Low-grade intraductal carcinoma of the lower lip

Lucyene Miguita, Paulo Sérgio Souza Pina, Décio dos Santos Pinto Junior, Bruna Parrillo Santos, Suzana Cantanhede Orsini Machado de Sousa

ABSTRACT

Introduction: Low-grade intraductal carcinoma (LGIC) is a rare neoplasm of the salivary glands, composed of a single or multiple cystic space with intraductal or intracystic proliferation of neoplastic epithelial cells. It involves predominantly parotid glands and rarely occurs in minor salivary glands. Presently, a case of LGIC in an uncommon location is reported and compared with the clinical, histopathological, and immunohistochemical findings of other cases reported in minor salivary glands. Case Report: A 53-year-old male patient reported with swelling in lower lip since four months. Histological findings showed neoplastic cells lining a large cystic space presenting intracystic proliferation formed by epithelial luminal cells, and sometimes a cribriform aspect. Neoplastic cells were positive for CK7 and S100 protein, and a rim of outer cells were p63 and S100 positive. Ki67 index was below 5%. The patient underwent surgical excision. One year later the patient is free of disease. Conclusion: The present case report adds information pertinent to document a rare salivary gland tumor located in an unusual site, being the present one the fifth reported case of a LGIC, in the English literature, arising from minor salivary glands and the first reported in the lower lip.

Keywords: Carcinoma, Intraductal, Lip, Minor, Salivary glands

INTRODUCTION

Low-grade intraductal carcinoma (LGIC), also known as low-grade cribriform cystadenocarcinoma, intraductal carcinoma, intraductal carcinoma with microinvasion, or low-grade salivary duct carcinoma, is a rare and non-life-threatening neoplasm of the salivary glands, first described as a variant of salivary duct carcinoma by Delgado et al. in 1966 [1]. In 2005, the World Health Organization (WHO) defined it as “a rare, cystic, proliferative carcinoma that resembles the spectrum of breast lesions from atypical ductal hyperplasia to micropapillary and cribriform low-grade ductal carcinoma in situ” [2]. In 2017, the new WHO definition characterized the lesion as intracystic or intraductal proliferations of neoplastic epithelial cells [3].

It occurs mostly in elderly people with a predominance of 2:1 in women, being the parotid gland the main site of involvement [4]. Only four cases involving minor
salivary glands have been reported in the literature [5–8]. Clinically, the tumor behavior is that of an indolent slowly growing cystic mass [3, 4] and histologically, it is usually described as a nonencapsulated mass composed of single or multiple cysts with intraductal proliferation, arranged in a cribriform pattern [2, 5].

Regarding therapeutic management of LGIC, a complete resection of the lesion seems to be curative and no additional therapy, such as chemotherapy or radiotherapy, seems to be necessary [9]. It presents an excellent prognosis with a very low index of recurrence [9].

Presently, a case of LGIC unusually arising from minor glands of the lower lip is described.

CASE REPORT

A 53-year-old white man, social drinker and non-smoker, attended a private dental clinic with an asymptomatic nodular lesion on the lower lip (Figure 1). The patient first noticed the lesion four months before and stated no baseline diseases or previous history of trauma.

An irregular, soft, and elastic nodule, no change in mucosal color, measuring approximately 1.4 × 0.9 cm, was surgically excised under local anesthesia and the specimen was fixed in 10% formalin. The surgeon referred the specimen to the histopathologic analyses with a provisional diagnosis of mucocele. The gross section showed a cystic cavity with a viscous and yellowish fluid inside (Figure 2).

Hematoxylin and eosin stained sections revealed a large cystic space lined predominantly by papillary and cribriform patterns of growth, frequently presenting duct-like structures (Figure 3). Those structures were composed by two layers of cells, an inner one with cuboidal luminal cells, and the external one composed by ovoid or spindle cells. The presence of micropapillae lining on the cystic cavity and the presence of islets of neoplastic cells in the capsule were conspicuous. A mucinous secretion could be seen within the cystic cavities.

The luminal cells of duct-like structures and the cells rimming the cystic space showed strong expression of Cytokeratin 7 (CK7) (Figure 4) and a weak expression of Cytokeratin 14 (CK14) (Figure 5). S100 protein was positive in the outer cells of duct-like structures and in cystic lining epithelium (Figure 6). The expression of p63, also known as Tumor protein 63 (TP63), displayed a continuous rim of cells underlying the luminal cells (Figure 7) and smooth muscle actin (SMA) was negative (data not shown). The proliferation marker Ki67 was positive in a few cells (less than 5%) (Figure 8). The final diagnosis established was of low-grade intraductal carcinoma. After diagnosis, the patient was referred for medical care, where a complete surgery was performed with margins analyzed. No further treatment was indicated. One year later the patient is free of disease.
DISCUSSION

Intraductal carcinoma is a rare neoplasm of the salivary glands, characterized by intracystic proliferation of neoplastic epithelial cells [3]. This tumor is more common in adults, occurring in a frequency of 57% in females and, the parotid is affected in 80% of the cases against 8% in minor salivary glands, especially in the palate [9]. It appears usually as an asymptomatic swelling [3], and, macroscopically, these tumors have been typically described as a small, non-encapsulated cystic lesion. The present case showed clinical and microscopic features in accordance with the literature [3–8], except for the uncommon location.

To the best of our knowledge, this is the first case of intraductal carcinoma arising from a minor salivary gland of the lips. Only four cases have been reported in the English literature involving minor salivary glands, one in the buccal mucosa [5] and the three others in
the palate [6–8]. Besides arising in the lip, the lower lip is even a rarer location for salivary gland tumors. In a recent multicentric retrospective study, da Silva et al. (2018) [10] found 2292 salivary gland tumors, being 970 malignant and among those only 14 cases affecting lower lip.

The main characteristics of LGIC include cells arranged in cribriform, micropapillary or even in solid patterns [4–8], lining cystic spaces [4–7]. Also, the “Roman-bridge” architecture lining the cystic areas, constituted by two layers of cells, one luminal/epithelial and a second layer of myoepithelial cells, is frequently seen [4–8]. These microscopic characteristics described are quite similar to our findings. Within cystic areas we could observe a basophilic material. Some authors described it as mucous positive for mucicarmine and periodic acid-Schiff diastase resistant [1, 5, 11], when negative for these two types of staining, other authors described as a central necrosis area [7–9].

Dystrophic calcification can also be present focally in some cases, as described in a LGIC on the palate [7]. It can be due to the proximity of alveolar bone present in this region. These structures were not observed in the LGIC of the lip.

Differential diagnoses of low-grade intraductal carcinoma include cystadenoma, cystadenocarcinoma, sclerosing polycystic adenosis, high-grade intraductal carcinoma (HGIC), papillary cystic variant of acinic cell carcinoma, and mammary analogue secretory carcinoma (MASC) [3, 5]. In the present case, cystadenoma and cystadenocarcinomas were both discarded due to the presence of cribriform architecture and of non-neoplastic myoepithelial cells, which are not seen in cystadenocarcinomas [3, 5, 9, 11, 12]. Also, a low-grade mucoepidermoid carcinoma could be a possibility [8], however, the lack of mucous and epidermoid cells aligned with the presence of a single cystic space ruled out this hypothesis. Still a cystic degeneration of an excretory duct could be thought, but cells morphology also excluded this diagnosis.

Table 1 summarizes the four cases reported in the literature from minor glands [4–7] and the present case. Regarding the age of patients, 80% (4/5) of the cases occurred in the fifth decade and the rate male/female was 3:2, including the present case. The most frequent findings among microscopic characteristics were the cribriform arrangement with “roman bridge” and the mucous present within cystic areas [4–7]. Immunohistochemically, only in the present case CK7 was used, and intensely positive. Protein S100 was positive in the majority of cases, in ours and the three other cases [4–6], and p63 was positive in a rimming of outer cells in the present case and also in two others, probably denoting myoepithelial cells as a previous report also showed positivity to calponin in these cells [4, 5]. Smooth muscle actin was negative in our case, but positive in Ide et al. (2004) [7] report (although not shown). The detection of cell markers such as SMA, CK14 on epithelial components and a low expression for p63 justify an in situ nature of the lesion as the neoplastic epithelial component is apparently retained intraductally [3].

Besides, some histologic characteristics such as comedo necrosis and the expression of S100 protein may help to separate HGIC from LGIC. While, HGIC can be either negative or only partially positive for S100 protein [1, 12], LGIC is positive [4–6].

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Sex/Age (Year)</th>
<th>Site</th>
<th>Microscopic findings</th>
<th>S100</th>
<th>CK7</th>
<th>CK14</th>
<th>SMA</th>
<th>P63</th>
<th>Ki67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimura et al. (2016) [5]</td>
<td>M/72</td>
<td>Buccal mucosa</td>
<td>Cribriform arrangement and “Roman-bridge” architecture, with mucus presence</td>
<td>+</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>+</td>
<td>+ (&lt;2%)</td>
</tr>
<tr>
<td>Ide et al. (2004) [7]</td>
<td>M/58</td>
<td>Palate</td>
<td>Cribriform arrangement, cell nests on capsule and “Roman-bridge” architecture</td>
<td>+</td>
<td>NI</td>
<td>NI</td>
<td>+</td>
<td>NI</td>
<td>+ (&lt;9%)</td>
</tr>
<tr>
<td>Tatemoto et al. (1996) [8]</td>
<td>F/58</td>
<td>Palate</td>
<td>Cribriform arrangement, cell nests on capsule and mucus presence within cystic areas</td>
<td>–</td>
<td>NI</td>
<td>NI</td>
<td>–</td>
<td>NI</td>
<td>–</td>
</tr>
<tr>
<td>Present case</td>
<td>M/53</td>
<td>Lower lip</td>
<td>Cribriform arrangement with “Roman-bridge” architecture, cell nests on capsule and mucus presence within cystic areas</td>
<td>+</td>
<td>+</td>
<td>+weak</td>
<td>–</td>
<td>+</td>
<td>+ (&lt;5%)</td>
</tr>
</tbody>
</table>

New evidences demonstrate that genetically intraductal carcinoma presents two distinct types. The first type is classic intercalated type, which commonly presents a fusion transcript of nuclear receptor Coactivator 4 (NCOA4) exon 6 to exon 12 of the RET proto-oncogene (RET) gene and rarely presents widespread invasion. The second type is named as apocrine intraductal lesions that are more invasive and show phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) (p.E545K/p.H1047R) and HRas proto-oncogene, GTPase (HRAS) (p.Q61R) mutations similar to salivary duct carcinoma [13]. These RET rearrangement mutations could be found only in 47% of the cases studied which also presented S100 expression and a phenotype of intercalated duct [13]. Despite the lack of the genetic analysis in the present case, the intercalated duct pattern with low invasion and S100 positive cells was also observed in our case, suggesting the presence of RET rearrangement. But further analysis is necessary to infer this hypothesis.

Regarding treatment of LGIC, as it is a malignant tumor, the complete resection of the lesion is recommended, however, without the necessity to apply adjuvant therapy as chemotherapy or radiotherapy [9]. It presents a particularly good prognosis with low recurrence rate [9] as also observed in the present case.

CONCLUSION

The diagnosis established to the case reported was low-grade intraductal carcinoma, elucidating this as the first case reported in the English literature of a LGIC arising from a minor salivary gland of the lower lip, and the fifth one of minor salivary glands.

REFERENCES


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Paulo Sérgio Souza Pina – Conception of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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