SMALL CELL NEUROENDOCRINE CARCINOMA WITH PRIMARY SITE IN TONSIL: CASE REPORT

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ABSTRACT

Aims: This study aims to report a case of small cell neuroendocrine carcinoma with a primary site in the tonsil in a 76-year-old male patient and review the main aspects. **Presentation of Case:** In this study, the patient had a palpable cervical mass on the right (predominantly affecting level V) and a large primary tumor in the tonsillar site on the right, making it necessary to perform a biopsy for histopathological and immunohistochemical studies. **Discussion:** Primary small cell neuroendocrine carcinomas (SNEC) are poorly differentiated neoplasms with poor prognosis and low incidence in the head and neck regions. SNEC originating in the head and neck, which have the tonsils as their primary sites, are even rarer, with only 14 cases being reported in the English literature over the last 40 years. **Conclusion:** Due to the scarcity of data in the literature on this pathology due to its rarity, therapeutic strategies have not yet been formulated. The clinical and imaging data in this study were essential for staging and primary site definition. Despite the favorable initial response to treatment with radiotherapy and chemotherapy, the patient progressed with the disease, conferring the poor prognosis expected for this type of neoplasm.

Keywords: Tonsillar fossa, Neuroendocrine carcinoma, Small cell carcinoma.

1. INTRODUCTION

Primary small cell neuroendocrine carcinomas (SNEC) are poorly differentiated neoplasms with a gloomy prognosis and low incidence in the head and neck regions [1]. There are other sites of origin, such as the lungs, the most common site; gastrointestinal and genitourinary tracts; breasts; and unknown primary sites [2].

Among SNECs originating in the head and neck, those with the tonsils as primary sites are even rarer, with only 14 cases reported in the English literature over the past 40 years [2]. Therefore, due to the scarcity of data in the literature regarding this condition, therapeutic strategies have yet to be formulated [2,3].

From this perspective, the present study aims to report a case of small cell neuroendocrine carcinoma with the primary site in the tonsil and to review the main aspects of this pathology.

2. PRESENTATION OF CASE

A 76-year-old patient attended an oncology center in Brazil in June 2019 with a complaint of a cervical tumor. He had a neck contrast enhanced computed tomography (CECT) scan on March 3, 2019, which revealed an expansive lesion in the right tonsillar fossa measuring 5.1 x 4.7 x 2.9 cm, with multiple nodal lesions in the right cervical region. In terms of personal history, he reported a smoking habit since the age of 15 and denied hypertension and diabetes mellitus.

He underwent an incisional biopsy of the palpable right cervical mass (predominantly affecting level V), measuring 4.7 x 3.9 x 2.8 cm in its largest dimensions. Four tissue fragments were collected and fixed in 10% formaldehyde.

On May 27, 2019, the immunohistochemistry described the fragment as infiltrated by a malignant small cell neoplasm with hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm. (**Fig.1**). During the immunohistochemical study, after dewaxing and treating the tissues with specific solutions to recover the epitopes, the histological sections were exposed to a set of monoclonal and/or polyclonal antibodies. A polymer-based detection system was then used. Positive and negative controls were included to check the accuracy of the reactions (**Fig.2**). The immunohistochemical study revealed the expression of cytokeratin in a Golgi pattern, INSM-1, and synaptophysin (**Fig.3**).

The combination of these findings is indicative of small cell neuroendocrine carcinoma. Therefore, the healthcare team conducted a correlation with clinical and imaging data for the primary site staging and investigation.

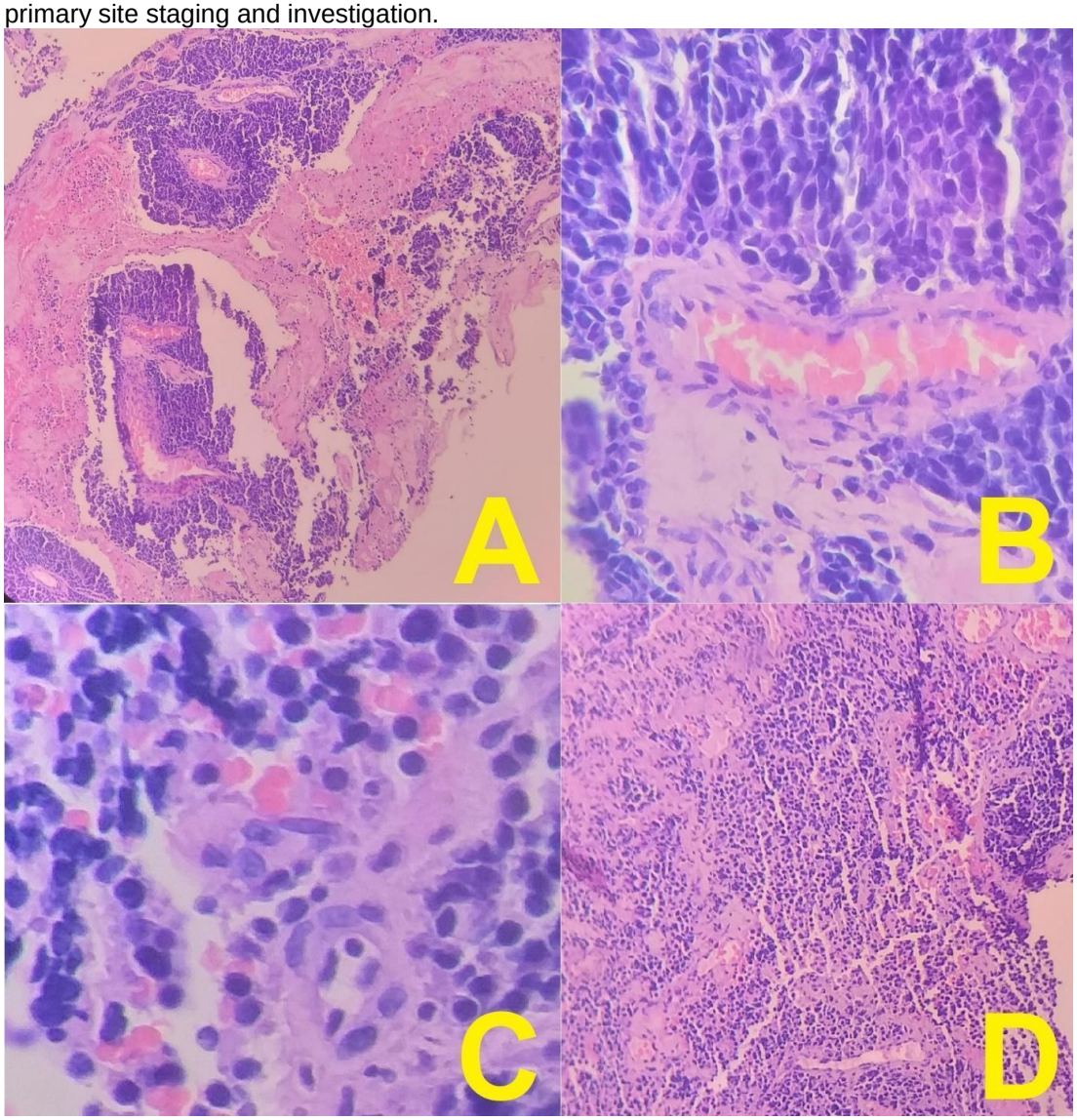

Fig.1. A) Connective tissue showing poorly differentiated malignant neoplastic cell proliferation, sometimes in a diffuse, blocky or rosette arrangement; B) Cells with small,

relatively monomorphic nuclei, with scarce cytoplasm, forming an amorphous cell block; C) Atypical neoplastic cells with a pseudorosette arrangement; D) Irregular infiltration of connective tissue by primitive cells.

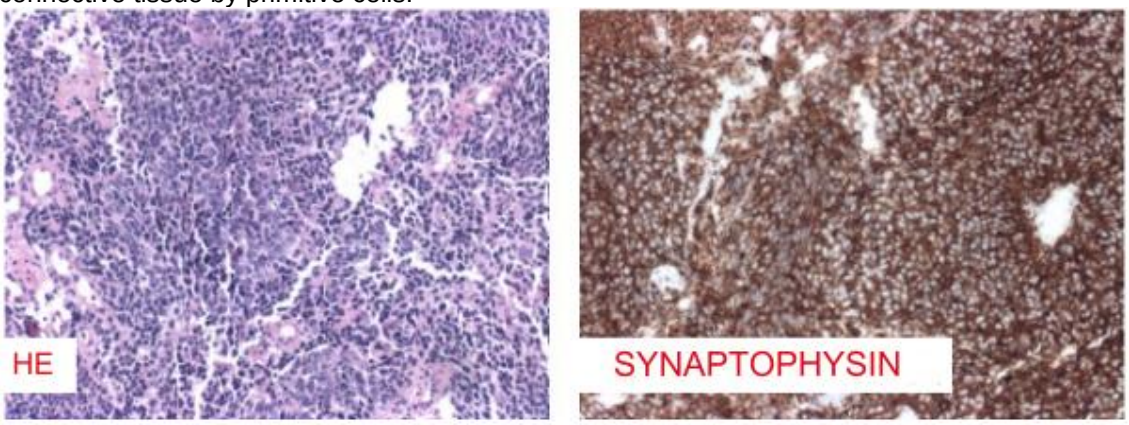

Fig.2: Immunohistochemistry.

Antibodies	Clone	Result	Note/Block
ki-67 - Cell prolifertion antigen	**MIB1**	Positive	**>95% (B-693/19)**
Cytoceratins of 40, 48, 50 and 50.6	**AE1/AE3**	Positive	**Golgi pattern (B-693/19)**
Synaptophysin	**DAK-SYNAP**	Positive	**(B-693/19)**
Insulinoma-associated protein 1	**BSB-123**	Positive	**(B-693/19)**
Citoceratina 20	**KS20.8**	Negative	**(B-693/19)**
P63 protein (squamous/transitional epithelia; myoepithelial cells)	**DAK-P63**	Positive	**(B-693/19)**

Fig.3: Markers and their interpretation: Ki67 95% - high cell proliferation; Cytokeratins (AE1/AE3) positive: origin of the neoplasm is epithelial (carcinoma); Synaptophysin positive: presence of a neuroendocrine component in the neoplasm (which defines it as carcinoid); Insulinoma-related protein positive: neuroendocrine differentiation marker; Ck20 negative: cytokeratin which may be negative in neuroendocrine carcinomas; P63 positive: cytokeratin indicative of squamous cell carcinoma, but can be positive in neuroendocrine carcinomas.

Subsequently, the team requested a chest, total abdomen, and neck CECT scan, central nervous system MRI with contrast, and laboratory tests. The exams did not detect distant lesions.

Thus, the clinical, laboratorial, and imaging evaluations diagnosed the lesion as small cell neuroendocrine carcinoma with the primary site in the tonsil, T3N2M0 stage IVa, locally

advanced. The patient underwent chemotherapy (EP x C3) and radiotherapy performed in 3 cycles with a 48-hour interval between them on days 1, 4, and 7, consisting of cisplatin (80 mg/m2) and etoposide (100 mg/m2). On January 27, 2020, he was discharged following radiotherapy, with a total dose of 70 Gy/35 fx.

In a post-treatment follow-up, a CECT scan was performed on December 21, 2021, with no evidence of expansive formations in the oropharyngeal region, persisting with no significant changes. There was localized lymphadenopathy in the right cervical level IIA, measuring 1.4 x 1.1 cm, along with other non-enlarged lymph nodes in the right level III, the largest measuring 0.9 cm in the smallest axis. With good response to treatment, the patient was kept under clinical observation. The patient then experienced disease control but was lost to follow-up until June 2022.

Unfortunately, the patient showed signs of recurrence. A control ultrasound was performed on July 4, 2022, which revealed enlarged lymph nodes in the right at levels II and III, measuring 3.0 cm and 1.5 cm, respectively, along with a 0.6 cm nodule in the left lobe of the thyroid, suggesting disease progression. After this, he developed complications due to benign prostatic hyperplasia, requiring surgery and delaying monitoring. In addition, due to Brazil's public health system, there was a delay in the patient's oncological follow-up.

On December 30, 2022, a fine-needle aspiration biopsy was performed on the right cervical lymph node at level II, with the results indicating a poorly differentiated malignant neoplasm, possibly a neuroendocrine tumor based on the clinical history.

Following this, a biopsy was requested for histopathological examination. The histopathology report from January 30, 2023, indicated a poorly differentiated malignant neoplasm of small cells infiltrating connective and striated muscle tissue, consistent with a lesion secondary to a neuroendocrine carcinoma.

3. DISCUSSION

SNECs are highly invasive neuroendocrine tumors that have the lungs as the most frequent primary site. The larynx is the most affected site in the head and neck region, followed by the salivary glands, nasal cavity, and paranasal sinuses. [4].The extrapulmonary incidence of this pathology is 0.1 to 0.4%, being extremely rare in the tonsil region, where the most common tumor type is squamous cell carcinoma, also including minor salivary gland tumors, lymphomas, melanomas, and sarcomas [4].

Previous studies have reported that SNEC often presents in older patients, ranging from 50 to 66 years of age, and has no gender bias, except for those with a primary site in the tonsils, in which there is a greater involvement of male patients, with a male to female ratio of 1.75. However, due to the rarity of this condition, more comprehensive studies on the incidence of this pathology are still needed [1].

This type of neoplasm usually presents as a painless cervical mass, with or without odynophagia, dysphonia, and a foreign body sensation in the region, whose progressive enlargement raises the possibility of its malignant character [3, 5]. In addition, a local mucosa asymmetrical tonsillar edema or ulceration may be found on physical examination, but in some cases it may also be within normal parameters [6].

A tonsillectomy is essential for diagnosing SNEC of the tonsils, and it is only replaced by a biopsy if the patient has a high bleeding risk [4]. Histopathology integrates these procedures and allows visualization of the lesion's neuroendocrine component, which is characterized by architectural cellular characteristics that include organoids, nesting, rosettes, ribbons, trabeculae, and peripheral palisades [7].

These tumor cells have a very characteristic oat-like shape and are called oat cells [8]. In addition, they have a round to oval shape and are arranged in cords or nests, containing hyperchromatic nuclei, scarce cytoplasm, and a high mitotic index [3, 9]. Therefore, based on its cellular characteristics, SNEC is considered, according to the most recent 2005 World

Health Organization (WHO) classification for head and neck tumors, to be a poorly differentiated neoplasm, thus falling into grade III [7].

Given the histopathological findings and the increased suspicion of the diagnosis, immunophenotyping is used to confirm the diagnosis. The leading marker for SNEC is the neural cell adhesion molecule (CD56), which is found in 90–100% of cases. However, as it is not specific to this tumor, morphological findings should be associated with this marker [4]. In addition to this, the immunohistochemical panel can also include synaptophysin and chromogranin, as well as pan-cytokeratin, calcitonin, S100, INSM-1, and TTF17 [7].

Although the diagnosis of these tumors is based on their clinical, histopathological, and immunohistochemical characteristics, some cases, such as submucosal tumors, can go unnoticed without a radiographic evaluation, especially through CECT and MRI [5]. These tests help assess the size and depth of tumor infiltration and identify whether the neoplasm is a metastatic site, such as in the lungs [1, 11]. Combined with these, positron emission tomography (PET-CT) is considered the gold standard for determining the origin of a mass compatible with SNEC in the head and neck region [11].

Some of the findings that can be identified on imaging tests in patients with SNEC are: the presence of a tumor with moderate enhancement located on the tonsils associated with unilateral or bilateral lymphadenopathy [8].

Due to its rare incidence, no recommendations have been established for the treatment of this pathology. Based on a comparison of the treatment of SNEC in the larynx and lung regions, the interventions include surgical resection, radiotherapy, chemotherapy, and a combination of these [2].

Some authors argue that chemotherapy should be considered in all patients with this pathology due to its propensity for early metastasis. Concerning local control, there are frequently mentioned opinions in favor of using radiotherapy to the primary tumor site and neck, preferably rather than surgery, or even their combination. However, guidelines for the management of patients with this pathology, depending on the stage of the disease, have not yet been established [3]. Among the chemotherapeutic agents used, platinum-based compounds such as cisplatin (CDDP) and etoposide are the most frequently used. Despite multimodal treatment, the prognosis of patients with SNEC of the head and neck is unfavorable. In a review of 12 cases, recurrence or distant metastases were found in 66.7% of them, and these patients ended up dying from the disease in 2.5 years with a median overall survival of 18 months [2].

4. CONCLUSION

Due to the scarcity of data in the literature on this pathology due to its rarity, therapeutic strategies have not yet been formulated. In this study, the patient had a palpable cervical mass on the right (predominantly affecting level V) and a large primary tumor in the tonsillar site on the right, making it necessary to perform a biopsy for histopathological and immunohistochemical studies, given the differential diagnoses for cervical lymph node enlargement, which include paraganglioma (positive for S-100, but negative for cytokeratin) and malignant lymphoma (immunoreactive for LCA, but negative for neuroendocrine markers).

The clinical and imaging data in this study were essential for staging and primary site definition. Despite the favorable initial response to treatment with radiotherapy and chemotherapy in 2019, the patient in question progressed with the disease in 2022, conferring the poor prognosis expected for this type of neoplasm.

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COMPETING INTERESTS

The authors have no competing interests to declare that are relevant to the content of this article.

AUTHORS' CONTRIBUTIONS

FAP: preparation of the research, preparation of the timetable, survey of the literature, collection and analysis of the data, writing of the article, correction of the writing of the article, and approval of the final version; **IFGG:** survey of the literature, writing of the article; correction of the writing of the article and approval of the final version; submission and processing of the article **MHBF**: writing the article, correcting the writing of the article and approving the final version; **TJMBSV:** writing the article, correcting the writing of the article and approving the final version; **KFSV:** writing the article, correcting the writing of the article and approving the final version; **JMSD:** writing the article, correcting the writing of the article and approving the final version; **LMQOB**supervision,correcting the writing of the article and approving the final version. and **PFS:**supervision,correcting the writing of the article and approving the final version.

CONSENT

The authors report that they have the patient's consent, which is available upon request.

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

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