Neuroendocrine Tumors of the Submandibular Gland: Literature Review and Report of a Case

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Abstract

Primary salivary neuroendocrine neoplasms are extremely rare, with only 1 case of carcinoid tumor and 7 cases of primary large-cell neuroendocrine carcinomas having been reported. Salivary small-cell neuroendocrine carcinomas are more frequent, accounting for less than 2% of all salivary malignancies. In addition to a literature review on the subject, the authors describe a rare case of malignant intermediate-grade neuroendocrine tumor of the submandibular gland.

Keywords

neuroendocrine tumors, salivary gland, immunohistochemistry

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms, with a wide range of histotypes, rarely arising in salivary glands.[1,2] The World Health Organization (WHO) classification of NETs in different organs and tissues of the body is detailed and complex; however, the current WHO classification of salivary gland tumors, given the rare occurrence of neuroendocrine neoplasms in this site, includes only 2 histotypes—small- and large-cell carcinoma—but low- and intermediate-grade NETs are not considered.[1,2]

The rarity of neuroendocrine neoplasms in salivary glands is probably correlated with the scarcity of neuroendocrine cells in this tissue. Considering the few in-depth studies,[3-5] we investigated the presence and distribution of neuroendocrine cells in archival normal human salivary tissues by immunohistochemistry with antibodies against neuroendocrine markers, Chromogranin A and Synaptophysin.

In addition, we reported a malignant, moderately differentiated NET of the submandibular gland, tentatively classified as a NET G2, according to the 2010 WHO of gastroentero-pancreatic NETs,[6] suggesting the need of possible future update of the current classification of salivary gland neuroendocrine neoplasms.

Case Report

Clinical Findings

A 72-year-old woman was referred to the Department of Otorhinolaryngology of the Catholic University, Rome, Italy, complaining of swelling and tension in the left submandibular region. The patient was referred for a total thyroidectomy in 1987 for thyroid papillary carcinoma. On palpation, a firm and painless small nodule was detected in the submandibular region; radiological examinations, ultrasound scans, and magnetic resonance imaging revealed a nodular, well-enhanced tumor, about 1.4 cm in maximum diameter, in the left submandibular gland, with a moderate swelling of some locoregional lymph nodes of the homolateral neck region. Upper-respiratory tract examination, esophagogastroscopy, and routine chest X rays did not show any pathologies. The fine-needle aspiration cytology of the nodule was suspicious for epithelial neoplasia, and the patient underwent total left submandibular gland removal with wide local excision and

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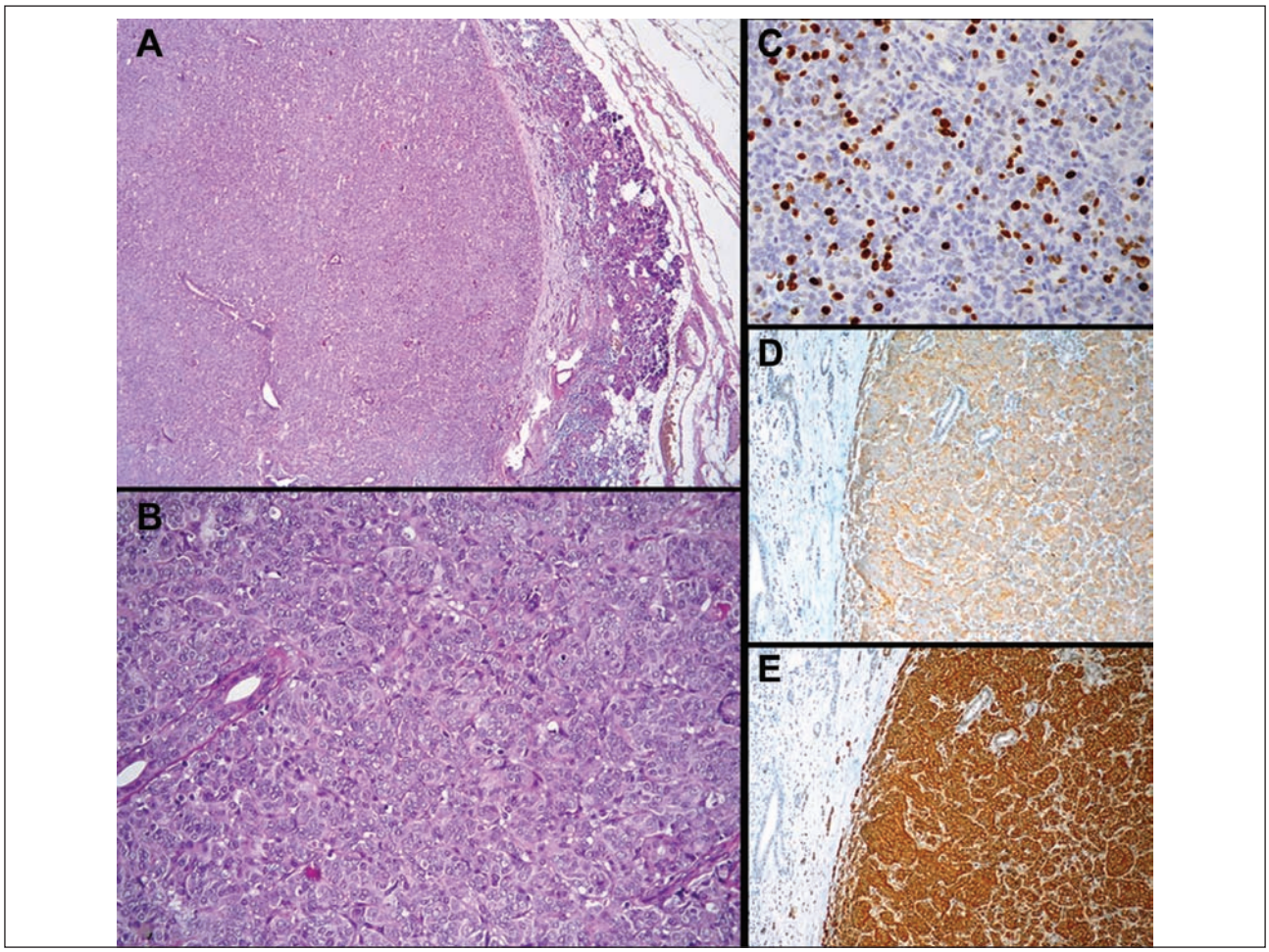

Figure 1. A. Microscopic overview of the small subcapsular nodule in the submandibular salivary tissue, completely comprised in the gland parenchyma (×40, hematoxylin and eosin stain). B. The submandibular lesion is composed of neoplastic cells, with eosinophilic cytoplasm, rounded or ovoid nuclei, and coarse chromatin, organized in solid nests. Normal salivary intercalated ducts are intermingled with the neoplastic tissue (×200, hematoxylin and eosin stain). C. Section of the salivary tumor immunostained by MIB1/Ki67 showing a proliferative index less than 20% (×200, MIB1/Ki67). D, E. After immunohistochemistry, the neoplastic cells appear diffusely stained positively for Synaptophysin (D) and Chromogranin A (E); D and E, ×100

selective neck dissection. No other body lesions were detected by thoracic and abdominal computerized tomography and OctreoScan at 11 months' follow-up.

Histopathological and Immunohistochemical Findings

On gross examination, the submandibular gland presented a firm and solid subcapsular nodule, measuring 1.4 cm in maximum diameter, *grayish-white in color, and completely comprised in the gland parenchyma and could be totally examined*" to "*...grayish-white in colour, comprised in the gland parenchyma and totally examined* Necrosis and hemorrhage were not found. In the lateral neck dissection, 4 lymph nodes were identified.

On microscopic examination, the submandibular lesion was composed of neoplastic cells, with a moderate amount of eosinophilic cytoplasm, round or ovoid nuclei, and coarse chromatin, organized in solid nests with occasional rosette-like arrangement (Figures 1A and 1B). In peripheral areas, intercalated ducts were found among neoplastic cells (Figure 1B). The mitotic count was less than 10 mitoses per 10 high-power fields (HPFs); mean = 6 per 10 HPFs. The proliferative index was less than 20% (MIB1/Ki67; Figure 1C). One of the 4 isolated lymph nodes revealed a small subcapsular tumoral deposit of 5 mm in maximum diameter, with the same morphological characteristics of the salivary neoplasm.

The neoplastic cells were stained positively with CAM5.2, cytokeratin 7 (CK7; in a dot-like pattern), Synaptophysin (Figure 1D), and Chromogranin A (Figure 1E). No immunostaining was observed for thyroid transcription factor-1, Thyreoglobulin, CDX2, CK20, and Calcitonin. The same immunophenotype was detected in

the nodal metastasis. The salivary ducts, admixed with neoplastic cells and in the remaining normal salivary tissue, did not reveal the presence of cells immunostained by neuroendocrine markers.

Based on the cell morphology, growth pattern, mitotic count, proliferative index (MIB1/Ki67), immunophenotype, and the presence of a locoregional nodal metastasis, we classified this lesion as primitive NET G2, according to the WHO classification of NETs of the digestive system.[6]

In archival normal salivary gland tissue, the immunohistochemistry for Chromogranin A showed only rare stained gangliar cells located in the interstitium, adjacent to vessels or ducts; on the other hand, a diffuse network of fine nerve fibers, around acini and ducts, and sparse gangliar cells were found after immunohistochemistry with Synaptophysin antibody; no neuroendocrine cells located in the ductal or acinar epithelium appeared to be stained by any of the antibodies.

Discussion

NETs have been described as arising anywhere in the body, but they are extremely rare in salivary glands.[1,2] The infrequency of NETs in salivary glands is probably because of the absence or only rare presence of neuroendocrine cells in normal salivary tissue, as suggested by our present investigation. In fact, no cells immunostained by neuroendocrine markers were detected either in ductal epithelium or in acini, with nerve fibers and ganglion cells being only labeled. Although expression of Chromogranin A by the salivary gland was reported in other mammals,[7] the presence and distribution of neuroendocrine cells in human salivary glands has been the topic of few reports, and the issue is still far from being clarified.[3,4]

NETs are a heterogeneous family of neoplasms with a broad spectrum of histomorphologies, tissue origins, and clinical outcomes. However, there is lack of consensus on the exact classification of neuroendocrine neoplasms of the salivary glands because of their rarity.[1,2] The present WHO classification of salivary gland tumors (2005) considers only the 2 categories of small- and large-cell neuroendocrine carcinomas, and the whole morphological and biological spectrum of NETs, as in other sites, is not considered.[1,2]

The small-cell carcinoma subtype, the most common variant in both major and minor salivary glands, accounts overall for less than 2% of salivary malignancies.[1] Hui et al[8] found that neither cell size nor a neuroendocrine differentiation influenced the prognosis, concluding that a distinction between subsets of small-cell carcinomas is no longer useful. Small-cell neuroendocrine carcinomas with Merkel-cell-like features in salivary glands were first reported by Kraemer et al.[9] More recently, on the basis of CK20 expression patterns, Nagao et al[10] proposed different prognostic implications for 2 categories of small-cell neuroendocrine carcinomas, which they named the Merkel cell type and the pulmonary type.[10]

On the other hand, large-cell neuroendocrine carcinoma of salivary glands has rarely been documented, being most likely underdiagnosed or misinterpreted.[2,11,12] In 1982, Eusebi et al[13] described the first case of large-cell neuroendocrine carcinoma of the parotid gland. This tumor represents a small subset of large-cell carcinoma,[2] with only 7 cases reported in the literature.[8,11-16] It affects older patients and is characterized by a high mitotic count and MIB1/Ki67 index and a rapidly aggressive course, with frequent occurrence of hepatic and pulmonary metastases.

Recently, Modlin et al[17] described a primary carcinoid tumor of the parotid gland, stressing the rarity of this type in salivary glands. The salivary gland tumor that we have reported was composed of medium-sized cells with a moderate grade of cellular atypia, with mitotic figures lower than 10 per 10 HPFs, a proliferative index (MIB1/Ki67) less than 20%, and absence of necrosis. After immunohistochemistry, diffuse positivity for Chromogranin A and Synaptophysin was found, confirming the neuroendocrine nature of the neoplasm. A metastatic origin for this neoplasm was ruled out by the results of immunohistochemistry, with negativity for thyroid transcription factor-1, CDX2, CK20, Thyreoglobulin, and Calcitonin; by the absence of any lesion on upper-respiratory tract examination, esophagogastroscopy, and routine chest X rays; and by negativity of thoracic and abdominal computerized tomography and OctreoScan at 11 months' follow-up; moreover, the only lymph node with metastasis was a locoregional one, near the gland. All these findings are strongly in favor of a primitive origin from the salivary gland. On the basis of the guidelines of the current WHO classification of neuroendocrine neoplasms of the gastro-entero-pancreatic tract, we consider this neoplasm as a NET G2.[6] In light of the discussion above, we suggest the need of minor additions in the present salivary gland NET classification of WHO to include rare entities, such as low- and intermediate-grade NETs.

Authors' Note

GP and AS have contributed equally to this work.

Declaration of Conflicting Interests

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