Wart on fire: A rare entity of verruciform xanthoma arising on a lower leg in a setting of chronic lymphedema

Simon F. Roy,[a] Robert Prokopetz, MD, FRCPC,[b] Yasmine Ayroud, MD, FRCPC,[b] Laura Pickett, MD,[c] and Ivan V. Litvinov, MD, PhD, FRCPC[c]
Montreal, Quebec, Canada and Ottawa, Ontario, Canada

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INTRODUCTION

Verruciform xanthoma (VX) is an uncommon papillomatous lesion occurring most frequently in the oral mucosa. We present a rare case of VX arising within a leg ulcer in a patient with a longstanding history of lymphedema in both legs.

CASE PRESENTATION

A 71-year-old white man was evaluated in the dermatology department for a nonhealing cutaneous ulcer on the right lower leg. This patient had multiple comorbidities including previous spinal injury, right hemiparesis from a stroke, venous insufficiency, gastroesophageal reflux, hypertension, well-controlled hyperlipidemia, osteoarthritis, and lymphedema secondary to previous trauma. Historic fasting lipid profile evaluations in this patient from 2005 documented only a mild elevation of triglycerides at 209.7 mg/dL (normal, <200 mg/dL), unremarkable total and high-density lipoprotein cholesterol findings. Following a statin therapy initiated in 2008, his hypertriglyceridemia resolved, and 2016 fasting lipid profile showed normal values. His venous insufficiency was managed with 30- to 40-mm Hg compression bandages. Approximately 3 years before presenting to our service, he noticed a small nodule on his right leg, which slowly grew over the last 2 years and developed both an exophytic and ulcerating aspect. It was mostly asymptomatic and occasionally bled. He recalls having sustained multiple minor injuries to his shins in the past. Because this patient was wheelchair bound, treating his venous insufficiency and lymphedema was challenging. The ulcer on his right leg was managed with weekly wound dressings and leg elevation.

Abbreviations used:

HPV: human papilloma virus
VX: verruciform xanthoma

Physical examination found a 5- by 7-cm oval shallow ulcer on the right anterior shin, with a soft "cauliflowerlike" mass at the upper border of the ulcer (Fig 1, *A*). There were no signs of necrosis or expanding erythema. The stemmer sign for lymphedema was positive, and nonpitting edema was observed. Inguinal lymph node examination was unremarkable. To rule out Marjolin ulcer, or a squamous cell carcinoma arising in a chronic venous ulcer, a deep shave biopsy of the papillomatous mass and the ulcer border was performed. Histopathologic analysis found a keratotic verrucous papillomatous lesion on low power (Fig 1, *B*). On higher power, foamy histiocytes filled the expanded papillary dermis of the lesion (Fig 1, *C*). Dissecting parakeratosis was also noted on high magnification (Fig 1, *D*). These findings established the diagnosis of a VX. The tumor expressed p16 protein, compared with the adjacent uninvolved epidermis (Fig 1, *E* and *F*). This finding strongly suggests direct involvement of human papilloma virus (HPV) in the pathogenesis

From the Faculty of Medicine, McGill University[a]; the Department of Pathology, the Ottawa Hospital, University of Ottawa[b]; and the Division of Dermatology, Ottawa Hospital Research Institute, University of Ottawa.[c]

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Correspondence to: Ivan V. Litvinov, MD, PhD, FRCPC, Box 926, 501 Smyth Road, Ottawa, Ontario K1H 8L6, Canada. E-mail: ilitvinov@toh.on.ca.

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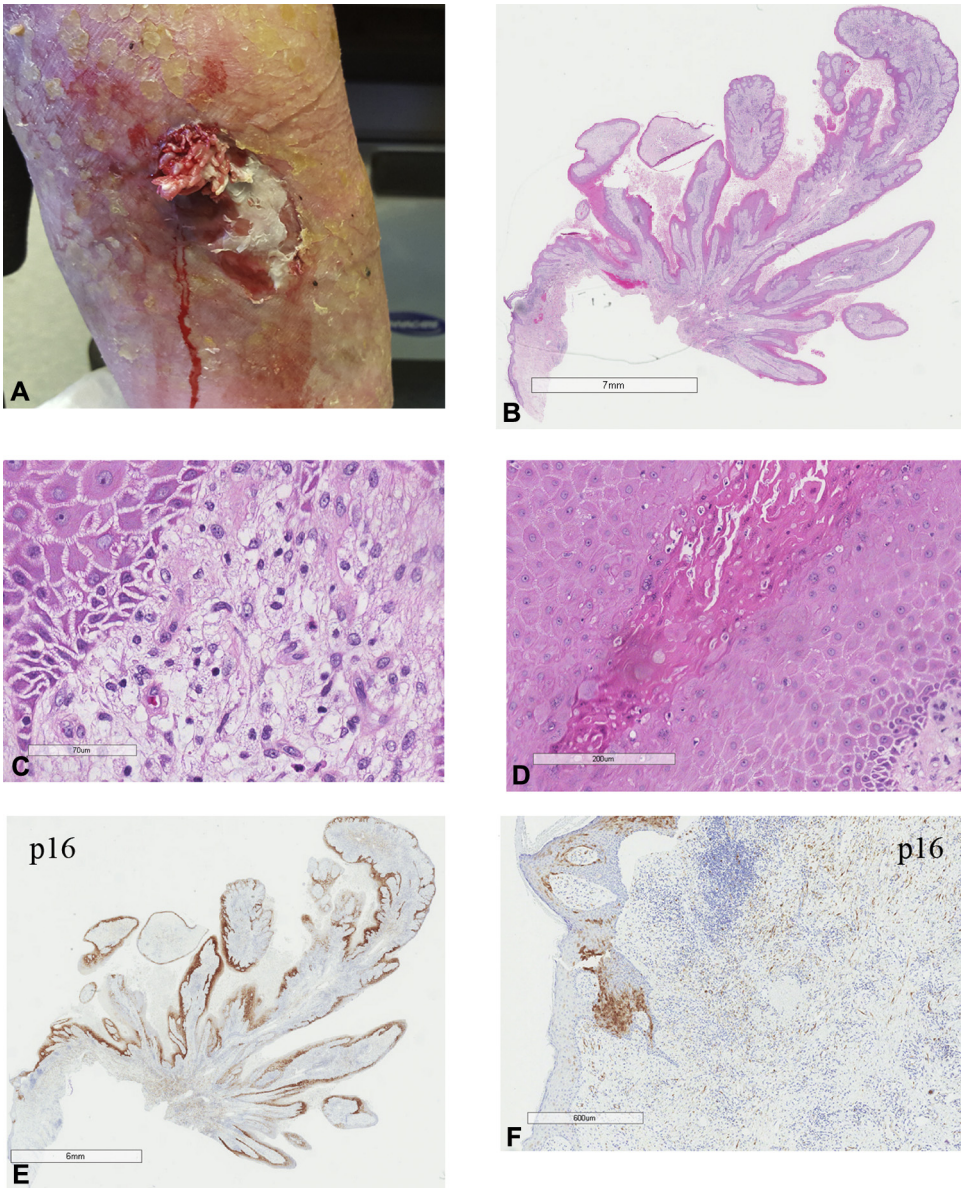

Fig 1. Clinical and pathologic presentation of VX. **A**, Soft papillomatous tumor arising within the proximal border of a shallow ulcer on the right anterior tibia. **B**, Low-power view of the papillomatous (fingerlike) appearance of the mass. **C**, Foamy histiocytes infiltrating the dermis. **D**, Brightly eosinophilic parakeratosis dissecting into the dermis. **E**, Low-power view of p16 staining of the lesion. **F**, High-power view of p16 staining of the lesion.

of this lesion. After saucerization of the lesion, the ulcer healed within 3 months.

DISCUSSION

VX is a rare benign papillary nodule that typically occurs in the oral mucosa. It may have a reddish color and a rough cobblestonelike surface and is usually a solitary lesion. The base may be sessile or pedunculated.[1] First reported in 1971 by Shafer,[2] who coined the term *verruciform xanthoma*, a worldwide literature survey from 1971 to 2001 reported 282 cases of oral VX. Extraoral cases tend to involve the scrotum or anogenital mucosa and amounted in 2001 to 46 cases.[3] Fewer than 40 cases of extraoral/extragenital VX are reported in the English-language literature.[4] Based on our literature review, to our knowledge, this is the first known case of VX arising in an ulcer.

Clinically, cutaneous or extraoral/extragenital VX resembles oral VX. A useful clinical hint is that the lesion is often soft on palpation compared with verrucous carcinoma or other malignancies. The

differential diagnosis of this exophytic lesion may include squamous cell carcinoma, squamous papilloma, giant molluscum contagiosum, and verruca vulgaris.[5] VX is slightly more frequent in whites and men. Even though most cutaneous xanthomas are associated with hyperlipidemia, VXs are often not linked to the disorders of lipid metabolism.[6]

On histologic examination, the major pathognomonic feature is the presence of foamy macrophages filled with lipids (or so-called xanthoma cells) in the papillary dermis. The second main feature is the papillomatous appearance best seen on low-power magnification. This appearance may also be described as a verrucous acanthosis, with the absence of hypergranulosis and koilocytes that would favor a diagnosis of verruca vulgaris.[7] It is not commonly known, however, that the presence of brightly eosinophilic focal dissecting parakeratin is a helpful histologic feature. In light of this, Rush and Bennett[7] coined the term a *wart on fire* to illustrate this histologic feature. We believe it is important to look for this classic feature on histopathology when a diagnosis of VX is suspected.

Immunohistochemistry for these tumors is seldom done, but it has been found that the foamy cells forming these lesions originate from a macrophage lineage. Neutrophils may also be incidentally present along with a mild lymphocytic infiltrate.[3] It remains unknown whether HPV is involved in the pathogenesis of VX.[8] Some studies, similar to this one, found the presence of HPV, whereas others failed to confirm this association.[9] Notably, the negative reports were criticized for using condylomas as a positive control, with usual high HPV DNA copies, and their assay may not have been sensitive enough to detect small copy numbers of the HPV genome in VX lesions.[9]

Analysis of 40 case reports of extraoral/extra-anogenital VX found that several of them were associated with the congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, cutaneous trauma, inflammatory disorders, and lymphedema.[8] Interestingly, for patients with lymphedema, ultrastructural studies documented that the foamy xanthoma cells use the degenerating epidermis as a lipid source. Hence, supporting theories proposed by Zegarelli[10] and Mohsin[11] indicate that any cutaneous insult such as chronic lymphedema or trauma may be in part responsible for the appearance of VX. Trauma may induce the secondary xanthomatous changes in VX, without requiring a primary pathologic process of perturbed lipid metabolism, which is often present in other true xanthomas such as xanthelasma and tuberous xanthoma. In addition, consumption of the excess of lipoproteins in the extracellular lymphatic fluid by the dermal histiocytes was also proposed as a pathogenic mechanism for these lesions.[8] In that regard, it is known that improving lymphedema and venous insufficiency may help treat VX, and compression therapy may be the only therapeutic modality necessary to prevent additional lesions.[12]

Although extraoral/extragenital VXs are extremely rare, we believe this diagnosis should be considered in patients with longstanding lymphedema and a history of trauma. We also propose that a p16 staining for HPV should be considered and, if positive, cryotherapy or other first-line therapies for warts could be used to treat these lesions in case of recurrence.

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