Nonhealing Wounds with Verrucous Presentation in the Neuropathic Patient

A Report of Two Cases

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Verrucous skin lesions on the feet of diabetic patients in conjunction with a neuropathic foot ulcer is an uncommon incident. Currently, there are approximately 20 reported cases in the literature. Herein we report two cases of verrucous lesions superimposing a chronic diabetic ulcer. Patients failed several conservative treatments, and several biopsies were performed with inconclusive results, suggesting possible underlying verrucous carcinoma. Given the possibility of underlying malignancy, both patients were treated with wide excision, and both were negative for malignancy, thus confirming verrucous skin lesions on the feet in diabetic neuropathy. We also summarize the current literature on verrucous skin lesions on the feet in diabetic neuropathy. (J Am Podiatr Med Assoc 109(6): 471-476, 2019)

Gerbig and Hunziker[1] coined the term *verrucous skin lesions on the feet in diabetic neuropathy (VSLDN)* in 1995. The lesion itself is very difficult to treat, and its pathogenesis is unclear. Several authors have speculated that the etiology of the lesion is related to chronic pressure in an area of sensory loss.[1-4] Currently, there are approximately 20 reported cases in the literature. The worldwide incidence is unknown given the rarity of the condition. The etiologies of VSLDN and diabetic ulcers are similar in that both develop at the site of chronic irritation with sensory loss.

Categorized as a pseudoepitheliomatous hyperplasia, VSLDN causes exophytic and endophytic keratinocyte proliferation triggered by chronic irritation.[5] It is associated with diabetes because diabetic patients have vascular disturbance, which may lead to adipose and muscle atrophy. Increased focal pressure at bony areas of the foot may cause chronic irritation. In addition, autonomic neuropathy causes skin dryness, which will result in epidermal thickening and hyperkeratosis.[3]

Verrucous carcinoma (VC) is rare and is a low-grade variant of squamous cell carcinoma. It is characterized by its slow-growing and exophytic nature.[6-11] Typically, VC develops at sites of chronic irritation and inflammation. Fortunately, most cases have a good prognosis, local recurrence is uncommon, and metastasis is rare. It is most commonly seen in middle-aged white men.[12,13] The condition was first described in the oral cavity by Ackerman in 1948,[14] with the first case in the foot reported by Mayron et al in 1988.[15] Currently, more than 50 cases have been described in the literature pertaining to the foot.[12,14,15] Because of its slow-growing nature and verrucous appearance, it is commonly misdiagnosed as a plantar wart when presented in the foot and is treated as such for years until it becomes more invasive.[6,8-11,16] Fortunately, it is only locally invasive, affecting underlying periosteum and causing gradual destruction of bone.[16]

Clinically, VSLDN and VC have similar presentations, making it difficult to distinguish one from the other. Treatment of VSLDN is challenging because of its location and because it is usually recalcitrant to common verruca treatment. We present two cases of VSLDN, both with biopsy suspicious for VC.

Case 1

A 66-year-old man, former smoker, with a medical history significant for atrial fibrillation (treated with rivaroxaban), hyperlipidemia, and congenital ab-

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sence of one kidney presented with a chronic right foot ulcer under the first metatarsal head. The patient experienced footdrop and neuropathy of the right lower extremity after previous back surgery. He presented with an open wound under the right first metatarsal measuring 2.5 × 4.0 × 0.5 cm. Clinically, the wound had mild serosanguinous drainage, was 75% fibrotic and 25% granular at the wound base, and had a macerated skin margin, with no probing, tunneling, tracking, or malodor. Initial treatment included sharp debridement, gel foam to the center of the wound, sterile cadexomer gel with iodine, and dry dressing daily. The patient was instructed to be partial weightbearing in a forefoot relief shoe. Deep wound culture showed moderate *Staphylococcus aureus*, and radiographic findings were nonsignificant.

A shave biopsy revealed the stratum corneum with parakeratosis and intracorneal hemorrhage, with the possibility of higher-grade underlying epithelial dysplasia. A repeated biopsy showed sparse portions of superficial macerated papillomatous epidermis without significant cytologic atypia. Microscopic differential diagnosis included stratum corneum overlying a verruca, but it could also represent VC (Figs. 1 and 2).

The lesion continued to persist after 10 months of treatment despite continued local wound care and use of a total-contact cast (Fig. 3). Given the chronicity of the wound, inconclusive repeated biopsies, and verrucous presentation of the wound, we suspected possible underlying VC. The patient was then referred to a plastic surgeon for wide excision of the lesion (Fig. 4). Frozen section was negative for malignancy. The wound then received six applications of skin substitute; the patient was then lost to follow-up.

The patient presented to the emergency department 10 months later with cellulitis of the right foot and admitted to noncompliance. The wound had a fibrogranular wound base, purulence drainage, malodor, probing to bone, periwound erythema, sinus tracking, and undermining. Radiographs showed signs of osteomyelitis, resulting in a partial first-ray resection, with bone biopsy confirming osteomyelitis.

Case 2

A 52-year-old man with a medical history significant for chronic kidney disease, type 2 diabetes (hemoglobin A_{1c} level of 9.2%), dyslipidemia, hypertension, heart failure, stroke, and coronary arterial disease presented with preulcerative lesions under

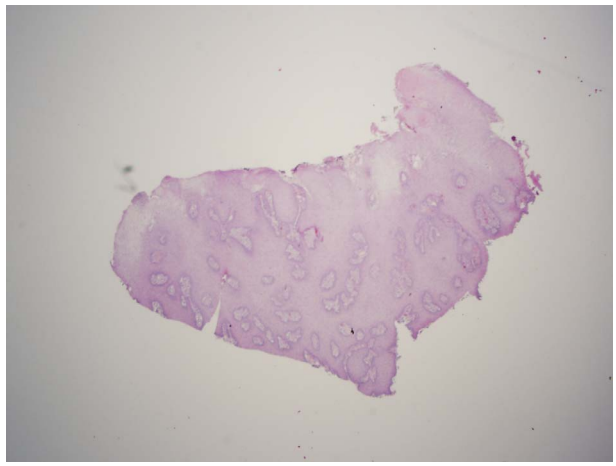


Figure 1. Skin biopsy sample from the wound under the first metatarsal head (×20).

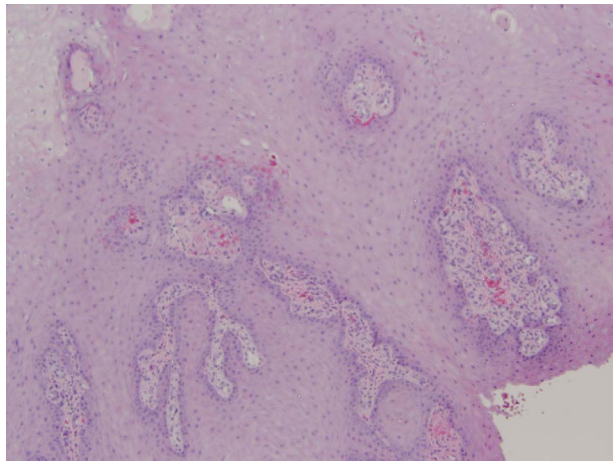


Figure 2. Sparse portions of superficial macerated papillomatous epidermis without significant cytologic atypia (×100).



Figure 3. Wound presentation at 10 months. The wound had been recalcitrant to various conservative treatments.



Figure 4. Wound presentation 1 month after surgical wide excision.

the first and fourth metatarsal heads on the right foot. Preulcerative lesions were treated conservatively.

He returned 2 weeks later with open wounds at the preulcerative areas. On debridement, the wound under the first metatarsal head measured $3.0 \times 3.0 \times 0.7$ cm, and the wound under the fourth metatarsal head measured $2.0 \times 2.0 \times 0.5$ cm. There was positive erythema, warmth, and malodor from the wounds, and the patient was started on cephalexin and off-loading with a forefoot relief shoe. A punch biopsy sample was taken at that time, and the pathology report revealed pseudoepitheliomatous hyperplasia; with a portion of the specimen having a verrucous appearance, we were unable to exclude VC. We called the pathologist to discuss the pathology result, and the pathologist recommended serial wound biopsy. Deep wound culture grew *Enterococcus* species.

The wounds were closed with local wound care and off-loading after 7 months. No advanced biological agents were used. During the 7-month treatment course, a repeated biopsy was performed and yielded similar pathology results.

Within 3 weeks of healing the patient developed a blister under the first metatarsal head, medial to the previously closed wound. The blister was drained and measured $5.0 \times 5.0 \times 0.1$ cm (Fig. 5). A culture was taken and it grew back *Pantoea* species. After an additional 3 months of local wound care, the wound closed, but it reopened again shortly after.



Figure 5. Wound presentation after blister drainage.

Moreover, the verrucous presentation of the wounds worsened each time (Fig. 6). Given that there had been multiple inconclusive biopsies and VC could not be excluded, the patient was referred to a plastic surgeon for wide excision of the wound (Fig. 7).

The frozen section of the wound was negative for malignancy. The wounds were excised and left open to heal via secondary intention. The wounds were treated with a combination of 0.25% acetic acid wet-to-moist (changed three times a day), collagenase, and off-loading. At the most recent visit, the patient's wound under the fourth metatarsal head had closed, and the wound under the first metatarsal head measured $0.6 \times 1.0 \times 0.2$ cm full thickness with hyperkeratotic verrucous periwound and no erythema, warmth, malodor, active drainage, tunneling, or undermining (Fig. 8). He is currently undergoing management at a wound care center secondary to proximity to his home.



Figure 6. The wound worsened despite conservative treatment and off-loading.



Figure 7. Wound presentation 1 month after wide excision.



Figure 8. Wound presentation 10 months after wound excision.

Discussion

The VSLDN has proved to be difficult to treat. It is recalcitrant to typical verrucous treatments. Previous studies have shown that cryotherapy, electrocoagulation, debridement, salicylic acid, and tropical glutaraldehyde are ineffective.[2,5] Sakai et al[5] successfully treated one patient with a combination of tacalcitol, 5-fluorouracil, and tretinoin for 16 days. Murao et al,[2] on the other hand, treated their patient only with topical maxacalcitol, and the lesions resolved after 6 weeks. Yamauchi et al[3] treated their patient with 8 weeks of off-loading using a hollowed-out sponge. This suggests that using multiple topical medications is more effective than single-drug therapy (Table 1).

Both patients presented with VSLDN and had the lesions treated as neuropathic ulcers with superimposed verruca initially. After weeks of conservative treatment with no improvement, skin punch biopsies were performed and the results were inconclusive and suggested possible underlying VC. The pathologist recommended serial biopsies. Repeated biopsy yielded similar results. Ideally, both patients should have been treated with topical 5-fluorouracil, tretinoin, and vitamin D_3, but secondary to potential underlying malignancy and inconclusive biopsy results, the authors decided to refer the patients to a plastic surgeon for wide excision of lesions. Pathology reports came back negative for malignancy, thus confirming VSLDN.

This article highlights the rare condition of VSLDN. It is important to recognize VSLDN and to distinguish it from plantar verruca and VC; VSLDN requires a unique treatment approach because typical verrucous treatments are ineffective. With delayed diagnosis or misdiagnosis, patients may undergo futile verruca treatments, affecting quality of life and increasing the financial burden of treatment. Whereas with VC, there are multiple treatment options (Table 2).

The main limitation of this report is the small number of patients, but VSLDN is an uncommon condition that is rarely reported in the literature. In addition, the patient in the first case did not have diabetes, but he did have neuropathy secondary to low-back surgery. The second patient changed his wound care provider, thus preventing us from further follow-up after the surgical wound excision. Potential further research on VSLDN is needed, including identifying its pathogenesis and a larger cohort study to evaluate current treatment modalities.

Table 1. Current Treatment Options for Verrucous Skin Lesions on the Feet in Diabetic Neuropathy

Drug	Class	Mechanism of Action
5-fluorouracil[5]	Chemotherapeutic agent	Potent antiproliferative agent Primarily affects cells actively synthesizing DNA
Maxacalcitol Tacalcitol	Vitamin D_3 analogue	Regulate proliferation and differentiation of keratinocytes May help reepithelialization
Tretinoin	Vitamin A derivative	Inhibitory effect on keratinocyte differentiation Enhance percutaneous absorption of chemicals Synergistic effect when used with above drugs

Table 2. Treatment Options for Verrucous Carcinoma

Treatment	Advantage	Disadvantage
Surgical excision	Highly effective	Arbitrary margin, excess tissues are often taken, causing a large wound[18]
Mohs surgery	Maximum cure with minimal local tissue loss Great for sensitive areas, such as the anogenital and oral regions	Not as beneficial in late stage due to deeper tissue involvement[12,17,19,20] Procedure can be tedious and prolonged
Cryotherapy	Safe and cost-effective	Lacks precision Low cure rate[21,22]
Radiation	Potentially avoid trauma to the soft tissue Viable option for patients who are not ideal surgical candidates	High risk of transforming a low-grade SCC into a high-grade aggressive SCC[23–25] Cost Requires multiple treatments Risk of developing osteoradionecrosis

Abbreviation: SCC, squamous cell carcinoma.

Conclusions

VSLDN is an uncommon condition that clinically mimics VC. Its pathogenesis is obscure, and it is recalcitrant to normal verruca treatments. It is important to distinguish VSLDN from VC because VSLDN requires a unique multitherapy treatment approach. If VC is detected early, Mohs surgery is the preferable technique for optimal cure with minimal local tissue damage.

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