Vulvar Verruciform Xanthoma: A Comprehensive Literature Review

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Abstract: Verruciform xanthoma (VX) is a rare, benign, mucocutaneous, verrucous, papillary lesion. This paper retrospectively summarizes clinical and pathologic features of 32 vulvar verruciform xanthoma reported from China and abroad. The skin lesions are generally single, mainly in labia minora, clitoris and fourchette with partly extending to the groin, buttocks and anus. The possible inducing factors include long-term scratching, local itching, severe lymphedema or lymphangioma circumscriptum. Severe cutaneous trauma and chronic inflammation may be the main causes. Clinically, it can easily be misdiagnosed as condylomata acuminata, squamous cell carcinoma, Bowenoid papulosis, etc. It is reported to be related to underlying disorders. The main treatment is complete resection.

Keywords: verruciform xanthoma, vulvar, clinical features, immunohistochemistry, treatment, etiology

Introduction

Verruciform xanthoma (VX) is a rare, benign, mucocutaneous, verrucous, papillary lesion characterized by collections of foamy histiocytes in the papillary dermis, lipid-laden macrophages (xanthoma cells), epidermal hyperplasia with hyperkeratosis and parakeratosis. It was first described in 1971 on the oral mucosa. Since then, the extraoral cases have also been reported, especially cases with lesions on anogenital area, thumb, esophagus and other areas, which are usually presented as painless polypoid or sessile papules with a verrucous or pebbly surface and pink-yellowish hue.

Among them, vulvar verruciform xanthoma can easily be misdiagnosed as a genital wart and HPV-independent TP53-independent vulvar intraepithelial neoplasia, etc. The diagnostic test of this disease is mainly through biopsy and pathological examination. Herein, we retrospectively summarized clinical and pathologic features of vulvar verruciform xanthoma reported from China and abroad through searches of PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and China National Knowledge Infrastructure (http://www.cnki.net/).

Clinical Features

To our knowledge, only thirty-two cases have been reported so far (Table 1). In the review of previously reported 32 vulvar VX cases, the mean age was 46 years (range from 1.5 to 84 years), the mean duration was 72 months (range from 1 to 300 months), and the main place of occurrence was labia minora, clitoris and fourchette with partly extending to the groin, buttocks and anus.

Among the 32 patients, 21 cases showed single skin lesions, 10 cases showed multiple skin lesions, and 1 case did not mention single or multiple skin lesions. Seven of 32 cases presented as mild itching, excluding 5 cases not mentioned, and the skin lesions ranged in size from 2 to 115 mm. Clinically, it can easily be misdiagnosed as condylomata acuminata.
| Case | Year | Age (Yrs) | Duration (Mo) | Inducing Factors | Location | No. | Morphology | Size (mm) | Subjective Symptoms | Clinical Impression | Associated Condition | Laboratory Examination | IH | Treatment | Follow-Up (Mo) |
|------|------|-----------|---------------|------------------|-----------|-----|------------|-----------|-------------------|-------------------|----------------------|------------------------|----|------------|---------------|
| 1    | 1979 | 29        | 204           | Nil              | Vulva     | Multiple | Verrucous lesions | NI        | None              | Condylomata acuminata | Nil                   | Nil                    | Nil | Nil        | Nil            |
| 2    | 1979 | 43        | Nil           | Nil              | Clitoris  | Single   | Polypoid, sessile mass, grayish-white | 13        | None              | Epidermod carcinoma | LS                    | Nil                     | Nil | Nil        | Nil            |
| 3    | 1980 | 16        | Lifelong      | Nil              | Left inguinal area | Single | Yellow-tan verrucous lesion | 60 ×30   | NI                | Epidermal nevus syndrome | Nil                   | Nil                     | Nil | Vitamin A followed by partial excision and persistence of lesion | Nil |
| 4*   | 1989 | 65        | Nil           | Nil              | Vulva     | Single   | Plaque like | 15       | None              | Leiomyomatosis of uterus | Nil                   | Nil                     | Nil | Nil        | Nil            |
| 5*   | 1990 | 15        | 173           | Nil              | Left groin, external genitalia, buttocks and anus | Multiple | Soft, pink, fleshy proliferations | NI       | NI                | Epidermal nevus syndrome or CHILD | Hypergammaglobulinemia of 3.36, total proteins of 9.24 g/100 mL | Nil | Nil        | Nil            |
| 6    | 1997 | 49        | 10            | Nil              | Left labium majus | Single  | Yellowish lesion with a granular surface | NI       | None              | Fibroepithelial polyp | Dyslipidemia, HPV (—) | CD68 +, S100 - | SE | No/60      |                |
| 7    | 1998 | 84        | Nil           | None             | Left vulva | NI       | Verrucous lesion | 5×4×3   | NI                | Carcinoma          | Dyslipidemia+ | CD68+ | SE | Nil        |                |
| 8    | 1998 | 1.5       | Nil           | Nil              | Right labium majus | Single  | Broad band or plaque | NI       | NI                | CHILD             | Nil                    | Nil | Nil        | Nil            |
| 9    | 2004 | 30        | Nil           | Nil              | Left labium minus | Single  | Warty red polypoid lesion | 50       | Itching           | Bowenoid papulosis | Dyslipidemia, HPV16, 18 (—) | CD68+, S100—, scanty PAS + | CO2 laser | Yes/96       |                |
| 10   | 2004 | 42        | 240           | Nil              | Feet and hands, genital area, ear | Multiple | Polypoid verrucous indurated vulvar lesions | 3–25     | Nil               | None              | Dyslipidemia, HPV 6, 11, 16, 18, 31 and 33 (—) | Nil | Nil        | Nil            |
| 11   | 2007 | 30        | 1             | Nil              | Right labia minora | Single  | Cauliflower | 20       | None              | Condylomata acuminata | Dyslipidemia, HPV (—) | CD68, α 1-AT, M ac387, PAS+, S100, Ki67 | SE | No/Nil      |                |

Table 1 Vulvar Verruciform Xanthoma Cases Reported to Date

https://doi.org/10.2147/CCID.S371979

Dove Press

Clinical, Cosmetic and Investigational Dermatology 2022:15

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| Case | Year | No. | Age | Region | Vaginal Part | Presence | Type | Lesion | Histopathology | Associated Factors | Presentations | Management | Outcome |
|------|------|-----|-----|--------|-------------|----------|------|--------|----------------|------------------|---------------|------------|---------|
| 12   | 2007 | 81  | 12  | NI     | Left labia minora | Single    | Verrucate | 10 | None | Condylomata acuminata | Dyslipidemia | SE | No/NI |
| 13   | 2007 | 47  | 6   | NI     | Clitoris | Single    | Pebbly surface | 30 | 15×10 | N/A | N/A | N/A | Dyslipidemia | CD68+ | SE | No/9 |
| 14   | 2011 | 75  | NI  | NI     | Fourchette | Single    | Yellowish-orange verrucous plaques | 2 | Itching | Condyloma | LS | Dyslipidemia | SE | No/NI |
| 15   | 2011 | 80  | NI  | NI     | Labia majora | Single    | Yellowish-orange verrucous plaques | 2 | Itching | None | Vulvar Paget’s disease | Dyslipidemia | SE | No/14 |
| 16   | 2011 | 77  | NI  | NI     | Clitoris | Single    | Yellowish-orange verrucous plaques | 2 | Itching | Keratotic papule | LS | Dyslipidemia | SE | NI |
| 17   | 2011 | 63  | NI  | NI     | Labia minora | Single    | Yellowish-orange verrucous plaques | 5 | None | Condyloma, SCC, VX | LS | No | SE | No/17 |
| 18   | 2011 | 51  | NI  | NI     | Labia minora | Single    | Yellowish-orange verrucous plaques | N/A | None | Verrucous lesion | LP | No | SE | No/108 |
| 19   | 2011 | 51  | NI  | NI     | Clitoris | Single    | Yellowish-orange verrucous plaques | 4 | None | VX | LS | No | SE | No/60 |
| 20   | 2011 | 57  | NI  | NI     | Labia minora | Multiple  | Yellowish-orange verrucous plaques | 20 | None | SCC | LS | Dyslipidemia | SE | NI | No/died |
| 21   | 2011 | 77  | NI  | NI     | Labia minora | Single    | Yellowish-orange verrucous plaques | 15 | None | Condyloma | LP | No | SE | Laser, SE | Yes/96 |
| 22   | 2011 | 79  | NI  | NI     | Fourchette | Single    | Yellowish-orange verrucous plaques | 3 | None | None | Radiodermatitis | Dyslipidemia | SE | NI |
| 23   | 2011 | 73  | NI  | NI     | Labia minora | Single    | Yellowish-orange verrucous plaques | 4 | None | Leucoplasia | LS | No | SE | SE |
| 24   | 2012 | 16  | 12  | Long-term scratching | Superior left labia majora | Single    | White-tan granular verrucous lesion | 15 | Itching | NI | NI | NI | SE | No/12 |

(Continued)
| Case | Year | Age (Yrs) | Duration (Mo) | Inducing Factors | Location | No. | Morphology | Size (mm) | Subjective Symptoms | Clinical Impression | Associated Condition | Laboratory Examination | IH | Treatment | Follow-Up (Mo) |
|------|------|-----------|---------------|------------------|----------|-----|------------|-----------|---------------------|---------------------|---------------------|----------------------|----|-----------|---------------|
| 25   | 2012 | 2         | 12            | After treatment of diarrhea with penicillin | Left labia minora, external anus and left inguinal area | Multiple | Pink oval verrucous growth, pale yellow papules | 70×50      | None                | NI                  | NI                  | Dyslipidemia—         | NI | Imiquimod cream for 6 weeks | No/NI         |
| 26   | 2013 | 2         | 12            |                    | Vulva, around the anus | Multiple | Yellowish verrucous plaque | 70×50      | None                | NI                  | NI                  | Dyslipidemia, HPV—     | NI | Imiquimod cream 5%    | No/9          |
| 27   | 2015 | 11        | 72            |                    | Vulva | Multiple | Verruciform erythematous mass | 60        | None                | NI                  | CHILD               | High- and low-risk HPV— | CD68, vimentin+, antikeratin ±, S100— | SE | Staged SE   | Ni            |
| 28   | 2017 | 35        | 300           |                    | Vulva | Multiple (9) | Yellowish flesh-colored, cauliflower-shaped lumps | 115×90    | None                | Genital warts        | NI                  | 19 high- and 9 low-risk HPV, CRP—Dyslipidemia + | SE | Ni         | Ni            |
| 29   | 2017 | 50        | 12            | SL, LC            | Vulva | Multiple | Orange-red, well-demarcated nodule with a verrucous surface | NI        | None                | NI                  | Localized lymphedema  | Ni                  | CD68, D2-40+           | Ni | Ni         | Ni            |
| 30   | 2018 | 61        | 36            | None              | Left labia minora | Single | White neoplasm, rough surface, slightly moist | Bean like  | None                | NI                  | NI                  | Dyslipidemia—         | SE | No/8       | Ni            |
| 31   | 2018 | 58        | 48            | Chronic pruritus of vulva | Right labia minora | Single | Pink proliferative mass, Oval like, unsmooth surface, the boundary is not clear | 12×6      | None                | Vulvar leukoplakia    | NI                  | Dyslipidemia—         | SE | No/NI      | No/NI         |
| 32   | 2019 | 22        | 6             | None              | Left vulva | Multiple | Light red soybean nodules, rough surface and rice grain large skin papule | Bean like  | None                | NI                  | NI                  | Dyslipidemia —        | SE | No/18      | Ni            |

**Abbreviations:** IH, immunohistochemistry; NI, not indicated; LS, lichen sclerosis; CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; SE, surgical excision; HPV, human papilloma virus; LP, lichen planus; SCC, squamous cell carcinoma; VX, verruciform xanthoma; CRP, serum C-reactive protein; SL, severe lymphedema; LC, lymphangioma circumscriptum.
acuminata, squamous cell carcinoma, Bowenoid papulosis, etc. And it was reported to be related to underlying disorders, such as lichen sclerosis (8 patients), congenital hemidyseplasia with ichthyosiform erythroderma and limb defects (3 patients), lichen planus (2 patients), epidermal nevus syndrome (2 patients), Paget’s disease (1 patient), radiodermatitis (1 patient), fibroepithelial polyp (1 patient), leiomyomatosis of uterus (1 patient) or localized lymphedema (1 patient).

**Histologic Examination**

We note that histopathology plays a key role in the recognition and diagnosis of VX. The major pathognomonic feature is the collections of foamy histiocytes in the papillary dermis, lipid-laden macrophages (xanthoma cells), epidermal hyperplasia with hyperkeratosis and parakeratosis. The second main feature is the papillomatous appearance, including plaque-like configurations, more polyoid papular proliferations to lesions, discrete frondular papillae overlying ectatic basal vessels and variable chronic inflammation.

**Immunohistochemistry**

In retrospective cases, immunohistochemistry revealed the foam cells were positive for the histiocytic marker CD68 (9 patients), α1-AT (2 patients), Mac387 (2 patients), vimentin (1 patient), PAS (2 patients); Weak positive for CK (AE1/AE3) (2 patients), antikeratin (1 patient); and negative for antibodies to S-100 (5 patients) and Ki67 (1 patient).

**Treatment**

Two patients were treated with laser, and both recurred; two patients were treated with imiquimod cream and satisfactory results have been obtained; the lesions of the other patients were typically managed successfully with surgical excision and no recurrence.

**Etiology**

The possible inducing factors include long-term scratching (1 patient), local itching (1 patient), severe lymphedema (1 patient) or lymphangioma circumscriptum (1 patient). The exact etiology of VX is unclear, and several main hypotheses have been proposed. ① Most studies deny the association between HPV and VX. Although HPV was found in several studies, others failed to confirm this association. ② It may be related to hyperlipidemia, but the majority of patients with VX do not have associated hyperlipidemia. ③ Severe cutaneous trauma and chronic inflammation seem to be a more plausible theory. First, rapid proliferation and release of chemokines that attract neutrophils may be stimulated by damaged keratinocytes. Then, the recruitment of neutrophils may accelerate the keratinolysis, when parakeratotic cells caused by the rapid proliferation of keratinocytes accumulate on the surface of the VX lesions. Finally, as keratinocytes degrade and degenerate toward the dermis, the necrotic keratinocyte debris is phagocytized by dermal macrophages and transformed into lipid-laden macrophages (foam cells).

**Conclusion**

When verrucous plaques occur in vulva or anus, the diagnosis of VX should be considered, which can be confirmed by histopathology, and the other tests are performed to rule out other entities on the differential diagnosis. Clinically, vulvar VX should be differentiated with condyloma acuminatum, verrucous carcinoma, squamous cell carcinoma and intraepithelial neoplasia. Therefore, the correct diagnosis requires histopathologic examination. The typical pathological feature is the dense accumulation of macrophage foam cells in papillary dermis. It is generally believed that xanthoma cells were positive for CD68, indicating monocyte/macrophage participation in the disease. The main treatment was complete resection.

**Funding**

This work was supported by the Construction Project of Hainan Province Clinical Medical Center.

**Disclosure**

The authors declare no conflicts of interest.
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