Verruciform Xanthoma (VX) is a rare benign tumor which was first described in the oral cavity by Shafer in 1971. Only a few cases of vulvar VX have been reported since its first description in 1979 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. Herein, we describe the clinicopathologic features of 10 cases of vulvar VX and focus on their 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
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

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

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

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

*There was histologic confirmation in all patients listed except patient 1.

Clinical description is given rather than diagnosis.
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 sclerosus 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 sclerosus. On the 8 surgical samples of VX, histologic examination also identified 3 cases of lichen sclerosus, 1 case of Paget disease, and 1 case of radiodermatitis. Three of the surgical samples did not display the known associated disease.

The 10 vulvar VX cases in this series are all associated with an underlying disorder: lichen sclerosus (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, 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 far (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). Three of 9 cases published in the literature were associated with an underlying condition (lichen sclerosus in 2 cases and fibroepithelial polyp in 1). In contrast, all cases in the present study were associated with a condition, usually a lichen sclerosus 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 sclerosus 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

<table>
<thead>
<tr>
<th>Source</th>
<th>Age, y</th>
<th>VAC</th>
<th>Clinical Hypothesis</th>
<th>Size, mm</th>
<th>Location</th>
<th>No.</th>
<th>Duration, mo</th>
<th>Dyslipidemia</th>
<th>HPV</th>
<th>Recurrence/ Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santa Cruz and Martin²</td>
<td>29</td>
<td>None</td>
<td>Condyoma</td>
<td>NI</td>
<td>Vulva</td>
<td>Multiple</td>
<td>204</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>de Rosa et al³</td>
<td>39</td>
<td>LS</td>
<td>SCC</td>
<td>13</td>
<td>Near clitoris</td>
<td>Unique</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Orchard et al⁴</td>
<td>44</td>
<td>None</td>
<td>None</td>
<td>13 × 10</td>
<td>Vulva</td>
<td>Unique</td>
<td>8</td>
<td>No</td>
<td>Test results negative for CAMVIR-1 and BPV-1 antibodies</td>
<td></td>
</tr>
<tr>
<td>Kishimoto et al⁵</td>
<td>49</td>
<td>Fibroepithelial polyp</td>
<td>NI</td>
<td>10 × 20</td>
<td>Left side of labia majora</td>
<td>Unique</td>
<td>10</td>
<td>Normal serum lipid levels</td>
<td>Test results negative for CAMVIR-1 and BPV-1 antibodies</td>
<td></td>
</tr>
<tr>
<td>Leong and Meredith⁶</td>
<td>84</td>
<td>None</td>
<td>Cutaneous carcinoma</td>
<td>22 × 17</td>
<td>Left side of vulva</td>
<td>Unique</td>
<td>NI</td>
<td>NI</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Reich and Regauer⁷</td>
<td>30</td>
<td>LS</td>
<td>Bowenoid papulosis</td>
<td>25</td>
<td>Inner left side of labia minora</td>
<td>Unique</td>
<td>NI</td>
<td>Normal serum lipid levels</td>
<td>Negative results from PCR for HPV types 16 and 18</td>
<td></td>
</tr>
<tr>
<td>Sopena et al⁸</td>
<td>42</td>
<td>None</td>
<td>None</td>
<td>3-25</td>
<td>Disseminated</td>
<td>Multiple</td>
<td>240</td>
<td>Normal serum lipid levels</td>
<td>Negative results from PCR for HPV types 8, 11, 16, 18, 31, and 33</td>
<td></td>
</tr>
</tbody>
</table>

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 warth dyskeratoma,¹³ discoid lupus erythematosus,¹³ “leucoplakia,”¹⁴ amyloidosis,¹⁴ oral submucous fibrosis,¹⁵ and SCC.¹⁵ Further, 7 cases of oral VX associated with lichen planus have been reported,¹⁴,¹⁵,¹⁷,¹⁸ 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,¹²¹,²² glans,¹³ or coronary sulcus 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,²³ 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.³³,³⁴ Zegarelli et al.³⁵,³⁶ 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.²⁶,²⁴,²⁵,²⁶,²⁷ Indeed, Takiwaki et al.²⁸ 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.1-7,9,36-44 To our knowledge, only 3 studies identified HPV DNA in 1 of 12 cases of oral VX (HPV-6 and HPV-11).43 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.35 However, most of the reported VX patients were normolipemic.3-5,9,16,22,34,48-50 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 3β-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).
Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Fite, Planier, and Moyal-Barracco. Acquisition of data: Fite, Planier, and Moyal-Barracco. Analysis and interpretation of data: Plantier, Dupin, Avril, and Moyal-Barracco. Drafting of the manuscript: Fite, Plantier, and Moyal-Barracco. Critical revision of the manuscript for important intellectual content: Planier, Dupin, Avril, and Moyal-Barracco. Statistical analysis: Fite. Administrative, technical, and material support: Dupin. Study supervision: Planier, Dupin, Avril, and Moyal-Barracco.
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REFERENCES


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 translation). This Latin translation may have misled historians into thinking of the beauty of the face, which has all the air of a true ancient statue, also, the same may be said.... Tosay noth-...torian Giorgio Vasari as follows:

Leonard J. Hoenig, MD

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

Leonard J. Hoenig, MD