

An unusually severe case of bullosis diabeticorum with marked morbidity ultimately resulting in bilateral trans-tibial amputation

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Abstract

Bullosis diabeticorum is a spontaneous, non-inflammatory, blistering condition seen in patients with diabetes mellitus that can be diagnosed after excluding similar conditions. The lesions described in bullosis diabeticorum have been reported to typically resolve without any specific treatment or scarring and are often considered to be self-limiting.

We report a case of a 49-year-old man with type 1 diabetes who presented with recurrent episodes of bullosis diabeticorum, complicated by infection and ultimately resulting in bilateral major amputations.

This case highlights the fact that bullosis diabeticorum may not follow an uncomplicated self-limiting course and also the need for early recognition and prompt treatment of infection. Copyright © 2016 John Wiley & Sons.

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Key words

bullosis diabeticorum; diabetic bullae; bullous disease; diabetes

Introduction

Bullosis diabeticorum was first reported by Kramer in 1930.¹ In 1963, Rocca and Pereyra described the same condition in a case series of 14 patients as ‘phlyctenar’, because the bullous lesions appeared similar to burn blisters.² Four years later, Cantwell and Martz published a case series of four patients and named the condition ‘bullosis diabeticorum’.³ It is also known as bullous disease of diabetes and diabetic bullae.

The incidence of bullosis diabeticorum in the diabetes population is difficult to determine but is reported as 0.16–2%.^{4,5} Bullosis diabeticorum more frequently, although not exclusively, occurs in men who have long-standing diabetes with peripheral neuropathy.^{4,6} The lesions tend to affect the peripheral parts, especially the feet, but have been reported elsewhere.^{4,6} The exact pathophysiology remains unclear, but it is likely to be multifactorial. Proposed mechanisms include trauma,⁷ impaired microvascular perfusion,⁸ poor or variable glycaemic control,^{4,9} disturbances in calcium, magnesium and carbohydrate metabolism,^{7,10} and excessive exposure to ultraviolet light.¹⁰ The lesions described in bullosis diabeticorum have been reported to typically resolve without any specific treatment or scarring and are

often considered to be self-limiting.⁶ Despite this perception, there are many cases of bullosis diabeticorum in the literature reporting complications such as chronic ulceration,¹¹ secondary infection,⁴ necrosis,^{11,12} and occasionally osteomyelitis.^{13,14}

Here we report a case of severe bullosis diabeticorum associated with marked morbidity, which has ultimately resulted in major amputation in a patient with type 1 diabetes mellitus.

Case history

A 49-year-old man with type 1 diabetes of 21 years’ duration presented to the podiatry clinic with new spontaneous painless blistering to the dorsum of his left foot and ulceration to the dorsal apex of the hallux (Figure 1). There were no preceding illness, changes to his medication or recent trauma. His past medical history included type 1 diabetes with peripheral sensory neuropathy, autonomic neuropathy, retinopathy and nephropathy (chronic kidney disease stage 3B). He also suffered from ischaemic heart disease with a previous myocardial infarction and coronary artery bypass. Glycaemic control was previously poor but now satisfactory (last HbA_{1c} level was 54mmol/mol [7.1%]).

He first described the eruption of bullae five years prior to this,

where they appeared overnight on his calves and were complicated by soft tissue infection. Following antibiotic treatment, these two areas healed to leave scars. No similar episodes occurred in the following two years. During the subsequent three years, the patient suffered with recurrent bullae formation. The site of bullae eruption was frequently over the dorsum of his right foot, but had also occurred on his hands, legs and buttock. Multiple skin biopsies have shown non-specific histological findings and negative immunofluorescence. Duplex ultrasound showed no significant stenosis and good arterial flow. A trial of immunosuppressive therapy (cyclosporin and prednisolone) was of no benefit. One year prior to this presentation, due to recurrent bouts of right foot soft tissue infections and osteomyelitis, the patient opted for an elective right-sided trans-tibial amputation.

Examination revealed a firm intact bulla on the dorsum of his left foot and an ulcer on the dorsal apex of his left hallux measuring 9x8mm (Figure 1). Both dorsalis pedis and posterior tibialis pulses were intact. He had reduced sensation bilaterally up to mid-thigh with a healthy looking stump site on the right. The bulla on the dorsum of his left foot was deroofed, exposing the wound bed (Figure 2).

Histology showed abundant fibrin together with superficial curettings of skin that show sub-epidermal blister, filled with neutrophils and fibrin. Examination of some of the overlying epidermis showed almost full epidermal necrosis. MRI excluded osteomyelitis. Duplex ultrasound of the lower limbs was unremarkable.

He was treated for a severe soft tissue infection with intravenous antibiotics, and had daily foot dressings. Following discharge from hospital, he continued to be troubled by recurrent bullae eruption on his left foot, complicated by slow healing, chronic ulcerations and secondary infections. He underwent a second trial of immunosuppressants (mycophenolate, cyclophosphamide) combined with prophylactic antibiotics (doxycycline) without improvement. He later electively underwent a trans-tibial amputation of



Figure 1. Extensive diabetic bullae on the dorsum of the left foot



Figure 2. Deroofed bullae exposing the wound bed



Figure 3. Bulla over the left trans-tibial stump site



Figure 4. Left trans-tibial stump site after treatment

the left foot and now mobilises with the aid of prosthesis.

Since his amputation, his time in hospital has been dramatically reduced. He has only required one hospital admission over an 18-month period to treat an infected bulla over his left trans-tibial stump site (Figures 3 and 4). His management continues to focus on wound care when ulcers occur, and supportive measures.

Discussion

To our knowledge, this is the first case of bullosis diabeticorum where complications of the disease have required major amputation. The patient in this case report has clearly compromised his quality of life and has put a strain upon health care resources. Despite the extreme surgical measures taken in this case and good healing over the stump site, the patient has since required hospitalisation for management of an infected bullae eruption on the stump. On review of the literature, we found four patients from three articles that required minor amputations due to complications that ensued from bullosis diabeticorum, including: partial toe amputation,⁴ trans-metatarsal ray amputation,⁴ greater toe amputation⁶ and multiple digital amputations.¹⁴ Reasons

given were necrosis, infection and osteomyelitis. Other reports of severe morbidity associated with bullosis diabeticorum include a patient who underwent a femoro-popliteal bypass for bullous disease complicated by an infection and gangrene due to peripheral vascular disease who died in the postoperative period of a myocardial infarction.¹² A different patient managed in hospital for a secondary bullous site infection had a cardiac arrest and died.⁶

Diagnosis and clinical course

The diagnosis of bullosis diabeticorum is based on characteristic findings, clinical course and the exclusion of similar conditions. The bullae in bullosis diabeticorum have been reported to be variably sized and painless, and arise from a non-erythematous skin usually in a peripheral part of the body, particularly the feet. They occur spontaneously and evolve rapidly, often overnight. The largest case series (n=25) available in the literature reports a median healing time of 2.5 months, with a range of 0.5–23 months.⁴ Although often considered to be a self-limiting disease, there are reports of scarring, chronic ulceration, soft tissue infection, osteomyelitis and minor amputations.^{4,6}

Histopathology

The findings on immunofluorescence and histology of skin biopsy are not specific for the condition but useful in excluding similar conditions, such as bullous pemphigoid, epidermolysis bullosa (simplex and acquista), dermatitis herpetiformis, porphyria cutanea tarda, pseudoporphyria and blistering due to drugs or burns.

Histopathological examination can be used to determine the level at which skin separation has occurred in the bulla, with variability in the literature.^{3,8,12} The patient in this case had sub-epidermal blistering. Basarab *et al.* attempted to explain this variability in the literature by suggesting that skin separation at intra-epidermal level can be explained by re-epithelialisation.¹² Basarab *et al.* proposed that the level of separation in true cases of bullosis diabeticorum occurs at the lamina lucida within the sub-epidermal level due to poor vascularisation.¹² This depth of skin separation could explain why the patient in this case showed signs of scarring and atrophy.

Disease mechanisms

The causes of bullosis diabeticorum are not known but are considered to be multifactorial. The bullae are usually painless or occasional associated with a burning sensation,⁵ which implicates the role of sensory neuropathy as a mechanism for the disease. The diabetic population has been shown to have a lower threshold for suction-induced blister formation compared to controls⁷ which supports the role of trauma. The distal prominence of bullae formation further supports trauma and/or neuropathy. It is possible that a combination of factors may result in a susceptibility to bullae formation with trivial trauma.

Goodfield *et al.* proposed a theory of impaired microvascular perfusion due to microangiopathy and sympathetic autonomic denervation, causing the premature aging of connective tissue or collagen.⁸ Similar ideas about tissue damage and susceptibility to bullae can be inferred about reports of excessive exposure to ultraviolet light.¹⁰ Toxicological studies during the Second World War examining

patients with lewisite and arsenical induced blisters report failure of carbohydrate oxidation at the pyruvate enzyme level.¹⁵ These findings support the importance of the metabolic control, leading to theories due to dysregulation of calcium, magnesium and carbohydrate metabolism.^{7,10}

It has also been suggested that glycaemic control has a role in bullosis diabeticorum formation.^{4,9} Larsen *et al.* suggested poor glycaemic regulation, particularly hypoglycaemia and highly variable glycaemia, has an important role in diabetic bullae formation.⁴ They report hypoglycaemic episodes near the time of bullae formation in 20 out of 35 outbreaks in their retrospective case series analysis. Wilson *et al.* published a retrospective case study analysis examining a patient with bullosis diabeticorum over an 11-year period and recorded blood glucose on 50 occasions during bullae occurrence and 50 occasions when bullae were not present.⁹ The study revealed the patient was more likely to experience bullae formation when his blood glucose level was elevated (t-test analysis, $p < 0.007$).

These theories of pathophysiology do not account for the cases of bullosis diabeticorum in patients with impaired glucose tolerance or in those as their first presentation of diabetes mellitus.^{5,16,17} It is also important to note that these theories do not explain why there is an absence of bullosis diabeticorum in the majority of patients with chronic and complicated diabetes.

Management

There is no clinical trial to inform best clinical practice. While some have advocated aspiration of the bulla,¹⁸ others have opposed this citing risk of introducing infection.¹⁹ The management focuses on good wound care when ulcers occur. Treatment with antibiotics is indicated if infection is suspected.

Conclusion

This report describes an unusually severe case of bullosis diabeticorum that resulted in prolonged hospitalisation, significant morbidity with bilateral below knee amputations, reduced quality of life and a strain on health care resources.

Key points

- Bullosis diabeticorum is a recognised skin condition associated with diabetes
- Bullosis diabeticorum does not always follow a benign uncomplicated self-limiting course
- The underlying disease mechanism is not well established
- Management focuses on good wound care and antibiotic therapy when indicated

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Declaration of interests

There are no conflicts of interest declared.

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