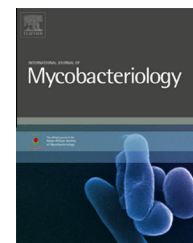


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## Management of complications of *Mycobacterium ulcerans* disease: A three-year review

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### ABSTRACT

**Background:** Infection with *Mycobacterium ulcerans* (MU) causes extensive destruction of tissues with the formation of large ulcers on exposed parts of the body. Healing leads to extensive scarring and other complications which may impair function.

**Objective:** To document the complications of MU disease and the reconstructive surgery performed to correct them.

**Study design:** Prospective from January 2010 to December 2012.

**Setting:** Ahafo Ano, Amansie West, Asunafo, and Upper Denkyira districts of Ghana.

**Methods:** Patients with unhealed lesions after completing 8 weeks of rifampicin and streptomycin treatment, and patients with complications of MU disease were selected and prepared for surgical treatment.

**Results:** 61 patients were treated successfully with rifampicin and streptomycin without complications. 65 patients presented with complications; they comprised 34 males and 31 females. Their ages ranged from 1 year 3 months to 80 years with mean age of 29.7 (S.D. 20.1). The types of lesions seen were ulcers (54), contractures (7), chronic osteomyelitis (one), subluxation of knee joint (one), salivary gland fistula (one) and Marjolin's ulcer (one). The lesions were distributed as follows: 69.2% on the lower, and 23.1% on the upper limbs, 6.2% on the head and neck and 1.5% on the trunk. Wound excision with or without skin grafting was done in 84.6% of patients, surgery for contractures in 10.8%, and sequestrectomy, exploration and ligation of fistula, groin dissection and above knee amputation in 4.6%.

**Conclusion:** Whilst ulcers, the commonest MU lesions, are being controlled with antibiotics, rare complications of the disease are also emerging.

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### Introduction

The mycolactone toxin produced by *Mycobacterium ulcerans* (MU) is mainly responsible for the pathology of Buruli ulcer disease [1]. This toxin is produced when the organism is infected with a transmissible plasmid [2]. The toxin has

cytotoxic and immunosuppressive properties [3]. Infection with MU leads to extensive destruction of the tissues with the formation of large ulcers especially on exposed parts of the body such as the limbs, head, and neck [4]. Healing of MU lesions may occur spontaneously by secondary intention after sloughing of the epidermis and subcutaneous fat with

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later re-epithelialization. Considerable deformity results from this mode of healing. Lesions are usually on the extremities of children. Scarring often leads to contractures, subluxation of joints, disuse atrophy, and distal lymphedema [5].

Treatment of MU disease with antibiotics, namely rifampicin and streptomycin, in accordance with WHO recommendations [6] led to a reduction in the number of early active lesions in some series [7]. Even for those requiring surgery after antibiotic treatment, the extent of surgery was also reduced, with most patients requiring only simple skin grafting [8]. However, for patients presenting with extensive ulcers for the first time, recurrent ulcers, or complications of the disease, the management tends to involve complicated reconstructive surgical procedures to improve form and function.

The objective of the study was to document the complications of MU disease, including those occurring after antibiotic treatment, and to determine the type of reconstructive surgery that was required to correct them.

## Patients and methods

A three-year prospective study was undertaken in four Buruli ulcer endemic districts located in the middle belt of Ghana. The communities were Tapa in Ahafo Ano (in 2010), Agroyesum in Amansie West (in 2011), Kukuom in Asunafo (in 2012), and Dunkwa in Upper Denkyira (in 2012) districts.

Patients with lesions suspected to be MU disease were identified by specially trained health workers in the communities, and referred to the district hospitals for confirmation of the diagnosis by the doctor, either by direct smear examination, polymerase chain reaction (PCR), or by histopathology of tissue obtained by punch biopsy, or by excision. PCR and histopathology were either done at the Kumasi Centre for Collaborative Research (KCCR) into Tropical Diseases or Komfo Anokye Teaching Hospital (KATH) in Kumasi. Culture and sensitivity for MU was not done routinely for confirmation of MU disease during the current study. All the patients with active disease were treated with rifampicin at 10 mg/kg body weight orally daily for 8 weeks and streptomycin 15 mg/kg body weight by intramuscular injection daily for 8 weeks in accordance with WHO recommendations.

Patients whose lesions were not completely healed after 8 weeks of antibiotic treatment, and patients who had developed complications, or were presenting with complications at the time of first clinical diagnosis were selected for surgical treatment. Surgery involved wound debridement, wound excision with or without skin grafting, release and repair of contractures, and sequestrectomy, depending on the type of MU lesions. The surgeries were performed at the district hospitals by a team comprising one plastic surgeon and one theatre nurse from Komfo Anokye Teaching Hospital, who were assisted by a doctor, an anesthetist and theatre nurses from the district hospitals.

Surgery was also performed for four patients who presented with four uncommon complications of MU disease:

- (1) A 19-year-old girl presented with a recurrent Buruli ulcer involving the right knee. She has had two previous wound excisions and split thickness skin grafting

done, but they failed on both occasions. She presented with a granulating ulcer on her right knee joint, about 10 cm by 6 cm on the anterior aspect. Wound excision and split thickness skin grafting was done. The limb was splintered in an above-knee plaster of paris (POP) back-slab for 2 weeks before weight bearing was allowed, and walking started.

- (2) A 14-year-old girl presented with chronic osteomyelitis of the right humerus, following Buruli ulcer of the right arm for 3 years. Sequestrectomy was performed for her.
- (3) A 14-year-old boy with a healed Buruli ulcer of the left cheek presented with a fistula in the scar discharging copious amount of saliva, which soaked his clothes continuously. The fistula was explored, cannulated and ligated under general anesthesia.
- (4) A 19-year-old boy who had had a Buruli ulcer for 10 years, presented with a malignant ulcer of the distal third of the right thigh and right knee. He also had a pathological fracture of the right tibia. In addition, he had palpably enlarged right inguinal lymph nodes. He underwent a block dissection of the right inguinal lymph nodes, and an above-knee amputation of the right lower limb. Histological examination of the resected tissue confirmed squamous cell carcinoma.

The case notes of all the patients who were treated by the author during the study period were compiled and analyzed.

## Results

The study period extended from January 2010 to December 2012. A total of 126 patients were treated for MU disease. In 61 patients, the wounds healed completely with the antibiotics rifampicin and streptomycin without complications. They did not require any surgery, and were hence excluded from the study.

65 patients presented with complications of MU disease, and were entered into the study. They comprised 10 patients from Tapa, 9 from Agroyesum, 33 from Kukuom, and 13 from Dunkwa. They comprised 34 men and 31 females, giving a male to female ratio of 1.1:1. Their ages ranged from 1 year 3 months to 80 years, with a mean age of 29.7 (SD 20.1). The age distribution of the patients is shown in Fig. 1.

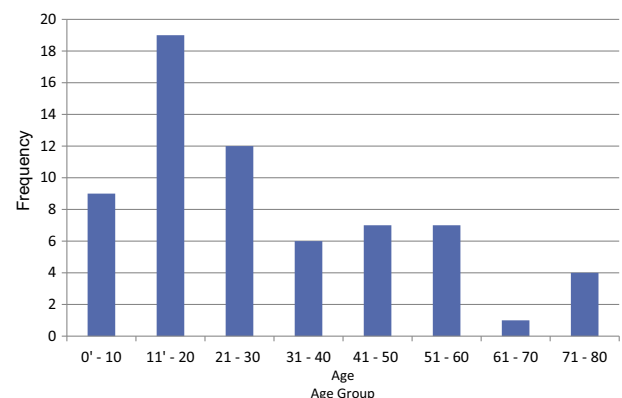


Fig. 1 – Age distribution of 65 patients with complications of *Mycobacterium ulcerans* disease.

**Table 1 – Distribution of *Mycobacterium ulcerans* lesions on various parts of the body.**

Site	Frequency (percentage)
Head and neck	4 (6.2%)
Scalp	1
Temple	1
Cheek	2
Upper limb	15 (23.1%)
Shoulder	1
Arm	2
Elbow	4
Forearm	3
Wrist	4
Hand	1
Trunk	1 (1.5%)
Chest wall	1
Lower limb	45 (69.2%)
Thigh	1
Knee	7
Leg	26
Ankle	4
Foot	7

The distribution of the lesions on various parts of the body is shown in Table 1. About 92% of the lesions were on the limbs, with the lower limbs comprising about 69% of the lesions. This distribution of the lesions confirms the prevalence of MU lesions on exposed parts of the body, especially on the limbs, seen in some series [9].

The types of MU lesions seen were ulcers (54, 83.1%), contractures (7, 10.8%), and 4 (6.1%) other uncommon complications: subluxation of the knee joint, chronic osteomyelitis of the humerus, salivary (parotid) gland fistula (Fig. 2), and Marjolin's ulcer from a recurrent Buruli ulcer (Fig. 3).

The sizes of the ulcers were: 5 cm or less (category 1, 9 patients); 5–15 cm (category 2, 34 patients); more than 15 cm (category 3, 11 patients).

There were four patients who presented with contractures of the wrist; three involved the hand and wrist; one involved only the wrist. The deformity caused by the hand and wrist contractures were dorsiflexion in two cases and volar flexion in two cases (Figs. 4a and 4b). A knee contracture caused a fixed-flexion deformity of about 80°.

The types of surgical procedures that were performed for the 65 patients who presented with complications are shown in Table 2. Since ulcers were the commonest lesions seen, the commonest procedures were wound excision and skin grafting.

## Discussion

The efficacy of antibiotic treatment, namely rifampicin and streptomycin, for MU disease has been demonstrated in several series [10–12]. Initially it was demonstrated to be effective only in small (less than 10 cm diameter) and early (less than six months old) lesions. Recently, it has been found that all forms of MU disease – plaques, nodules, edema and ulcers – however extensive, respond well to antibiotic treatment [12].



**Fig. 2 – Salivary gland fistula of the left cheek following MU disease.**



**Fig. 3 – Marjolin's ulcer of right knee with pathological fracture of the right tibia as complications of MU disease.**



**Fig. 4a – Contracture of right wrist from MU disease (pre-operative).**

However, not only antibiotics promote healing of MU lesions; spontaneous healing of MU lesions, without any form of treatment, has been known to occur [5]. The scar tissue resulting from this slow, normal healing process causes



**Fig. 4b** – Right wrist after release of contracture and groin flap repair.



**Fig. 5** – MU disease of right arm treated with herbs.

**Table 2** – Surgical procedures performed for 65 patients with complications of *Mycobacterium ulcerans* disease.

Surgical procedure	Frequency (%)
Excision and skin grafting	43 (66.2)
Excision	5 (7.7)
Skin grafting	4 (6.2)
Release of contracture and groin flap repair	4 (6.2)
Release of contracture and skin grafting	3 (4.6)
Re-grafting	3 (4.6)
Sequestrectomy	1 (1.5)
Exploration and ligation of salivary (parotid) fistula	1 (1.5)
Right groin dissection and above knee amputation	1 (1.5)

adhesions to and between adjacent structures which limit movement. Thick or tight scars resist injuries poorly, may limit movement, distort appearance and prevent function. Herbal medicines used in some endemic communities by local people to treat MU disease also lead to this kind of healing. In the latter two situations, and also sometimes with antibiotic treatment unsupported by physiotherapy, healing leads to contracture formation which seriously impairs function (Fig. 5). In the current study, 10.8% of the surgical procedures were performed for the release and repair of contractures, second only to surgery for ulcers.

Scars from MU disease are usually dry and may crack or ulcerate during play or work. Such unstable scars may, over many years, develop into squamous cell carcinoma–Marjolin's ulcer [13]. Even though only a single such case was encountered in the current study, it is significant in terms of the magnitude of surgery performed and the resulting loss of limb.

These difficult complications of MU disease usually require complex reconstructive surgery and physiotherapy to correct. Such services are usually not available at the district hospitals in the endemic communities, and patients have to be transferred to a tertiary centre (KATH).

The usefulness of antibiotic treatment is limited by patients who report late with advanced disease. Early lesions of MU disease are usually painless [5] and do not usually prevent patients from performing their activities of daily living. They are, therefore, likely to be ignored by the patient until they become bigger, or painful from secondary bacterial infection [5]. Patients presenting the first time with severe contractures or malignant complications may not have the MU organisms in the tissues to be treated with antibiotics. Surgical management in such cases is the only option. For antibiotic treatment to be more effective in achieving a cure for MU disease, and also to reduce the need for extensive surgery, early case detection for MU lesions should be emphasized in all endemic communities.

## Conclusion

Whilst ulcers, the commonest MU lesions, are being controlled with rifampicin and streptomycin, rare complications of the disease which require skillful reconstructive surgery and physiotherapy to correct are also emerging.

## Conflict of interest

None declared.

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