Squamous Cell Carcinoma of the Submandibular Gland With Cutaneous Fistula: A Case Report and Literature Review

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Abstract

Squamous cell carcinoma (SCC) of salivary glands, also referred to as epidermoid carcinoma, is a very rare neoplastic tumor. It occurs as metastasis of a cutaneous or mucosal squamous carcinoma of the head and neck or as a primary SCC. In the latter case, the most known risk factor is previous irradiation to the gland. Common clinical symptoms are represented by cervical swelling and hyposialia. The treatment is essentially surgical, most often supplemented by a radical neck dissection and postoperative radiation therapy.

A 75-year-old male patient with a history of chronic smoking was consulted for a tumefaction in the right submandibular region evolving for three months. No cervical lymphadenopathy in the submandibular and superior jugulo-carotid areas was palpable. CT scan showed an enhancing heterogeneous process of the right cervical region, invading the mylohyoid and stylohyoid muscles. A biopsy-excision of the lesion has shown a keratinizing tumor with cytonuclear atypia, consistent with SCC. Radical resection of the mass was associated with the removal of the infiltrated skin. The cutaneous defect was repaired with a rhomboid flap. The patient was started on sessions of adjuvant radiotherapy and chemotherapy. Eight months postoperatively, the patient came for follow-up, with no signs of local disease.

The EGFR protein is found in ~70% of salivary neoplasms and is considered as a factor of poor prognosis and rapid proliferation. PET CT is currently the best examination to detect the existence of a concomitant malignant lesion. Diagnosis of primary SCC (PSCC) of the submandibular gland is made on histopathology. Differential diagnoses include mucoepidermoid carcinoma, lymphoepithelial carcinoma and submandibular metaplasia. There is an increased prevalence of nodal involvement in the PSCC, which justifies neck dissection (regions I, II and III of the neck). The RAS mutation leading to resistance to anti-EGFR therapies may be assessed. This would allow for a treatment depending on molecular features for metastatic PSCCs.

PSCC of major salivary glands is a very rare lesion with local and general aggressiveness. The diagnosis is based on a combination of clinical examination, MRI, fine needle aspiration and histological examination. Immunotherapy constitutes a ground of research to treat metastatic and advanced pathological cases.

Introduction

Most neoplastic lesions of the major salivary gland are benign. The malignant lesions are rare and include mainly mucoepidermoid carcinoma [1]. Squamous cell carcinoma (SCC) of salivary glands, also referred to as epidermoid carcinoma, is a very rare malignant tumor. It represents around 1.8 % of all salivary neoplasms and is a proliferation of squamous epidermoid cells [2].

SCC usually develops in mucosal surfaces of the upper aerodigestive tract. It is associated with chronic smoking and alcohol intake. The SCC of the major salivary glands, do not present the same pathophysiological mechanisms. It mostly occurs as metastasis of a cutaneous or mucosal squamous carcinoma of the head and neck. The most known risk factor is previous irradiation to the gland [3]. Common clinical symptoms are cervical swelling and hyposialia. At the time of diagnosis, cervical node metastases have an incidence of 21% to 45% [4].

Histologically, the presence of squamous cells that are round to polygonal with eosinophilic cytoplasm, is the hallmark feature of this lesion. Immunohistochemistry (IHC) is useful for determining positive CK and...
p63 markers [5]. The treatment is determined after a multidisciplinary consultation meeting. It is essentially surgical, most often supplemented by a radical neck dissection and postoperative radiation therapy. Surgical removal is often disfiguring, given the difficulty to achieve resection in free margins. We report the case of a rare case of SCC of the submandibular gland with a sialo-cutaneous fistula and a review of the previously reported cases of SCCs of major salivary glands in the literature.

**Case Presentation**

We report a case of a 75-year-old male patient with a history of chronic, with no hypertension, diabetes or general illness. He consulted on February 2021 in the Otorhinolaryngology Department at the Cheikh Khalifa International University Hospital (CKIUH). He presented a swelling in the right submandibular region evolving for three months. The patient did not report any symptoms of dyspnea, dysphonia, or epistaxis. The submandibular mass was hard, firm and was accompanied by local inflammation.

There was a fistulous orifice adjacent to the mass, discharging a mucoid fluid at palpation. Intraoral examination showed normal-aspect mucosa. The floor of the mouth, palatine tonsils and oropharynx were not the sites of any suspicious lesion. No cervical lymphadenopathy in the submandibular and superior jugulo-carotid areas was palpable. The patient underwent a nasofibroscopy to explore the rest of the upper aerodigestive tract. No synchronous malignancy was ruled out through the examination.

The cervical ultrasonography revealed a hypoechoic lesion of the right submandibular gland, highly suggestive of neoplasia. CT scan showed an enhancing heterogeneous process of the right cervical region of 4×3.2×4.2 cm, causing a defect of the skin, invading the mylohyoid and stylohyoid muscles, coming into close contact with the right parotid gland and the jugular vein (Figures 1, 2). There were several suspicious lymph nodes of the submental (I), superior and middle jugulo-digastric areas (II and III) of the right neck.
FIGURE 1: Scannographic presentation of the right submandibular swelling (heterogeneous mass with irregular contours extending into the right parapharyngeal space and palatine fossa).
A biopsy excision of the lesion has shown a keratinizing tumor with cytonuclear atypias and numerous mitoses. The chorion was infiltrated by spans, cords and nests of the carcinomatous lesion (Figure 3). Diagnosis of a moderately differentiated SCC of the submandibular gland was made. The objective of the therapeutic protocol was to avoid revision surgery and allow for complete removal of the lesion. After a multidisciplinary consultation meeting, we decided to perform a neck dissection comprising levels I, II and III (Figure 4). The neck dissection material showed no signs of malignancy.

FIGURE 2: Scannographic presentation of the right submandibular mass showing high enhancement after injection of the contrast product.

Contrasted areas (blue arrow)
FIGURE 3: Tumoral proliferation made of squamous cells with cytonuclear atypias and numerous mitoses, consistent with SCC. Hematoxylin-eosin stain, original magnification *40.

FIGURE 4: Post-operative aspect after complete resection of the lesion.

Radical resection of the mass was associated with the removal of the infiltrated opposite skin. The cutaneous defect was repaired with a rhomboid flap (Figure 5).
The final pathological examination confirmed the diagnosis of SCC of the submandibular gland. As the deep margins of the tumor were invaded, our patient underwent revision surgery. Multiple biopsies of the suspected site confirmed the complete removal of the carcinoma after a histopathological study. The patient was started on 35 sessions of adjuvant radiotherapy (70 Gy). The treatment was completed by 10 courses of cisplatin-based chemotherapy. Eight months postoperatively, the patient came for follow-up, with no signs of cervical swelling, pain or hyposialia. Nasofibroscopy and control CT scan showed no sign of local disease.

Discussion

Primary SCC (PSCC) of the submandibular gland is a particular entity of the SCC of major salivary glands. The latter represents ~2% of all malignant salivary gland tumors and arises most of the time in the parotid (~80%). Patients with PSCC present a poor overall survival outcome, approaching ~50% at 5 years [6]. This can be related to the highly recurrent nature of the disease (~66% in the first year) [7]. Studies have shown that patients with primary and metastatic SCC of the major salivary glands have both the same prognosis [6]. Also, the presence of lung metastases is a life-threatening prognostic factor [7].

The EGFR protein is found in ~70% of salivary neoplasms and is considered a factor of poor prognosis and rapid proliferation. It has been demonstrated that the Wnt/β-catenin pathway induces tumor development by increasing self-renewal. Indeed, Wnt glycoprotein activation permits signal transduction. This generates an elevation of the intracellular level of the β-catenin complex. The nuclear translocation of β-catenin is then followed by the transcription of multiple targeted genes (i.e., Cyclin D1). Loss of membrane β-catenin has been shown to distort cell adhesion, allowing for migration and metastatic invasion. This is combined with the aggressive nature of the tumor and its drug resistance [8].

PSCC of the submandibular gland remains a diagnosis of exclusion. Differential diagnoses have to be excluded: (1) metastasis from a distant primary site, (2) mucoepidermoid carcinoma, and (3) cutaneous SCC extending locally. It is difficult in histopathology to differentiate between a PSCC and a secondary or metastatic localization. Indeed, both are keratinizing lesions with no specific features for the primary tumor. The radiological investigations are necessary due to the fact that the identification of the site of origin is often not obvious at the time of presentation. PET CT is currently the best examination to detect the existence of a concomitant malignant lesion [9]. In the case of our patient, PET CT evaluations have not revealed any secondary metastatic site.

This disease occurs mainly in men with a male to female ratio of 2:1. The highest incidence was found to be in the sixth and seventh decades of life [9]. This correlates to our case study. The main described risk factor is cervical radiotherapy, with an onset interval of 10 years [9]. In our case, there was no history of irradiation.
Part of a document discussing the treatment and management of metastatic salivary gland squamous cell carcinoma (PSCC), highlighting the importance of early diagnosis and the role of multimodal therapy. The text emphasizes the need for accurate imaging and histological examination to confirm the diagnosis of SCC, and the potential for immunotherapy in treating metastatic cases. It also mentions the aggressive nature of these tumors, their association with known risk factors, and the importance of surveillance for local recurrences and distant metastases. The conclusion reiterates the rarity of PSCC in major salivary glands and the need for comprehensive management plans.
Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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