Verruciform Xanthoma with Equivocal Exfoliative Cytological Diagnosis

Takeshi Onda¹, Kamichika Hayashi¹, Naoki Shiraishi¹, Nobuo Takano² and Takahiko Shibahara³

¹ Department of Oral and Maxillofacial Surgery, Tokyo Dental College, 1-2-2 Masago, Mihama-ku, Chiba 261-8502, Japan
² Oral Cancer Center, Tokyo Dental College, 5-11-13 Sugano, Ichikawa, Chiba 272-8513, Japan

Received 31 August, 2017/Accepted for publication 6 November, 2017

Abstract

Verruciform xanthoma (VX), a papillary or wart-like lesion of the mucosa, is histopathologically characterized by papillary projection of the epithelium and an aggregation of foam cells in the lamina propria. Here, we describe a case of VX in the posterior mandibular gingiva, initially suspected to be a benign lesion based on clinical findings and cytology prior to an excisional biopsy. The patient was a 62-year-old man who had visited a local dentist approximately 1 year earlier, presenting with a white lesion in the left posterior mandibular gingiva that resisted removal by scraping. The lesion was left untreated as there were no subjective symptoms. Thereafter, the surface of the lesion roughened and the patient was referred to our department for a comprehensive examination. A circumscribed, granular mass, 15-mm in diameter, with a red and white surface was observed in the left posterior mandibular buccal gingiva. Exfoliative cytology was performed. The diagnosis was a class III lesion. Excisional biopsy was performed under local anesthesia. Histopathological examination led to a diagnosis of VX. At 1 year postoperatively, the patient is making satisfactory progress without recurrence. Verruciform xanthoma is difficult to diagnose preoperatively, and is commonly resected under a clinical diagnosis of papilloma or benign tumor. A benign lesion was also initially suspected in the present case and cytological analysis performed to confirm absence of malignancy. The lesion could not be diagnosed as VX preoperatively. Verruciform xanthoma can be over-diagnosed based solely on cytological examination because it often involves cellular atypia reflecting its characteristic extension of rete pegs and keratinization of surface cells, indicating the need for care in arriving at a definitive diagnosis.

Key words: Verruciform xanthoma — Cytology — Gingiva
Introduction

Verruciform xanthoma (VX), a papillary or wart-like lesion of the mucosa, is histopathologically characterized by papillary projection of the epithelium and an aggregation of foam cells in the lamina propria \(^3\). It is relatively rare in the oral cavity \(^3\). Here, we describe a case of VX in the posterior mandibular gingiva initially suspected to be a benign lesion based on clinical findings and cytology prior to an excisional biopsy.

Case Report

Patient: A 62-year-old man.
Chief complaint: A white lesion in the left posterior mandible.
Past medical history: Hypertriglyceridemia, hypertension, and chronic hepatitis B virus infection.
Family history: Nothing significant.
History of present illness: Approximately 1 year before presenting at our department, the patient’s local dentist had noted a white lesion in the buccal gingiva of the left posterior mandible. The lesion proved resistant to removal by scraping, however. It was subsequently left untreated as the patient reported no subjective symptoms. Later, however, the surface of the lesion roughened and the patient was referred to our department for a comprehensive examination, the findings of which were as follows:

General findings: Nothing significant.
Facial findings: Symmetrical.
Intraoral findings: A circumscribed, granular mass, 15-mm in diameter, with a red and white surface on the left posterior mandibular buccal gingiva (Fig. 1).

Imaging findings: No obvious bone adsorption or abnormal findings were observed in the area concerned on panoramic X-ray or CT images (Fig. 2).

Blood test: No significant findings.
Clinical diagnosis: Suspected benign tumor in the left posterior mandible.
Treatment and clinical course: Exfoliative cytology was performed and a class III (suspicious; suggestive of malignancy, but not conclusive) lesion diagnosed. An excisional biopsy was performed under local anesthesia. Iodine staining was performed to determine the extent of resection required. No unstained areas were observed, however. Resection with a sufficient surgical margin including the periosteum was performed. Verruciform xanthoma was diagnosed based on histopathological findings. Twelve months have passed postoperatively at the present time, and the patient is making satisfactory progress without recurrence.

Cytological findings: Orange G-stained squamous cells were scattered and an overlap of these cells was also observed at various sites. Keratinized squamous cells exhibited mild nuclear enlargement, and some of these cells also presented augmented cytoplasmic brightness, irregular nuclear shape, increased nuclear-cytoplasm ratio, and darkened nuclear staining (Fig. 3a, b).

Histopathological findings: The rete pegs of the covering epithelium were irregularly extended, and an aggregation of foam cells with bright and granular cytoplasms was observed in the connective tissue papillae. Mild keratinization and papillary projection of the epithelium were also observed at the extended rete pegs (Fig. 3c, d).

Histopathological diagnosis: Verruciform xanthoma.
Discussion

First described in 1971, VX is a papillary or wart-like lesion of the mucosa\textsuperscript{20}. Histopathologically, it is characterized by extended rete pegs with aggregations of foam cells in the lamina propria between them. It remains to be fully described and its pathogenesis is still unknown, but is generally considered to be the result of inflammatory change rather than a true tumor\textsuperscript{3,30}. A number of reasons have been reported for this supposition: the foam cells do not autonomously proliferate and are localized to the papillary portion of the subepithelial connective tissue; Touton giant cells, which are observed in a true xanthoma, are absent; and inflammatory cell infiltration is observed in the subepithelial connective tissue\textsuperscript{21,32}. There are two hypotheses regarding the association between papillary projection of the epithelium and foam cells in the subepithelial connective tissue: the first postulates that papillary projection of the epithelium occurs through chronic stimuli, followed by degeneration and disintegration of epithelial cells that have invaginated the connective tissue, resulting in transformation of these epithelial cells into xanthoma cells, which responsively appear localized to the papillary area\textsuperscript{21,32}; the second postulates that a localized lipid metabolism abnormality occurs at the papillary portion through some type of stimulation, histiocytes aggregate in the subepithelial area and phagocytose lipids, thereby transforming into xanthoma cells, and the papillary projection of epithelium occurs as a response to this\textsuperscript{2,13}. No evidence was found in the present case to support either of these hypotheses, however. It is possible, though, that some form of stimulation had been applied to the gingiva. Immunohistochemically, foam cells are likely to be negative for epithelial markers and positive for mesenchymal markers. They are also likely to

Fig. 2 Imaging findings at initial visit

a: Panoramic X-ray image. No obvious abnormalities observed in left posterior mandibular teeth or alveolar bone. b, c: X-ray CT image. No obvious bone adsorption or abnormality observed or neoplastic lesion detected.
be positive for CD68 and α1-antitrypsin, which are believed to be derived from histiocytes. Although VX predominantly occurs in the oral region, some reports have shown its appearance at the penis and vulva. One earlier statistical analysis of 173 clinical cases revealed that oral VX occurred most commonly in the gingiva and alveoli (n = 85), followed by the palate (n = 25), tongue (n = 16), buccal mucosa (n = 12), and floor of the mouth (n = 10). In the present case also, VX had developed in the gingiva, which is considered to be its most common location. Gingival VX was first reported in Japan in 1977. To our knowledge, only 54 cases, including the present one, were reported in Japan over the 40-year period between 1977 and 2016. Among these, patient age ranged widely, from 16 to 84 years, with a mean age of 53.4 years and median age of 54 years. It showed a tendency to occur in middle-aged patients in their 40s to 60s. It appears to affect men (n = 31) slightly more than women (n = 23), with a male-to-female ratio of 1:0.74 (Fig. 4). It occurred commonly in the posterior area, with the posterior mandible being the most common location (n = 30), followed by the posterior maxilla (n = 18) (Fig. 5). The most common surface type was granular (n = 32), followed by papillary (n = 11), and wart-like (n = 10). The most common color is white (n = 12), followed by a mixture of red and white (n = 10), and red and yellow (n = 6 each) (Fig. 6). Most lesions were relatively small, with a maximum diameter of 3 to 30 mm, mean diameter of 10.7 mm,
and median diameter of 10 mm. No giant lesions were observed (Fig. 7). Cytology was performed in only 9 cases (16.7%)\(^\text{18,19,29}\). The results revealed that class III (suspicious) was the most common (n = 5, 55.5%), with class V (false-positive) in 2 cases, resulting in a false-positive rate of 22.2% (Fig. 8). The most common clinical diagnosis was papilloma (n = 24, 44.4%), followed by leukoplakia and malignant tumor (n = 6 each, 11.1%). Only one case (1.9%) was diagnosed as VX preoperatively (Fig. 9). It is difficult to diagnose preoperatively, and has been commonly resected under a clinical diagnosis of papilloma or a benign disease in previous reports of gingival VX. The macroscopic properties of VX vary widely, and it should thus be differentiated from other diseases, including papilloma, papillary hyperplasia, verrucous carcinoma, and squamous cell carcinoma\(^\text{1,7,9,12,17,25}\). The treatment and prognosis for VX and malignant lesions such as verrucous carcinoma and...
Squamous cell carcinoma differ markedly, necessitating caution in arriving at a diagnosis. In the present case, the initial diagnosis was a suspected benign tumor based on clinical findings. Exfoliative cytology was also performed, however, to confirm the absence of malignant disease, which resulted in a diagnosis of a class III lesion (suspicious). This required differentiation from malignant tumors such as verrucous carcinoma and squamous cell carcinoma, making a definitive diagnosis of VX impossible at this point. As the lesion was relatively small, a biopsy to attain a definitive diagnosis was not performed; instead, a total biopsy under local anesthesia at the outpatient department was carried out. A full explanation was given to the patient preoperatively that additional treatment such as additional resection as well as strict follow-up would be required if a malignant tumor was diagnosed histopathologically. The procedure was performed with the patient’s consent. Iodine staining was performed to determine the extent of resection required. No unstained areas were observed, however. In accordance with established guidelines for resection of a malignant tumor, the margin (10 mm) was set and resection of the lesion, including the periosteum, performed. The tooth adjacent to the lesion was preserved. A layer of alveolar bone directly beneath the lesion was removed and the inferior surface wrapped with a periodontal pack. A definitive diagnosis of VX was obtained based on the results of postoperative pathological analysis. Verruciform xanthoma is sometimes over-diagnosed by cytology because it often involves cellular atypia reflecting its characteristic extension of rete pegs and keratinization of surface cells, indicating the need for care in arriving at a definitive diagnosis. If the preoperative cytological diagnosis had been negative (class I or II), then resection could have been performed under a diagnosis of a benign lesion, and this could have resulted in a shorter recovery period due to a reduction in the extent of resection and preservation of the periosteum. On the other hand, according to one report, the presence of foam cells in specimens obtained for exfoliative cytological diagnosis prior to biopsy can lead to a presumptive diagnosis of VX. In the present case, however, it was not possible to determine the presence of foam cells after staining with Papanicolaou stain. Therefore, it was difficult to assume VX cytologically before excisional biopsy, which required us to set wider safety margins for resection, just in

Fig. 8 Cases of VX that received preoperative cytology. Cases of periodontal VX occurring in Japan over 40-year period. Cytology was rare and performed in only 9 cases (16.7%). Among these, class III (suspicous) was most common diagnosis.

Fig. 9 Clinical diagnosis in previous Japanese cases of periodontal VX. Cases of periodontal VX occurring in Japan over 40-year period. VX was most frequently resected under diagnosis of papilloma. Only 1 case (1.9%) was diagnosed as VX preoperatively.
case. With VX, foam cells are often observed in the subepithelial lamina propria, which may explain why none were harvested by scraping. This was compounded by the absence of conditions that might indicate another type of lesion such as an ulcer, for example. Histopathological and immunohistochemical examination in one earlier study of the basement membrane in the epithelium in cases of VX revealed a tendency toward blurring, partial denaturation, and disappearance in cases of inflammatory cell infiltration. Some studies have also reported that no foam cells were observed in VX scrape cytology specimens. This suggests that VX should be considered as a potential diagnosis, even in the absence of foam cells when confronted with granulating or verruciform lesions accompanied by minor atypia.

Surgical resection is generally considered to be the first-line therapy for VX. The prognosis after resection of VX is favorable, with no reports suggesting further malignant development, to our knowledge. Neither, as far as we know, have there been any reports of recurrence in Japan, although it has been reported in a few cases in Western countries. Twelve months have passed since surgical intervention in the present case, and the patient is making satisfactory progress without recurrence.

Acknowledgements

The authors would like to thank Dr. Kei Nakajima for his technical assistance.

References

1) Akashi Y, Shigematsu Y, Okada M, Saito K, Magoshi S, Suzuki S (2000) Verruciform xanthoma arising from the upper gingival mucosa. Nihon Kokuka Gakkai Zasshi 49:108–111. (in Japanese)
2) Cobb CM, Holt R, Denys FR (1977) Ultrastructural features of the verruciform xanthoma. J Oral Pathol 5:42–51.
3) Hayashi T, Yamada K, Iseki T, Tsuji K, Yasuda N, Morita S (2015) A case of verruciform xanthoma of the palate that showed enlargement during 17 years of follow-up. Nihon Koku Geka Gakkai Zasshi 61:277–281. (in Japanese)
4) Higo T, Yamamoto T, Nishida N, Tsutsumi Y, Nakai A, Saito S, Nishikawa M, Yamamoto G (2009) A case of verruciform xanthoma occurring in the maxillary gingiva caused by poor oral hygiene. Nihon Koku Shindan Gakkai Zasshi 22:279–282. (in Japanese)
5) Kamino Y, Okada H, Kobayashi R, Yamaguchi F, Fukumoto M, Yamamoto H, Nagura H (2002) A case of verruciform xanthoma; A comparative study of proliferative activity of the epithelium. Nihon Koku Kagaku Zasshi 28:158–161. (in Japanese)
6) Kawarada K, Suwa W, Suwa H, Hirano M, Ehara M, Nagayama M, Muraki T, Taniguchi K, Ehara Y, Shikimori M, Tanuma J (2013) A case of verruciform xanthoma arising from the lower gingival mucosa. Gifu Shi Gaku Shi 40:155–158. (in Japanese)
7) Kikuchi M, Iizuka Y, Teshima S, Hayashi S, Okabe H (1977) A cases of verruciform xanthoma. Michinoku Shi Gakkai Zasshi 8:35–36. (in Japanese)
8) Kimura M, Ohto H, Shibata A, Enomoto A, Umemura M (2016) Clinicopathological and immunohistochemical characteristics of verruciform xanthoma of the lower gingiva: A case report. J Clin Diagn Res 10:5–6.
9) Kraemer BB, Schmidt WA, Foucar E, Rosen T (1981) Verruciform xanthoma of the penis. Arch Dermatol 117:516–518.
10) Li MH, Ito D, Horiguchi H, Manabe M, Nagumo M (2003) Verruciform xanthoma arising in the mandibular gingiva: Report of two cases. Nihon Koku Nenmaku Gakkai Zasshi 9:74–78. (in Japanese)
11) Matsuda K, Murayama I (1984) Two cases of verruciform xanthoma. Nihon Koku Geka Gakkai Zasshi 30:406–410. (in Japanese)
12) Matsudomi S, Tsuji T, Hirayama J, Suzuki M, Matsumura K, Shinozaki F (1989) A cases of verruciform xanthoma and its DNA histogram of nuclei. Nihon Koku Geka Gakkai Zasshi 35:2554–2556. (in Japanese)
13) Murakami K, Yamamoto K, Sugiyama T, Imai Y, Kurihara M, Shimaoka H, Nishi S, Kiritani T (2008) Two cases of verruciform xanthoma in the oral cavity. Nihon Koku Shindan Gakkai Zasshi 21:95–99. (in Japanese)
14) Nakamura T, Iida S, Ikeda N, Kawaj T, Kawai T, Kameyama Y (1992) A case of verruciform xanthoma of the mouth floor. Nihon Koku Geka Gakkai Zasshi 38:1576–1577. (in Japanese)
15) Philipsen HP, Reichart PA, Takata T, Ogawa I (2003) Verruciform xanthoma—biological profile of 282 oral lesions based on a literature survey with nine new cases from Japan. Oral Oncol 39:325–336.
16) Santa Cruz DJ, Martin SA (1979) Verruciform xanthoma of the vulva. Report of two cases. Am J Clin Pathol 71:224–228.
17) Sato K, Segawa K, Fukuda K, Yamaguchi K, Osa H, Nara E, Fujiyoka Y, Takeda Y (1991) A case of verruciform xanthoma of the palatal gingiva. Nihon Kokka Shuyu Gakkai Zasshi 3: 79–81. (in Japanese)
18) Sato K, Ushioda T, Bessho H, Tonogi M, Katakura A, Yamane G, Tanaka Y (2012) Oral cytology in patients with verruciform xanthoma. Jpn J Oral Diag/Oral Med 25: 103–107.
19) Sato T, Mizukami R, Hamada K, Yamanaka K, Asada K, Ishibashi K, Kojima H (1989) Two cases of verruciform xanthoma of mandibular gingiva. Nihon Koku Geka Gakkai Zasshi 35: 2115–2120. (in Japanese)
20) Shafer WG (1971) Verruciform xanthoma. Oral Surg Oral Med Oral Pathol 31:784–789.
21) Shibata M, Takahashi R, Kodani I, Kataoka S, Ueyama Y, Ryoke K (2002) A case of verruciform xanthoma arising in the floor of the mouth. Nihon Kokka Gakkai Zasshi 51: 273–276. (in Japanese)
22) Suka N (2007) Histogenetic study of verruciform xanthoma. Meikai Shika Igaku 36:74–89. (in Japanese)
23) Takeshita N, Satoh N, Suzuki A, Chiba K, Tanifuji M, Kudoh K (1979) A case of verruciform xanthoma—light and electron microscopic observation. Iwate Ikadaigaku Shi Gakkai Zasshi 4: 34–38. (in Japanese)
24) Takigawa T, Sato H, Terakado M, Osawa K, Shimizu T, Inada M, Hirayama H, Konuro Y, Nakamura T, Fukumoto K, Onuma C, Kimura M (1981) A case of verruciform xanthoma of mandibular gingiva. Nihon Daigaku Shi Gakkai Zasshi 55:21–25. (in Japanese)
25) Terakado M, Takigawa T, Honda M, Adachi Y, Ohki H, Sekiwa T, Ono M, Sato H (1991) A case of verruciform xanthoma in the mandibular gingiva. Nihon Koku Geka Gakkai Zasshi 37:2091–2092. (in Japanese)
26) Uchida R, Ikebe T, Ozeki S (2009) Verruciform xanthoma with dysplasia in situ in the palatal gingiva—A case report. Nihon Koku Shindan Gakkai Zasshi 22:292–298. (in Japanese)
27) Uemura S, Fukuda J, Kikuta T, Yamada N, Shimoda T (1991) A case of verruciform xanthoma of the palatal gingiva. Kyusyu Shi Gakkai Zasshi 9:729–736. (in Japanese)
28) Utsunomiya T, Matsumoto T, Morikawa M, Suemitsu M, Tanaka H, Ota Y, Saito T, Yamamoto H, Kuyama K (2014) Histopathological, immunohistochemical and exfoliative cytological studies of oral verruciform xanthoma. Open Journal of Stomatology 4: 435–440.
29) Yamada T, Wakimoto M, Ueno T, Mishima K, Matsumura T, Moritani N, Ota A, Hirata Y (2009) A case of verruciform xanthoma accompanied by oral lichen planus. Nihon Koku Shindan Gakkai Zasshi 22:64–68. (in Japanese)
30) Yamashita M, Jinbu Y, Noguchi T, Tsukinoki K, Mori Y (2016) Two cases of verruciform xanthoma in the oral cavity and a clinico-statistical study of Japanese cases. Nihon Koku Naika Gakkai Zasshi 22:29–34. (in Japanese)
31) Yoshitomi I, Kawasaki G, Baba N, Mizuno A, Fujita S, Ikeda T (2007) Two cases of verruciform xanthoma and a review of the literature. Nihon Koku Shindan Gakkai Zasshi 20:291–295. (in Japanese)
32) Zegarelli DJ, Zegarelli-Schmidt EC, Zegarelli EV (1975) Verruciform xanthoma. Further light and electron microscopic studies, with the addition of a third case. Oral Surg Oral Med Oral Pathol 40:246–256.

Correspondence:
Dr. Takeshi Onda
Department of Oral and Maxillofacial Surgery,
Tokyo Dental College,
1-2-2 Masago, Mihama-ku,
Chiba 261-8502, Japan
E-mail: ondatake@tdc.ac.jp