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Case Report

Oral squamous cell carcinoma with extensive mandibular involvement: Unveiling the role of bone invasion patterns, tumor biology and molecular prognosticators with c-Myc and PanCK expression

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Abstract

Background: Craniofacial and gnathic skeleton is primarily responsible for housing a myriad of benign and malignant neoplasms. Tumor biology and heterogeneity may have contributed to the lack of significant improvements in the clinical outcome of the disease despite advances in diagnosis and therapy. Although there is constant evolution of the TNM staging for oral squamous cell carcinoma, it does not encompass the complexities of the variation in bone invasion. Diving into the depths of the tumor microenvironment could significantly affect the prognosis and the treatment modality.

Case Report: A case of a 43-year-old male patient complained pain and swelling with pus discharge in left lower front and back tooth region for 6 months. Initial treatment was extraction of mandibular posterior teeth and diagnosing a hyperkeratotic patch in a private set up. On aggravation of symptoms, radiological investigation revealed extensive osteolytic, ill-defined radiolucent lesionextending from mesial of #43 region, crossing midline till the left molar and ramus region. Incisional biopsy demonstrated moderately differentiated OSCC. Histology of the resected specimen reconfirmed the squamous cell origin bone destruction. Assessment of the cervical lymph nodes revealed level IIa positive for tumor cell infiltration.

Discussion & Conclusion: Thorough assessment of the tumor microenvironment with a comprehensive set of immunomarkers and genomic analysis is vital to predict the biological behaviour of oral malignancies. Subsequently, there could be an alteration within the treatment modalities including surgical margins along with potential for targeted therapies.

Keywords: OSCC, Pan CK, C-myc, Bone invasion

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1. Introduction

The predominance of oral cancer within the Indian population surpasses more than 30% of all cancers.[1] The AJCC 8th edition Staging Manual accounts for a clear disparity among the anatomical sites namely the involvement of the underlying bone affected by oral cancer in the eastern vs western population.[1] Despite having much literature regarding other prognosticators like depth of invasion, pattern of invasion and perineural invasion in tumor cells there is an existing lacunae in correlating bone invasion and metastatic potential of OSCC.

The existing patterns of bone invasion in OSCC comprises of either infiltrative, erosive and mixed. Predominantly consisting of osteoclastic areas and fibrosis within the tumor front is characteristic of erosive pattern. On the other hand, infiltrative pattern exhibits residual bony islands and tumor nests along the irregular front. This histological picture of mandibular invasion has also been successfully correlated with the biological behavior.[2] A better prognosis is associated with an erosive compared to the infiltrative pattern owing to the surgical efficiency obtained with clear margins. Furthermore, there is still an existing controversy regarding the prognostic value of medullary vs cortical invasion.[3]

RANK/RANKL is likely the chief mediator of bone invasion by tumor cells. As a result, certain modifications

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affecting the cortical microarchitecture of the tumor margins remains debatable.[2] Furthermore, reprogramming energy metabolism and tumor associated inflammation might also be of importance in detecting bone invasion by OSCC.[4]

Once the bone is invaded, careful consideration regarding the treatment modality is primary which should excise the involved tissue with safe margins. Widespread medullary involvement is managed with a segmental resection aided by extensive use of panoramic radiographs, computed tomography (CT) and magnetic resonance imaging (MRI). Within oral cavity, 5 mm represents the most commonly used margin standard and the osseous margins have been traditionally determined before surgery.[2]

2. Case Report

A 43years old patient reported with a chief complaint of pain and swelling with pus discharge in left lower front and back tooth region since 6 months. After the initial onset of pain, the patient underwent serial extraction of #35, #36, #37 and #38 within 4months with no significant relief. One month post-extraction he reported further with pain and associated white patch for which biopsy was performed. A diagnosis of "Hyperkeratotic patch" was given and he was kept under follow-up. Despite a follow-up of two months, his symptoms aggravated and he reported with pain, swelling and pus discharge in the affected area. The pain was dull and continuous without any associated aggravating or relieving factors. He was a chronic tobacco smoker and chewer for 20 years with a habit of placing the tobacco in his left lower vestibular region.

Extra oral examination revealed gross asymmetry of the face with a diffused swelling on the left side of his face extending superiorly from the left ala-tragal line to the lower border of the mandible inferiorly and anteriorly from the corner of the mouth to the angle of the mandible posteriorly with obliteration of the nasolabial fold and left angle of mandible. The overlying skin showed no signs of inflammation and extra-oral sinus formation. On palpation, it was soft to firm and tender with no regional lymphadenopathy.

On intraoral examination an ulceroproliferative lesion of size 2x1 cm in the left buccal mucosa anterioposteriorly extending from mid buccal mucosa to the retromolar region and superoinferiorly from at the level of mid occlusal plane of maxillary teeth to the mandibular vestibular region was observed.The superior aspect of the lesion was erythematous whereas the inferior most part had white keratotic tissue with a sinus tract. It was tender on palpation with indurated margins and active pus drainage on compression was observed. A provisional diagnosis of suspected Malignancy with secondary infection was made. Differential diagnosis was given as Osteomyelitis, secondarily infected odontogenic cyst and tumor and metastatic carcinoma was made. (**Figure 1**a)

2.1. Radiographic findings

Reconstructed panoramic view showed evidence of destruction extending from the fourth quadrant crossing the midline till the left molar and ramus region with thinning and effacement of the post border. The central part of the lesion also depicts haphazardly arranged trabeculae with a characteristic moth-eaten pattern. (**Figure 1**)

CBCT - An extensive osteolytic, ill-defined radiolucent lesion was noted in the mandible involving the crestal, middle, apical alveolus and basal mandible along with lower border of the mandible extending anterio-posteriorly from mesial of #43 region, crossing midline till the left molar and ramus region. Superio-inferiorly it extended from the crestal region till the lower border of the mandible in dentate region and in posterior extent from ramus till the lower border of mandible/angle. Evidence of multiple areas of destruction of both cortical plates were seen along the lesion; severely affecting the buccal and lingual cortices with pathological effacements and perforations. The superior and inferior cortex of inferior alveolar canal could not be delineated due to the bone destruction around the canal region thus the lesion is completely involving the inferior alveolar nerve. Radio graphically, it was difficult to distinguish between carcinoma and osteomyelitis but due to absence of involucrum and sequestrum, a radiographic diagnosis of malignancy of mandible was given along with a differential of chronic suppurative osteomyelitis. (**Figure 1**b,c,d)

Histopathological evaluation from incisional biopsy demonstrated parakeratinised stratified squamous epithelium invading into the underlying connective tissue in form of sheets. The extensive tumor islands exhibited exaggerated anaplastic features including cellular and nuclear pleomorphism, nuclear hyperchromatism, abnormal mitosis, prominent nucleoli and few keratin pearls. Focal areas with clear cell differentiation were also appreciated. The connective tissue stroma was minimal with chronic inflammatory infiltrate which was associated with ample resorptive areas within the bony trabeculae (**Figure 2**a). To confirm the squamous cell origin, panCK immunohistochemical analysis was performed which was positive within the tumor cells. Moderately differentiated squamous cell carcinoma was given as the diagnosis after reviewing the slides. (**Figure 3**a)

CECT – A heterogenous space occupying lesion measuring 77*40*59mm arising from the gingivobuccal sulcal margin with extension noted into and along the left mandible reaching upto the coronoid process with resultant destruction and abutment into the anterior 2/3rd of the left hemi tongue. Few enlarged homogeneously enhancing bilateral level Ib, II and ipsilateral level III group of cervical lymph nodes were noted, largest measuring upto 22 x 20 mm at right level II.

PETSCAN – It corroborated the findings of CECT suggesting an extensive lytic lesion causing entire destruction of left hemi-mandible including angle, body, ramus and cornu. Mildly FDG avid few small subcentric bilateral cervical level Ib, II, III and IV were noted.

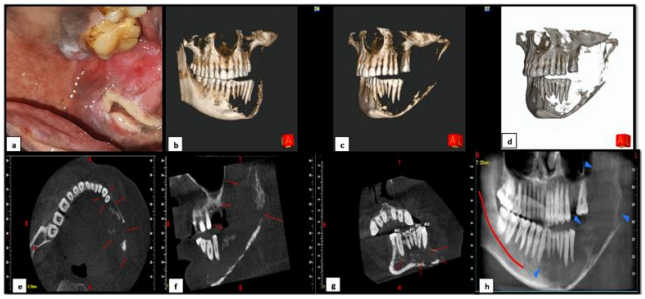

Figure 1: a: An ulceroproliferative lesion is seen in the left buccal mucosa extending from anteroposteriorly from the mid buccal mucosa to the retromolar region and superoinferiorly from at the level of mid occlusal plane of maxillary teeth to the mandibular vestibular region; **b,c,d:** CBCT- An extensive osteolytic, ill-defined destructive radiolucent lesion is noted in the mandible involving the crestal, middle, apical alveolus and basal mandible along with lower border of the mandible; **e:** Axial view; **f:** Saggital view; **g:** Coronal view; **h:** reconstructed Panoramic View

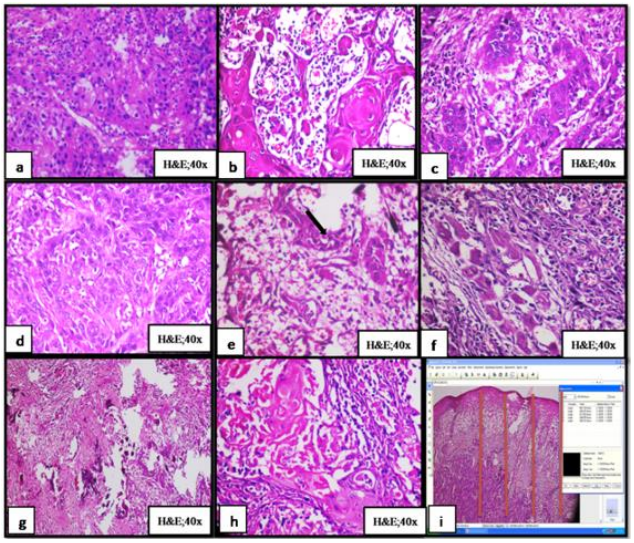

Figure 2: a: H/E stained section showing areas of tumor cells infiltrating connective tissue stroma in form of sheets, islands and showing aggressive features; **b:** Anterior margin of the tumor showing squamous cell infiltration; **c:** Posterior margin of the tumor showing squamous cell infiltration; **d:** Superior margin of the tumor showing squamous cell infiltration; **e:** Inferior margin of the tumor showing squamous cell infiltration; **f:** Sarcolemmal invasion; **g:** Tumor cells surrounding bony trabeculae causing resorption of bone; **h:** Level Ila lymph node was found to be positive for tumor cell infiltration; **i:** Depth of inavsion-4.07mm

Owing to the initial histopathological and radiological investigations, a preliminary AJCC TNM staging was performed which came out to be Stage IVa which makes radiotherapy mandatory. Following this, tumor resection was planned via arch mandibulectomy with supraomohyoid dissection. A reconstructional attempt was also made with a PMMC flap.

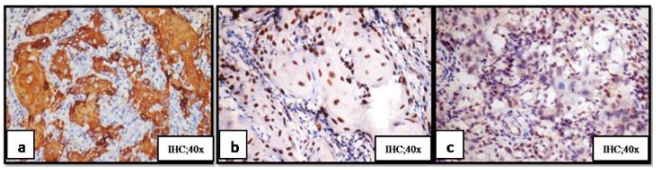

Figure 3: a: Positive Immunoexpression of Pan CK indicating Epithelial in origin; **b:** Nuclear expression of p53 indicating aggressive behavior; **c:** positive immunoexpression of c-myc indicating the process of bone resorption in squamous cell carcinoma.

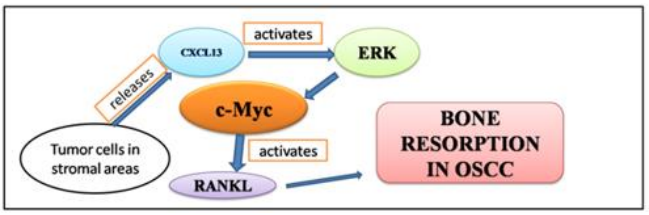

Figure 4: Mechanism of bone resorption in cases of Oral Squamous cell carcinoma where tumor cells release cytokines and activates RANKL pathway by suppression of OPG thus causing bone resorption in cases of OSCC.

Excisional specimen on histopathological analysis revealed positive anterior, posterior, superior and inferior margins and pronounced anaplasia along with evidence of sarcolemmal and bone invasion. Depth of invasion was 4.06mm and level IIa node was positive for tumor cell infiltration (**Figure 2**b,c,d,e,f,g,h,i). TNM classification remained unchanged post reviewing excisional biopsy. Additional workup with cMyc immunohistochemistry yielded strong cytoplasmic positivity within tumor cells indicating the activation of RANKL which in turn is responsible for Bone resorption (**Figure 3**b,c)

3. Discussion

Current literature would suggest that it is not necessarily bone invasion that affects prognosis, but rather the pattern of bone invasion as initially described by Slootweg and Muller.[5] The treatment aspect for OSCC is dependent on the classic TNM staging which neglects the tumor biology.[6] Furthermore, shortcomings in imaging deny a better classification of tumors originating from soft tissues in complex anatomical locations, such as the oral cavity.[4]

The incidence of mandibular bone involvement ranges from 12 to 56%.[7] Several patterns of bone invasion have been documented in the literature but its prognostic significance is rather disputed. Certain reports highlight an invasive pattern along with medullary extension having poor survival rates.[8] Our case illustrates a classic example of an infiltrative type of bone invasion. The panCK immunopositivity suggests a squamous origin of the cells whereas a strong cMyc positivity indicating deregulated DNA synthesis, thereby uncontrolled

cellular proliferation and malignant transformation. It also plays a role in activating RANKL.[9] In comparison to the erosive type, infiltrative pattern of bone invasion is associated with rise in levels of tumor necrosis factor alpha (TNFα), interleukins (IL-6 & 11) and parathyroid hormone related protein (PTHrP). Subsequently, they lead to either suppression of osteoprotegrin (OPG) or expression of RANKL in stromal and tumor cells promoting osteoclastogenesis (**Figure 4**).[1] To sustain bone homeostasis, the phenomenon of osteomimicry is a researched area where tumor cells are known to acquire osteomimetic characteristics expressing analogous molecules.[10] Therefore, this creates a metamorphosed microenvironment with adapted tumor biology which in turn draws our attention to employing a more radical treatment approach to mandible resection.[4,8]

The prognostic impact of mandibular invasion remains controversial. Majority of the studies side with medullary invasion having a poor prognosis with less overall survival and disease-free survival. The different invasion patterns affect treatment protocols used worldwide, as safe (bone) margins are essential for better survival rates.[4] The plight of mandibular carcinomas is poor with high recurrence rate of 70% and a survival rate of 26% both of which are interrelated.[7] Pandey et al. performed a univariate analysis suggesting a significant role of inferior alveolar nerve sensory disturbances in predicting bone invasion.[5] On the other hand, Gomez et al. performed a study on 83 cases of gingival tumors and inferred that bone invasion is not a characteristic predictor of advancing disease.[5]

4. Conclusion

To conclude, a comprehensive set of diagnostic modalities including the initial examination, advanced radiography and well oriented biopsy is mandatory to delineate the treatment approach which can drastically affect the prognosis and quality of life. Furthermore, careful exploration of the etiopathological routes is vital to ascertain the tumor microenvironment and eventually the biological behaviour of oral cancer.

5. Source of Funding

None.

6. Conflict of Interest

None.

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