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Genital Verruciform Xanthoma: Lessons from a Contemporary Multi-Institutional Series

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ABSTRACT

AIMS: Verruciform xanthoma (VX) is an uncommon lesion, seen in the oral mucosa and rarely occurring at cutaneous genital sites. Reports of exceptional VX presentations dominate the literature; herein we assess the clinical and histologic features of a cohort of routine, consecutive cases.

METHODS/RESULTS: Clinicopathologic features of genital VXs from four academic centers were reviewed. A cohort of 25 lesions from 24 patients (22 M, 2 F; median age 62), occurred on the scrotum (84%), penis (8%), and perineum/vulva (8%). VX was never suspected clinically; considerations ranged from fibroepithelial polyps to squamous cell carcinoma. Classic diagnostic criteria were present at least focally in each lesion, including verrucous architecture, prominent

wedge-shaped parakeratosis extending between exophytic epidermal projections, and neutrophils in the stratum corneum. Xanthomatous cells were present in all cases, but scattered to rare in 24%.

CONCLUSIONS: Consecutive genital VXs reliably exhibited classic histopathologic features, although the essential finding of xanthomatous cells may be scarce. Our comparison to meta-analyses of published cases found relatively fewer penile and vulvar examples. Additionally, the median age was older than in published series, which have emphasized syndromic associations.

INTRODUCTION:

Verruciform xanthoma (VX) is an uncommon, benign mucocutaneous lesion that most commonly affects the oral mucosa of middle aged adults[1]. The classic histopathology of VX consists of a verrucous squamous proliferation, with compact parakeratosis and foamy macrophages within the dermal papillae, as reviewed recently[2]. Beyond the oral cavity, VX also occurs on the extremities, anal, and genital sites[3]. Due to the rarity of VX in the anogenital region, VX may be misclassified as one of the more commonly encountered warty lesions in this area, particularly condyloma acuminatum, or for larger lesions, verrucous carcinoma and other variants of squamous cell carcinoma. Case reports of unusual VX presentations, pitfalls, and rare syndromic associations (as well as meta-analyses thereof) dominate the literature, such that from the standpoint of prospective routine diagnosis the spectrum of expected clinical and histologic features are uncertain. Herein, reviewing the experience of multiple centers with contemporary, consecutive cases, we provide a clinicopathologic reappraisal of 25 VXs, detailing histopathologic features including some not previously emphasized, and correlating our findings with a recent comprehensive meta-analysis[3] of the published literature.

METHODS:

After IRB approval at each institution, clinicopathologic features of VXs of genital sites from four academic centers were identified and reviewed retrospectively. Clinical information were collected from the medical record, including demographics, lesion location, size, co-existing dyslipidemias, genital dermatitides, and systemic conditions. Each case was reviewed by both genitourinary pathology and dermatopathology subspecialists to confirm the diagnosis and qualitatively evaluate a series of histopathologic features. These features included low magnification architecture, presence and configuration of parakeratosis, presence of intracorneal neutrophils, presence of surface organisms, degree and type of lichenoid and dermal inflammation, and relative quantity of xanthomatous macrophages. If evaluable, the adjacent skin was assessed for the presence of concomitant pathologies. Whole slide imaging was performed (Leica/Aperio AT2 and Hamamatsu Nanozoomer), with white balance, contrast adjustment, and white space histologic artifacts removed (spot tools, Adobe Photoshop CS3) from non-lesional areas to provide clear low power images.

RESULTS:

A total of 25 VXs of genital sites from 24 patients (22 M, 2 F) were identified and reviewed. Median age was 62 years (range 37-≥89 years), with lesions located most frequently on the scrotum (21; 84%) compared to the penis or perineum/vulva, (each 2; 8%). The usually (23/24; 96%) solitary lesions ranged in size from 0.2 to 2.5 cm, with a median greatest dimension of 0.6 cm. Clinical considerations documented ranged from wart to benign vascular lesions, fibroepithelial polyps, seborrheic keratoses, and squamous cell carcinomas. A specific, coexisting genital dermatitis was documented with one specimen, that of mild radiation dermatitis from radiotherapy for penile squamous cell carcinoma; history of eczema, tinea cruris, and xerosis was documented in three additional cases). In no case was any documentation of a syndromal dyslipidemia documented, and in no case was the VX submitted with concern for cutaneous manifestation of systemic dyslipidemia. Clinical features, including incidental comorbidities are detailed in **Supporting Documentation – Table 1**.

Architecturally, VXs exhibited variable exophytic verrucous architecture (**Figure 1**), correlating a frequent clinical impression of a papule (**Figure 2A**). Histologically, prominent wedge-shaped parakeratosis, extension of compact eosinophilic keratotic scale between epidermal projections, and neutrophils in the stratum corneum were present in all cases (**Figure**

2B-C); neutrophils were abundant in 88% and focal in 12%. Surface and intracorneal bacterial organisms were identified in 24 (96%), albeit only focally in 32% (**Figure 2D**). Xanthomatous macrophages were abundant in 19 cases (76%), scattered in 4 cases (16%), and scarce in 2 cases (8%) (**Figure 2E-F**). While mild perivascular lymphoplasmacytic inflammation was present in all cases, a lichenoid arrangement of inflammatory cells was present in 8 (32%). Significant keratinocyte atypia was absent, with the exception mild atypia in one case; koilocytosis was absent in all cases.

DISCUSSION

Verruciform xanthoma (VX) is a benign squamous proliferation that presents clinically as a well circumscribed white, yellow, or erythematous papule or plaque with a verrucous surface and a flat or pedunculated base[3,4]. Lesions arising in the oral cavity are most common and have been described in series of significant numbers[4,5]. However, an infrequent subset arise at cutaneous sites[6], often involving the genitals[7], where they can pose diagnostic challenges clinically as well as histopathologically.

The definitive pathogenetic mechanism for VX remains unknown. While subsets of cases have been loosely associated with dermatologic and systemic conditions in male patients, there appears to be a stronger association with lichenoid dermatitides in female patients[8], a setting in which eight of ten vulvar VXs were associated with lichen sclerosus et atrophicus or lichen planus in one study[9]. Although HPV infection has been detected and postulated to be the etiologic source[10,11], HPV detection is infrequent [7,12] and has been interpreted overall as superinfection[2] with a prevalent human pathogen. Bacterial colonization has been described, particularly among lesions of the oral cavity[7,13,14], with multiple bacterial types detected[15]. To the authors' knowledge, this histologic feature has not been previously studied in large numbers of cutaneous VXs, or observed in small series [7] prior to our multi-institutional contemporary review. We have interpreted the presence of superficial bacteria as colonization secondary to altered barrier function; yet, we must note that chronic bacterial infections are associated with a number of xanthomatous/xanthogranulomatous lesions in the genitourinary area (e.g. malakoplakia), such that greater study is needed. Overall, for VX, most authors favor a chronic inflammatory etiology, involving keratinocyte damage, neutrophilic infiltration, induction of proliferation into a verrucoid lesion, with reactive xanthomatous accumulation in the papillary dermis[3,7,16].

While case reports and meta-analyses thereof have composed much of the literature concerning VX, our study represents the largest multi-institutional, retrospective study of consecutive cases of sporadic VXs. An excellent, recent comprehensive review of published genital VXs by Stiff *et al.*[3] provides a resource for comparison to our findings. We found that the overwhelming majority of VXs (92%) occur in males, which is close to the proportion documented (85%) by Stiff et al. Our experience suggests that in terms of sites, published case reports have somewhat over-represented (though not statistically significantly; p>0.3) the less prevalent penile (8% versus 16%) and vulvar cases (8% versus 14%), as compared to the most common site of the scrotum. While cases with inverted, endophytic, or cystic features have been described [3,7,17–19], all those we encountered were polypoid and exophytic.

The main difference, however, between our series and those reported previously, pertains to the median age, which was 51 years in the cases presented in the Stiff et al., as compared to our 62 years (P<0.01, U-test). This difference relates, at least in significant part, to the emphasis in the published literature of the association of VX with congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome [20–22], a genetic disease that almost exclusively manifests in females due to its X-linked dominant mode of inheritance and lethality in males. In patients with CHILD syndrome, VXs appear as multiple papules or nodules arranged in linear streaks with midline demarcation[23]. Of particular note, mutations involving the gene encoding *NSDHL (NADP Dependent Steroid Dehydrogenase-Like)* have been identified not only in CHILD syndrome but reportedly also in a subset of apparently sporadic VXs[24] .

Beyond comparing reported versus consecutive clinical features, we also endeavored to assess the prevalence and reliability of the classic diagnostic criteria, across an unselected consecutive cohort from diverse institutions. We note that in our series, the entity of VX, given its rarity, was not documented in the clinical differential diagnosis of any of our cases, emphasizing the key role of histopathology in its recognition and diagnosis. In this regard, our focus on histopathologic features can provide some guidance. We would particularly emphasize the low magnification configurations of these lesions, which in our opinion have not been well depicted or in significant numbers in prior case reports and small series. Examples ranged from broad, plaque-like configurations, whether of coalescent papillae or widened rete (Figure 1A,C respectively) to more polypoid papular proliferations (Figure 1D,F, and G) to lesions with discrete frondular papillae (Figure 1B,E, and H) overlying ectatic basal vessels and variable chronic inflammation. However variable the lesional silhouette, the higher magnification histopathologic features of VX (Figure 2) were quite consistent and reliable across all demographics, regardless

of gender, age of onset, and anatomic site. VX frequently displays wedge shaped, dense parakeratosis with an orange hue which commonly extends to fill the space between the epidermal papillomatous fronds. Additionally, the neutrophilic infiltrate in the parakeratotic stratum corneum represents a uniform characteristic feature, which is generally abundant and nearly always associated with bacterial colonies, at least focally. Consistent with anecdotal experience and prior teaching[2] that diagnostic xanthomatous macrophages may be infrequent or scarce, we observed they were only scattered or scarce 24% of VXs, necessitating recognition of ancillary features to prompt careful inspection for these cells. Interestingly, a subset (32%) of our cohort demonstrated lichenoid inflammation, which was characteristically mild. No clear association with a specific dermatologic or systemic comorbidity was identified, though many were documented at this cohort's age range. Nonetheless, we stipulate that one limitation of the series is that all cases studied were identified initially by searches for unequivocal diagnosis of VX, such that morphologic outliers or atypical/equivocal lesions would not have been included.

In summary, our experience suggests that beyond unusual case reports and published pitfalls, in routine practice genital VX is a predominantly a solitary lesion of the scrotum of middle aged to order men. Classic features, including the lack of significant cytologic atypia and koilocytosis, the abundance of neutrophils within the stratum corneum, and the usually prominent, even wedge-shaped parakeratosis between epidermal projections, are consistent characteristic findings in VX. These, in conjunction with xanthoma cells (which may be subtle) in the dermal papillae, should be helpful in distinguishing VX from its malignant and premalignant mimics.

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MCM, AMU; MBR; AOO, MBA, & SCS designed the study; GW, MCM, MBR, JSG, AMU, MPC, RMP, & SCS performed the research; GW, MCM, & SCS analyzed the data; GW, MCM, and SCS wrote the first draft of the paper; all authors edited/revised and approved the final paper.

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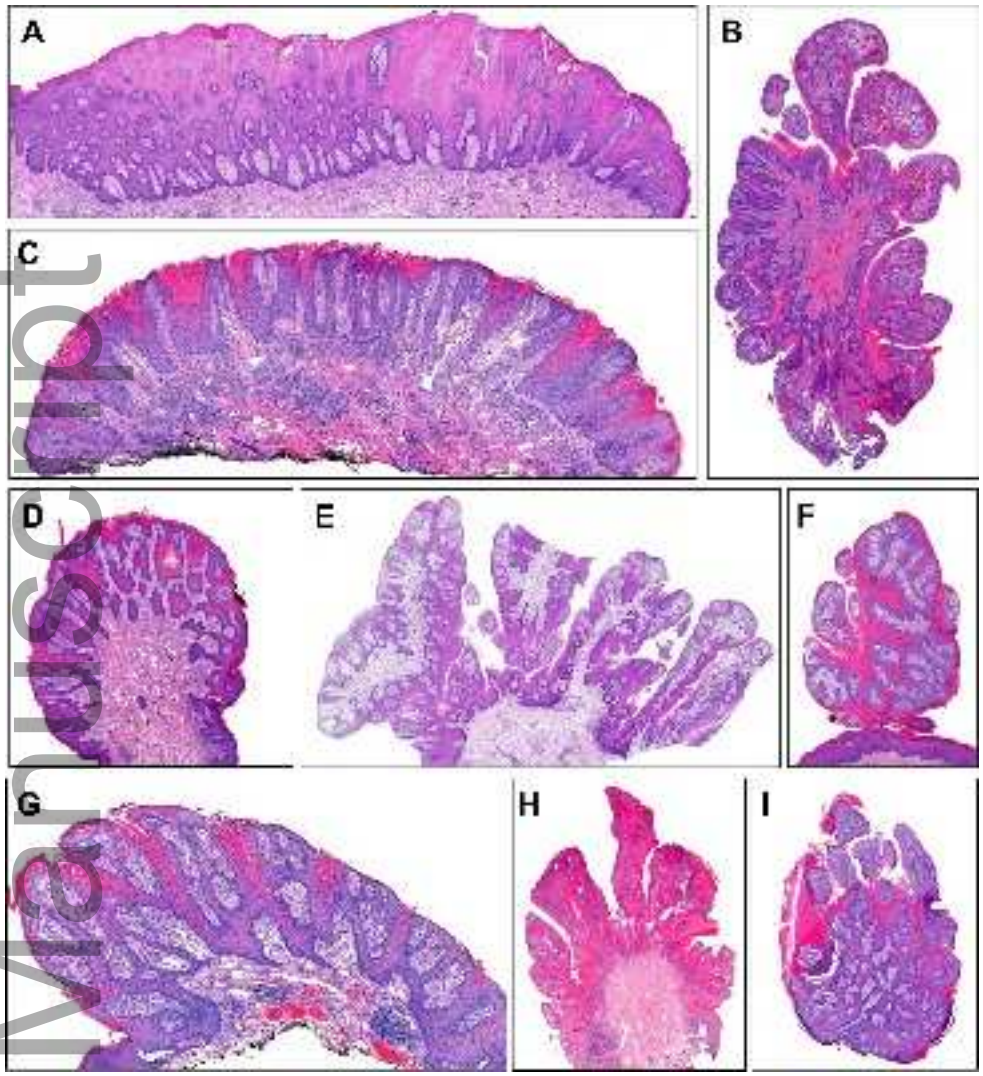
FIGURE LEGENDS

Figure 1. At low power, all VX cases encountered were exophytic, with varying degrees of plaque-like, to frondular/papillary, to pedunculated growth. Those depicted include (A) 2.1cm vulvar lesion from a 77 year old; (B) 1.3cm left anterior scrotal lesion from a 71 year old; (C) 0.6cm right scrotal lesion from an ≥89 year old; (D) 0.5cm left scrotal lesion from a 67 year old; (E) 1.8cm scrotal lesion of an 86 year old; (F) 0.5cm right scrotal lesion of a 68 year old; (G) 0.6cm right scrotal lesion of a 78 year old; (H) 1.6cm right scrotal lesion of a 79 year old; (I) 0.6cm right lateral scrotal lesion of a 62 year old.

Figure 2. Clinically, VXs presented most frequently as small scrotal papules, with variable scale crust (A). Key histologic features present in all cases included parakeratosis, often prominent and wedge-shaped (B), extending inward between papillary projections (C). Within parakeratosis (D), neutrophils were present in all cases (open arrowheads), with superficial bacterial colonies present in nearly all cases (black arrowhead). A subset of cases (24%) showed scattered or scarce xanthoma cells (E), often alternately present in the stroma of some (black arrowhead) but not all (open arrowhead) dermal papillae. Most cases, however, showed readily identified xanthoma cells filling the papillary dermis (F).



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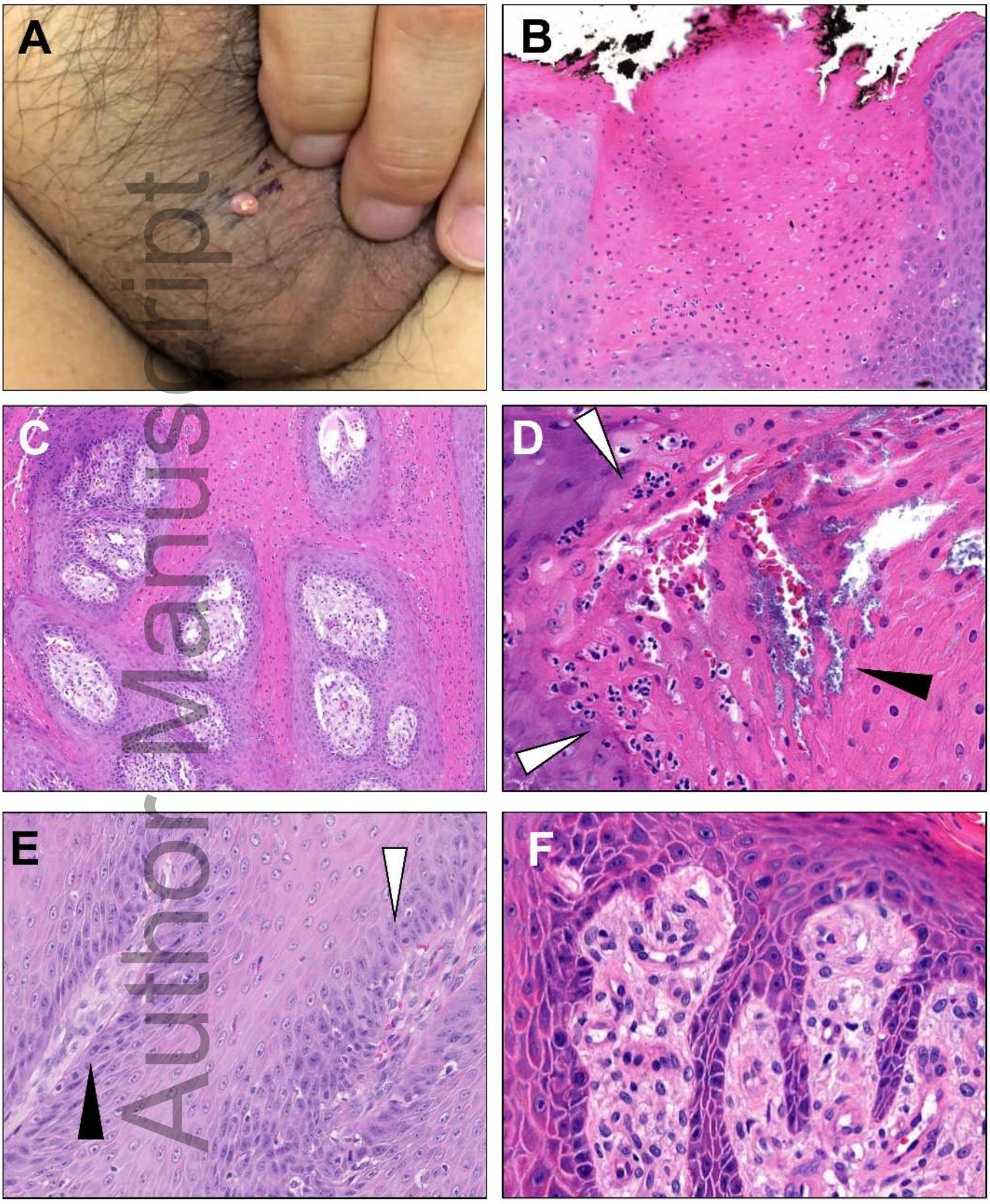

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