Primary signet-ring squamous cell carcinoma of the oral cavity: The first intraoral case

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Abstract
Introduction
The aim of this paper was to report a case of primary signet-ring squamous cell carcinoma in the floor of the mouth and highlight the importance of complete oral examination.

Case report
We report the case of a 54-year-old man who complained of pain and difficulty to open the mouth. The patient presented to the outpatient clinic after he had visited 18 dentists without any definite diagnosis. Oral examination showed a mass in the submandibular gland and an ultrasound revealed an expansive lesion. Histopathological analysis showed the presence of a tumour infiltrating adjacent tissue with groups of cells exhibiting a signet-ring appearance. PAS and mucicarmine was negative. Immunohistochemical staining for CK7 and EMA was strongly positive and Ki67 staining was weakly positive. The lesion was completely submucosal and no ulceration was observed.

Conclusion
This case of signet-ring cell SCC originating from the excretory duct of the submandibular gland represents a rare variant of oral SCC and highlights the importance of complete oral examination, including palpation.

Introduction
According to the World Health Organization, oral and oropharyngeal carcinomas are the most frequent malignant neoplasms of the head and neck¹ and squamous cell carcinoma (SCC) is the most common oral cancer². However, the signet-ring variant is extremely rare and only eleven cases have been reported in the English literature³,⁴,⁵.

We report a case of primary signet-ring squamous cell carcinoma in the floor of the mouth and highlight the importance of complete oral examination.

Case report
The study was approved by the Ethics Committee of Institute of Science and Technology, UNESP - Univ Estadual Paulista and the patient agreed to participate in the study by signing a free informed consent form.

A 54 year old white man complaining of pain and difficulty to open the mouth presented to the outpatient clinic for treatment after he had visited 18 dentists without any definite diagnosis. His medical history included no relevant information. He smoked for 30 years and stopped smoking twenty years ago. Extra- and intraoral examination revealed a mass in the submandibular gland. An ultrasound showed an expansive lesion in the right submandibular gland (Figure 1). Clinical impression was a malignant salivary gland tumour.

An incisional biopsy was performed and histopathological analysis showed the presence of a tumour infiltrating adjacent tissue. The tumour consisted of hyperchromatic epidermoid cells that exhibited loss of polarity and cohesion. The tumour infiltrated adjacent tissue in continuity with the normal excretory duct. In addition, groups of cells with large vacuolated cytoplasm and hyperchromatic nuclei displaced towards the periphery, exhibiting a signet-ring appearance, were seen (Figure 2). Staining with periodic acid-Schiff or mucicarmine was negative.

Immunohistochemical evaluation of CK7, EMA and Ki67 markers (Dako Corporation, Glostrup, Denmark) was performed to better characterize the tumour. The tumour cells were strongly positive for CK7 and EMA and weakly positive for Ki67 (Figure 3).

Figure 1: Ultrasound findings.

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All authors abide by the Association for Medical Education (AME) ethical rules of disclosure.

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Chest and abdominal multislice computed tomography was performed to rule out the possibility that the lesion was a metastatic tumour, as well as the presence of distant metastases. Both exams were negative. The final diagnosis was SCC with signet-ring cells. Treatment consisted of surgical resection, unilateral neck dissection, and postoperative irradiation with 200cGy/day (total dose of 6,000 cGy) for 30 days.

Two years follow-up of the patient detected either local recurrence and skull base metastatic. Patient is undergoing chemotherapy.

Discussion

Oral and oropharyngeal carcinomas are the most frequent malignant neoplasms of the head and neck, with about 264,000 new cases and 128,000 deaths reported in 2008. SCC is the most common oral cancer and the tongue is the site most frequently affected. In the present case, the tumour involved the floor of the mouth, particularly the submandibular gland region.

SCC is strongly associated with environmental factors and lifestyle habits such as smoking and alcohol consumption. The present patient reported smoking but no drinking habit. The diagnosis of SCC is usually made in advanced stages of the disease, a fact resulting in a poor prognosis, high treatment costs and high mortality. As a consequence, an early diagnosis of the disease is extremely important. In this study, the patient complained of pain and difficulty to open the mouth and he had visited 18 dentists without any definite diagnosis before he was seen at our outpatient clinic. The lack of palpation resulted in diagnostic difficulties and a delayed diagnosis, a fact indicating the importance of this procedure in daily practice.

The signet-ring variant of SCC is rare. To our knowledge, only twelve cases of signet-ring SCC of the head and neck (including the present case) have been reported in the English literature (Table 1). In the first case reported by Cramer and Heggeness, 1989, the authors observed recurrent ulcerative nodules on the forehead and contiguous scalp. The initial tumour was well differentiated and derived from keratoacanthoma, whereas cells in the recurrent lesions became acantholytic, dyskeratotic and more anaplastic. A progressively larger number of signet-ring cells were also observed. This case culminated in lymph node metastasis and death of the patient.

McKinley et al. reported a solitary ulcerated nodule detected in the lateral neck, the histopathological analysis revealed areas of signet-ring cells surrounded by foci of keratinization.

El Demellawy et al. reported a case that the patient presented an ulcerated lesion on the upper lip. Histologically, the lesion consisted of cell nests.
exhibiting keratinization and areas displaying prominent signet-ring cell features.

The others cases reported in the English literature are cited in table 1. In the present case, the tumour infiltrated adjacent tissue in continuity with the normal excretory duct.

To our knowledge, this is the first case of signet-ring intraoral SCC involving the submucosa.

The morphological change seen in signet-ring cells probably reflects a degenerative phenomenon related to anaplastic progression. However, not all signet-ring formations have a degenerative origin and can be secondary to the production of mucin, immunoglobulin accumulation or deposition of thyroglobulin, among others. The prognostic significance of this rare variant is not clear, but it should be differentiated from other malignant tumours that are likely to contain signet ring cells, such as adenocarcinoma, basal cell carcinoma, malignant melanoma, lymphoma, liposarcoma, and leiomyosarcoma. In this respect, immunohistochemistry is essential for a correct diagnosis.

When signet-ring cells are present, in addition to clinical history and morphological analysis, immunohistochemistry is important to establish the differential diagnosis. The absence of expression of CK7, CK20, CK19, CAM5.2, CEA, Hepbar, TTF1, thyroglobulin, ER, PR, BRST-2, CA125, vimentin, and CD10 in tumour cells makes the diagnosis of adenocarcinoma unlikely. Negative staining of tumour cells for BerEP4 and CD10 rules out basal cell carcinoma. Negative staining for vimentin, S-100, HMB45 and mel A excludes melanoma. The absence of LCA, CD20, CD10, CD3, CD5 and CD30 expression particularly rules out the signet-ring variant of follicular lymphoma. Negative staining for actin, vimentin and desmin excludes sarcomas, particularly liposarcoma and leiomyosarcoma.

In the present study, tumour cells were strongly positive for CK7 and EMA and weakly positive for Ki67. The presence of CK7 in salivary duct epithelium has been well documented. Linking the information of immunohistochemical findings, assessments in PAS, mucicarmine, deep location within submucosal tissue and lack of ulceration, we postulated an origin from CK7-positive cells from ductal system of the salivary gland, rather than from the surface epithelium.

Regauer et al. also reported cases of CK7-positive SCCs originating from the excretory ducts of submucosal minor salivary glands.

Table 1: Summary of clinical and histochemical findings in cases of signet-ring squamous cell carcinoma reported in the literature (NA: not available).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Mucicarmine</th>
<th>PAS</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>Male</td>
<td>Forehead and scalp skin</td>
<td>NA</td>
<td>Negative</td>
<td>Positive</td>
<td>Lymph node metastasis and death</td>
</tr>
<tr>
<td>79</td>
<td>Female</td>
<td>Right cheek skin</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>82</td>
<td>Male</td>
<td>Left temple skin</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>83</td>
<td>Male</td>
<td>Right ear skin</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>80</td>
<td>Male</td>
<td>Forehead skin</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>87</td>
<td>Male</td>
<td>Frontal scalp skin</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>76</td>
<td>Male</td>
<td>Forehead skin</td>
<td>NA</td>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>50</td>
<td>Male</td>
<td>Lateral neck skin</td>
<td>0.6</td>
<td>Negative</td>
<td>Positive</td>
<td>multiple local recurrences and skin others sites</td>
</tr>
<tr>
<td>84</td>
<td>Female</td>
<td>Upper lip</td>
<td>1.1</td>
<td>Negative</td>
<td>Negative</td>
<td>Died one year after for unrelated reason</td>
</tr>
<tr>
<td>67</td>
<td>Male</td>
<td>Skin near the left lateral canthus</td>
<td>1.5</td>
<td>Negative</td>
<td>Negative</td>
<td>Without local recurrence distant metastases 13 months postoperatively</td>
</tr>
<tr>
<td>54</td>
<td>Male</td>
<td>Mouth floor</td>
<td>2.7</td>
<td>Negative</td>
<td>Negative</td>
<td>Without local recurrence or distant metastases after one year after</td>
</tr>
</tbody>
</table>

N/A: Not available
Conclusion
This case of signet-ring cell SCC originating from the excretory duct of the submandibular gland represents a rare variant of oral SCC and highlights the importance of complete oral examination, including palpation.

References