Gingival squamous cell carcinoma masquerading as necrotizing ulcerative periodontitis

Saif Khan, Kafil Akhtar,1 Abdul Ahad,2 Jaiti Uppal

Abstract:
Necrotizing ulcerative periodontitis (NUP) is a painful and debilitating condition seen mostly in an immunocompromised state. Although squamous cell carcinoma (SCC) on gingiva is not uncommon, its presentation as a benign necrotizing lesion on gingiva is rare. Such presentations may lead to delayed diagnosis and poor prognosis. This report describes a case of a 34-year-old male presenting clinically with NUP around mandibular posterior teeth. Clinical features were misleading, but the histological findings established the diagnosis of well-differentiated SCC. Immunohistochemistry also showed features of epithelial–mesenchymal transition with decreased expression of E-cadherin and increased vimentin expression showing local invasion and metastasis. The patient was referred to the oncology department for evaluation of possible metastasis and further management of carcinoma.

Key words: Gingiva, immunohistochemistry, periodontal disease, squamous cell carcinoma

INTRODUCTION
Oral squamous cell carcinoma (SCC) comprises more than 90% of all malignant lesions in the oral cavity.1,2 Gingiva is a less frequent site to be involved, comprising about 10% of all oral SCCs. Gingival SCC is more likely to be present on the mandible as compared to the maxilla, and the majority of these are found in the molar region.3 Unlike its presentation in other parts of the oral cavity, it can mimic a variety of other lesions, especially those of inflammatory origin when present on the gingiva. Clinical presentations of SCCs of the gingiva can be quite variable and hence are misdiagnosed as benign tumors or other inflammatory responses. Gingival SCC has been mostly reported as an exophytic mass with granular, papillary, or verrucous surface. Sometimes, it also presents as an ulcerative lesion. It is more often a slow-growing lesion with initial symptoms including but not limited to swelling with ulceration, pain, mobility of teeth, or nonhealing extraction site, while it may sometimes be asymptomatic.4 However, its presentation as a necrotizing periodontal lesion has not been reported.

Necrotizing ulcerative periodontitis (NUP) is a debilitating condition caused by fusospirochetal microbes. It is commonly observed in immunocompromised states, especially in individuals with human immunodeficiency virus (HIV) infection. It clinically presents as a necrotizing ulcerative lesion of the gingiva accompanied by the loss of teeth, supporting connective tissue, and the alveolar bone. There is severe pain along with gum bleeding and gingival necrosis with or without pseudomembrane formation and alveolar bone loss. NUP may be accompanied by fever and regional lymphadenopathy. Moreover, if not treated, it may progress to necrotizing ulcerative stomatitis and/or gangrenous stomatitis at later stages, which can be potentially life-threatening. The diagnosis of NUP can be easily made using its diagnostic triad of pain, ulceration, and gingival bleeding.5,6

This report describes a case of the gingival lesion clinically presenting as NUP but diagnosed as oral SCC by routine histopathological examination and immunohistochemical evaluation using E-cadherin and vimentin biomarkers.

CASE REPORT
A 34-year-old male patient reported with the chief complaint of severe pain in the right...
mandibular region for 1½ months. According to the patient, he was apparently well around 1½ months ago when he noticed swelling and tightness in his gums. He reportedly found a pustule appearing on the gums that increased in size and became extremely painful. The pain was spontaneous and continuous, severe in intensity, increased on touching, eating, and at night and decreased on taking analgesics. A few days later, he noticed ulceration, bleeding, and sloughing of gums while the teeth in that region became progressively loose. Because of the pain and bleeding, he discontinued brushing in the affected area for the past 2 weeks. There was no significant medical history, no history of smoking, tobacco or alcohol use, and no positive family history of malignancy. On extraoral examination, the right submandibular lymph nodes were tender on palpation, soft in consistency, and mobile. Intraoral examination revealed severely inflamed, redish-pink gingiva with loss of interdental papilla between the mandibular right second premolar and first molar, abundant plaque and calculus, pseudomembrane formation, and crater-like lesions in the interdental regions [Figure 1]. The lesion extended from the mesiobuccal aspect of the first premolar to the distal aspect of the first molar with irregular necrotic margins and sloughing of tissues. Exudation of sanguineous pus was also observed on the application of digital pressure. There was gingival recession till the mucogingival junction on the buccal aspect along with deep pockets interproximally. The tooth #45 was Grade III mobile, whereas #46 and #44 were Grade II and Grade I mobiles, respectively. All three were tender on percussion. Further, multiple small, white nonscarable patches were observed on the edentulous premolar area of the ipsilateral maxillary arch [Figure 1].

**Investigations**

Periapical radiograph of the region in question #44, #45, and #46 revealed severe periodontal bone loss extending to the apical third of #45 and mesial root of #46 [Figure 2]. Routine blood investigations, including complete blood count, bleeding time, and clotting time, were in the normal range without any significant findings. Serological examination for HIV-1 and HIV-2 serotypes and CD4 count were advised as patients with NUP have a high susceptibility to HIV infection. However, the patient was seronegative for HIV-1 and HIV-2 antigens, and the CD4 count was also within normal limits.

Since tooth #45 was Grade III mobile and extremely painful, the patient insisted on getting it extracted. The tooth #45 was extracted, and a portion of the soft tissue around the extracted tooth was sent for histopathological and immunohistochemical evaluations.

**Histopathology and immunohistochemistry**

Microscopic examination of the biopsy specimen showed features of well-differentiated SCC with sheets and clusters of large polygonal atypical tumor cells with a hyperchromatic nucleus, prominent nucleoli, irregular nuclear membranes, and well-defined eosinophilic cytoplasm with prominent foci of keratin pearls [Figure 3]. The immunohistochemical expression of E-cadherin marker showed foci of tumor cells with mild and decreased intensity of membranous staining [Figure 4]. Similarly, vimentin immunomarker showed tumor cells with mild focal cytoplasmic positivity signifying epithelial-to-mesenchymal transition (EMT) of the tumor lesion, thus deciphering its malignant nature [Figure 5]. Considering the histopathological and immunohistochemistry findings, the patient was referred to the department of oncology for evaluation of possible metastasis and management of SCC.

**DISCUSSION**

NUP is a periodontal disease that is often observed in immunocompromised individuals, particularly in HIV-positive patients. This condition is a marker of deterioration of the immune system with a 95% predictive value of the CD4+ counts as <200 cells/mm³. Therefore, it is necessary to screen NUP patients for HIV infection. In the case of NUP, the decreased immunity makes the periodontal microorganism breach the epithelial lining leading to invasion and further evasion of host defense mechanism.

To our surprise, the histopathological examination revealed the lesion clinically presenting as NUP to be a well-differentiated SCC. Furthermore, the immunohistochemistry of E-cadherin showed its decreased membranous expression, which marks the initiation of EMT where epithelial cells lose their polarity and cohesion and resemble mesenchymal cells and tend to form the invasive front of the lesion. In addition to this, the immunohistochemical expression of vimentin biomarker showed focal cytoplasmic positivity [Figure 5]. Usually, vimentin is not expressed in the epithelial cells, but its expression in the transforming tumor cells is suggestive of EMT, tumor invasion, and metastasis.

The clinical presentation of oral SCC in the gingiva can be deceptive and may be confused with periodontal inflammatory conditions leading to diagnostic delays. In an interesting case reported by Brooks et al., a 60-year-old female presented with persistent gingival bleeding, periodontal pocket measuring 2–3 mm in the maxillary right first and second molar region with moderately inflamed and ulcerated margin without any paresthesia, swelling, or lymph node involvement. She had a history of Stage 2 breast cancer of the right side for which she underwent surgery 19 years ago and was under chemotherapy and periodic physical examination and mammogram without any disease recurrence. Taking cognizance of her medical history for suspected metastasis, an incisional biopsy was performed. The histopathological evaluation revealed the lesion to be moderate to well-differentiated SCC of the gingiva.

In another similar intriguing case by Bornstein et al., a 64-year-old female presented with long-standing refractory periodontal disease with the moderately deep pockets, loss of papilla, and a red mucosal lesion with respect to left maxillary incisors and canine. There was no history of smoking or alcohol intake. She had osteoporosis and was initially treated with ibandronic acid and later with injections of denosumab twice a year. The patient was nonresponsive to conventional and surgical periodontal therapy. The radiographic examination revealed horizontal bone loss; however, cone-beam computed tomography revealed the mottled radiographic appearance of the inter-radicular bone between the lateral incisor and canine. The incisional biopsy of the lesion was done, and histopathological examination confirmed it as gingival SCC.
Therefore, the clinician needs to be more vigilant and to have a skeptical eye on any oral/gingival morphological changes such as desquamations, ulcerations, loss of papillae, and verrucous and hyperplastic epulis growths in the refractory chronic periodontal lesions, as these could be early clinical signs of the impending malignancy. Thus, chronic, long-standing, and refractory periodontal disease cases should always be in the suspicion radar of being malignant unless proven otherwise as delay in the diagnosis increases the chances of metastasis and invasion, leading to decreased survival rates.\[8,9\] Nevertheless, suspicious gingival lesions that persist for more than 2 weeks after removal of etiological agents should undergo thorough history, clinical examination, and biopsy for histopathological evaluations to rule out any malignancy for better treatment outcomes and increased survival.\[10\]

**CONCLUSION**

SCC of the gingiva should be considered in the differential diagnosis while dealing with uncommon periodontal conditions. Periodontists can play a lifesaver’s role in such cases where it is essential to rule out this aggressive disease
even when no risk factor is present. A proper history and thorough clinical examination followed by histopathological and immunohistochemistry can easily identify any malignant involvement. Early diagnosis in such cases can help in initiating appropriate treatment and thereby improve prognosis with minimal morbidity, mortality, and health-care costs.

Declaration of patient consent
The authors declare that they obtained the required patient consent regarding the use of his clinical image and data for publication and research work. The patient has given his consent and understands that his name and identity will not be disclosed.

Financial support and sponsorship
The study has been funded by the authors and their institution.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Bharanidharan R, Dineshkumar T, Raghavendhar K, Kumar AR. Squamous cell carcinoma of the gingiva: A diagnostic enigma. J Oral Maxillofac Pathol 2015;19:267.

2. Soo KC, Spiro RH, King W, Harvey W, Strong EW. Squamous carcinoma of the gums. Am J Surg 1988;156:281-5.

3. O'Sullivan B, Shah J. New TNM staging criteria for head and neck tumors. Semin Surg Oncol 2003;21:30-42.

4. Glick M, Muzyka BC, Salkin LM, Lurie D. Necrotizing ulcerative periodontitis: A marker for immune deterioration and a predictor for the diagnosis of AIDS. J Periodontol 1994;65:393-7.

5. Novak MJ. Necrotizing ulcerative periodontitis. Ann Periodontol 1999;4:74-8.

6. Horning GM, Cohen ME. Necrotizing ulcerative gingivitis, periodontitis, and stomatitis: Clinical staging and predisposing factors. J Periodontol 1995;66:990-8.

7. Costa LC, Leite CF, Cardoso SV, Loyola AM, Faria PR, Souza PE, et al. Expression of epithelial-mesenchymal transition markers at the invasive front of oral squamous cell carcinoma. J Appl Oral Sci 2015;23:169-78.

8. Brooks JK, Kleinman JW, Lubek JE, Price JB, Ghita I, Scurnick SA, et al. Gingival squamous cell carcinoma: An unexpected clinical presentation. Quintessence Int 2019;50:50-7.

9. Bornstein MM, Andreoni C, Meier T, Leung YY. Squamous cell carcinoma of the gingiva mimicking periodontal disease: A diagnostic challenge and therapeutic dilemma. Int J Periodontics Restorative Dent 2018;38:253-9.

10. Khan SM, Gossweiler MK, Zunt SL, Edwards MD, Blanchard SB. Papillary squamous cell carcinoma presenting on the gingiva. J Periodontol 2005;76:2316-21.