinical trial of this drug.

We would like to thank the refugees who took part in this study; their trust and co-operation were a continuous encouragement. We would like to thank the doctors in Masindi, Hoima, Apac, and Lira hospitals for their help. Special acknowledgement is due to the Uganda Ministry of Culture and Community Development and to the United Nations High Commission for Refugees for permission to work in the settlements.

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