

**Case presentation**

**Verruciform Genital-Associated (Vegas) Xanthoma: report of a patient with verruciform xanthoma of the scrotum and literature review**

**Bryce D Beutler<sup>1</sup>, Philip R Cohen<sup>2</sup>**

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**<sup>1</sup>School of Allied Health Sciences, University of Nevada, Las Vegas, Nevada**

**<sup>2</sup>Department of Dermatology, University of California San Diego, San Diego, California**

**Correspondence:**

Bryce D. Beutler, BS  
1060 Wiegand Road  
Encinitas, CA 92024  
brycebeutler@hotmail.com

Philip R. Cohen, MD  
10991 Twinleaf Court  
San Diego, CA 92131-3643  
mitehead@gmail.com

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**Abstract**

**Background:** Verruciform xanthoma is a benign verrucous lesion characterized by epithelial acanthosis and lipid-laden foamy histiocytes in the connective tissue papillae. It typically presents as a papillomatous, polypoid, or sessile lesion. Verruciform xanthoma is most commonly observed within the oral cavity. However, albeit less frequently, it develops on the penis, scrotum, or vulva.

**Purpose:** We describe the clinical and pathologic findings of a man who developed a verruciform xanthoma on his scrotum. We also summarize the associated conditions, the differential diagnosis, the postulated pathogenesis, and the treatment options for this tumor.

**Materials and methods:** The features of a man with a scrotal verruciform xanthoma are presented. Using PubMed, the following terms were searched and relevant citations assessed: anogenital, foam cells, penis, scrotum, verruciform, verruciform xanthoma, vulva, and xanthoma. In addition, the literature on verruciform xanthoma is reviewed.

**Results:** Our patient developed an asymptomatic, exophytic, red filiform papule on his scrotum. A shave biopsy, attempting to remove the entire lesion, was performed. Based on correlation of the clinical presentation and histopathologic findings, a diagnosis of verruciform xanthoma was established. The patient applied mupirocin 2% ointment to the biopsy site, which subsequently healed without complication or recurrence.

**Conclusion:** Verruciform xanthoma is a benign tumor commonly located within the oral cavity and characterized by the development of a small verrucous, papillomatous, polypoid, or sessile growth. Extraoral sites of verruciform xanthoma often include the penis, scrotum, or vulva; we introduce the term 'Vegas' (Verruciform Genital-Associated) xanthoma for these lesions. The lesions are often mistaken for viral warts or malignancies. Although the mechanism of pathogenesis is unknown, verruciform xanthoma may have a multifactorial etiology involving inflammation, local immunosuppression, and/or metabolic dysfunction. It has also been postulated that verruciform xanthoma is a secondary reaction to trauma-induced epithelial damage or degeneration. A biopsy for histopathologic examination is required to diagnose verruciform xanthoma. The treatment of verruciform xanthoma typically involves simple surgical excision.

**Keywords: anogenital, foam cells, penis, scrotum, verruciform, verruciform xanthoma, vulva, xanthoma**

## Introduction

Verruciform xanthoma is a benign lesion that is most commonly observed within the oral cavity. However, albeit rarely, verruciform xanthoma can develop on the penis, scrotum, or vulva [1-3]. Lesions often morphologically mimic other conditions, including malignancies and infections. Therefore, microscopic assessment is required for diagnosis. Verruciform xanthoma has a distinctive pathology; the presence of foamy histiocytes in the connective tissue papillae, which enables it to be distinguished from similar-appearing lesions.

We describe a man who developed verruciform xanthoma on his scrotum. We also review associated conditions, the differential diagnosis, the postulated pathogenesis, and the treatment options of verruciform xanthoma.

## Case presentation

A 59-year-old man presented for evaluation with an asymptomatic lesion on his scrotum that was present for three weeks. Physical examination revealed an exophytic, red filiform papule measuring 5 mm x 4 mm x 4 mm on the left side of his scrotum (Figure 1). He was monogamous, heterosexual, and had no known history of sexually transmitted infections, including condylomas.

A shave biopsy was performed. Histopathologic examination showed an exophytic papule with a papillomatous epidermis. The epidermis showed prominent parakeratosis. In the dermal papillae were numerous foamy histiocytes as well as a dense lymphocytic and neutrophilic inflammatory infiltrate (Figure 2).

Based on correlation of the clinical presentation, lesion morphology, and pathology findings, a diagnosis of verruciform xanthoma was established. The lesion had been completely removed by the shave biopsy. The patient applied mupirocin 2% ointment to the biopsy site, which subsequently healed without complication or recurrence.

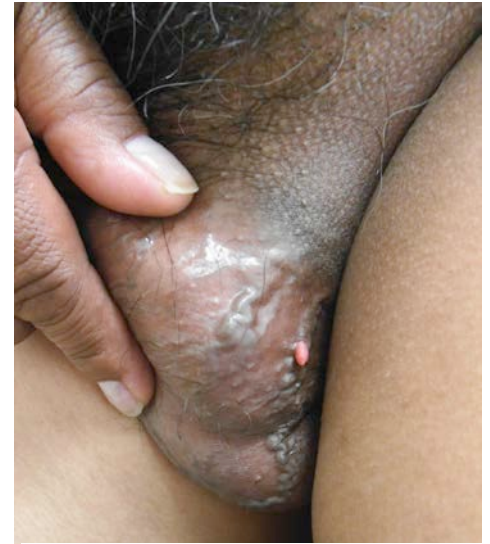
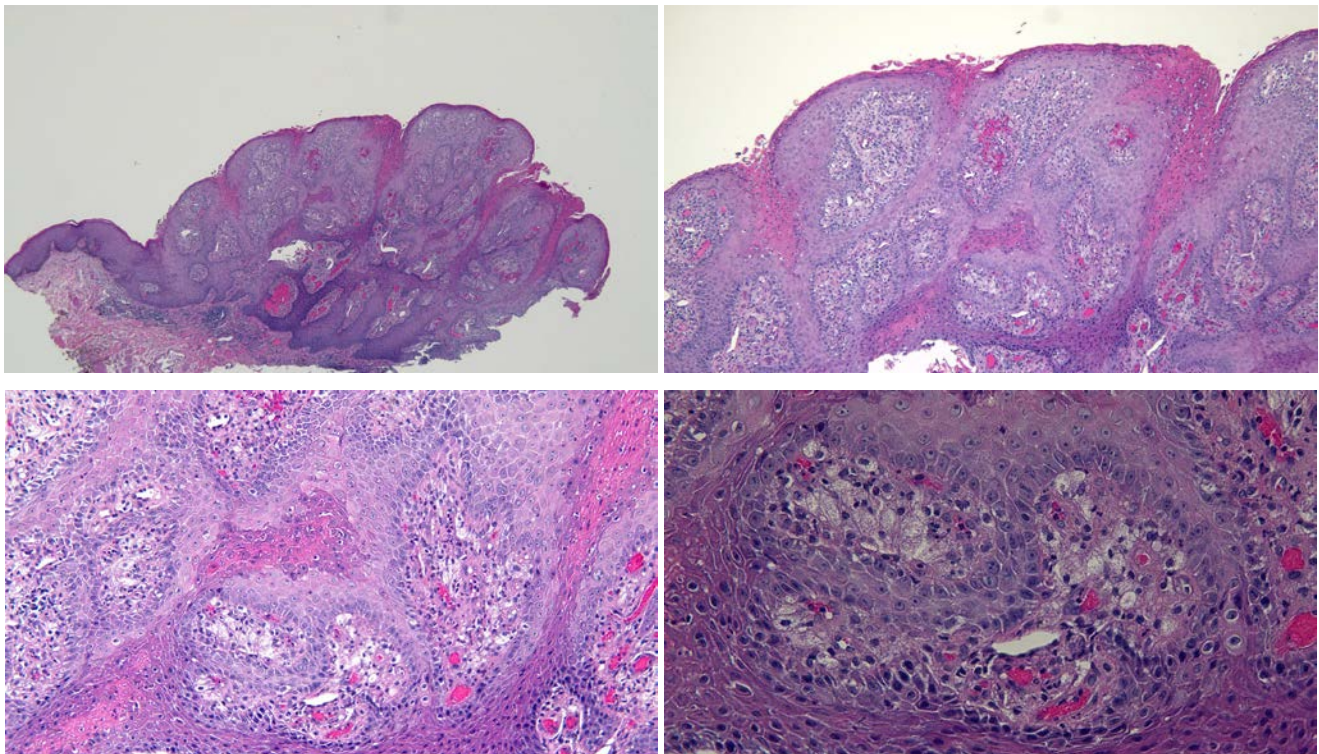
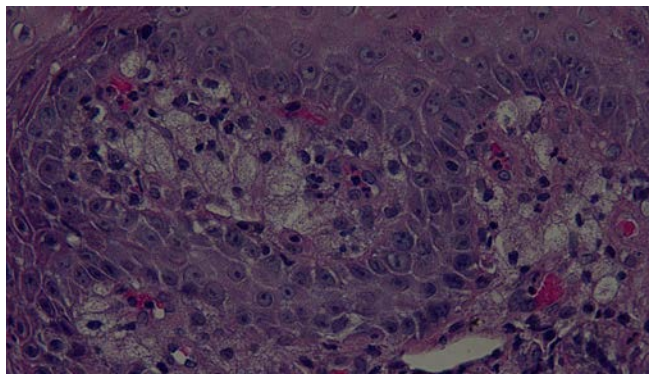


Figure 1. An exophytic red filiform nodule protruding from the left side of the patient's scrotum.





**Figure 2 (a-e).** Low (a), intermediate (b, c), and high (d, e) magnification views of a verruciform xanthoma located on the scrotum. Low magnification view (a) shows an exophytic tumor with a papillomatous epidermis. Intermediate magnification views (b, c) show parakeratosis of the rete ridges which surround areas of the upper dermis. High magnification views (d, e) show aggregates of foamy histiocytes in the dermal papillae; lymphocytes and neutrophils comprise the inflammatory infiltrate.

## Discussion

Verruciform xanthoma was originally described as xanthoma-like nevus by Sachs in 1903 [4]. In 1971, Shafer identified the condition in fifteen patients and proposed the name verruciform xanthoma [5]. The mechanism of pathogenesis for verruciform xanthoma remains to be determined.

Verruciform xanthomata most commonly occur within the oral cavity. The most frequent sites of extraoral verruciform xanthoma include the penis, scrotum, and vulva. Isolated reports of verruciform xanthoma on the ear, forearm, foot, hand, leg, and nose have also been described [6-10].

Oral verruciform xanthoma is typically observed in adults, with a mean age of presentation of 50 years [11]. However, the onset of verruciform xanthoma in either childhood [12] or old age [3] has also been reported. Prior to the age of 50, oral verruciform xanthoma occurs more frequently in men than in women, with a male-to-female ratio of 1.6:1. After the age of 50, however, the ratio reverses in favor of women, the male-to-female ratio becoming 0.8:1 [13]. Most oral verruciform xanthomata are reported in Caucasians, although the condition can also occur in African-Americans (as in our case) and Asians [14].

Extraoral verruciform xanthomata, particularly of the genital skin sites, are extremely rare and there is limited data concerning incidence and prevalence. However, it is interesting to note that there are more reports of genital verrucous xanthomata occurring on the scrotum than the vulva despite the two structures having homologous embryological origins. In a report on extraoral verruciform xanthoma in Japanese men, Nakamura et al. noted that 88% of the lesions developed on the scrotum [11]. Kono later postulated that the condition may be triggered by irritation of the scrotum associated with the Japanese custom of sitting on the floor [15]. It is thus conceivable that genital verrucous xanthomata are more likely to develop on the scrotum than the vulva simply because the anatomical location and structure of the scrotum makes it more vulnerable to pressure, trauma, or irritation.

Verruciform xanthoma typically presents as a solitary red or pink lesion that ranges in size from 0.15 to 2.0 cm [16], although - albeit less common - the lesion may be substantially larger [17]. The surface may appear verrucous, papillary, or granular with a sessile or pedunculated base. The lesions are usually asymptomatic and often persist for months or years prior to the patient seeking evaluation and the diagnosis being established [18-20].

The diagnosis of verruciform xanthoma is established by its pathologic findings. The epidermis commonly shows verrucous acanthosis with hyperkeratosis. In some lesions, as in our patient, there is prominent parakeratosis. In the dermis, a dense lymphocytic and neutrophilic inflammatory infiltrate may be present. The distinguishing feature of verruciform xanthoma is the presence of lipid-laden foamy histiocytes confined to the dermal papillae. PAS-positive, diastase-resistant granules have been found within xanthoma cells [21].

The clinical and pathologic differential diagnosis of verruciform xanthoma is listed in Table 1 [22-24]. It includes several localized benign or malignant tumors or infections.

Table 1. Differential diagnosis of verruciform xanthoma

Clinical	Pathologic
Bowenoid papulosis	Fibrous histiocytoma

Condyloma acuminatum Erythroplasia of Queyrat Granular cell myoblastoma Seborrheic keratosis Squamous cell carcinoma Verruca vulgaris Verrucous carcinoma Vulvar intraepithelial neoplasia	Granular cell epulis Granular cell tumor
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Verruciform xanthoma typically occurs in isolation. However, several conditions - listed in Table 2 - have been associated with verruciform xanthoma [6,25-37]. In addition, verruciform xanthoma has been described in both bone marrow transplant recipients [38] and renal transplant recipients [39]. Notably, many of the conditions associated with verruciform xanthoma either are associated with immunosuppression or are treated with immunosuppressive therapy. Indeed, Kanitakis et al. and Hsia et al. both observed that immunocompromised patients have a higher risk of developing cutaneous verruciform xanthoma [39,40].

Table 2. Conditions and syndromes associated with verruciform xanthoma

Actinic keratoses [6] Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome [26] Discoid lupus erythematosus [27] Epidermolysis bullosa (regressive dystrophic) [36] Epidermal nevus or epidermal nevus syndrome [28] Graft-versus-host disease [29] Human immunodeficiency virus infection [30] Lichen planus [31,35] Lichen sclerosus [32,35] Lymphedema [33] Paget disease [35] Pemphigus vulgaris (oral) [34] Radiodermatitis [35] Snuff dipper's keratoses [37] Squamous cell carcinoma (in situ and invasive) [25,37]
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The mechanism of pathogenesis for verruciform xanthoma is unknown. Indeed, to the best of our knowledge, only a single verruciform xanthoma associated with human papillomavirus has been reported [41]. However, this may have been an incidental finding. Subsequent research to determine if there is a relationship between human papillomavirus and verruciform xanthoma has failed to detect the presence of human papillomavirus antigen by immunohistochemistry, polymerase chain reaction, or in situ hybridization [12,29,42].

In 1974, Zegarelli et al. proposed a multifactorial etiology for the development of verruciform xanthoma [43]. In Zegarelli's model, local irritation induces epithelial degeneration, triggering a neutrophil-mediated inflammatory response. Lipids are subsequently released from damaged keratinocytes and engulfed by macrophages, which ultimately accumulate in the connective tissue papillae as foam cells.

Zegarelli's hypothesis is supported by Mohsin et al., who observed that chemotactic cytokines released by degenerating keratinocytes attract neutrophils and stimulate rapid epidermal growth, conceivably generating a grossly visible lesion [42]. Furthermore, Travis et al. suggested that foamy macrophages release epithelial growth factors that induce epithelial hyperplasia, a feature characteristic of the lesion [12]. However, other investigators argue that verruciform xanthoma would be far more prevalent if the precipitating event was merely local trauma or irritation [14].

It has also been postulated that verruciform xanthoma has an immunological origin. Kanitakis et al. speculated that immunosuppression results in decreased epidermal Langerhans cell density and function [39]. Consequently, lipids and other products released by degenerated keratinocytes must be phagocytized by dermal macrophages, which in turn accumulate in the connective tissue papillae as foam cells.

Mostafa et al. suggested an alternative immunopathogenesis [44]. In a case series of ten verruciform xanthoma, Mostafa et al. identified T lymphocytes as the predominant infiltrating lymphocytes in the lesion; they proposed that the tumor may be a local immunological disorder with a cell-mediated mechanism. However, the specific underlying cause of the immune reaction could not be elucidated.

A third immunologic etiology was recently proposed by Oliveira et al. [45]. They hypothesized that the pathogenesis of verruciform xanthoma is similar to that of lichen planus, in which an autoimmune reaction triggers apoptosis of epithelial cells. Notably, verruciform xanthoma has been observed within oral lichen planus [31].

In 1981, Nowparast et al. introduced a metabolic hypothesis for the origin of verruciform xanthoma [20]. They suggested that the verrucous and papillary architecture of the lesion results from the presence of foam cells, which affect the metabolism of epithelial cells and thereby induce hyperkeratotic changes. Nowparast also noted that the lipid products found within xanthoma cells are similar to those found within foam cells in chronic inflammatory reactions such as periapical cysts and dental granulomas, in which epithelial degeneration is common.

Interestingly, some of the genital verrucous xanthomas appear to have several unique features not seen in oral verruciform xanthoma. In case reports of pedunculated nodular verrucous xanthomas of the vulva and scrotum, Kishimoto et al. identified capillaries and dilated blood vessels in the deep dermis underneath the nodules [46,47]. They hypothesized that some unknown factor could induce vascular ectasias and trigger the following cascade of events: (1) activation of endothelial cells and pericytes in the papillary dermis, (2) release of cytokines and growth factors from the activated cells that stimulate hyperplasia of epidermal keratinocytes, (3) keratinocyte degeneration and release of lipids, (4) accumulation of macrophages, and (5) engulfment of lipids by macrophages, which subsequently accumulate in the dermal papillae as foam cells.

Simple surgical excision is typically effective for the treatment of both oral and extraoral verruciform xanthoma [18,23,28,48]. For most patients, excision of the tumor is curative and the lesion does not recur. However, albeit rarely, alternative interventions may need to be considered.

In a 2013 report, Guo et al. describe a case of verruciform xanthoma of the vulva that was successfully treated with imiquimod [49]. Multiple lesions were present, including one 7 x 5 cm verrucous plaque on the left labia minora. Surgical excision presented substantial risks because of the size and location of the lesions. Therefore, imiquimod cream 5% was applied to the lesions, which began to decrease in size after several weeks and were nearly cleared after four months. Nine months after withdrawal of the medication, the lesions had not recurred and the characteristic foam cells of the lesion had almost disappeared.

Fractionated carbon dioxide laser therapy has also been used to treat verruciform xanthoma of the scrotum [50]. However, there are only a few patients for whom this treatment option has been reported [22,50,51].

Verruciform xanthoma is asymptomatic. If the diagnosis of verruciform xanthoma is confirmed by histological assessment and the patient is not concerned about the cosmetic appearance of the lesion, observation of the tumor may also be a reasonable alternative.

## Conclusion

Verruciform xanthoma is a rare asymptomatic lesion that is distinguishable only by histologic examination. When the tumor is extraoral and involves the penis, scrotum, or vulva, we suggest that they be referred to as 'Vegas' (Verruciform Genital-Associated) xanthoma. Vegas xanthomas are extremely rare and often mistaken for benign or malignant tumors, neoplasms, or viral infections on clinical examination.

The pathogenesis of verruciform xanthoma is unknown. Irritation or trauma may be a precipitating event in the development of the condition. Alternatively, verruciform xanthoma may have an immunological or metabolic origin.

Simple surgical excision is the standard treatment for both oral and extraoral verruciform xanthoma. Infrequently, topical imiquimod cream 5% or fractionated carbon dioxide laser therapy have also been used as treatment alternatives to surgical excision. If the lesion is asymptomatic and the patient is not concerned about the cosmetic appearance of the lesion, clinical observation - without additional intervention - may be appropriate.

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