Oral Verruciform Xanthoma Associated with Chronic Graft-Versus- Host Disease: A Report of Five Cases and a Review of the Literature

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Abstract Verruciform xanthoma (VX) is an uncommon benign inflammatory mucocutaneous condition that chiefly occurs in the oral cavity. It is often associated with pre-existing epithelial and/or inflammatory disorder and is characterized histopathologically by papillary epithelial hyperplasia and the presence of foamy macrophages in connective tissue papillae. We report of a series of five cases with VX who concurrently had chronic oral graft-versus-host disease following hematopoietic stem cell transplantation.

Keywords Verruciform xanthoma · Chronic GVHD · Oral GVHD · Oral mucosa · Hematopoietic stem cell transplantation

Introduction

Verruciform xanthoma (VX) is an uncommon, benign, and usually solitary papillary lesion with a predilection for oral mucosa [1]. It was first reported in 1971 by Shafer [2] who

described 15 cases occurring in the oral mucosa. The frequency of occurrence is from 0.025 to 0.094% [3, 4] and may also affect the skin especially of the genital area [5–8]. VX affects mostly adults in the 4th and 5th decades without sex predilection [1].

Although most of the cases of VX occur in otherwise healthy individuals, it has been reported in association with inflammatory conditions such as pemphigus vulgaris [9], lichen planus [10–14], discoid lupus erythematosus [15, 16], warty dyskeratoma [17], psoriasis [18], epidermal nevus/CHILD nevus [5, 19, 20], dystrophic epidermolysis bullosa [21], and seborrheic keratosis [22]. It has also been associated with carcinoma in situ [23], and squamous cell carcinoma [24]. Multifocal cases of VX involving the upper aerodigestive tract have been also reported in a patient with systemic lipid storage disorder [25] and in a patient using snuff [26]. An association of VX with chronic graft-versus-host-disease (cGVHD) after allogenic hematopoietic stem cell transplantation (aHSCT) has also been documented and only four cases have been reported [24, 27–29]. Here, we report a series of five cases of VX that arose in patients who developed GVHD following HSCT. All patients were seen in the Division of Oral Medicine and Dentistry, Brigham and Women's hospital, Boston, for evaluation and management of their oral lesions.

Case Report

Case 1

A 45-year-old Caucasian male presented with a 1.0 cm, well-demarcated, non-tender, sessile, papillary reddish plaque on the left buccal mucosa in the area of the first and

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second molars that had been present for 6 months (Fig. 1). There was an area of white striae in a reticular pattern with mild erythema and ulceration on the posterior of left buccal mucosa consistent with a known history of oral GVHD. He had undergone aH SCT 22 months prior for acute lymphoblastic leukemia and had developed GVHD of the eyes, mouth, liver and lungs 8 months after transplantation.

Case 2

A 13-year-old African-American female presented with a 1.2 cm, pedunculated, non-tender papillary mass on the right posterior tongue that was present for 6 months (Fig. 2). She had undergone an aH SCT 4 years prior for aplastic anemia and had a history of GVHD involving the skin, mouth, eyes, and lungs.

Fig. 1 Case 1 showing a well-demarcated papillary reddish plaque of the left buccal mucosa

Fig. 2 Case 2 showing a pedunculated papillary nodule on the right posterior tongue dorsum

Case 3

A 63-year-old male presented with a 1.0 cm, ovoid, non-tender, well-demarcated, rough plaque on the left posterior lateral tongue, which developed in 3 months (Fig. 3). He also had generalized white striae in a reticular pattern of the right and left buccal mucosa typical for oral cGVHD. He had undergone HSCT 5 years prior for chronic lymphoblastic leukemia and subsequently developed GVHD involving the skin and mouth.

Case 4

A 48-year-old female presented with a 1.5 cm, erythematous, well-demarcated, non-tender, sessile plaque of the left upper labial mucosa (Fig. 4). The tongue and buccal

Fig. 3 Case 3 showing a well-demarcated yellowish verrucous plaque on the left lateral ventral tongue

Fig. 4 Case 4 showing a well-demarcated erythematous papillary plaque on the maxillary labial mucosa

mucosa demonstrated extensive white striae in a reticular pattern typical for GVHD. She had undergone aHSCT 4 years prior for chronic myelogenous leukemia and developed GVHD of the skin, mouth, and eyes.

Case 5

A 45-year-old male presented with 0.5 cm, well-demarcated, non-tender, sessile erythematous granular plaque on the right hard palate in the area of the first premolar (Fig. 5). He had undergone aHSCT 5 years prior for chronic lymphoblastic leukemia and had a history of extensive GVHD of the skin, mouth, and eyes. He also had several unrelated distinct leukoplakias in his mouth which were biopsied and diagnosed “verruccous hyperplasia without significant cytologic atypia, extending to tissue edges”.

Histopathology

The histopathological findings of all five cases were identical and typical for VX. Each lesion consisted of a papillary proliferation of stratified squamous epithelium covered by brightly eosinophilic parakeratin with desquamating cells on the surface; neutrophilic exocytosis was frequently noted. The epithelium formed uniformly long bulbous rete ridges often confluent at the tips (Fig. 6a). Many foamy macrophages were located in the papillary lamina propria (Fig. 6b).

Discussion

VX occurs mainly in the oral cavity, although it may arise from any surface or lining epithelium such as vulva,

Fig. 5 Case 5 showing a well-defined reddish granular plaque (solid arrow) and a separate unrelated area of leukoplakia (dotted arrow) on the right hard palate

Fig. 6 **a** Photomicrograph of a verruciform xanthoma (case 4) with papillary epithelial hyperplasia, hyperkeratosis, parakeratin plugging, and uniformly elongated rete ridges, (H&E, $\times 40$). **b** Photomicrograph (case 4) showing numerous large, vacuolated foam cells that fill the connective tissue papillae with overlying parakeratosis (H&E, $\times 200$)

scrotum, and skin [1, 5, 6, 30]. Similar lesions have also been reported in dogs [31]. VX manifests as an asymptomatic solitary, slow-growing plaque or nodule with a papillary, granular or verrucous surface and sharply delineated margins that may appear pink, red, yellow, or white in color [1]. The occurrence of multiple or disseminated VX is extremely rare [24, 32, 33]. Approximately 75% of all oral VX lesions occur on the masticatory mucosa of the palate, gingiva or the alveolar ridge [1].

Histopathologically, VX is characterized chiefly by hyperparakeratosis and papillary surface configuration; however non-papillary or flat variants have been described [34]. The parakeratin layer exhibits a bright orange hue, the spinous layer is hyperplastic and the rete ridges are uniformly elongated. The hallmark feature of VX is the presence of large, lipid-laden foam cells within the connective tissue papillae [1]. These foam cells were found to be histiocytes or macrophages based on immunohistochemical findings demonstrating positivity for CD68, macrophage scavenger receptor-I (MSR-I), monocyte chemo-attractant protein-I (MCP-I), CCR2, and oxidized

Table 1 Previously and current reported cases of oral verruciform xanthoma associated with oral lichen planus (OLP) and oral chronic GVHD (cGVHD)

Condition	Reference	Gender	Age	Site
OLP	Hume et al. [10]	Female	55	Buccal mucosa
	Miyamoto et al. [11]	Female	68	Lateral tongue
	Polonowita et al. [12]	Male	65	Mandibular gingiva
		Female	73	Mandibular alveolar mucosa
		Female	42	Lateral tongue
		NS	NS	NS
		NS	NS	NS
	Yu et al. [13]	NS	NS	NS
	Anbinder et al. [14]	Male	70	Buccal mucosa
	Allen et al. [28]	Male	22	Lower lip vermillion
Oral cGVHD	Helm et al. [27]	Female	23	Thigh
	Mannes et al. [24]	Male	12	Axilla
	Sibaud et al. [29]	Male	57	Gingiva
	Shahrabi Farahani et al.	Male	45	Buccal mucosa
		Female	13	Tongue dorsum
		Male	63	Lateral tongue
		Female	48	Labial mucosa
		Male	45	Hard palate

NS not specified

low-density lipoprotein (OX-LDL) [35, 36]. A cystic variant of VX has also been reported [37].

The etiopathogenesis of VX is unclear but appears to be associated with localized inflammation [38]. Immunologic factors [39] and viral etiologies [5] have been also suggested. The prevailing theory is that epithelial tissue damage results in the breakdown of the phospholipid-rich cell membranes releasing lipids that are then taken up by macrophages in the connective tissue that become lipid-laden or foamy in appearance [38, 40, 41]. An immunologic pathogenesis has been suggested because of the predominant T cells infiltrate, and decreased number of Langerhans cells in oral VX compared to normal tissue [34, 39]. Human papillomavirus (HPV) has not been demonstrated in VX lesions [24, 26, 35, 41, 42] and viral particles have not been identified ultrastructurally [35].

Chronic GVHD is a common complication after allogeneic HSCT in which functional donor immune cells recognize the recipient cells as foreign and attack the host tissues [43]. Oral mucosal manifestations of chronic GVHD are common and include reticular/hyperkeratotic striations and plaques, erythema, and ulcerations [44]. Histopathologically, GVHD is similar to oral lichen planus, exhibiting apoptosis of keratinocytes and destruction of the basal cells and apoptosis [45]. It is therefore not surprising that VX has been reported in association with both lichen planus [10–14] and chronic GVHD (Table 1).

Here we report a series of five cases of oral VX that developed in association with oral GVHD, bringing the total number of cases in the literature to nine (Table 1). All five cases were non-tender, erythematous, granular or papillary lesions with distinct borders similar to previous reports. All nine cases of VX associated with GVHD had a

history of or concurrent skin or oral chronic GVHD. Although 75% of oral VX involves gingiva and hard palate, only one each of the seven oral cases (29%) was located on the gingiva or hard palate and the rest were on the buccal mucosa, tongue, and labial mucosa. Similarly, only two of six cases with known site of involvement of reported VX cases associated with oral lichen planus were located on the gingiva with the rest located on the buccal mucosa and tongue (Table 1). Because oral GVHD and oral lichen planus most commonly affect the buccal mucosa, tongue, and labial mucosa, this further supports the hypothesis that the pathogenesis of VX is related to localized epithelial damage. It is likely that damage to the basal cell and apoptosis seen in lichen planus and oral chronic GVHD release lipids that are phagocytosed by histiocytes or dermal dendrocytes. Other associated conditions that suggest a role for epithelial damage include pemphigus vulgaris and epidermolysis bullosa [9, 21].

The clinical differential diagnosis of VX includes squamous papilloma, verruca vulgaris, condyloma acuminatum, verrucous leukoplakia, and squamous cell carcinoma. Patients who have undergone allogeneic HSCT are on many immunosuppressive agents and those who develop chronic GVHD are at substantially increased risk for developing squamous cell carcinoma of the skin and mouth [46, 47], so these lesions must be correctly diagnosed. The presence of foamy macrophages and the distinctive papillary epithelial proliferation with brightly eosinophilic parakeratin with keratin squames and neutrophilic exocytosis can easily distinguish VX from malignancy [48]. Especially in patients with history of chronic GVHD, VX requires biopsy for definitive diagnosis, and treatment of oral VX is generally simple excision although

once diagnosed lesions can be watched without further intervention.

References

- Philipsen HP, Reichart PA, Takata T, et al. Verruciform xanthoma-biological profile of 282 oral lesions based on a literature survey with nine new cases from Japan. *Oral Oncol*. 2003;39:325–36.
- Shafer WG. Verruciform xanthoma. *Oral Surg Oral Med Oral Pathol*. 1971;31:748–9.
- Buchner A, Hansen LS, Merrell PW. Verruciform xanthoma of the oral mucosa. Report of five cases and review of the literature. *Arch Dermatol*. 1981;117:563–5.
- Cheng YS, Wright J, Lucente J, et al. Oral and maxillofacial pathology case of the month. Verruciform xanthoma. *Tex Dent J*. 2010;127(1):126–7, 130–1.
- Santa Cruz DJ, Martin SA. Verruciform xanthoma of the vulva. Report of two cases. *Am J Clin Pathol*. 1979;71:224–8.
- Kraemer BB, Schmidt WA, Foucar E, et al. Verruciform xanthoma of the penis. *Arch Dermatol*. 1981;117:516–8.
- Kimura S. Verruciform xanthoma of the scrotum. *Arch Dermatol*. 1984;120:1378–9.
- Barr RJ, Plank CJ. Verruciform xanthoma of the skin. *J Cutan Pathol*. 1980;7:422–8.
- Gehrig RD, Baughman RA, Collins JF. Verruciform xanthoma in a young male patient with a past history of Pemphigus vulgaris. *Oral Surg Oral Med Oral Pathol*. 1983;55:58–61.
- Hume WJ, Smith CJ, Franklin CD. Verruciform xanthoma. *Br J Oral Surg*. 1980;18:157–61.
- Miyamoto Y, Nagayama M, Hayashi Y. Verruciform xanthoma occurring within oral lichen planus. *J Oral Pathol Med*. 1996;25:188–91.
- Polonowita AD, Firth NA, Rich AM. Verruciform xanthoma and concomitant lichen planus of the oral mucosa. A report of three cases. *Int J Oral Maxillofac Surg*. 1999;28:62–6.
- Yu CH, Tsai TC, Wang JT, et al. Oral verruciform xanthoma: a clinicopathological study of 15 cases. *L Formos Med Assoc*. 2007;106:141–7.
- Anbinder AL, de Souza Quirino MR, Brandao AA (2010) Verruciform xanthoma and neurofibromatosis: a case report. *Br J Oral Maxillofac Surg*. [Epub ahead of print].
- Meyers DC, Woosley JT, Reddick RL. Verruciform xanthoma in association with discoid lupus erythematosus. *J Cutan Pathol*. 1992;19:156–8.
- Poulpoulos Ak, Epivatianos A, Zaraboukas T, et al. Verruciform xanthoma coexisting with oral discoid lupus erythematosus. *Br J Oral Maxillofac Surg*. 2007;45:159–60.
- Neville BW, Coleman PJ, Richardson MS. Verruciform xanthoma associated with an oral warty dyskeratoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;81:3–4.
- Yamamoto T, Katayama I, Nishioka K. Verruciform xanthoma in a psoriatic patient under PUVA therapy. *Dermatology*. 1995;191:254–6.
- Ko JY, Shin H, Lee CW. A verruciform xanthoma-like phenomenon in a linear epidermal naevus in the absence of a syndromic association. *Br J Dermatol*. 2008;159:493–6.
- Hashimoto K, Prada S, Lopez AP, et al. CHILD syndrome with linear eruptions, hypopigmented bands, and verruciform xanthoma. *Pediatr Dermatol*. 1998;15:360–6.
- Orpin SD, Scott IC, Rajaratnam R, et al. A rare case of recessive dystrophic epidermolysis bullosa and verruciform xanthoma. *Clin Exp Dermatol*. 2009;34:49–51.
- Wu YH, Hsiao PF, Lin YC. Verruciform xanthoma-like phenomenon in seborrheic keratosis. *J Cutan Pathol*. 2006;33:373–7.
- Drummond JF, White DK, Damm DC, et al. Verruciform xanthoma within carcinoma in situ. *J Oral Maxillofac Surg*. 1989;47:398–400.
- Mannes KD, Dekle CL, Requena L, et al. Verruciform xanthoma associated with squamous cell carcinoma. *Am J Dermatopathol*. 1999;21:66–9.
- Travis WD, Davis GE, Tsokos M, et al. Multifocal verruciform xanthoma of the upper aerodigestive tract in a child with a systemic lipid storage disease. *Am J Surg Pathol*. 1989;13:309–16.
- Neville BW, Weathers DR. Verruciform xanthoma. *Oral Surg Oral Med Oral Pathol*. 1980;49:429–34.
- Helm KF, Hopft RM, Kreider JW, et al. Verruciform xanthoma in an immunocompromised patient: a case report and immunohistochemical study. *J Cutan Pathol*. 1993;20:84–6.
- Allen CM, Kapoor N. Verruciform xanthoma in a bone marrow transplant recipient. *Oral Surg Oral Med Oral Pathol*. 1993;75:591–4.
- Sibaud V, Marit G, Deminiere C, et al. Multiple verruciform xanthomas of the oral mucosa associated with graft versus host disease. *Ann Dermatol Venereol*. 2006;133:995–9.
- Herrera-Goepfert R, Lizano-Soberón M, García-Perales M. Verruciform xanthoma of the esophagus. *Hum Pathol*. 2003;34:814–5.
- Balm E, Thuilliez C, Lejeune T, et al. Multiple atypical xanthomas in a dog similar to human verruciform xanthoma. *J Vet Diagn Invest*. 2009;21:124–8.
- Blanco C, Miranda C, Fernandez F, et al. Verruciform xanthoma of the lip: two lesions in a woman. *Am J Dermatopathol*. 1988;10:176–8.
- Sopena J, Gamo R, Iglesias L, et al. Disseminated verruciform xanthoma. *Br J Dermatol*. 2004;151:717–9.
- Nowparast B, Howell FV, Rick GM. Verruciform xanthoma. A Clinicopathologic review and report of fifty-four cases. *Oral Surg Oral Med Oral Pathol*. 1981;51:619–25.
- Mostafa KA, Takata T, Ogawa I, et al. Verruciform xanthoma of the oral mucosa: a clinicopathological study with immunohistochemical findings relating to pathogenesis. *Virchows Arch A*. 1993;423:243–8.
- Ide F, Obara K, Yamada H, et al. Cellular basis of verruciform xanthoma: immunohistochemical and ultrastructural characterization. *Oral Disease*. 2008;14:150–7.
- Poblet E, McCaden ME, Santa Cruz DJ. Cystic verruciform xanthoma. *J Am Acad Dermatol*. 1991;25:330–1.
- Zegarelli DJ, Zegarelli-Schmidt EC, Zegarelli EV. Verruciform xanthoma. A clinical, light microscopic, and electron microscopic study of two cases. *Oral Surg Oral Med Oral Pathol*. 1974;38:725–34.
- Rowden D, Lovas G, Shafer W, et al. Langerhans cells in verruciform xanthoma: an immunoperoxidase study of 10 cases. *J Oral Pathol*. 1986;15:48–53.
- Zegarelli DJ, Zegarelli-Schmidt EC, Zegarelli EV. Verruciform xanthoma. Further light and electron microscopic studies, with the addition of a third case. *Oral Surg Oral Med Oral Pathol*. 1975;40:246–56.
- Mohsin SK, Lee MW, Amin MB, et al. Cutaneous verruciform xanthoma: a report of five cases investigating the etiology and nature of Xanthomatous cells. *Am J Surg Pathol*. 1998;22:479.
- Imaroon A, Vickers RA. Characterization of verruciform xanthoma by in situ hybridization and immunohistochemistry. *J Oral Pathol Med*. 1996;25:395–400.
- Cutler C, Antin JH. Chronic graft-versus-host disease. *Curr Opin Oncol*. 2006;18:126–31.
- Treister NS, Cook EF Jr, Antin J, Lee SJ, Soiffer R, Woo SB. Clinical evaluation of oral chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2008;14:110–5.

45. Woo S-B, Lee SJ, Schubert MM. Graft-vs-host disease. *Crit Rev Oral Biol Med*. 1997;8:201–16.
46. Cutris RE, Metayer C, Rizzo JD, et al. Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study. *Blood*. 2005;105:3802–11.
47. Khan FM, Sy S, Louie P, et al. Genomic instability after allogeneic hematopoietic cell transplantation is frequent in oral mucosa, particularly in patients with history of chronic graft-vs-host disease, and rare in nasal mucosa. *Blood*. 2010; [Epub ahead of print].
48. Woo SB. In: McKee PH, Calonje E, Granter SR, editors. *Pathology of the skin with clinical correlations*. 3rd ed. Philadelphia, PA: Elsevier-Mosby, 2005; pp. 385–472.