Human papillomavirus involvement in a diabetic foot ulcer: A case report

Shelly Griffiths, David Fish, Brian T Andrews

Article points

1. Foot callus is highly predictive of later ulcer formation in people with diabetes.
2. The authors report a case of diabetic foot ulceration in association with verruca.
3. A patient presented with a plantar ulcer with a wart-like lesion in close proximity; the ulcer had features typically seen in plantar warts.
4. The possible relationship between HPV infection, callus formation and subsequent ulceration deserves more thorough investigation

Keywords
- Human papillomavirus
- Infection
- Verruca
- Wart

Author details can be found on the last page of this article.

Callus on the sole of the foot has been found to be highly predictive of subsequent ulcer formation among people with diabetes (Murray et al, 1996). It is generally accepted that such a callus is secondary to altered loading of the metatarsal heads seen in people with diabetic peripheral neuropathy, and possibly also as a consequence of soft tissue glycation (Reddy, 2003). Such calluses could be plantar warts caused by human papillomavirus. Here, the authors report a case of diabetic foot ulceration in association with verruca.

Diabetic foot ulcers are a common health problem. It is estimated that 15% of people with diabetes require hospitalisation as a result of the complications of diabetic foot ulcers (Frykberg et al, 2006). Diabetic foot ulceration is the most common cause of non-traumatic lower extremity amputations, acting as a precursor in 85% of cases (Pecoraro et al, 1990; Jeffcoate, 2005). The incidence of diabetes-related amputation is 5.7 per 100 000 people per year (Deerochanawong et al, 1992). Given the increasing incidence of diabetes in the general population, with the World Health Organization estimating the prevalence of diabetes in the UK at 2.7 million by 2030 (World Health Organization, 2012), this is a significant health problem.

The presence of a callus on the sole of a diabetic foot has been found to be highly predictive of subsequent ulcer formation (Murray et al, 1996). It is generally accepted that such a callus could be secondary to the altered loading of the metatarsal head, possibly as a consequence of soft tissue glycation (Reddy, 2003). However, it is not entirely inconceivable that such a callus could in fact be a plantar wart caused by human papillomavirus (HPV) types 1, 2, 4, 27 and 57 (Gibbs et al, 2003).

It has been suggested elsewhere that warts in the immunocompromised person with diabetes are a potential trigger for ulceration (Li et al, 2010). Here, the authors report a case of diabetic foot ulceration in association with verruca.

Case report

A 44-year-old man (Mr J) with type 2 diabetes presented with a painful, full-thickness plantar ulcer underlying the first metatarsal head on his left foot. Mr J described the ulcer as being of 18 months' duration and having originated

from an area of hyperkeratotic skin. There was a second small wart-like lesion in close proximity which had appeared prior to ulcer formation (*Figure 1*). The ulcer demonstrated macroscopic features typically seen in plantar warts (*Figure 2*), i.e. a change in the regular papillary skin lines, thrombosed dermal capillaries and bleeding from dilated capillaries following debridement (Stulberg and Hutchinson, 2003), which was undertaken on a fortnightly basis.

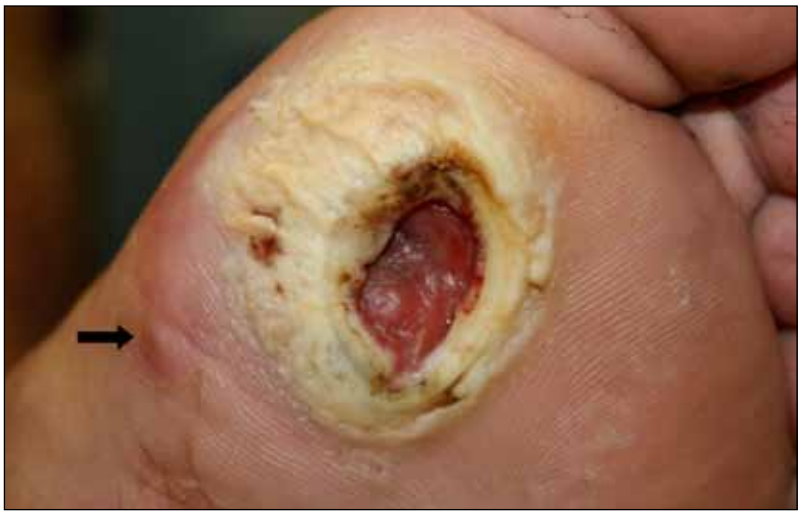
Histological examination of the ulcer edge (at ×200 magnification) demonstrated a hyperkeratotic, mildly papillomatous epidermis with the presence of koilocytes (*Figure 3*), suggestive of viral aetiology of the lesion. P16 immunohistochemical labelling of infected koilocytes was negative; however, because this only detects high risk strains, this is not surprising. A series of three plain films over 5 months failed to demonstrate any evidence of osteomyelitis.

Diabetic control, achieved with metformin (500 mg three times a day) and NovoMix 30 (biphasic insulin aspart; Novo Nordisk, Crawley); 30–40 units three times a day), was moderate with an HbA_{1c} of 64–86 mmol/mol (8–10%). Diabetic complications included moderate to severe bilateral pre-proliferative retinopathy but no peripheral vascular disease, with peripheral pulses present and no evidence of ischaemia. Wound swabs were negative.

Topical treatment with Duofilm® (Stiefel, Uxbridge) was initiated, both to the peri-wound surface and to the neighbouring wart-like lesion. Pressure-relieving orthotics were also supplied, initially with an Aircast® (DJO Global, Vista, USA) removable boot and then with a VACO®diaped (OPED, Valley, Germany), as the patient declined a total-contact cast.

The smaller lesion responded well to topical salicylate and cleared quickly. However, little improvement was seen in the ulcer after 16 weeks of treatment, probably owing to a combination of pressure effects and impaired immunity. The patient did not want to try further medical treatment and requested a transmetatarsal amputation of the left hallux, allowing total excision of the ulcer.

Figure 1. Ulcer on the left foot, located over the first metatarsal head. Note the second, small lesion resembling a plantar wart (arrow).



Discussion

The propensity of people with diabetes to develop foot ulceration may be the result of a combination of impaired pedal vascularity and bony deformities secondary to peripheral neuropathy and soft tissue glycation. These deformities may initially cause a callus and subsequent pressure necrosis, leading to eventual ulceration of the sole of the foot. However, it is conceivable that in people with diabetes callosities from plantar warts may either contribute to pressure necrosis or ulcerate as

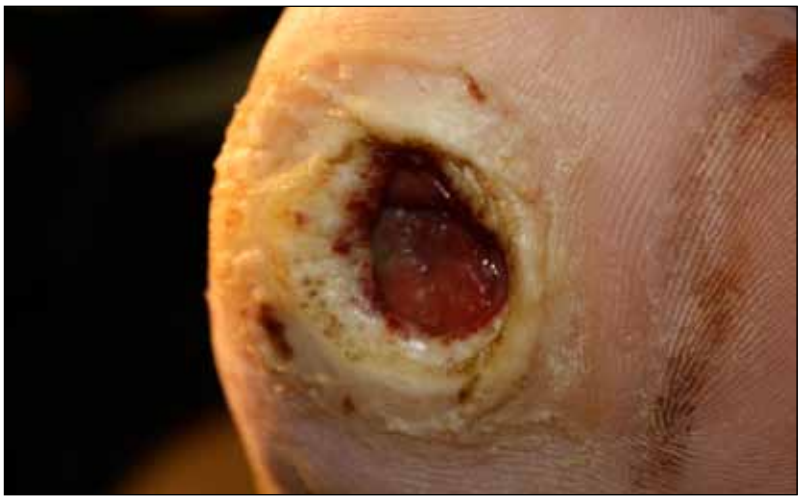


Figure 2. Characteristically abnormal dermatoglyphics distorted by the ulcer and prominent thrombosed dermal capillaries in the skin of the ulcer crater.

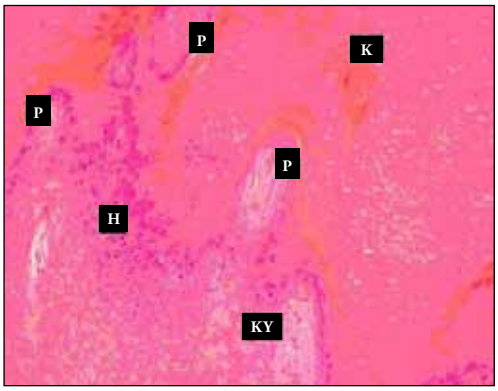


Figure 3. Skin section showing features consistent with a plantar wart hyperkeratosis (K), papillomatosis (P), hypergranulosis (H) and occasional koilocytes (KY). Magnification ×200.

Authors

Shelly Griffiths is Senior House Officer, Department of Surgery, Medway Maritime Hospital, Gillingham; David Fish is Consultant Histopathologist and Clinical Lead in Cellular Pathology, Department of Histopathology, Maidstone & Tunbridge Wells NHS Trust, Maidstone, Kent; Brian T Andrews is Consultant General and Vascular Surgeon, Department of Surgery, Medway Maritime Hospital, Gillingham, Kent.

a result of uncontrolled viral activity in the context of the impaired immunity seen in people with diabetes (Moutschen et al 1992).

Viral warts are most common in children and adolescents, with an estimated prevalence of 20% (Sterling et al, 2001). The prevalence in an adult population is 3.28% (Rea et al, 1976). In people without diabetes, plantar warts do not generally progress to ulceration, with up to 83% healing spontaneously or as a result of topical treatment (Gibbs et al, 2003).

Given that diabetic foot ulcers and plantar warts are relatively common conditions, it is surprising that there is such little discussion in the literature on the possible association between HPV and diabetic foot ulcers. If HPV infection were found to be a significant cause of diabetic foot ulceration this would certainly be clinically significant and could well alter the management of such lesions. A study of six patients (Li et al, 2010) did not find evidence of HPV infection on nested polymerase chain reaction. This is not surprising given the small number of participants in relation to the 3% prevalence of viral warts in the adult population. There have been no studies of large enough size to draw adequate conclusions.

The possible relationship between HPV infection, callus formation and subsequent ulceration deserves more thorough investigation in order to evaluate the efficacy of a novel therapeutic approach aimed at eradicating HPV in patients with histological evidence of such an infection. ■

Deerochanawong C, Home PD, Alberti KG (1992) A survey of lower limb amputations in diabetic patients. *Diab Med* **9**: 942–6

Frykberg RG, Zgonis T, Armstrong DG et al (2006) Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg* **45**(5 Suppl): S1–66

Gibbs S, Harvey I, Sterling JC, Stark R (2003) Local treatments for cutaneous warts. *Cochrane Database Syst Rev* **3**: CD001781

Jeffcoate WJ (2005) The incidence of amputation in diabetes. *Acta Chir Belg* **105**: 140–4

Li L, Iwamoto S, Cha J, Falanga V (2010) Diabetic foot ulcer calluses show histological similarities to HPV infection without evidence of HPV involvement by nested PCR. *Int J Low Extrem Wounds* **9**: 84–9

Moutschen MP, Scheen AJ, Lefebyre PJ (1992) Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. *Diabete Metab* **18**: 187–201

Murray HJ, Young MJ, Hollis S, Boulton AJ (1996) The association between callus formation, high pressures and neuropathy in diabetic foot ulceration. *Diabet Med* **13**: 979–82

Pecoraro RE, Reiber GE, Burgess EM (1990) Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care* **13**: 513–21

Rea JN, Newhouse ML, Halil T (1976) Skin disease in Lambeth. A community study of prevalence and use of medical care. *Br J Prev Soc Med* **30**: 107–14

Reddy GK (2003) Glucose-mediated in vitro glycation modulates biomechanical integrity of the soft tissues but not hard tissues. *J Orthop Res* **21**: 738–43

Sterling JC, Handfield-Jones S, Hudson PM, British Association of Dermatologists (2001) Guidelines for the management of cutaneous warts. *Br J Dermatol* **144**: 4–11

Stulberg DL, Hutchinson AG (2003) Molluscum contagiosum and warts. *Am Fam Physician* **15**: 1233–40

World Health Organization (2012) *Prevalence of diabetes in the WHO European Region*. Available at http://bit.ly/I2LLyO (accessed 23.04.12)