International Journal of Dental Research and Allied Sciences
2021, Volume 1, Issue 1, Page No: 76-83

Available online at: www.tsdp.net

ISSN: 3062-3502

Original Article

Role of M2-Polarized Foamy Macrophages in Oral Verruciform Xanthoma: VEGF Expression and Angiogenesis

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Received: 15 June 2021; **Revised:** 15 September 2021; **Accepted:** 15 September 2021

ABSTRACT

Oral verruciform xanthoma (OVX) represents a rare, nonmalignant mucosal disorder histologically distinguished by numerous lipid-laden (foamy) macrophages within the papillary layer of the lamina propria. Although the exact mechanism underlying OVX formation remains unclear, prior evidence has demonstrated that macrophage polarization—namely, M1 with antitumor functions and M2 with protumor and angiogenic activity—plays a crucial biological role. The present investigation aimed to clarify the participation of foamy macrophages in OVX development, emphasizing their involvement in angiogenesis. Four patients who underwent complete surgical removal or total excisional biopsy of OVX lesions were included. Immunohistochemical analysis was conducted to assess macrophage-related markers CD68 (general macrophage marker) and CD163 (M2 subtype), as well as CD34-positive microvessel density (MVD) within the lesions. In every case, foamy macrophages showed strong reactivity for both CD68 and CD163. Microvessel density and vascular endothelial growth factor (VEGF) expression were further analyzed in relation to tissue morphology. The MVD in OVX lesions was markedly greater than that observed in adjacent healthy mucosa. Notably, the verrucous-type OVX exhibited higher MVD compared with the other morphological variants. VEGF immunoreactivity was consistently detected in the foamy macrophages across all specimens. Collectively, these findings suggest that CD163-positive foamy macrophages may contribute to OVX formation through VEGF-mediated angiogenic mechanisms.

Keywords: Oral verruciform xanthoma, Foamy macrophages, CD163, Angiogenesis, VEGF

How to Cite This Article: Shimizu A, Hayashi T, Ogawa N. Role of M2-Polarized Foamy Macrophages in Oral Verruciform Xanthoma: VEGF Expression and Angiogenesis. Int J Dent Res Allied Sci. 2021;1(1):76-83. https://doi.org/10.51847/gwxwpAiTJm

Introduction

Oral verruciform xanthoma (OVX) is an uncommon, non-cancerous mucosal disorder that was initially described in 1971 [1]. Histopathologically, it presents as a papillary or warty elevation of stratified squamous epithelium accompanied by surface keratin buildup and the presence of foamy macrophages concentrated within the connective tissue papillae.

The etiology of OVX is still uncertain. Some investigators have proposed that it represents a reparative or reactive lesion in which lipid-filled macrophages emerge following epithelial degeneration [2–5]. Others have postulated that the accumulation of these cells may secondarily alter epithelial metabolism, giving rise to the characteristic papillary or verrucous surface and keratotic features [6].

Macrophages are functionally divided into two major phenotypes—M1, which is associated with anti-tumor activity, and M2, which promotes tumor growth and tissue remodeling [7–9]. The M2 phenotype expresses distinctive receptors, including CD163 (hemoglobin scavenger receptor), CD204 (macrophage scavenger receptor I), and CD206 (mannose receptor) [10]. Multiple studies have demonstrated that secreted

factors from M2 macrophages facilitate angiogenesis [11, 12]. Our earlier findings indicated a significant involvement of CD163-positive macrophages in the progression of oral epithelial malignancies [13, 14]. Nonetheless, to date, no research has examined whether macrophages influence angiogenic pathways in the development of OVX.

Given this context, we hypothesized that the accumulation of foamy macrophages contributes to the tissue morphology of OVX by stimulating angiogenesis.

Materials and Methods

Patient data

Five OVX cases were retrieved from the Kobe University Hospital Pathology System using the search keyword "verruciform xanthoma." Four of these patients, who had undergone complete excision or excisional biopsy in the Department of Oral and Maxillofacial Surgery, Kobe University Hospital (Kobe, Japan) between 2001 and 2015, were included in this study. Cases diagnosed only through incisional biopsy were excluded.

All participants provided written informed consent allowing the use of their tissue samples and clinical data for retrospective analysis. Ethical clearance was obtained from the Kobe University Institutional Review Board (Approval No. B190043, dated 29 May 2019).

Patient records were reviewed for demographic details, site of occurrence, preliminary clinical diagnosis, and medical history.

Histopathological review

Surgically excised specimens were preserved in 10% formalin and subsequently paraffin-embedded. Based on previously established morphological criteria [6, 15], lesions were categorized into one of three patterns—verrucous, papillary, or flat. Hematoxylin and eosin–stained sections were examined independently by three oral pathologists (M.S., Y.-i.K., and M.N.) to confirm both diagnosis and subtype classification.

Immunohistochemical protocol

Immunohistochemical staining was conducted using the EnVision Dual Link System–HRP with 3,3′-diaminobenzidine (DAB) as the chromogen (DakoCytomation, Glostrup, Denmark). Primary antibodies used included:

- Mouse anti-CD68 (1:100; clone Kp-1, Dako)
- Mouse anti-CD163 (1:100; clone 10D6, Novocastra, Newcastle upon Tyne, UK)
- Mouse anti-CD34 (1:50; clone NU-4A1, Nichirei, Tokyo, Japan)
- Rabbit polyclonal anti-VEGF (1:100; A-20, Santa Cruz Biotechnology, Santa Cruz, CA, USA)

All slides were reviewed by three independent examiners (M.S., Y.-i.K., and T.K.), who were blinded to patient identities and clinical data.

Evaluation of microvessel density

Microvessel density (MVD) was determined using CD34 staining within a stromal area located 100 μm beneath the epithelial surface. Under ×200 magnification, three regions exhibiting the highest vascular concentration were selected. Only distinct, lumen-forming vessels were counted. The final MVD score for each case represented the mean vessel count across the three selected fields, in accordance with the criteria described previously [16].

Statistical treatment

Statistical calculations were performed using SPSS Statistics version 22 (IBM, Chicago, IL, USA). Paired and independent t-tests were applied for comparing MVD values, and $p < 0.05$ was set as the threshold for statistical significance.

Results and Discussion

Clinical overview

The demographic and clinicopathologic information of the four OVX cases is summarized in **Table 1**. Among the four individuals, three were male and one was female. The patients' ages ranged between 15 and 54 years, with a mean of 40.0 years at the time of histological diagnosis.

Three lesions were situated on the gingiva, while one was identified on the hard palate. The lesion diameters varied from 3.0 to 5.0 mm, averaging 4.3 mm.

Provisional diagnoses included epulis (Case 1), gingival tumor (Case 2), squamous papilloma (Case 3), and erosion (Case 4). Three of the four individuals had relevant medical histories:

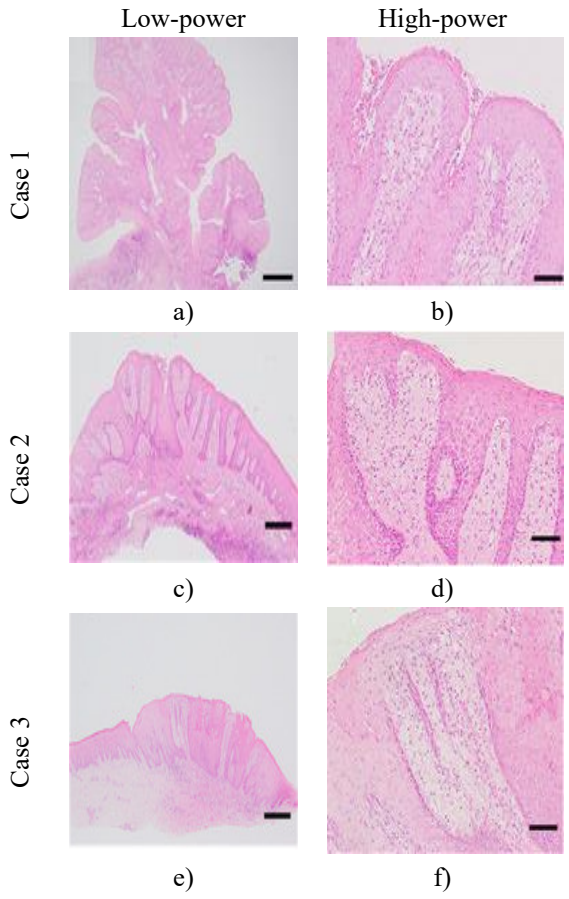
- Case 1: pneumonia and macroscopic hematuria nine years before presentation
- Case 2: dyslipidemia and hyperuricemia under medical treatment
- Case 3: no systemic diseases recorded
- Case 4: appendicitis and Basedow's disease

Table 1. Clinical and Histopathological Profiles of Patients with Oral Verruciform Xanthoma

Case	Gender	Age (Years)	Location	Size (mm)	Clinical Impression	Histological Type	Past Medical Conditions
1	Male	15	Gingiva	5.0	Epulis	Verrucous	Pneumonia, Gross hematuria
2	Male	54	Gingiva	5.0	Gingival mass	Flat	Dyslipidemia, Hyperuricemia
3	Male	43	Palate	3.0	Papilloma	Flat	None
4	Female	48	Gingiva	4.0	Erosive lesion	Flat	Appendicitis, Graves' disease

Morphological findings

Histopathological analysis was conducted on hematoxylin and eosin (HE)-stained slides. All OVX samples exhibited epithelial acanthosis without evidence of cellular atypia. In each specimen, numerous foamy macrophages were seen gathered within the connective tissue papillae, accompanied by mild-to-moderate chronic inflammatory infiltration, primarily composed of lymphocytes. Case 1 was identified as the verrucous variant, distinguished by its raised and distinctly demarcated morphology. The remaining three lesions were categorized as flat-type, presenting a level epithelial surface with proliferative changes confined beneath it **(Figures 1a–1h and Table 1)**.



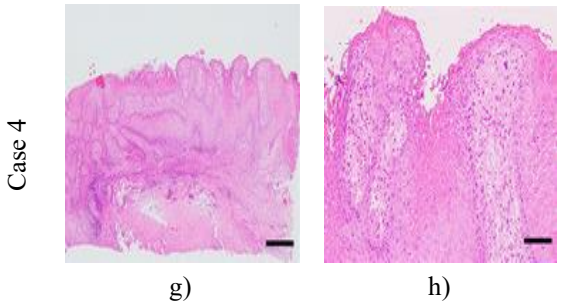
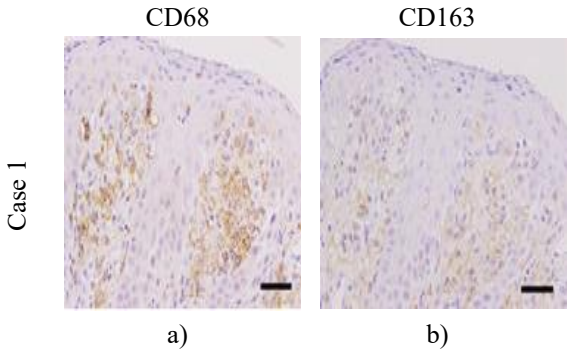


Figure 1. Microscopic morphology of oral verruciform xanthoma. All cases showed epithelial thickening without atypia. (a, c, e, g) Chronic inflammatory infiltrate was visible within the connective tissue. (b, d, f, h) Abundant foamy macrophages were present in the papillary stroma. Case 1 demonstrated a verrucous form of OVX ((a): scale bar = 500 µm, original magnification ×20; (b): scale bar = 50 µm, original magnification ×200). Cases 2–4 were flat-type OVXs ((c, e, g): scale bar = 200 µm, magnification ×40; (d, f, h): scale bar = 50 µm, magnification ×200).

Expression of macrophage markers in OVX

Immunohistochemical staining revealed cytoplasmic positivity for CD68 (a general macrophage marker) and membranous reactivity for CD163 (an M2 macrophage marker) in the foamy macrophages of every case. No notable difference in the expression levels of these markers was observed between the verrucous and flat-type lesions **(Figures 2a–2h)**.



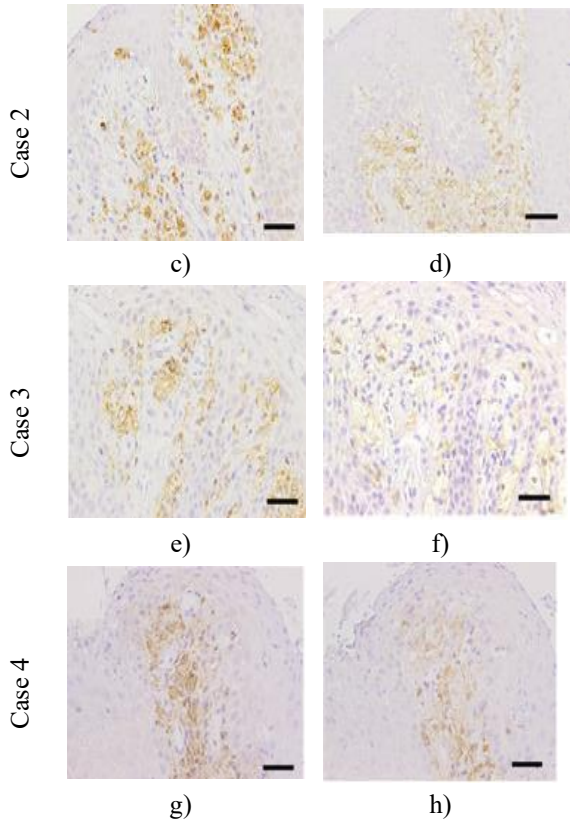
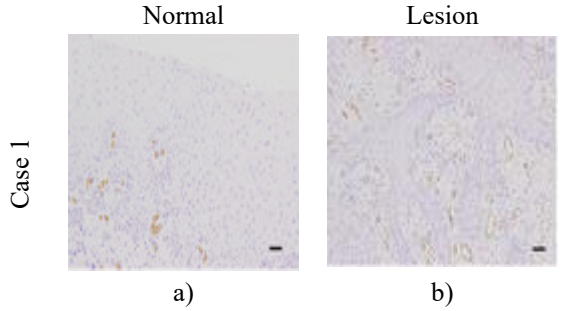
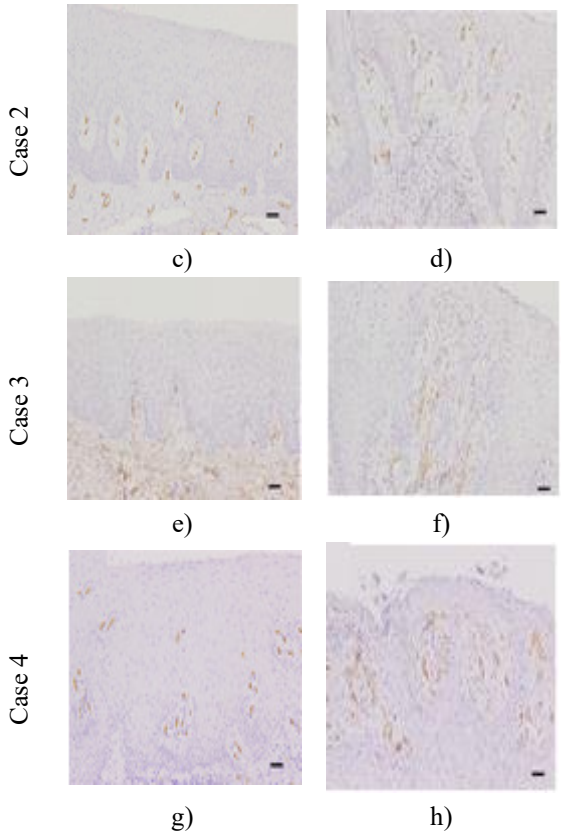


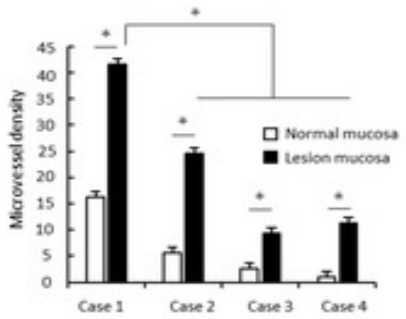
Figure 2. Representative immunostaining for macrophage markers in OVX. (a, c, e, g) CD68 showed diffuse cytoplasmic positivity in foamy cells. (b, d, f, h) CD163 demonstrated distinct membranous staining in the same cell populations (scale bar = 20 μm; magnification ×400).

Angiogenesis in OVX

Since M2 macrophages are known to promote tumor-associated angiogenesis [17, 18], angiogenic activity within OVX tissues was examined using anti-CD34 antibody staining. While the normal oral epithelium showed few or no small-caliber vessels, pronounced vascular formation with elongated microvessels was evident in OVX lesions **(Figures 3a–3h)**. Statistical comparison revealed that microvessel densities (MVDs) in all OVX samples were significantly elevated compared with the adjacent normal mucosa. Among these, the verrucous-type case (Case 1) demonstrated the highest MVD values **(Figure 3i)**.







i)

Figure 3. CD34 immunostaining demonstrating angiogenesis in OVX. (a, c, e, g) Minimal CD34-positive vessels were found in the normal mucosa. (b, d, f, h) Numerous elongated microvessels were observed in lesional connective tissue papillae (scale bar = 50 μm; magnification ×200). (i) Quantitative analysis showed that MVD values within 100 μm of the epithelial stroma were significantly higher in all OVX samples than in normal tissues. The verrucous-type lesion showed the greatest MVD count. CD34-positive vessels were enumerated per 200× field; $p < 0.05$ by t-test.

Expression of VEGF in the OVX microenvironment

To further investigate angiogenic mechanisms, VEGF expression was evaluated by immunostaining. Both the epithelial layer and the foamy macrophages in OVX tissues exhibited positive VEGF signals. No substantial difference in epithelial VEGF expression was detected

between normal and affected mucosa **(Figures 4a–4h)**. However, foamy cells in the flat-type lesion (Case 4) displayed weaker VEGF staining intensity than those in other cases **(Figure 4h)**.

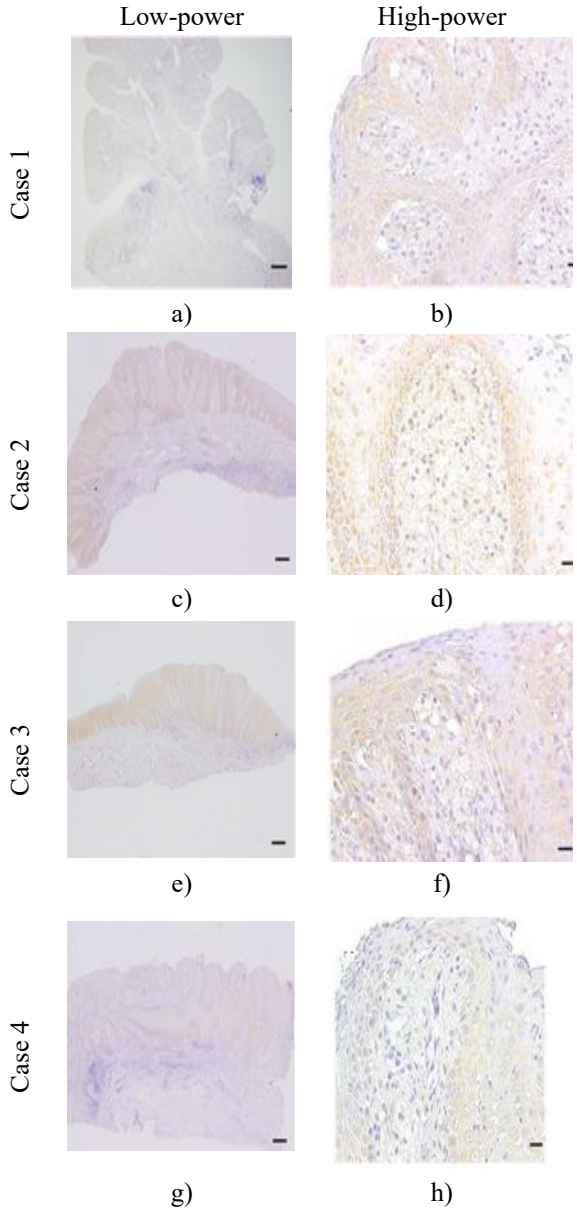


Figure 4. VEGF expression in oral verruciform xanthoma. (a, c, e, g) Low-power views revealed similar epithelial VEGF staining in OVX and control tissues (scale bar = 1000 µm; magnification ×12.5). (b, d, f, h) High-power images showed strong VEGF positivity in foamy macrophages across all samples, except Case 4, where staining was weaker (scale bar = 20 µm; magnification ×400).

Epidemiological studies have estimated OVX prevalence rates ranging between 0.025% and 0.094% over a 12-year observation period [19, 20]. Tamiolakis *et al*. (2018) documented 13 OVX cases, representing 0.04% of 35,617 specimens examined from 1971–2017 [21]. In our series, approximately 0.06% of 6,499 histopathologically assessed samples were confirmed as OVX, aligning closely with earlier reports and reaffirming the lesion's rarity.

Consistent with prior investigations [6, 15, 22], our OVX cases were localized predominantly to masticatory mucosa sites, such as the gingiva and hard palate, and displayed stromal inflammation. Supporting previous observations [23], lymphocytic infiltrates in the lesions showed stronger CD3 than CD20 immunoreactivity (data not shown). Ide *et al*. (2008) proposed that factors such as periodontal pathogens, mechanical irritation, smoking, alcohol consumption, medications, or sensitizing substances from food and dental materials may contribute to OVX pathogenesis [23]. Similarly, Belknap *et al*. (2020) emphasized subepithelial inflammation as a key pathogenic factor [24], and de Andrade *et al*. (2015) also concluded that inflammatory responses play a central role [15].

In this study, foamy macrophage aggregates were mainly located in the superficial lamina propria rather than in deeper layers—consistent with earlier descriptions [1]. Moreover, Ki-67 expression was absent in both squamous epithelial cells and foamy macrophages across all four cases (data not shown). Collectively, these observations suggest that mechanical irritation–induced inflammation represents a major driving mechanism in OVX formation.

In contrast, several previous studies have proposed a potential link between OVX and certain systemic disorders, such as hyperlipidemia, graft-versus-host disease, and congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome [25–27]. Within our cohort, only Case 2 presented with dyslipidemia, suggesting that a possible connection between OVX and systemic conditions cannot be entirely ruled out.

Macrophages constitute a major component of inflammatory infiltrates. CD163, a hemoglobin–haptoglobin scavenger receptor, is expressed on the surface of both monocytes and macrophages [28]. In this analysis, the majority of foamy macrophages demonstrated immunopositivity for the general macrophage marker CD68 as well as for CD163, a marker indicative of the M2 phenotype. Consistent with our observations, de Andrade *et al*. [15] also noted CD163 expression in foamy macrophages associated with OVX. Nonetheless, the precise biological function of CD163-positive macrophages in OVX remains to be fully clarified.

Within neoplastic environments, M2 macrophages are known to facilitate angiogenesis by secreting several proangiogenic factors, including VEGFA, epidermal growth factor, and interleukin-8 [12, 17, 29, 30]. Our earlier investigations demonstrated that M2 macrophages promote vascular development in the microenvironment of esophageal squamous cell carcinoma [18]. Similarly, prior studies have shown that CD163-positive macrophages enhance angiogenic activity in oral squamous cell carcinoma [31–33]. However, data regarding vascularization in OVX lesions are extremely limited.

In this work, the MVD of OVX tissues was markedly greater than that of the adjacent normal mucosa. For the first time, we analyzed VEGF expression patterns in OVX and confirmed that both epithelial cells and foamy macrophages exhibited positive immunoreactivity. No clear difference in VEGF levels was found between the epithelium of normal and affected mucosa, suggesting that epithelial VEGF is unlikely to influence OVX morphogenesis. Instead, we propose that VEGF secreted by foamy macrophages contributes significantly to the angiogenic processes observed in these lesions. This assumption is further supported by the high density of CD34-positive microvessels observed in areas rich in foamy macrophages. Interestingly, the verrucous-type lesion displayed a notably higher MVD compared to the other variants, implying that vascular density may correlate with architectural variations among OVX subtypes. Nonetheless, the relatively weak VEGF expression noted in Case 4 remains unexplained.

A major limitation of our investigation is the small sample size (n = 4) and the absence of papillary-type OVX among the cases examined. Future studies involving a larger cohort will be necessary to validate these preliminary findings. Another constraint is our inability to delineate the exact molecular mechanism underlying angiogenesis in OVX. Nakayama *et al*. (2015) previously observed that polypoid colorectal adenomas exhibit clusters of newly formed vessels, while flat-type adenomas maintain vascular patterns similar to those of normal mucosa [34]. Drawing on this analogy, we infer that angiogenesis could be associated with OVX morphogenesis through mechanisms yet to be identified. Further molecular-level analyses are required to define the nature of this association.

Moreover, distinguishing between M1 and M2 macrophages remains challenging due to the absence of specific immunohistochemical markers for M1 macrophages [30]. Although CD68/STAT1 and CD163/STAT1 combinations have been proposed as possible indicators [35], CD163 expression alone cannot definitively classify a foamy macrophage as M2. It is also worth noting that a few rare instances of OVX have been reported in association with malignant lesions [36–38]. In addition, other investigations have demonstrated links between CD163-positive macrophage activity, epithelial dysplasia, and malignant transformation in oral precancerous conditions [13, 14, 39, 40]. Thus, despite OVX being generally regarded as a benign reactive lesion, the possibility of malignant potential within the associated squamous epithelium should not be dismissed. Future prospective studies are warranted to explore the potential for malignant transformation in OVX.

Conclusion

To our knowledge, this is the first study to demonstrate that CD163-positive foamy macrophages are implicated in the morphogenesis of oral verruciform xanthoma through VEGF-mediated angiogenic mechanisms.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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