

ONLINE FIRST

Vulvar Verruciform Xanthoma

Ten Cases Associated With Lichen Sclerosus, Lichen Planus, or Other Conditions

Charlotte Fite, MD; Françoise Plantier, MD; Nicolas Dupin, MD, PhD;
Marie-Françoise Avril, MD; Micheline Moyal-Barracco, MD

Background: Verruciform xanthoma (VX) is a rare benign tumor that usually involves the oral cavity. Since the first report of this tumor in 1971, only 9 cases have been reported on the vulva, and 3 of these were associated with another vulvar condition. We describe the clinicopathologic features of 10 patients with vulvar VX and focus on their associated conditions.

Observation: The mean age of the patients was 68 years (range, 51-80 years). The VX lesions were asymptomatic, yellowish-orange verrucous plaques. The diagnosis was clinically suspected in 2 cases; other suggested diagnoses were condyloma or squamous cell carcinoma. All of the patients had an associated vulvar condition: lichen sclerosus (6 patients), lichen planus (2 patients), Paget disease, or radiodermatitis. Under microscopy, the VX lesions displayed parakeratosis,

acanthosis without atypia, and elongated rete ridges. Xanthomatous cells were aggregated in the papillary dermis.

Conclusions: Vulvar VX is a benign tumor with misleading clinical features. All 10 cases were associated with a vulvar condition, mainly a lichen sclerosus. Therefore, VX might represent a reaction pattern induced by different conditions, mainly characterized by damage to the dermoepidermal junction. When confronted with the diagnosis of vulvar VX, clinicians may look for an associated vulvar condition.

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VERRUCIFORM XANTHOMA (VX) is a rare benign tumor which was first described in the oral cavity by Shafer in 1971.¹

Only a few cases of vulvar VX have been reported since its first description in 1979,²⁻⁸ and the pathogenesis of this condition remains unclear. Anecdotal cases of mucosal or skin VX associated with an underlying disorder have been reported, and it has been suggested that oral VX might be secondary to an underlying inflammatory disorder.⁹ Herein, we describe the clinicopathologic features of 10 cases of vulvar VX and focus on their associated vulvar conditions.

METHODS

All consecutive cases of vulvar VX encountered between February 1989 and March 2010 by 1 pathologist (F.P.) working in 2 public hospitals of Ile de France and a private pathology center were listed. Biopsy specimens were fixed in acetic-formaldehyde-alcohol solution, paraffin embedded, and routinely processed. For each case, we retrospectively collected the following information from the patients' medical records: age, clinical description of VX,

location, histologic findings, history of dyslipidemia, treatment, follow-up, and associated vulvar conditions.

RESULTS

CLINICAL DATA

During the study period, 10 patients (mean age, 68 years [range, 51-80 years]) were registered with a diagnosis of VX (**Table 1**), which presented as a single lesion in 9 of the cases and as multiple lesions in 1 case. Lesions were asymptomatic, slow-growing, sharply demarcated, indurated, yellowish-orange verrucous plaques (**Figure 1** and **Figure 2**). The size of the lesions ranged from 2 to 20 mm. Three of the lesions were located on the labia minora, 3 were on the labia majora, 2 were on the clitoris, and 2 were on the fourchette. One patient had 3 concomitant VX lesions, all located on the labia minora. Three patients complained of vulvar itching related to lichen sclerosus (2 patients) and Paget disease (1 patient). Diagnosis of VX was clinically suspected in only 2 cases, other suggested diagnoses being condyloma (3 patients), squamous cell carcinoma (SCC) (2 patients), or "leucoplasia" (1 patient). In 2 cases, there was no recorded diagnosis but

Author Affiliations:

Departments of Dermatology (Drs Fite, Dupin, Avril and Moyal-Barracco) and Pathology (Dr Plantier), Assistance Publique des Hôpitaux de Paris, Hospital Cochin, Paris Descartes University, Paris, France.

Table 1. Characteristics of the Vulvar Verruciform Xanthoma (VX) of the Present Series

| Patient No./ Age, y | Vulvar Associated Condition ^a | Clinical Description or Hypothesis | Diameter, mm | Location | No. | History of Dyslipidemia | Recurrence/ Follow-up, mo |
|------------------------|---|---------------------------------------|--------------|--------------|----------|----------------------------|---------------------------------|
| 1/75 | LS clinically obvious | Condyloma | 10 | Fourchette | Unique | No | NA |
| 2/80 | Vulvar Paget disease | None | 2 | Labia majora | Unique | Yes | No/14 |
| 3/77 | LS | "Keratotic papule" ^b | 2 | Clitoris | Unique | Yes | NA |
| 4/63 | LS | Condyloma, SCC, VX | 5 | Labia minora | Unique | No | No/17 |
| 5/51 | LP | "Verrucous lesion" ^b | NA | Labia minora | Unique | No | No/108 |
| 6/51 | LS | VX | 4 | Clitoris | Unique | No | No/60 |
| 7/57 | LS | SCC | 20 | Labia minora | Multiple | Yes | NA/died |
| 8/77 | LP | Condyloma | 15 | Labia majora | Unique | No | Yes/96 |
| 9/79 | Radiodermatitis | None | 3 | Fourchette | Unique | Yes | NA |
| 10/73 | LS | "Leucoplasia" ^b | 4 | Labia majora | Unique | No | NA |

Abbreviations: LP, lichen planus; LS, lichen sclerosus; NA, not available; SCC, squamous cell carcinoma.

^aThere was histologic confirmation in all patients listed except patient 1.

^bClinical description is given rather than diagnosis.



Figure 1. Clinical photograph of a condyloma-like verruciform xanthoma of the left labia minora associated with a lichen sclerosus (pallor, architectural changes).



Figure 2. Clinical photograph of a condyloma-like verruciform xanthoma of the right labia minora associated with an erosive lichen planus (erosions, architectural changes).

only the clinical descriptions "keratotic papule" and "verrucous lesion."

All of the patients had an associated vulvar condition: lichen sclerosus (6 patients), lichen planus (2 patients), Paget disease (1 patient), or radiodermatitis consecutive to cervical cancer treatment (1 patient). All of the associated diagnoses were histologically confirmed except for 1 case of lichen sclerosus that was clinically obvious. Indeed, this patient was diagnosed as having chronic recurrent vulvar pruritus with typical architectural changes in the vulva.

In 5 cases, VX was diagnosed in patients whose associated condition had been previously followed up for a mean period of 30 months (range, 24-48 months). For 2 patients, VX and lichen sclerosus were diagnosed simultaneously. The time delay between the respective diagnosis of VX and the associated vulvar condition was unavailable for the last 3 patients. A medical history of high lipid levels was reported in 4 patients. Of these, 2 patients were receiving specific treatment.

Verruciform xanthoma was unresponsive to topical steroids prescribed for lichen sclerosus (in 5 patients). Surgical excision of the VX was offered to and performed in 8 patients. Complete removal of the lesion was

pathologically confirmed in 7 cases. One patient had laser ablation, but the lesion recurred 16 months later, and she was subsequently treated with surgery. However, removal was incomplete, and the VX recurred 2 years later. Two patients were not treated by surgery; both of these were lost to follow-up, and we were informed that 1 of them had died of myocardial infarction at the age of 63 years, 6 years after diagnosis of VX. The mean duration of follow-up for 4 of the patients was 48 months (range, 14-108 months); 5 of the patients were lost to follow-up. In 1 patient, local recurrence occurred first within 16 months after laser destruction of the lesion and then 2 years after the surgical procedure.

PATHOLOGIC RESULTS

Pathologic examinations were performed in specimens from 4 partial biopsies and in 8 surgical samples after excision. The VX lesions were usually well demarcated from the adjacent normal epithelium. The epithelium showed hyperkeratosis, acanthosis, and elongation of the rete ridges (**Figure 3**). A wedge-shaped hyperkeratosis formed invaginating crypts extending deep into the acanthotic

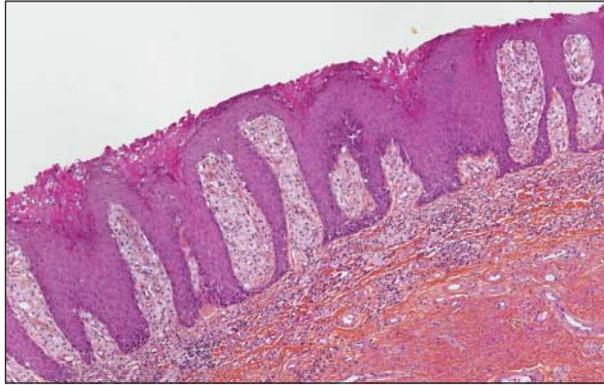


Figure 3. Characteristic wedge-shaped parakeratosis with an orange hue and xanthomatous cells aggregated between the rete ridges (hematoxylin-eosin, original magnification $\times 200$).

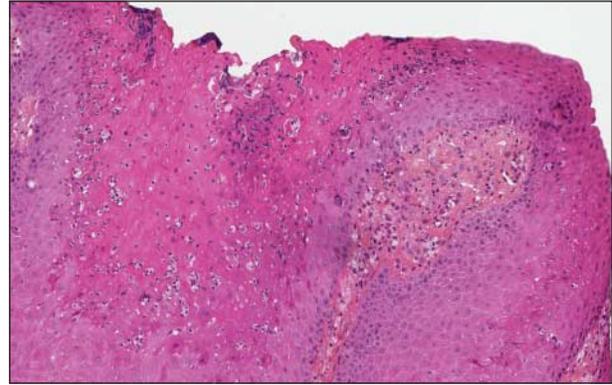


Figure 4. High magnification shows an inflammatory infiltrate of neutrophils, with microabscesses at the junction with the parakeratosis (hematoxylin-eosin, original magnification $\times 100$).

epithelium and exhibited a characteristic orange hue. The granular layer was absent. A neutrophilic infiltrate of varying density was noted at the junction of the parakeratotic layer and the stratum spinulosum (**Figure 4**). No atypia, mitosis, or koilocytes were seen.

Aggregates of xanthomatous cells were confined to the papillary dermis, between the rete ridges (**Figure 5**). These aggregates did not usually extend deeper into the connective tissue. Xanthomatous cells were lipid-laden histiocytes—also called foam cells—and displayed a single small central vesicular nucleus, abundant lipid vacuoles, and tiny granules in their cytoplasm that were periodic acid–Schiff positive and diastase resistant. We did not observe any multinuclear Touton giant cells.

The papillary dermis showed an increased number of prominent and often tortuous thin-walled vessels. Varying degrees of acute or chronic inflammatory infiltrate (lymphocytes, plasma cells, neutrophils, and a few eosinophils) were present in the subepithelial connective tissue. Fat stains were precluded because specimens were not frozen.

Four partial biopsies of VX were performed in patients with previously histologically confirmed lichen sclerosis or planus. Specimens from 3 of these biopsies displayed no histologic features of the known lichen. One of these 3 patients was subsequently treated with surgery, and the surgical sample showed both the VX and the lichen sclerosis. On the 8 surgical samples of VX, histologic examination also identified 3 cases of lichen sclerosis, 1 case of Paget disease, and 1 case of radiodermatitis. Three of the surgical samples did not display the known associated disease.

COMMENT

The 10 vulvar VX cases in this series are all associated with an underlying disorder: lichen sclerosis (6 patients), lichen planus (2 patients), Paget disease (1 patient), and radiodermatitis (1 patient). To our knowledge, this is the largest series of vulvar VX to be published, and it shows that these lesions mainly affect postmenopausal women and usually present as solitary, verrucous, yellowish-orange plaques (Table 1). Clinically, vulvar VX may be misdiagnosed as a genital wart, a verrucous carcinoma,

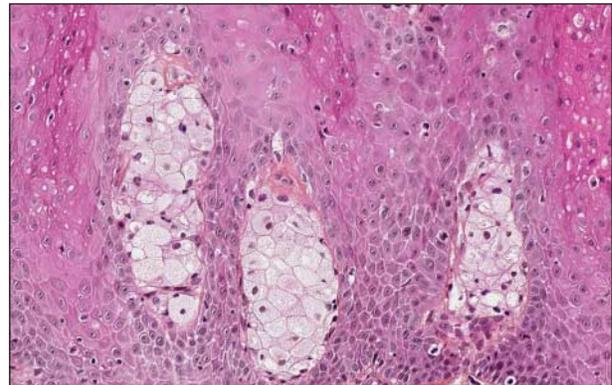


Figure 5. High magnification shows xanthomatous cells aggregated in the papillary dermis (hematoxylin-eosin, original magnification $\times 400$).

or an SCC. The outstanding histopathologic features were the wedge-shaped, orange-colored parakeratosis invaginating into the papillomatous epithelium and the presence of xanthomatous cells in the papillary dermis (Figure 3). No case of transformation into SCC was observed.

To our knowledge, only 9 cases of vulvar VX have been reported so far²⁻⁸ (**Table 2**). In agreement with our findings, the misleading clinical features of vulvar VX were highlighted. Our histologic findings are similar to those in previous reports (Figures 3-5).^{2-8,10,11} Three of 9 cases published in the literature were associated with an underlying condition (lichen sclerosis^{2,7} in 2 cases and fibroepithelial polyp⁵ in 1). In contrast, all cases in the present study were associated with a condition, usually a lichen sclerosis or planus. To our knowledge, an association of vulvar VX with lichen planus, radiodermatitis, or Paget disease has not been previously reported. This discrepancy may be partially because a quiescent lichen can be overlooked either clinically or pathologically. Indeed, a quiescent vulvar lichen, either sclerosis or planus, no longer shows typical clinical features (shiny pallor, white reticulated network, or erosions). The diagnosis is thus based only on architectural modifications, which may be subtle and therefore difficult to detect. Similarly, the specific pathologic features of a lichen may be absent when the dermatosis is quiescent. Association of VX with other conditions has also been described anec-

Table 2. Previous Reports of Vulvar Verruciform Xanthoma in the Literature

| Source | Age, y | VAC | Clinical Hypothesis | Size, mm | Location | No. | Duration, mo | Dyslipidemia | HPV | Recurrence/ Follow-up, mo |
|------------------------------------|--------|-----------------------|---------------------|----------|---------------------------------|----------|--------------|---------------------------|---|---------------------------|
| Santa Cruz and Martin ² | 29 | None | Condyloma | NI | Vulva | Multiple | 204 | NI | NI | NI |
| | 43 | LS | SCC | 13 | Near clitoris | Unique | NI | NI | NI | NI |
| de Rosa et al ³ | 65 | None | None | 15 | Vulva | Unique | NI | NI | NI | NI |
| Orchard et al ⁴ | 44 | NI | NI | 13 × 10 | Vulva | Unique | 8 | No | Test results negative for CAMVIR-1 and BPV-1 antibodies | NI |
| | 14 | NI | NI | 90 × 85 | Vulva | Unique | NI | No | Test results negative for CAMVIR-1 and BPV-1 antibodies | NI |
| Kishimoto et al ⁵ | 49 | Fibroepithelial polyp | NI | 10 × 20 | Left side of labia majora | Unique | 10 | Normal serum lipid levels | No | No/60 |
| Leong and Meredith ⁶ | 84 | None | Cutaneous carcinoma | 22 × 17 | Left side of vulva | Unique | NI | NI | NI | NI |
| Reich and Regauer ⁷ | 30 | LS | Bowenoid papulosis | 25 | Inner left side of labia minora | Unique | NI | Normal serum lipid levels | Negative results from PCR for HPV types 16 and 18 | Yes |
| Sopena et al ⁸ | 42 | None | NI | 3-25 | Disseminated | Multiple | 240 | Normal serum lipid levels | Negative results from PCR for HPV types 6, 11, 16, 18, 31, and 33 | NI |

Abbreviations: BPV-1, bovine papilloma virus-1; HPV, human papilloma virus; LS, lichen sclerosus; NI, not indicated; PCR, polymerase chain reaction; SCC, squamous cell carcinoma; VAC, vulvar associated condition.

dotally in the oral cavity, on the penis, and on the skin. Although no associated conditions were reported in the 162 cases of oral VX reviewed by Oliveira et al,¹⁰ some cases have been anecdotally reported to be associated with intraoral conditions, such as warty dyskeratoma,¹² discoid lupus erythematosus,¹³ "leucoplakia,"¹⁴ amyloidosis,¹⁴ oral submucous fibrosis,¹⁵ and SCC.^{15,16} Furthermore, 7 cases of oral VX associated with lichen planus have been reported,^{14,15,17-19} and 1 case of VX arising after radiotherapy treatment was described on the esophagus.²⁰ Interestingly, both lichen and radiodermatitis have been reported to be associated with VX in oral and vulvar locations. About 16 cases of penile VX involving the foreskin,^{21,22} glands,²³ or coronary sulcus²⁴ have been reported. One of these cases was associated with an SCC. Finally, a few cases of cutaneous VX have also been described in association with discoid lupus erythematosus,²⁵ recessive dystrophic epidermolysis bullosa,^{26,27} pemphigus vulgaris,²⁸ CHILD syndrome (Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects),²⁹ epidermal naevi,³⁰ sun-damaged facial skin,³¹ and solar keratosis.³²

Our series has both practical and theoretical implications. Owing to misleading clinical features, the diagnosis of vulvar VX is mostly ascertained by the pathologist. Thus, when confronted with a vulvar VX, both clinician and pathologist should scrutinize the vulva for an associated condition, mainly a lichen sclerosus or a lichen planus, which may have been overlooked in the previous examination. Even if histologic examination fails to detect these

conditions, clinical examination of the whole vulva is required to identify a possibly quiescent condition and ensure proper treatment and follow-up. We therefore recommend complete surgical removal of vulvar VX, all the more so if it arises on a lichen sclerosus or planus, which are both potential SCC precursors. It has been suggested that VX results from degenerative changes in the epidermis with a subsequent nonspecific histiocytic response.^{9,33,34} Zegarelli et al^{9,33} proposed that damage to the epithelium could trigger the following cascade: (1) entrapment of epithelial cells in the papillary dermis, (2) subsequent degeneration of these cells and lipid formation, (3) engulfment of released lipids by macrophages, and (4) accumulation of foam cells between the rete ridges. It is noteworthy that lichen planus and lichen sclerosus—found in 8 of our 10 cases—are both interface dermatitis, in which alteration of the dermoepidermal junction may allow the migration of epithelial cells into the papillary dermis. Therefore, VX might represent a reaction pattern induced by different conditions, mainly characterized by damage to the dermoepidermal junction.

Some limitations to this study should be considered. First, our follow-up data are too limited to completely exclude a risk of transformation into an SCC. Although there has never been a report of transformation of a vulvar VX into an SCC, VX can be associated with SCC.^{16,24,35,36} Indeed, Takiwaki et al²⁴ reported 1 case of SCC that seemed to arise within a penile VX; a 61-year-old patient was surgically treated for a VX of the coronary sulcus, and histologic features were initially interpreted as SCC, although

the final diagnosis was VX. Excision was incomplete, and the patient experienced recurrence 4 months later but refused any further surgery. Six years later, the lesion had grown, and histologic examination of partial penectomy revealed an SCC with many clusters of xanthomatous cells. Second, we did not search for human papillomavirus (HPV) in our cases. Owing to the clinical condyloma-like appearance of VX and its location in the mucosa, a role of HPV in the pathogenesis of VX has been suggested. However, at least 12 studies using techniques such as electron microscopic examination, Southern blotting, immunohistochemical analysis, polymerase chain reaction (PCR), nested PCR followed by sequencing, or in situ hybridization have failed to identify HPV in a total of 22 cases.^{4,7,8,36-44} To our knowledge, only 3 studies identified HPV DNA in 1 of 12 cases of oral VX (HPV-6 and HPV-11),⁴⁵ 1 case of scrotal VX (HPV-6),⁴⁶ and 3 cases of cutaneous VX (HPV-16, HPV-23, and HPV-36).⁴⁷ The low rate of HPV positivity published and the absence of specific pathologic features of HPV in our 10 cases lead us to consider HPV as being incidental rather than etiologic in cases of vulvar VX. Third, we did not explore the lipid metabolism of our patients. The presence of lipid-laden cells within the lesions of VX has led some investigators to suggest that VX is associated with a systemic lipid abnormality.³⁷ However, most of the reported VX patients are normolipemic.^{5,6,9,16,22,34,48-50} Four of our patients reported hyperlipidemia, but the age of these patients (Table 1) suggests that these lipid abnormalities should be considered as an incidental finding. In addition, cutaneous lipid deposition related to hyperlipidemia is usually associated with xanthomas, which are clinically and histologically different from VX (no acanthosis, presence of Touton giant cells located deeper in the dermis). Lipid-laden macrophages of VX could result from a local lipid clearance disorder of the degenerating epidermis. This could be related to a mutation of the β 3-hydroxysteroid dehydrogenase (*NSDHL*) gene, which is involved in cholesterol biosynthesis, as suggested by Mehra et al.⁵¹

In conclusion, vulvar VX is a rare and misleading yellowish-orange verrucous tumor that can simulate a genital wart, a verrucous carcinoma, or an SCC. Our 10 cases of vulvar VX were all associated with another vulvar condition, mainly lichen sclerosus or lichen planus. Both clinicians and pathologists should be aware of this association and search for a lichen, either active or quiescent, in the tissues surrounding the VX. Because we cannot strictly exclude the possibility of transformation of vulvar VX into an SCC, we recommend complete surgical removal of this tumor, all the more so if it arises on a lichen sclerosus or planus, which are both potential precursors of SCC.

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Correspondence: Charlotte Fite, MD, 25 rue Basfroi, 75011 Paris, France (charlotte.fite@noos.fr).

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Notable Notes

Shedding Light on Michelangelo's "Moses"

Michelangelo (1475-1564) was one of the greatest artists of the Renaissance. Among his most admired masterpieces is the sculpture of Moses, a magnificent artwork with one curious feature: it depicts Moses with 2 horns on his head. The story behind these horns actually involves a unique dermatologic phenomenon that characterized the face of the great Jewish prophet as described in the Book of Exodus (34:29). According to the biblical text, when Moses descended Mount Sinai, "the skin of his face had become radiant" (Hebrew transliteration: *karan ohr panav*) such that the rays of light would shine and project like horns off his face.¹

The Latin Vulgate version of the Bible, however, translates the verse in Exodus as "cornuta esset facies" ("his face was horned"). This Latin translation may have misled medieval artists and, later, Michelangelo to portray Moses with actual horns atop his head. The luminous nature of Moses' face was not due to the everyday light that normally reflects off our skin. Rather, this "light" represented some type of extraordinary brilliance that resulted from Moses' communion with God on Mount Sinai.

Maimonides explains that prophetic truth is experienced like flashes of lightning in the dark night.² For some prophets, these "flashes" come in rapid succession, and thus they seem to be in a continuous light. This was the degree of prophetic excellence attained by Moses as indicated by his radi-

ant face. At times, Moses wore a veil on his face both because of modesty and to allay the fears of the children of Israel, who were startled by his radiant skin. Whatever the nature of the light that emanated from Moses' face, he did not, according to the Hebrew biblical text, have actual horns on his head. Despite Michelangelo's erroneous portrayal of Moses, his sculpture of him is of such amazing beauty that one can almost imagine the majestic splendor that radiated from Moses' face.

These sentiments were also expressed by the noted art historian Giorgio Vasari³ as follows:

He finished the Moses, a statue in marble of five braccia, which no modern work will ever equal in beauty; and of the ancient statues, also, the same may be said. . . . To say nothing of the beauty of the face, which has all the air of a true Saint and most dread Prince, you seem, while you gaze upon it, to wish to demand from him the veil wherewith to cover that face, so resplendent and so dazzling it appears to you, and so well has Michelagnolo expressed the divinity that God infused in that most holy countenance.

Contact Dr Hoenig at 601 N Flamingo Rd, Ste 201, Pembroke Pines, FL 33028 (gooddoeljh@yahoo.com).

Leonard J. Hoenig, MD

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