CASE REPORT

Poor prognosis of oral squamous cell carcinoma developing in young patient without habits along with perineural invasion - A case report with review of literature

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Introduction

Oral squamous cell carcinomas (OSCC) generally occur in older (>50 years) population usually with a history of tobacco and/or alcohol use.¹-³ It is less frequent in young individuals (<40 years) and represents 3–6% of all OSCC. However, the incidence of tongue SCC is gradually increasing since 1973 in a particular group of patients without any known reasons.⁴

Usually, tongue SCC with perineural invasion (PNI) in young patient is associated with poor outcome. PNI is a distinct entity of tumor metastasis that can be seen in the absence of lymphatic or vascular invasion. Even, PNI is not an extension of lymphatic metastasis because there are no lymphatic channels within the inner sanctum of the nerve sheath.⁵ In 1930s, Jentzer first noted that cancer cells spread along nerves as an additional pathway of invasion.⁶ Dissemination of cancer cells along nerve fibers is a frequent pathological finding among several types of malignancy including pancreatic, prostate, upper gastrointestinal tract, and head and neck cancers.⁷ PNI is most commonly found in adenoid cystic carcinoma in salivary glands followed by SCC in the head and neck cancer.⁸,⁹ It is mainly involves the vicinity of the primary tumor (92%) compared with near nodal metastasis (8%) and this invasion is not dependent on the size of primary tumor or histological grading of the tumor in case of OSCC.¹⁰

Abstract

Vascular and lymphatic channels are well-established routes of metastatic spread of tumor cells from primary location to secondary site. However, another route of tumor spread is along nerves which have been described in several literatures since 1800AD. It is well accepted that perineural invasion (PNI) by tumor cells is a hallmark of poor prognosis and decreased survival rate. We are reporting a case of 28-year-old female without any deleterious oral habit complaining of pain and ulcer on the left lateral side of tongue for last 3 months. Regional lymph nodes were not palpable. Histopathological diagnosis was well differentiated squamous cell carcinoma (SCC) with PNI. The patient died within 5 months after diagnosis. Surgery was not performed due to rapid deterioration of general health. SCC of tongue in young patients without any habit showing PNI is essentially an aggressive lesion. This case report outlines the important issues pertaining to treatment planning of such patients.

Case Report

A 28-year-old female reported in the Outpatient Department of Dr. R. Ahmed Dental College and Hospital, Kolkata, India, with the chief complaint of pain and ulcer on the left lateral side of tongue for last 3 months. Ulcer was less than 1 centimeter in diameter [Figure 2] with irregular border and indurated base. The patient had no deleterious oral habit in the past and had not suffered from any major illness. The patient’s general health was good and the regional lymph nodes were free [Figure 1]. Selective grinding of teeth on the affected side was done. On the base of history and clinical findings, the presumptive diagnosis was malignancy. Routine hemogram was advised. Incisional biopsy under local anesthesia was performed in the Department of Oral Pathology of the institute after obtaining written consent from the patient and her relative. Tissue was preserved in 10% neutral buffered formalin and sent for tissue processing. Serial sections were made from embedded wax block at 4 µm thickness using Leica semiautomatic microtome.
Histopathological examination of H and E stained sections revealed the presence of infiltrating neoplastic cells in the underlying connective tissue [Figure 3]. Few of the nerve sheaths also showed invasion by neoplastic epithelial cells [Figures 4 and 5]. Histopathological features were conclusive of well-differentiated SCC with PNI. Immunohistochemical examination was not done for neural tissue since neoplastic epithelial cells were clearly visible in the H and E stained section. The patient was referred to the Department of Oral and Maxillofacial Surgery for further investigation and management. Subsequently, the patient reported to Christian Medical College and Hospital, Vellore, India. Surgery could not be performed due to her fast deteriorating health conditions. Only palliative treatment was done and the patient was discharged. The patient survived only 5 months after diagnosis.

**Discussion**

It has been reported that the incidence range of OSCC in patients younger than 40 years was 0.4–3.9% of all cases and tongue is the
Halder and Ray Oral squamous cell carcinoma

most commonly involved site followed by floor of the mouth.\(^\text{[10]}\)

Higher incidence of carcinoma involving tongue is observed in older male patients as compared to young patients.\(^\text{[11]}\) It rarely occurs below the age of 20 years.\(^\text{[12]}\) However, the subsequent reports were showing that the scenario was reversing according to change of time. Atula et al. in Finland found that SCC of tongue in young adults increased from 3% per year for the decade 1953–1962 to 7% per year for the decade 1983–1992.\(^\text{[13]}\) Myers et al. also reported the same that SCC of tongue was gradually increasing in young population during past 25 years.\(^\text{[14]}\) Mc Gregor et al. in their study of SCC tongue found that sex and site distribution are differ with respect to age of patients.\(^\text{[15]}\) It has been reported that the tongue was the most common site and the majority of the patients were women.\(^\text{[16]}\) The present case which is being reported also suggests the same. It has been opined that traditional risk factors such as tobacco consumption and alcohol intake are not associated with occurrence of OSCC, especially among young females.\(^\text{[17]}\) OSCC in younger patient is a distinct disease entity with respect to different biological behaviors and etiological factors of the diseases.\(^\text{[14-16]}\)

Batsakis defined PNI in his 1985 article that PNI is invasion of tumor cells in, around, and through the nerves.\(^\text{[17]}\) However, most widely accepted description of PNI is proposed by Liebig et al. tumor in close proximity to nerve that involves one-third of it circumscribe and/or tumor cells present in any three layers of nerve sheath.\(^\text{[18]}\) PNI is two types; one is called “incidental” or microscopic (mPNI) and other is clinical PNI (cPNI). mPNI is most commonly found which is diagnosed by the histopathological examination of the tissue sample without any neurological manifestation. Prognosis of cPNI is not good with respect to mPNI because it is diagnosed with neurological manifestation such as paresthesia, hypesthesia, and pain in the distribution of a trigeminal nerve branch or facial weakness. In the present case, the patient reported with mPNI but later on developed neurological manifestations such as severe pain and burning sensation in tongue and teeth before death.

OSCC is a “neurotropic malignancy” that reflects tropism of tumor cells to nerve bundles in the surrounding tissues.\(^\text{[18]}\) PNI is one distinct metastatic process associated with aggressive behavior, higher recurrence, and increased morbidity and mortality.\(^\text{[19]}\) Therefore, appropriate surgical management of primary tumor should include the removal of nerve bundles in the adjoining area because tumor cell can persist and grow within nerve that leads to high rate of recurrence as well as second primary. It is suggested in literature that PNI is an important parameter among other parameters used to predict the prognosis of malignant disease. Literatures reveal that PNI is a well-known indicator regarding the prognosis of colorectal carcinoma and salivary gland malignancies.\(^\text{[19-21]}\) PNI is found in almost all types of pancreatic cancer and the 5-year survival rate is only 5%.\(^\text{[22-25]}\)

Molecular mechanism of PNI is not well understood, but a recent theory explains that it is due to a reciprocal signaling interaction among tumor cells, nerve cells, and stromal cells. Ayala et al. demonstrated in mouse model that dorsal root ganglia exhibits directional outgrowth of neuritis in response to tumor cells.\(^\text{[26]}\) Some neurotrophic factors such as nerve growth factors are highly expressed in OSCC with neural invasion.\(^\text{[27]}\) There is a controversial report regarding the role of neural cell adhesion molecule (NCAM) in the pathogenesis of PNI in head and neck SCC. Vural et al.\(^\text{[28]}\) concluded that there is significant increase of NCAM with PNI. In 2009, Solares et al.\(^\text{[29]}\) contradicted the earlier hypothesis.

Neurotrophic factors and their possible functions are given in Table 1.\(^\text{[30]}\)

Epstein–Barr virus and human papillomavirus have been attributed to oral carcinogenesis.\(^\text{[31]}\) In the present case, viral load in the oral cavity was not evaluated due to inadequate facility. Genetic susceptibility of OSCC among young individuals is also reported in some literatures.\(^\text{[31]}\) Tremblay et al.\(^\text{[31]}\) reported that there was low expression of GSTP1 and underexpression of FANCE gene in younger patients suffering from OSCC compared with older group. Unfortunately, no clear etiology factors have been identified.

Treatment planning is excision of primary lesion along with free margin and comprehensive neck dissection if neck nodes are clinically detectable. Elective neck dissection may also be considered with clinically negative neck nodes along with external radiotherapy and chemotherapy. In our case, surgery could not be performed due to rapid deterioration of patient general health along with poor economic condition.

There is a debate about the outcome of tongue SCC in young patients (<40 years) compared with older patients. Several series have suggested that outcome of younger patient is very poor compared with older.\(^\text{[32-34]}\) Whereas, others have reported that there is no discrepancy between the two age group of patients suffering from tongue SCC.\(^\text{[19,32-35]}\) Goepfert et al. concluded that tongue carcinoma in young women was not associated with worse outcomes compared to a matched cohort of other patients.\(^\text{[36]}\) Tongue SCC shows high rate of locoregional recurrence and a high disease-specific mortality.\(^\text{[37]}\)

Table 1: Neurotrophic factors

<table>
<thead>
<tr>
<th>Factors</th>
<th>Possible function</th>
<th>Expression in cancer</th>
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<tbody>
<tr>
<td>NGF</td>
<td>May stimulate epithelial cancer cell growth and mediate nerve invasion</td>
<td>Overexpressed in pancreas cancer and prostate cancer cell lines</td>
</tr>
<tr>
<td>BDNF</td>
<td>May be overexpressed by tumor cells to promote neurite growth</td>
<td>Overexpressed in pancreas cancer and adenoid cystic carcinoma</td>
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<tr>
<td>GDNF</td>
<td>Exhibits a chemotactic and chemokinetic effect on tumor cells</td>
<td>Overexpressed in specimens of human neural plexi</td>
</tr>
<tr>
<td>NT-3</td>
<td>Stimulates tumor cell invasion at low-to-moderate concentrations</td>
<td>Overexpressed in pancreas cancer specimens</td>
</tr>
</tbody>
</table>

NGF: Nerve growth factor, NT-3: Neurotrophin-3, GDNF: Glial cell-derived neurotrophic factor, BDNF: Brain-derived neurotrophic factor
Conclusion
Sufficient data are not available of young patients (<40 years) suffering from tongue SCC without traditional habits and PNI. According to literature, it is suggested that etiology and pathogenesis of tongue cancer in young patient is different compared with older group. This case report suggests more aggressive behavior of this type of lesion. However, more data are required to make a conclusion of tongue SCC which should be studied with the following parameters tongue SCC with PNI, young patients <40 years of age, and without any traditional habits.

Clinical Significance
Pathophysiology of tongue SCC is quite different with other oral SCC. SCC of the tongue of a young patient should be treated as early as possible after confirmatory diagnosis.

References