Stomatologija. Baltic Dental and Maxillofacial Journal, 28: 29-32 2026

Diagnosis of secretory carcinoma of the upper lip: A rare case report and literature review

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SUMMARY

Secretory carcinoma (SC) is a rare malignant neoplasm of the salivary glands, first recognized in 2010 due to its resemblance to secretory breast carcinoma. Although classified as a low-grade tumor with generally favorable outcomes, some cases may exhibit high-grade features, including lymph node metastasis and aggressive histological architecture. The defining characteristic of SC is the ETV6-NTRK3 gene fusion; however, diagnosis can also rely on histopathological and immunohistochemical criteria when this fusion is absent. SC typically requires complete surgical excision with negative margins, with adjuvant radiotherapy considered in selected cases. Occurrence of SC in the upper lip is extremely rare, particularly in female patients, making accurate diagnosis essential. A 50-year-old woman with a history of sinusitis, arthritis, hypercholesterolemia, and thyroid nodules presented with a slow-growing, painless nodule on the upper labial mucosa. Clinically, the lesion resembled a benign mucocele. Histopathological analysis revealed a fibrous capsule surrounding proliferating cells with eosinophilic cytoplasm and a predominantly microcystic pattern with some papillary features. Immunohistochemistry confirmed SC, with strong positivity for CK7, S100, and mammaglobin, and negativity for CK14 and p63. Complete surgical excision was performed, and no residual tumor was found. Follow-up over nine months showed no recurrence. This case highlights the importance of recognizing SC in atypical locations, such as the upper lip. Given its clinical similarity to benign conditions like mucocele, thorough histopathological and immunohistochemical analyses are crucial. Early identification and complete excision are key to achieving favorable outcomes.

Keywords: secretory carcinoma, salivary gland, diagnosis, immunohistochemistry, lip neoplasms.

INTRODUCTION

Secretory carcinoma (SC) is a rare malignant salivary gland tumor first described in 2010, with histological similarities to secretory breast carcinoma (1). It is generally considered a low-grade lesion with an indolent clinical course and favorable survival rates (2). However, high-grade features—such as nodal metastasis, more solid and trabecular architecture with areas of necrosis, and ETV6-X gene fusion alterations – have also been documented (3, 4). The diagnosis of SC is typically based on the presence of the highly specific ETV6-NTRK3 gene fusion (5, 6). Nonetheless, cases diagnosed in the absence of this gene fusion, relying on morphological and immunohistochemical characteristics, have been reported (7). Treatment for SC usually involves complete surgical excision with negative margins, with adjuvant radiotherapy considered in select cases (8). This case report describes a rare SC lesion on the lip.

CASE REPORT

This case report followed ethical standards and was conducted in compliance with the Declaration of Helsinki. The informed consent was secured from

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the patient for both participation and publication of the findings. A 50-year-old fair-skinned woman with a medical history of sinusitis, arthritis, hypercholesterolemia, and thyroid nodules presented with a slow-growing, palpable nodule on the upper left labial mucosa, which had been present for three years. The patient denied pain, bleeding, or other associated symptoms. Intraoral physical examination revealed a slightly undulating submucosal lesion, well-circumscribed and approximately 1 cm in diameter, with no visible changes to the adjacent mucosa (Figure 1). Based on the clinical findings, the initial differential diagnosis included benign lesions such as a mucocele, given its location and clinical characteristics.

A biopsy of the lesion was performed under local anesthesia. Histopathological analysis revealed a fibrous capsule surrounding a proliferation of cells with eosinophilic cytoplasm and a granular appearance. The tumor exhibited a predominantly microcystic pattern with papillary areas (Figure 2). Periodic acid-Schiff (PAS) staining of the ductal structures demonstrated positive results (Figure 3). Immunohistochemical studies showed strong positivity for CK7, S100, and mammaglobin, confirming the features of secretory carcinoma. The lesion was negative for CK14, α-SMA, and p63. Ki67 immunostaining demonstrated less than 5% positivity, indicating a low proliferative index (Figure 4).

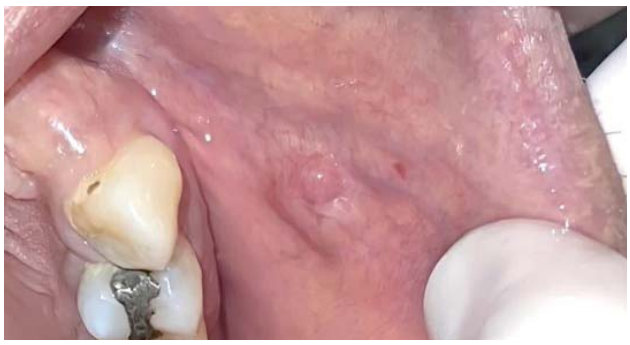

Fig. 1. Nodular lesion on the upper left labial mucosa

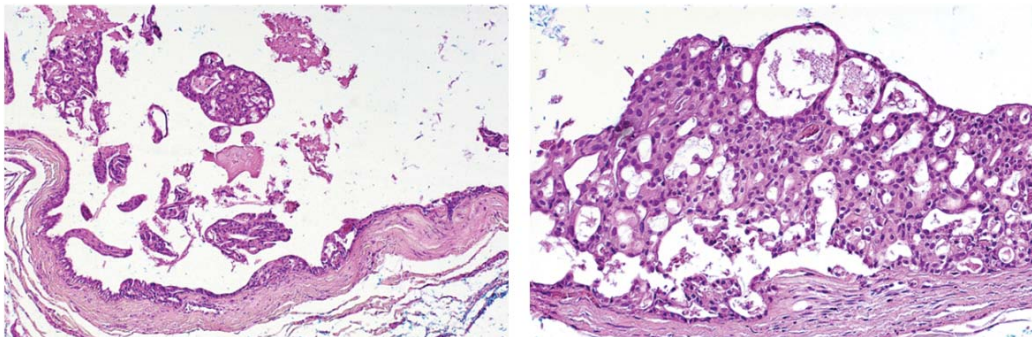

Fig. 2. Fibrous capsule surrounding a proliferation of cells with eosinophilic cytoplasm and granular appearance (Hematoxylin and eosin-stained section; original magnification 10× and 20×).

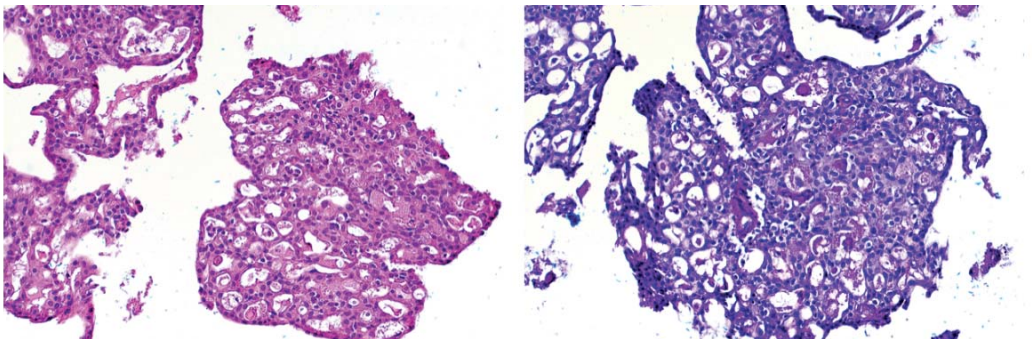

Fig. 3. Predominantly microcystic pattern with some papillary areas (Hematoxylin and eosin-stained section; original magnification 20×.; Periodic acid-Schiff stained section; original magnification 20×).

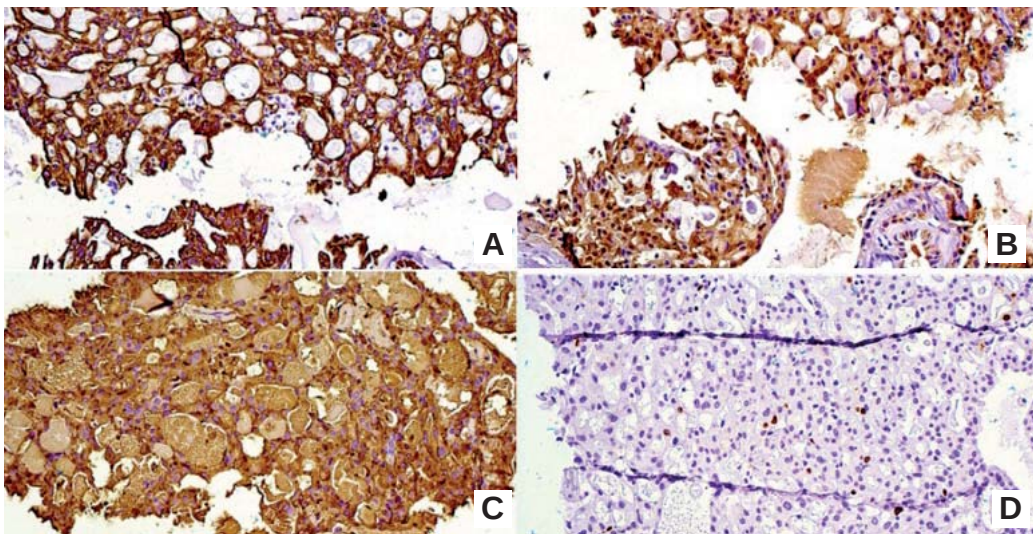

Fig. 4. The immunohistochemical panel showed strong and diffuse positivity for the markers. A – CK7, B – S100, and C – mammaglobin; D – immunohistochemistry showing Ki67 positivity in less than 5% of cells (Original magnification, 20×).

Following these findings, the patient underwent complete surgical excision of the lesion. Histopathological examination of the excised specimen confirmed the diagnosis of secretory carcinoma, with no evidence of residual tumor or microvascular invasion. Postoperative recovery was uneventful, and the patient was discharged. At the nine-month follow-up, there was no evidence of tumor recurrence or residual disease.

DISCUSSION

SC is a rare salivary gland tumor, with only a limited number of cases documented in the literature (4). Recently recognized as a distinct pathological entity, SC shares histological, immunohistochemical, and genetic characteristics with secretory breast carcinoma (1). This tumor is most notably associated with the ETV6-NTRK3 gene fusion, resulting from the t(12;15)(p13;q25) translocation (4). While major salivary glands are more commonly involved, occurrences in minor salivary glands are even rarer, as exemplified in this case (9).

Formally classified by the World Health Organization (WHO) in 2017 (10), SC was first described by Skalova *et al.* (1). It predominantly affects the parotid gland, followed by minor and submandibular glands, with a slight male predominance and a mean age of onset of 45 years (2). However, exceptions such as the female patient described in this report underscore the variability in epidemiological patterns.

Clinically, SC often mimics benign lesions due to its slow growth, painless nature, and benign-like features (11). In this case, the lesion on the patient's upper lip was initially misdiagnosed as a mucocele. Such presentations emphasize the need for heightened clinical awareness of SC, particularly in uncommon anatomical locations.

In this case, histopathology revealed features supporting the suspicion of SC, aligning with findings reported in other studies (3,12). The presence of a fibrous capsule surrounding a proliferation of cells with eosinophilic cytoplasm and granular appearance, along with a predominantly microcystic pattern and papillary areas, is consistent with typical features of this neoplasm. These histological patterns can sometimes resemble other low-grade salivary gland neoplasms (13).

The immunohistochemical profile was crucial in confirming the diagnosis. Positivity for CK7, S100, and mammaglobin strongly indicated the secretory nature of the tumor (11), differentiating it from other salivary gland neoplasms such as adenoid cystic carcinoma (ACC), which lacks mammaglobin expression (14). Furthermore, the low Ki-67 labeling index (<5%) aligned with SC's indolent clinical behavior and favorable prognosis (15).

Immunohistochemistry is crucial in diagnosing SC, particularly in distinguishing it from other salivary gland neoplasms (7). SC typically shows positivity for mammaglobin, S-100 protein, and CK7 (16). In contrast, markers such as DOG1 and p63 are usually negative or only focally positive (17). The t(12;15)(p13;q25) chromosomal translocation, which results in the ETV6-NTRK3 gene fusion, is a key molecular marker for SC diagnosis and can be detected by fluorescence in situ hybridization (FISH) or PCR (18). However, gene fusions unrelated to NTRK, such as ETV6-MET (19) and ETV6-RET (20), have also been reported, complicating detection in laboratories with limited resources. In settings with constrained resources, like Brazil, a basic immunohistochemistry panel combined with thorough histopathological analysis may suffice to establish the diagnosis.

The standard treatment for SC is complete surgical excision with negative margins, offering a favorable prognosis with low metastatic risk (12). Adjuvant radiotherapy or TRK inhibitors, such as larotrectinib, may be options in advanced cases (8).

In conclusion, SC is a rare but distinct entity with unique features requiring accurate diagnosis through combined histopathological and immunohistochemical approaches. Early recognition and appropriate treatment, particularly surgical excision, are crucial for optimal outcomes, even in resource-constrained settings.

STATEMENT OF CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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Received: 13 01 2025
Accepted for publishing: 20 03 2026