

***Mycobacterium ulcerans* disease management in Australian patients: the re-emergence of surgery as an important treatment modality**

Running head: *Mycobacterium ulcerans* surgical treatment

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Abstract

With the demonstration of the effectiveness of antibiotic treatment, the management of *Mycobacterium ulcerans* disease has changed from a predominantly surgically to a predominantly medically treated disease. However, research among Australian patients has revealed that antibiotic treatment alone is associated with prolonged wound healing times, high rates of treatment toxicity, and the potential for significant tissue destruction associated with severe paradoxical reactions. We present the current state of *Mycobacterium ulcerans* management in Barwon Health, Australia, where a close working relationship exists between the Plastic Surgical and Infectious Diseases units. Here treatment has evolved based on nearly 20 years of experience gained from managing more around 600 patients from a *Mycobacterium ulcerans* epidemic on the nearby Bellarine and Mornington Peninsulas. In our experience, surgery has re-emerged to play an important role in the treatment of *Mycobacterium ulcerans* in improving the rate of wound healing, minimising antibiotic associated toxicity and preventing further tissue loss associated with severe paradoxical reactions. For selected small lesions surgery without antibiotics may also be an effective treatment option, however aggressive surgical resection of lesions with wide margins through uninvolved tissue should no longer be performed. Furthermore, extensive surgery that will require the use of split skin grafts and vascularised tissue flaps to repair skin defects should be avoided if possible.

Introduction

Mycobacterium ulcerans disease is endemic in Australia, mainly in parts of coastal Victoria and the Daintree region of northern Queensland.(1, 2) It causes necrotising lesions of skin, soft-tissue and occasionally bone that, if left untreated, usually progress and can lead to significant tissue loss, morbidity and long-term deformity.(3, 4) The disease is known internationally as Buruli ulcer,(5) in Victoria as also the Bairnsdale ulcer(1) and in northern Queensland as the Daintree ulcer.(2) In recent years, for unknown reasons, there has been a dramatic increase in the number of cases reported in Victoria, increasing more than fourfold from 66 to 275 cases per year between 2013 and 2017.(6) Furthermore, the disease has emerged in new areas and cases have become more severe.(7) Therefore, clinicians both within and outside endemic areas are increasingly required to manage this disease.(8)

Up until the turn of the century, treatment of *Mycobacterium ulcerans* disease was considered to be surgical, with wide excision through uninvolved tissue the recommended treatment.(9, 10) However this often required extensive reconstructive surgery including the need in many cases for split skin grafts (SSG) and vascularised tissue flaps (figure 1). This resulted in long-term cosmetic deformities and significant treatment costs.(11) Despite this, up to one-third of patients would suffer disease relapse and require further treatment to ensure a cure.(12)

With the demonstration of the effectiveness of antibiotic treatment in the early 2000s,(13-15) the pendulum swung to *M. ulcerans* being considered a medically treated disease., An 8 week course of combination rifampicin-based antimicrobial therapy is now the recommended treatment,(5, 16) and curative outcomes are excellent.(17-19) In selected cases, surgery can be combined with a shortened duration of antibiotic treatment without compromising outcomes, presumably through the reduction of *M. ulcerans* organism burden.(20, 21)

However, research has revealed several limitations to treatment with antibiotics among Australian patients. Firstly, in the older populations managed in Australia, there is significant toxicity associated with antibiotic treatment. Overall 22% of patients suffer an antibiotic-associated complication severe enough to warrant cessation of that antibiotic; this figure increasing to 39% in those 65 and older.(22) Secondly, wound healing times with antibiotic treatment alone are long, with a median time to heal of 4.5 months from the start of antibiotic treatment.(21) This is further prolonged in larger wounds (more than 4 cm in diameter), with some wounds taking longer than 12 months to heal.(19, 21) Long healing times result in significant inconvenience and the cost of prolonged wound dressings and medical care. Thirdly, up to one-third of *M. ulcerans* lesions treated with antibiotics are complicated by paradoxical reactions.(23, 24) These result from the reversal of the immune inhibition mediated by the mycolactone toxin produced by living *M. ulcerans* which occurs when the antibiotics kill the mycobacteria.(25) This leads to a paradoxical worsening of the clinical appearance of lesions on treatment, after an initial improvement, and if severe can result in significant additional tissue loss, often requiring further surgery.(24) Additionally, paradoxical

reactions delay wound healing by a median 1-2 months, depending on the size of the lesion.(21) Fourthly, there are a number of patients who cannot take antibiotics due to previous drug allergy or drug-drug interactions and a proportion who do not wish to take them at all.

In this paper we present the current state of *M. ulcerans* management at Barwon Health, Australia, a tertiary referral medical centre. In this health service there is a close working relationship between the Plastic Surgical and Infectious Diseases units. This has led to treatment that has evolved based on nearly 20 years of experience gained from managing around 600 patients from a *M. ulcerans* epidemic on the nearby Bellarine and Mornington Peninsulas. In our health service, surgery has re-emerged to play an important role in *M. ulcerans* treatment. In our experience, appropriate surgical intervention improves the rate of wound healing, minimises antibiotic-associated toxicity and prevents further tissue loss associated with severe paradoxical reactions. This paper builds on our earlier surgical experience which was published in 2012,(26) and aims to inform protocol development to guide *M. ulcerans* management in Australia and other endemic countries.

Aim of Surgery in *M. ulcerans* disease

Three basic principles underlie the aims of surgery in our experience. Firstly, that surgery is not required to sterilise *M. ulcerans* lesions, as this is achieved very effectively by appropriate antimicrobials. Aside from selected situations where surgery is used without antibiotics for small lesions, we no longer recommend aggressive surgical resection of lesions with wide margins through uninvolved tissue as a primary treatment for *M. ulcerans*. Secondly, we try to avoid extensive surgery that will require the use of SSGs and vascularised tissue flaps to repair skin defects. This is reflected in the proportion of patients in our cohort treated with either a SSG or vascularised tissue flap significantly reducing over the time [38/61 (62%) patients during 1998-2004, 64/120 (53%) patients during 2005-2011, and 28/284 (10%) patients during 2011-2016, $p < 0.0001$). Thirdly, that wounds should be treated according to usual surgical principles and managed as they would be for other causes.

The aims of surgical treatment in our experience include: a) to improve the rate of wound healing. This is achieved by removing necrotic tissue and the mycolactone toxin which inhibit healing,(21) or by the use of reconstructive surgery to cover large wounds, b) to allow a reduction in the duration of the antibiotic treatment by reducing the burden of organisms,(20, 21) c) to prevent deformity or scarring from lesions with significant skin and soft-tissue necrosis, d) to remove dead tissue and organisms to prevent or treat paradoxical immune reactions that impair wound healing,(21) and e) to sterilise lesions when antibiotics are not used for selected small lesions.

Wide excision without antibiotics

Surgery without antibiotic treatment remains a treatment option in selected cases where they are contraindicated or the patient prefers not to take them.(12) This mode of treatment avoids the risks associated with antibiotic toxicity. In addition, the surgical wound will heal significantly faster than

ulcers treated with antibiotics alone(21) reducing the inconvenience and cost of prolonged wound dressings and regular medical visits. The surgery however requires wide excision of the lesion through uninfected tissue to minimise the risk of disease relapse.

Patient selection is important as a number of factors need to be considered. Firstly, there are a number of patient characteristics associated with increased rates of disease relapse if antibiotics are not given, and therefore caution would be advised in these patients. These characteristics include; positive histological margins of excised lesions, age 60 years or older, associated immune suppression, or a lesion requiring SSG or vascularised tissue flap (12, 13). In our experience, in lesions without these risk factors for relapse, cure rates with surgery alone are 94% (17/18 cases from 2001 to 2017). Secondly, the lesion should be amenable to excision and direct closure. We feel lesions requiring reconstructive surgery (eg SSG or flap) should not be managed with surgery alone due to the complexity and cost of treatment.(11) Therefore the size and position of the lesion is important, as large lesions or lesions on certain parts of the body (eg anterior shins, ankle) may preclude direct wound closure.

Importantly, the surgical wound following wide excision can be quite large (figures 2a, 2b). Therefore patients need to be made aware of this prior to surgery so they are comfortable with the predicted long-term cosmetic appearance of the wound. Furthermore, there may be financial costs to the patient in having the surgery performed that need to be considered.

Antibiotics + curette of lesion.

This involves a shallow surgical excision using a curette of all the macroscopically abnormal skin and subcutaneous tissue, including the wound edges, under local anaesthetic with the wound left open to heal by second intention. (Figure 3a-c) The main aim of this method is to reduce the duration of antibiotics for small lesions, because in our experience the duration of antibiotics can be reduced from eight to four weeks.(21) In our limited experience with this method, there has been a 100% cure rate with a median time to wound healing post commencement of antibiotics of 71 days (IQR 64-114 days).(21) The advantages of this method include that it is a minor surgical procedure which can be done in the surgeon's office under local anaesthetic, the wound heals relatively quickly, and the risk of antibiotic toxicity is reduced by about 50% as the treatment duration is halved.(22) However, this mode of treatment is only suitable for small lesions of less than 400mm² in size. We aim for the surgery to be performed after about 2 weeks of antibiotics. This takes advantage of the reduction in lesion size that occurs early in antibiotic treatment allowing a smaller excision.(21)

Antibiotics + surgical debridement

This involves debridement of necrotic or inflamed tissue in the base of wounds and underlying the wound edges. It does not involve the excision of wound edges or macroscopically abnormal skin. (Figure 5) It is aimed at increasing the rate of wound healing by removing necrotic tissue and mycolactone toxin which inhibit wound healing.(21) It is particularly useful for large lesions where

conservative excision and primary closure is not possible. Even for smaller lesions it can be beneficial as the final wound scar is usually smaller than the larger scar associated with conservative excision and primary closure. Debridement is generally not urgent and would usually be undertaken after the completion of antibiotic treatment. This is supported by evidence from a recent randomised controlled trial in Africa that showed delaying surgery from 8 to 14 weeks after antibiotic commencement made no difference to wound healing times but reduced the proportion of lesions that required surgery.(27)

Antibiotics + conservative surgical excision

This involves excision and direct closure of the lesion, with excision of the macroscopically involved tissue without taking wide margins through macroscopically normal tissue. It is generally only undertaken if direct closure can be obtained. This avoids the associated cost, complexity and morbidity of reconstructive surgery with SSGs or vascularised flaps which are generally not preferred over the more prolonged wound healing with antibiotics alone. Usually at least 4 weeks of antibiotics are given prior to surgery to shrink the lesion as much as possible so as to minimise the extent of surgery required.

This is generally used for one of two indications. Firstly, where the patient and clinician would prefer to heal the wound more rapidly, either to avoid prolonged healing times pre-emptively or in those experiencing prolonged healing times after antibiotic treatment. (Figure 4) Depending on lesion size, this method can reduce wound healing times by an average 1-2 months.(21) The second indication is for patients with lesions less than or equal to 1600mm² in size where there is a desire to reduce the duration of antibiotic treatment due to patient wishes or because of antibiotic toxicity. In these situations we have shown that 4 weeks of antibiotics with conservative surgical excision is highly effective in curing lesions.(20, 21) The disadvantage of this mode of treatment is that surgery involves a general anaesthetic and a cost, and that the length of the surgical wound required to allow its direct closure can be quite significant.

Antibiotics + wide surgical excision

This approach is undertaken if antibiotics were ceased due to toxicity before they were felt to be effective. In our experience this is usually less than 21-28 days duration(20). In this case, it is important to take wide margins through macroscopically normal tissue as in this instance there is a reliance on the surgery to help sterilize the lesion.

Treatment of severe paradoxical reactions

Severe paradoxical reactions result in significant tissue loss for reasons that are unknown, but may relate to tissue ischaemia from the associated wound swelling. Tissue loss can be minimised with the use of corticosteroids(28). However, as reactions can take many months to settle, they may need to be given for a prolonged period with the risk of side-effects. Furthermore, in our experience, in

many instances the ulceration continues to slowly enlarge despite prednisolone treatment. We have found that simple surgical debridement of lesions can dramatically settle the paradoxical lesions and lead to more rapid wound healing. (Figure 6) This likely relates to the removal of the mycobacterial antigens released by dead bacteria that drive the immune reaction allowing the wound to settle and heal. Thus surgical debridement has the advantage of preserving tissue, reducing the duration of corticosteroid therapy required and improving wound healing times. In our experience surgery should be employed soon after the severe paradoxical reactions have developed.

Conclusions

In our experience surgery remains an important mode of treatment for *M. Ulcerans* disease that can improve the rate of wound healing, minimise antibiotic-associated toxicity, prevent further tissue loss associated with severe paradoxical reactions and be an effective treatment option for selected lesions in the absence of antibiotics. However, apart from selected small lesions, aggressive surgical resection of lesions with wide margins through uninvolved tissue should no longer be performed. Additionally, extensive surgery requiring the use of SSGs and vascularised tissue flaps to repair skin defects should be avoided if possible. The key to optimal treatment of *M. Ulcerans* disease is a close working relationship between Surgical and Infectious Diseases teams.

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Figure legends:

Figure 1: Example of wide excision and reconstructive surgery prior to first-line treatment of *M. ulcerans* disease with antibiotics: a) ulcerative lesion left elbow region, b) vascularised free flap from forearm to elbow to repair defect from excision left elbow lesion

Figure 2: Small *M. ulcerans* lesion lateral aspect left leg a) before treatment, and b) 7 weeks after surgical and direct closure without antibiotics.

Figure 3: *M. ulcerans* lesion posterior aspect of calf at a) start of antibiotic treatment, b) post curette done after 11 days of antibiotics, and c) 6 weeks post curette.

Figure 4: Excision for slow wound healing: *M. ulcerans* lesion left thigh a) after 84 days since antibiotics commenced with slow wound healing, and b) 60 days after surgical excision and direct closure.

Figure 5: *M. ulcerans* lesion left leg a) after 4 weeks of antibiotics containing significant necrotic tissue, b) 4 weeks post surgical debridement, and c) healed at 8 weeks post debridement.

Figure 6: *M. ulcerans* lesion anterior aspect left ankle at a) start of antibiotics, b) 7 weeks after start of antibiotics whilst experiencing a severe paradoxical reaction, c) post surgical debridement, and d) healed 4 weeks post surgical debridement.

Table 1: Type of surgery stratified by indication, advantages, disadvantages and timing.

Type of treatment	Indication	Lesion size	Advantages	disadvantages	Timing
Wide excision without antibiotics	Antibiotics declined or contraindicated. No risk factors for relapse. Lesion amenable to excision and direct closure.	Small lesion (<400mm ²)	No risk of antibiotic toxicity. Wound healing less than 1 month.	Cost of surgery. Larger scar.	As soon as possible after diagnosis.
Curette of lesion + antibiotics	Desire to reduce antibiotic duration due to patient wishes	Small lesion (<400mm ²)	Reduced duration of antibiotics. Can be performed under local anaesthetic.	Cost of surgery.	After 2 weeks of antibiotics
Antibiotics + surgical debridement	Necrotic, inflamed or slowly healing wounds. Severe paradoxical reactions.	All wounds	More rapid wound healing. No large scar. Suitable for large lesions.	Cost of surgery. Requires general anaesthetic.	After 8 weeks of antibiotics
Conservative excision + antibiotics	Desire to reduce antibiotic duration due to toxicity or patient wishes. To expedite wound healing.	Small or moderate sized lesions (≤1600mm ²)	Reduced duration of antibiotics. More rapid wound healing.	Cost of surgery. Requires general anaesthetic. Larger scar	After at least 4 weeks of antibiotics
Wide excision + antibiotics	Achieve cure when antibiotics ceased early due to toxicity	Small or moderate sized lesions (≤1600mm ²)	Allows curative treatment in cases of reduced antibiotic duration due to toxicity. More rapid	Cost of surgery. Requires general anaesthetic. Larger scar	As soon as possible after antibiotics have been ceased

			wound healing.		
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Figure 1a.jpg



Figure 1b.jpg







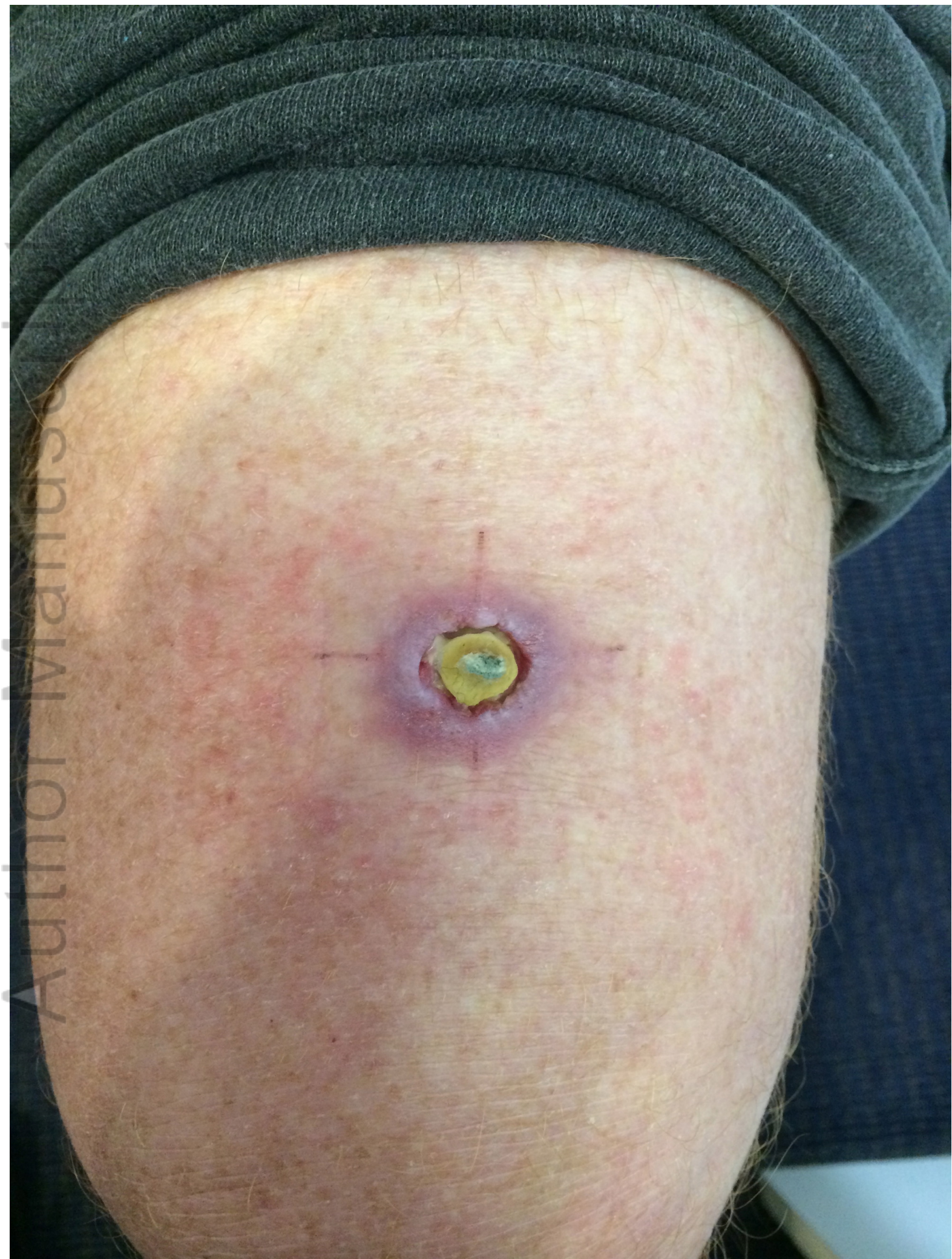
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