EDITORIAL

# Hemangiomatous Proliferation in Oral Squamous Cell Carcinoma and Its Mimicry in the Regional Lymph Nodes

Gargi S Sarode[1], Sachin C Sarode[2], Shankargouda Patil[3]

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## Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity with pathognomonic histopathologic features of invading nests, islands, or chords of malignant epithelial cells. Although the histological features are quite uniform across a majority of the cases, they can drastically change in different variants of OSCC, such as clear cell, spindle cell/sarcomatoid, adenoid/acantholytic/pseudoglandular, basaloid, papillary and adenosquamous, etc.[1]

The stromal component and response are also well known in the literature and involve immune cell invasion, angiogenesis, and lymphangiogenesis. While invading the surrounding structure, tumor cells also encounter other resident cells and tissues (muscles, nerves, salivary glands, etc.). Such interaction with resident structures might change the biological behaviors of the tumor cells.[2,3] Sometimes, the stroma shows distinctive features in the form of tumor-associated tissue eosinophilia, foreign body giant cells, etc.[4] Even the hemorrhagic areas in close proximity to the tumor cells have been envisaged as a modulator of tumor biology in OSCC,[5] all such tumors and stroma-associated features alone or together have been envisaged as a potential prognosticator for OSCC.[6]

The cellular and molecular changes in the metastatic lymph nodes (LNs) before the arrival of the tumor cells are very well known in the literature.[7] These changes are mediated by the systemic expression of various chemokines and cytokines, which act on the regional LNs. This brings out certain structural and molecular changes in the LNs that are conducive to the growth and development of tumor cells. However, the structural changes in the stromal component of the tumor and its mimicry in the LN have not been reported in the literature before.

In our routine diagnostic histopathology practice, we reported an unusual phenomenon in the stroma in the form of hemangiomatous proliferation of large vascular spaces near tumor islands with its mimicry in the regional LNs. This hemangiomatous proliferation was quite different from the well-known tumor-associated angiogenesis, which is usually present in the form of small capillary networks and sprouting of endothelial cells.

## Observations

A 35-year-old male patient reported a chief complaint of pain and growth in the right mandibular posterior region for 1 month. The medical and dental history was not remarkable. The patient gave a history of betel quid chewing of 7–8 packets per day for the last 10 years. Intraoral examination revealed an ulceroproliferative lesion in the mucobuccal fold measuring 4 cm × 3 cm. The lesion extends from the right second premolar to the retromolar region. Intriguingly, bleeding on provocation was reported during the examination. After confirmation of the OSCC diagnosis on incisional biopsy, the tumor was surgically excised along with right hemimandibulectomy (distal of the first premolar along with coronoid and neck of the condyle) and radical neck dissection.

Histopathologic examination of the excised specimen showed numerous chords and islands of dysplastic tumor cells with occasional keratin pearl formation. Intriguingly, in close proximity to the tumor islands, numerous large and sometimes cavernous vascular spaces were reported (Fig. 1). These spaces were lined by endothelial cells and engorged with red blood cells (RBCs), thus ruling out the possibility of lymphatic vessels. In a few places, these spaces were in direct contact with tumor islands but without any evidence of vascular invasion (Fig. 1).

A total of 15 LNs were retrieved from the radical neck dissected specimen for histopathological examination. Intriguingly, all the LNs of level I showed the same vascular spaces as reported in the primary tumor (Fig. 1). These spaces were lined by endothelial cells and engorged with RBCs. Moreover, we also reported the presence of tumor cell islands along with keratinization in two level I LNs.

## Discussion

Neoangiogenesis is a well-orchestrated phenomenon in carcinogenesis involving the interplay of various signaling pathways.[8] The carcinogenesis-induced neoangiogenesis is presented histologically as the sprouting of capillary networks is close to the tumor cells without engorgement with RBCs.[8] In contrast, the present case showed proliferation of vascular spaces in the form of large and occasionally cavernous spaces with engorged

[1,2]Department of Oral Pathology and Microbiology, Dr DY Patil Dental College and Hospital, Dr DY Patil Vidyapeeth, Pune, Maharashtra, India
[3]Department of Maxillofacial Surgery and Diagnostic Sciences, Division of Oral Pathology, College of Dentistry, Jazan University, Jazan, Saudi Arabia

**Corresponding Author:** Gargi S Sarode, Department of Oral Pathology and Microbiology, Dr DY Patil Dental College and Hospital, Dr DY Patil Vidyapeeth, Pune, Maharashtra, India, Phone: +91 9823871462, e-mail: gargi14@gmail.com

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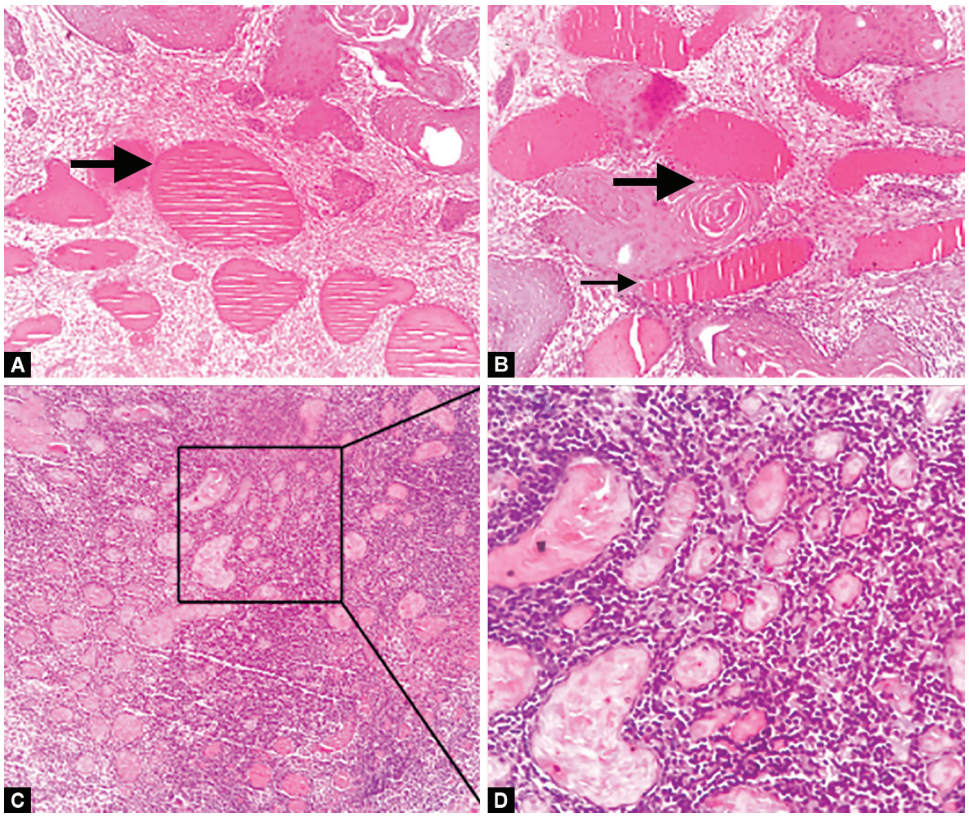


**Figs 1A to D:** (A and B) Photomicrograph showing numerous large vascular spaces engorged with red blood cells (black arrow) close to the tumor cells; (B) Some vascular spaces (black arrow) are in close contact with the tumor cell islands without evidence of intravascular invasion; (C) The regional lymph node shows similar-looking vascular proliferation surrounded by lymphoid tissues; (D) The high-power magnification clearly shows endothelial lining and red blood cell engorgement [Hematoxylin and eosin stain; total magnification: A, B, and D (400×) and C (100×)]

RBCs, thus ruling out the possibility of tumor-related angiogenesis. The size, distribution, and quantification of vascular spaces were close to any typical hemangioma. This unusual phenomenon could be an independent vascular malformation at the site of the tumor formation or an atypical tumor-induced stromal response. The possibility of this being a tumor-induced effect is more as a similar phenomenon was observed in the cervical LNs.

Despite the proximity and direct contact of such spaces with tumor islands, we could not be able to find any intravascular invasion by the tumor cells. All the large vascular spaces were engorged with RBCs. The absence of intravascular invasion could be attributed to the complete engorgement of the vessels with RBCs, thus preventing the invasion of tumor cells inside the lumen. If this proposition holds, then this could be a marker for the nonhematogenous spread of tumor cells with a better prognosis in terms of distant metastasis, which needs further exploration in the future.

The most intriguing finding was the presence of the same stromal vascular malformations inside the level I LNs. The cellular and molecular changes in the metastatic LNs before the arrival of the tumor cells are very well known in the literature.[7] These changes include increased lymphangiogenesis,[9] increased lymph flow,[10] remodeling of high endothelial venules,[10] recruitment of myeloid cells, and diminution of effector lymphocyte count and/or function.[11] Moreover, this tumor cell-induced premetastatic remodeling of LNs also includes expansion of immune cells and stromal cell population and appears to have a largely immunosuppressive cytokine environment.[12] These cytokines and molecules include IL-10, TGF-beta, granulocyte-macrophage colony-stimulating factor, and prostaglandin E2.[12] On these similar lines, we believe that the angiomatous malformation seen in the LNs could be related to some unknown factors secreted by the tumor cells. These unknown factors released by tumor cells could have acted locally as well as in the LNs via lymphatic vessels. This noncellular communication between primary tumors and the regional LNs needs further exploration in the literature.

When cancer cells enter the LNs, they are subjected to the challenges of the hypoxic environment. Under such circumstances, cancer cells can adapt to low-oxygen settings or secure oxygen and nutrient demand by recruiting blood vessels to meet their energetic and biosynthetic requirements.[13] The exuberant angiomatous proliferation within LNs observed in the present study could be related to the recruitment of blood vessels for the nourishment of future metastatic tumor cells. However, this could not explain the coexistence of the same phenomenon at the primary tumor site and within LNs as observed in the present case.

In conclusion, the present case reported a unique hemangiomatous proliferation of vascular spaces engorged with RBCs in OSCC. This unique presentation was also recapitulated in the regional LNs suggesting possible preconditioning of the regional LNs for future metastasis. Although this is a rare event, it would be interesting to investigate the potential of this phenomenon as a biomarker of prognosis.

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