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Verruciform xanthoma(เวอรูชิฟอร์มแซนโทมา)

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Verruciform xanthoma

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Abstract

Verruciform xanthoma is a rare, benign entity which preferentially affects the oral mucosa than any other tissue. The most frequent site of involvement is the gingiva. It affects mostly the middle-aged person with a predilection for male gender. Clinically, verruciform xanthoma appears as papillary or verrucous, flat or slightly raised lesions. Aggregates of lipid-laden foam cells confined to the connective tissue papillae between epithelial rete ridges in association with papillary or verrucous epithelial hyperplasia are the histolopathologic hallmark of this lesion. These foam cells are actually of macrophage/monocyte lineage. The histopathological distinction of verruciform xanthoma from other lesions, which it may clinically resembles, is straightforward. This review article also present the proposed etiology as well as the differential diagnoses.

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Keywords: clinico-pathological features; etiology; foam cells; verruciform xanthoma

Introduction

The term xanthoma was derived from the Greek word xanthos, meaning yellow. Xanthoma was used to describe a yellowish, slightly raised or flat lesion on the skin to reflect the accumulation of xanthoma cells beneath the epithelial surface thus imparting the yellow-tan hue to the cutaneous lesion. Many xanthomas are cutaneous manifestation of local or generalized diseases which are known to be related to metabolic disturbances of different lipids, but there is one condition in this category in which the etiology is unknown that is verruciform xanthoma.[1]

Review of the literatures

Verruciform xanthoma was first described as an entity by Shafer in 1971.[2] Verruciform xanthoma is a relatively uncommon lesion occurring chiefly in the oral cavity.[3] Since the original description by Shafer, extraoral presentations have been reported in vulva,[4] penis,[5] scrotum,[6] and skin.[7] Although most verruciform xanthoma tend to occur as isolated lesions, cases showing simultaneous presentation with other lesions such as snuff dipper's keratosis,[8] warty dyskeratoma,[9] lichen planus,[10] psoriasis,[11] epidermal nevus,[12] discoid lupus erythematosus,[13] carcinoma in situ,[3] pemphigus vulgaris,[14] dystrophic epidermolysis bullosa[15] have been reported.

Etiology

The etiology of verruciform xanthoma still remains uncertain. It seems that it is not associated with local or generalized diseases as in the case of most skin xanthomas which are known to be cutaneous manifestations of the metabolic disturbances of different lipids.[1,16] The supporting fact is that most patients with verruciform xanthoma have normal lipid metabolism and do not show hyperlipidemia.[17] A viral etiology was suggested by Santa Cruz.[18] Mohsin et al[17] also suspected HPV as a culprit in the pathogenesis of verruciform xanthoma due to clinical resemblance to condyloma acuminata and the proclivity of this lesion to occur preferentially in

the oral cavity and at genital skin. This may account for a possible role of transmittable viral infection, similar to HPV. Attempts to demonstrate HPV in the lesion of verruciform xanthoma by both the immunohistochemical means or the more sensitive detection methods such as PCR or Southern blot analysis did not bear fruit and negligible number of cases were positive for HPV when detected by in situ hybridization.[19] Rowden et al[20] proposed an immunologic basis for the etiology of verruciform xanthoma based upon the result of the immunoperoxidase study for S-100 protein in which they could demonstrate the positively stained dendritic cells among the mononuclear inflammatory cell infiltrate at the base of the lesion and to a lesser extent among the foam cells. The presence of S-100 positive dendritic cells was interpreted as Langerhans cells. The principal function of these putative Langerhans cells was to present the antigens so verruciform xanthoma was thought to be at least mediated by an immune mechanism.[19]

Zegarelli et al[21,22]suggested an inflammatory origin. They proposed that local irritation caused gradual degeneration of epithelial cells with subsequent release of lipid material. The lipid, in turn, was scavenged by macrophages which finally assumed the foamy appearance and were called xanthoma cells. Supporting evidence for this explanation was the ultrastructural finding of degenerating, lipid-containing epithelial cells. Mohsin et al[17] explained the presence of faint granular cytoplasmic staining by cytokeratin in the foam cells of papillary dermis as of keratin fragments derived from the degenerating keratinocytes. Therefore, lipid in foam cells may derive from the cytoplasmic membrane or organelles of keratinocytes.

Since verruciform xanthomas have been reported to associated with lesions such as pemphigus vulgaris, discoid lupus erythematosus, epithelial dysplasia, epidermolysis bullosa, graft-versus-host disease, and epidermal nevi, such examples lend support to the theory that epithelial degeneration with subsequent lipid release results in accumulation of xanthoma cells.[9]

Nowparast et al[1] accounted for the verrucous and papillary architecture of the lesion by the fact that these were secondary changes to the presence of foam cells which affected the nutrient status and metabolism of the epithelial cells and led to parakeratotic and hyperkeratotic changes while Kishimoto et al[4] postulated that deep dermal vascular ectasia by unknown inciting agent caused the activation of both endothelial cells and pericytes in the papillary dermis. These activated cells then released various cytokines and growth factors that induced hyperplasia of epidermal keratinocytes as well as the accumulation of macrophages. Finally, macrophages took up the lipids and converted to xanthoma cells.

Clinical features

Clinically, verruciform xanthoma has been described to present as a roughened, papillary or cauliflower-like surface with sessile or a pedunculated base. Colors may range from normal to varying shades of red, gray or white depending on the degree of keratinization.[1,23,24] Typically, this lesion is asymptomatic and slowly growing.[1,25,26] Verruciform xanthoma may occur anywhere in the oral cavity, but the gingiva and the alveolar ridge are the most frequent locations.[8,24] According to the studies of Bucher et al,[27] gingiva was the most affected site followed in decreasing order of occurrence by alveolar mucosa, palate, floor of the mouth and mucobuccal fold, lip and ventral surface of the tongue, respectively. Takehana et al[25] reported that the premolar-molar gingiva was the most frequent site of involvement in the jaws. The majority of cases affect the middle-aged patients.[8,23] Mean age of most reported series usually falls in the range of 40-51 years.[1,19,25,28] The lesion can cover a variable amount of surface area, but mostly less than 2 cm. in diameter.[8,24,25] However, there were reports of the lesions measured up to 4 cm. in diameter.[26,29] Males are affected with this entity more often than females.[1,25]

Differential diagnosis

The differential diagnoses for verruciform xanthoma are papilloma, papillomatosis, papillary hyperplasia, keratosis, condyloma acuminata, verrucous hyperplasia, verruca vulgaris, verrucous carcinoma and squamous cell carcinoma.[8,16,23,25,27]

Histopathology

Nowparast et al[1] classified verruciform xanthoma into 3 configurations when viewed with low-powered microscope as follows:

1) Warty or verrucal appearance in which the lesion was elevated and well circumscribed. There were hyperparakeratosis, acanthosis and elongation of the rete ridges but not thickened granular layer as in verruca vulgaris.

2) Papillary or cauliflower-like architecture which formed numerous fingerlike projections consisting of mature stratified squamous epithelium covering connective tissue cores and forming crypt-like spaces covered by

parakeratin. This abnormality extended above the mucosal surface and demonstrated minimal epithelial proliferation below the surface.

3) Flat type in which the epithelial proliferation was seen below the surface with variable elongation of rete ridges to a uniform depth. No mitotic activity or pseudoepitheliomatous hyperplasia is observed in the epithelium.[25] The striking histologic feature of verruciform xanthoma is the aggregate of large foam or xanthoma cells which fill the connective tissue papillae between epithelial rete ridges (Fig 1 & 2). None of these xanthoma cells extend deep into the connective tissue beyond the tips of the epithelial rete ridges.[1,2,10,25] These cells exhibit abundant amounts of foamy cytoplasm and small round or oval nuclei, most of which are eccentrically placed.[16,24] In frozen section, these cells are shown to contain appreciable amounts of lipid when stained with Sudan III.[25,26] No giant cells are encountered in verruciform xanthoma.[1] There is zonal infiltration comprising lymphocytes, neutrophils and plasma cells beneath the main xanthomatous lesion.[16,30]

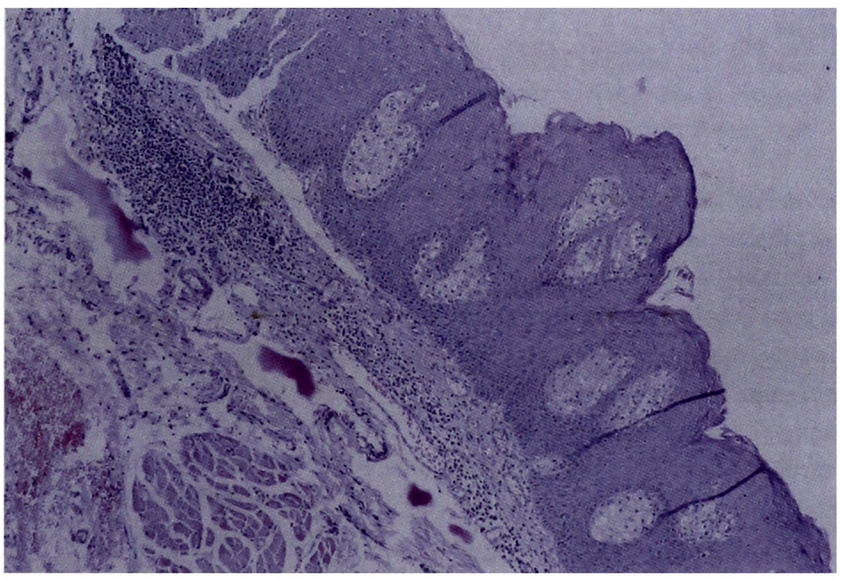

Fig 1 Photomicrograph showing the aggregate of foam cells in the connective tissue papillae between epithelial rete ridges. Hematoxylin and eosin stain. 42x

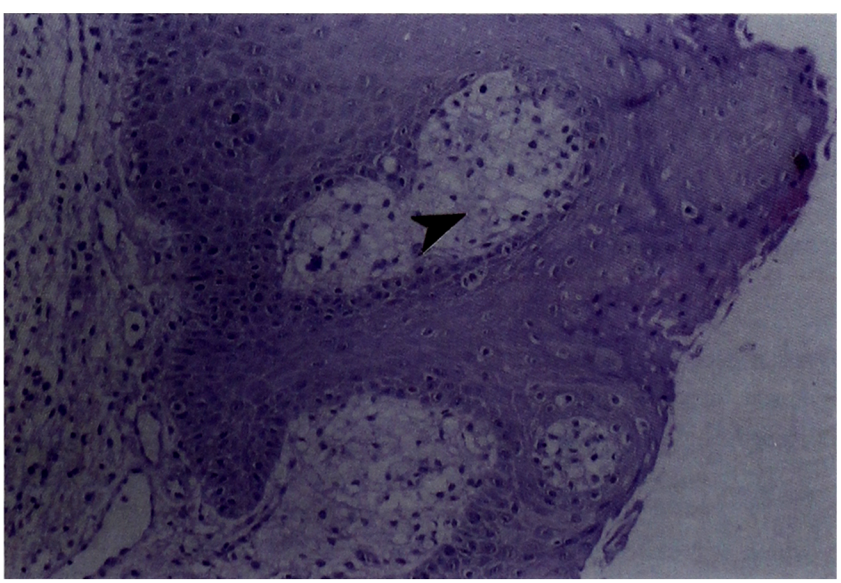

Fig 2 Photomicrograph showing higher magnification of foam cells (arrow) between epithelial rete ridges. Hematoxylin and eosin stain. 105x.

Immunohistochemistry

The characteristic foam cells of verruciform xanthoma are intensely stained by antibodies against cathepsin B, CD68 and vimentin,[4,9,19,31] less intensely stained by antibodies against MAC387, LeuMl, lysozyme and chymotrypsin[4,19,31] and negative staining for antibodies against neuron-specific enolase, desmin and keratin.[31] These findings support the origin of foam cells as cells derived from the monocyte/macrophage lineage. Cytokeratin shows a faint granular cytoplasmic staining in the foam cells in the papillary dermis and strong reactivity in keratinocytes.[17] S-100 protein highlights epidermal Langerhans cells in the suprabasal layer whereas foam cells in the papillary dermis show no reactivity.[17,19]

Ultrastructure

The foam cells assume an ellipsoidal morphology displaying irregular and undulating cytoplasmic membrane. The cytoplasm contains a variable number of electronlucent, spherical lipid droplets which correspond to the characteristic foamy appearance in the light microscope. Foam cells not only possess ordinary electronlucent lipid droplets, they also contain other lipid inclusions such as myelin figures and lipid inclusion in the form of amorphous matrix of uniform density. The myelin figures are found to be associated with lipid droplets. They are located both external to and within the lipid droplets. The cytoplasm also comprises numerous small vesicles and membrane-bound, electron-dense lysosomes. Due to the abundant amount of lipid inclusions, the nucleus is displaced to the eccentric position. The nucleus is ovoid or elongated with irregular outline. The nuclear chromatin is evenly dispersed except for regular condensation at the periphery. Its nucleolus is prominent. The subepithelial capillaries present with normal appearing endothelial cells showing multiple layers of basal lamina. The multiple laminae are of uniform density with pronounced granularity.[16,24]

Treatment

The treatment for verruciform xanthoma is usually accomplished through simple surgical excision with recurrence almost nonexistent.[1,25,28]

Discussion

All the lesions in which verruciform xanthoma mimics clinically can be distinguished on histopathological ground. Although these lesions may possess certain degree of epithelial proliferation, they consistently lack the characteristic aggregate of xanthoma cells between the epithelial rete ridges. Besides, papilloma, verruca vulgaris and condyloma acuminata also show the koilocytes which are regarded as the histopathological hallmark of the viral infection. The importance in recognizing this entity is to avoid the misdiagnosis as more serious disease as verrucous carcinoma or squamous cell carcinoma which leads to overtreatment and the devastating effect to the patient as a consequence since the treatment for verruciform xanthoma can be easily accomplished through simple surgical excision.

Although the etiology of this lesion is still unresolved, the most widely accepted theory concerning the origin of this lesion is the one put forward by Zegarelli et al[22] which stated that the unknown inciting agent caused the epithelial cells to degenerate and subsequently released the lipid content. These lipids were then taken up by macrophages that finally converted to xanthoma cells. Subsequent authors proposed that immune response also played a part in the pathogenesis of verruciform xanthoma based on the presence of Langerhans cells.[19,20]

Conclusion

Verruciform xanthoma is an uncommon lesion with special preference for occurring in the oral cavity. Verruciform xanthoma can display varied architectural features which may mimic clinical presentation of a host of other diseases, but the histologic appearance of verruciform xanthoma is very characteristic and should not pose any difficulty in rendering the correct diagnosis. From the immunohistochemical and ultrastructural studies, it can be concluded that the foam or xanthoma cells are acutually the macrophages, which engulf the lipid material.

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เวอรูซิฟอร์มแซนโทมา

กิตติพงษ์ ดนุไทย ท.บ., วท.ม.

ภาควิชาทันตพยาธิวิทยา คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

บทคัดย่อ

เวอรูซิฟอร์มแซนโทมาเป็นเนื้องอกชนิดที่ไม่ร้ายแรงที่พบได้ไม่บ่อยซึ่งมักจะพบบริเวณเนื้อเยื่อในช่องปากได้มากกว่าเนื้อเยื่อบริเวณอื่น ตำแหน่งที่พบได้บ่อยที่สุดคือบริเวณเหงือก เวอรูซิฟอร์มแซนโทมามักจะพบในผู้ป่วยวัยกลางคนโดยเฉพาะอย่างยิ่งในเพศชาย ในทางคลินิกเวอรูซิฟอร์มแซนโทมาจะแสดงลักษณะพื้นผิวที่ขรุขระโดยรอยโรคอาจจะแบนราบหรือยกตัวสูงขึ้นเล็กน้อย ลักษณะเฉพาะของโรคนี้ทางจุลพยาธิวิทยาคือมีการรวมกลุ่มกันของโฟมเซลล์ซึ่งมีไขมันบรรจุอยู่ภายในเซลล์โดยโฟมเซลล์เหล่านี้จะอยู่ในส่วนของเนื้อเยื่อยึดต่อซึ่งยื่นเข้าไปในส่วนของเอ็พพิทีเลียมร่วมกับการงอกเกินของเนื้อเยื่อบุผิวแบบเป็นปุ่มนูนเล็ก ๆ หรือลักษณะคล้ายหูด โฟมเซลล์เหล่านี้มีต้นกำเนิดมาจากเซลล์ในสายของแมกโครฟาจหรือโมโนซัยต์ เวอรูซิฟอร์มแซนโทมามีลักษณะทางจุลพยาธิวิทยาที่เฉพาะตัวแตกต่างจากรอยโรคอื่นซึ่งมีลักษณะทางคลินิกคล้ายคลึงกัน บทความปริทัศน์นี้ยังกล่าวถึงสาเหตุรวมทั้งการวินิจฉัยแยกโรคของโรคนี้

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