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REVIEW

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.[1] It was first described in 1971 on the oral mucosa.[2] Since then, the extraoral cases have also been reported, especially cases with lesions on anogenital area,[2] thumb,[3] esophagus[4] and other areas, which are usually presented as painless polypoid or sessile papules with a verrucous or pebbly surface and pink-yellowish hue.[1]

Among them, vulvar verruciform xanthoma can easily be misdiagnosed as a genital wart and HPV-independent TP53-independent vulvar intraepithelial neoplasia,[5] etc. The diagnostic test of this disease is mainly through biopsy and pathological examination.[6] 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[6–26] (Table 1). In the review of previously reported 32 vulval 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

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Table 1 Vulvar Verruciform Xanthoma Cases Reported to Date

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[1]	1979	29	204	NI	Vulva	Multiple	Verrucous lesions	NI	None	Condylomata acuminata	NI	NI	NI	NI	NI
2[1]	1979	43	NI	NI	Clitoris	Single	Polypoid, sessile mass, grayish-white	13	None	Epidermoid carcinoma	LS	NI	NI	NI	NI
3[2]	1980	16	Lifelong	NI	Left inguinal area	Single	Yellow-tan verrucous lesion	60 ×30	NI	NI	Epidermal nevus syndrome	NI	NI	Vitamin A followed by partial excision and persistence of lesion	NI
4[3]	1989	65	NI	NI	Vulva	Single	Plaque like	15	NI	NI	Leiomyomatosis of uterus	NI	NI	NI	NI
5[4]	1990	15	173	NI	Left groin, external genitalia, buttocks and anus	Multiple	Soft, pink, fleshy proliferations	NI	NI	NI	Epidermal nevus syndrome or CHILD	Hypergammaglobulinemia of 3.36, total proteins of 9.24 g/100 mL	NI	NI	NI
6[5]	1997	49	10	NI	Left labium majus	Single	Yellowish lesion with a granular surface	NI	None	NI	Fibroepithelial polyp	Dyslipidemia, HPV (—)	CD68 + S100 -	SE	No/60
7[6]	1998	84	NI	None	Left vulva	NI	Verrucous lesion	5×4×3	NI	Carcinoma	NI	Dyslipidemia+	CD68+	SE	NI
8[7]	1998	1.5	NI	NI	Right labium majus	Single	Broad band or plaque	NI	NI	NI	CHILD	NI	NI	NI	NI
9[8]	2004	30	NI	NI	Left labium minus	Single	Warty red polypoid lesion	50	Itching	Bowenoid papulosis	LS	Dyslipidemia, HPV16, 18 (-)	CD68+, S100— scanty PAS +	CO_2 laser	Yes/96
10[9]	2004	42	240	NI	Feet and hands, genital area, ear	Multiple	Polypoid verrucous indurated vulvar lesions	3 −25	None	NI	NI	Dyslipidemia, HPV 6, 11, 16, 18, 31 and 33 (-)	NI	NI	NI
11[10]	2007	30	1	NI	Right labia minora	Single	Cauliflower	20	None	Condylomata acuminata	NI	Dyslipidemia, HPV —	CD68, α 1-AT, Mac387, PAS+, S100, Ki67-	SE	No/NI

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12[10]	2007	81	12	NI	Left labia minora	Single	Verrucate	10	None	Condylomata acuminata	NI	Dyslipidemia, HPV —	CD68, α 1-AT, M ac387, PAS+, S100, Ki-67—	SE	No/NI
13[11]	2007	47	6	NI	Clitoris	Single	Pebbly surface	30 ×15 ×10	NI	NI	NI	Dyslipidemia—	CD68+	SE	No/9
14[12]	2011	75	NI	NI	Fourchette	Single	Yellowish-orange verrucous plaques	10	Itching	Condyloma	LS	Dyslipidemia—	NI	NI	NI
15[12]	2011	80	NI	NI	Labia majora	Single	Yellowish-orange verrucous plaques	2	Itching	None	Vulvar Paget 's disease	Dyslipidemia+	NI	SE	No/14
16[12]	2011	77	NI	NI	Clitoris	Single	Yellowish-orange verrucous plaques	2	Itching	Keratotic papule	LS	Dyslipidemia+	NI	SE	NI
17[12]	2011	63	NI	NI	Labia minora	Single	Yellowish-orange verrucous plaques	5	None	Condyloma, SCC, VX	LS	No	NI	SE	No/17
18[12]	2011	51	NI	NI	Labia minora	Single	Yellowish-orange verrucous plaques	NI	None	Verrucous lesion	LP	No	NI	SE	No/108
19[12]	2011	51	NI	NI	Clitoris	Single	Yellowish-orange verrucous plaques	4	None	VX	LS	No	NI	SE	No/60
20[12]	2011	57	NI	NI	Labia minora	Multiple	Yellowish-orange verrucous plaques	20	None	SCC	LS	Dyslipidemia+	NI	NI	NI/died
21[12]	2011	77	NI	NI	Labia minora	Single	Yellowish-orange verrucous plaques	15	None	Condyloma	LP	No	NI	Laser, SE	Yes/96
22[12]	2011	79	NI	NI	Fourchette	Single	Yellowish-orange verrucous plaques	3	None	None	Radiodermatitis	Dyslipidemia+	NI	SE	NI
23[12]	2011	73	NI	NI	Labia minora	Single	Yellowish-orange verrucous plaques	4	None	Leucoplasia	LS	No	NI	SE	SE
24[13]	2012	16	12	Long-term scratching	Superior left labia majora	Single	White-tan granular verrucous lesion	15	Itching	NI	NI	NI	NI	SE	No/12

(*Continued*)

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Table 1 (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[14]	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[15]	2013	2	12	NI	Vulva, around the anus	Multiple	Yellowish verrucous plaque	70×50	None	NI	NI	Dyslipidemia, HPV—	NI	Imiquimod cream 5%	No/9
27[16]	2015	11	72	NI	Vulva	Multiple	Verruciform erythematous mass	60	None	NI	CHILD	High- and low-risk HPV—	CD68, vimentin+, antikeratin ±, S100—	Staged SE	NI
28[17]	2017	35	300	NI	Vulva	Multiple (9)	Yellowish flesh-colored, cauliflower-shaped lumps	115 × 90	None	Genital warts	NI	19 high- and 9 low-risk HPV, CRP—Dyslipidemia +	NI	SE	NI
29[18]	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
30[19]	2018	61	36	None	Left labia minora	Single	White neoplasm, rough surface, slightly moist	Bean like	None	NI	NI	Dyslipidemia—	NI	SE	No/8
31[20]	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—	NI	SE	No/NI
32[21]	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 —	CD68+, S100—	SE	No/18

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 hemidysplasia with ichthyosiform erythroderma and limb defects (3 patients), lichen planus (2 patients), epidermal nevus syndrome (2 patients), Paget's disease (1 patients), 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.[1] The second main feature is the papillomatous appearance, including plaque-like configurations, more polypoid papular proliferations to lesions, discrete frondular papillae overlying ectatic basal vessels and variable chronic inflammation.[27]

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.[28] Although HPV was found in several studies,[29,30] 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.[28] 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).[31]

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.

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Disclosure

The authors declare no conflicts of interest.

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