CASE REPORT

Sinonasal neuroendocrine carcinoma – a case report

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ABSTRACT

BACKGROUND. Sinonasal neuroendocrine carcinoma (SNEC) was first described as a distinct entity by Silva in 1982, which he separated from esthesioneuroblastoma. It is usually diagnosed as an advanced lesion and most commonly involves the nasal cavity, ethmoid and maxillary sinuses. Given the rarity of the sinonasal neuroendocrine tumors, understanding their clinical progression and improving their outcomes is limited.

CASE REPORT. A 64-year-old male presented with left sided nasal obstruction, persistent headache, recurring left-sided epistaxis, diplopia, exophthalmia and left eyelid ptosis as the primary symptoms. Computed tomography (CT) demonstrated a soft tissue mass occupying the left nasal cavity, the ethmoid, maxillary and sphenoid sinuses, with bony destruction and extension into the left orbit. The histopathological examination, along with immunohistochemical staining, determined the diagnosis of sinonasal neuroendocrine carcinoma.

DISCUSSIONS. Sinonasal neuroendocrine carcinoma is a rare neoplasm, the clinical evolution of which is not well known, mainly due to the paucity of published literature on the topic. Clinical presentation is similar to other malignancies arising in the sinonasal tract, thus diagnosis is based on histopathological analysis. The differential diagnosis of sinonasal neuroendocrine carcinoma comprises other sinonasal malignancies with neuroendocrine differentiation, other tumors of neuroectodermal origin and other carcinomas. There is no specific recommendation regarding the management of this particular neoplasm and treatment options are extrapolated from neuroendocrine tumors of pulmonary origin.

CONCLUSION. Due to the infrequency of this pathology, overlapping features with other entities and histological heterogenicity, a delineation of this particular histological type within the group of neuroendocrine neoplasms remains to be determined.

KEYWORDS: neuroendocrine carcinoma, nasal cavity, paranasal sinuses, esthesioneuroblastoma, immunohistochemistry

INTRODUCTION

Although the sinonasal compartment is highly exposed to carcinogenic substances, malignancies arising in this area are uncommon, making up less than 5% of all head and neck cancers[1]. Their management is frequently challenging due to late diagnosis, aggressive histology and high morbidity associated with complete surgical removal of disease. Particular entities among neoplasms arising in the sinonasal tract are the tumors of neuroendocrine origin. Sinonasal neuroendocrine tumors are extremely rare and, unlike the lung and other extrapulmonary sites, there is no definite classification. There is also a bit of controversy regarding the terminology within this group of tumors. The World Health Organisation addressed it in 2005, stating that the terminology and classification used in the lung should be applied to the head and neck. Thus, sinonasal neuroendocrine malignancies are categorized as typical carcinoids, atypical carcinoids, small cell carcinoma, neuroendocrine type, sinonasal neuroendocrine carcinoma "not otherwise specified"[2] and paragangliomas. Esthesioneuroblastoma (ENB), which exhibits neuroendocrine differentiation, and sinonasal undifferentiated carcinoma (SNUC), which can express neuroendocrine markers, are not included in this classification.

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Sinonasal neuroendocrine carcinoma (SNEC) was first described as a distinct entity by Silva[3] in 1982, which he separated from esthesioneuroblastoma. It is usually diagnosed as an advanced lesion and most commonly involves the nasal cavity, ethmoid and maxillary sinuses[4]. Given the rarity of the sinonasal neuroendocrine tumors, understanding their clinical progression and improving their outcomes is limited.

This article describes the clinicopathological features of a patient with neuroendocrine carcinoma of the left nasal cavity and left maxillary, ethmoid and sphenoid sinuses. The natural history, pathologic findings and therapy choice are discussed.

CASE REPORT

A 64-year-old male presented to our Department with a three-month history of left sided nasal obstruction, persistent maxillary pressure, seromucous rhinorrhea, persistent headache and recurring left-sided epistaxis, with progression of symptom severity and accompanied by the onset of diplopia two weeks prior to presentation. Physical examination revealed left exophthalmia and left eyelid ptosis with restricted left medial gaze. His visual acuity was preserved. Upon examination of the nasal cavities, including rigid nasopharyngoscopy, the patient was found to have a bleeding soft tissue mass occupying the upper left nasal cavity. There were no palpable cervical lymph nodes on physical examination. A computed tomography (CT) scan of the head and neck was performed, which revealed a soft tissue mass occupying the left nasal cavity, the ethmoid, maxillary and sphenoid sinuses, with bony destruction and extension into the left orbit.

An endoscopic biopsy of the mass was performed and multiple tissue specimens were sent for histological examination. The specimens were fixed in formalin, routinely processed, embedded in paraffin, then cut 4 µm thick and stained with hematoxylin and eosin. Immunohistochemical staining was also performed for Leukocyte Common Antigen (LCA/ CD-45), S-100, cytokeratin (CK) AE1/AE3 and chromogranin.

On histological examination, the tumor was characterised by areas of large, round cells with moderate amounts of eosinophilic cytoplasm and large, round nuclei with finely dispersed chromatin (Figure 1). High mitotic activity was present. Lymphatic vascular invasion was identified (L1) and areas of necrosis were observed. The tumor cells did not show significant pleomorphism and no tumor nests, rosettes or neurofibrillary stroma were seen. The immunohistochemical profile showed tumor positivity for chromogranin and cytokeratin. The tumor cells were strongly positive for chromogranin, 50% of tumor cells exhibited the marker (Figure 2). Perinuclear dot-like cytokeratin
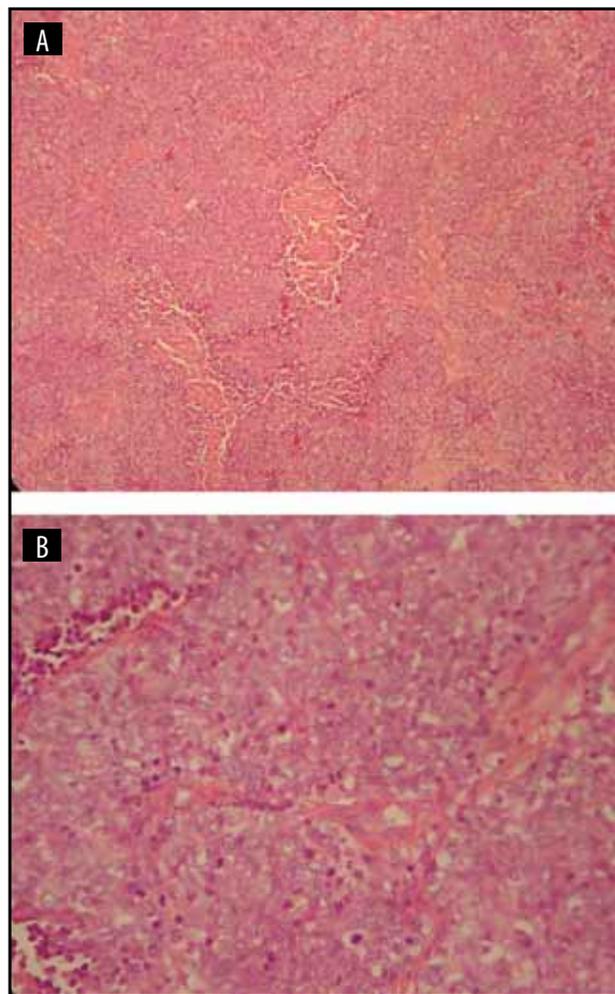
Figure 1 A: Neuroendocrine carcinoma demonstrating large sheets of tumoral cells with confluent necrosis (centre); **B:** Detail showing large, round cells with moderate amounts of eosinophilic cytoplasm and large, round nuclei with finely dispersed chromatin.
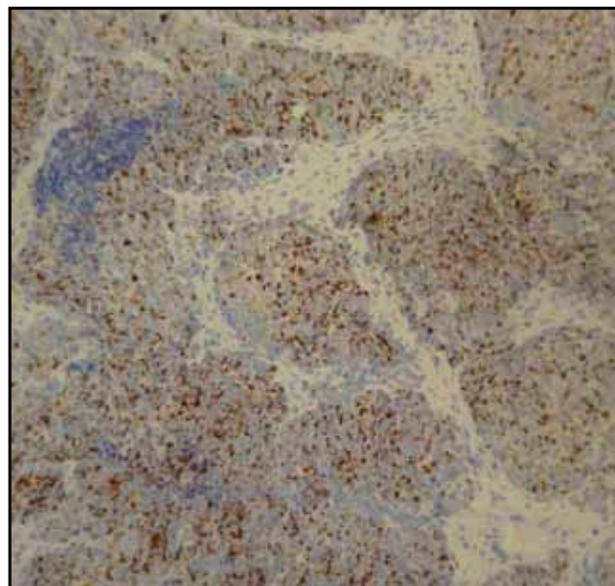
Figure 2 Immunohistochemical staining for chromogranin

staining was observed (Figure 3). There was no S-100 staining of the tumor cells and the tumor was negative for LCA.

Based on cellular architecture and immunohistochemical correlation, the diagnosis of sinonasal neuroendocrine carcinoma was favoured.

CT scan of the thorax and the upper abdomen following diagnosis was normal. The patient was referred for oncologic treatment and he never presented to our service for follow-up. However, we have found out that he received chemotherapy consisting of five cycles of carboplatin and etoposide with 90% tumor remission followed by radiotherapy; the patient received 60 Gray of external beam radiation therapy, divided in 30 fractions; residual tumor was found on the follow-up CT scan one month after treatment completion.

DISCUSSIONS

Sinonasal neuroendocrine carcinoma is a rare neoplasm, the clinical development of which is not well known, mainly due to the paucity of published literature on the topic. Clinical presentation is similar to other malignancies arising in the sinonasal tract, thus diagnosis is based on histopathological analysis[5].

Initial symptoms are nonspecific, such as nasal obstruction, rhinorrhea, facial pressure, headache, hyposmia, epistaxis, and patients are often initially treated for benign conditions, delaying diagnosis. Other presenting signs relate to an extensive lesion that involves multiple sites of the sinonasal compartment and may include facial pain, facial asymmetry, epiphora, diplopia, proptosis, altered visual acuity. Clinical series reports show that the median age of patients with SNEC is 50 to 57 years[6].

Radiological findings reveal an aggressive tissue mass that erodes and invades the adjacent bone rather than remodelling it, and can extend to nearby structures, as the orbit and cranium[1]. CT scan with intravenous contrast is the most effective early imaging study that helps characterizing the lesion, describing tumor vascularity, relevant skull base anatomy, bony destruction and the degree of invasiveness. MRI will further make a fine description of the tumor extension into the skull base, cavernous sinus and orbit, defining potential respectability more accurately[4]. Regional lymph nodes are best evaluated on CT and distant metastases should be excluded with at least a chest/upper abdomen CT.

The differential diagnosis of sinonasal neuroendocrine carcinoma comprises other sinonasal malignancies with neuroendocrine differentiation, other tumors of neuroectodermal origin and other carcinomas.

Of special interest is the differentiation from esthesioneuroblastoma and sinonasal undifferentiated car-
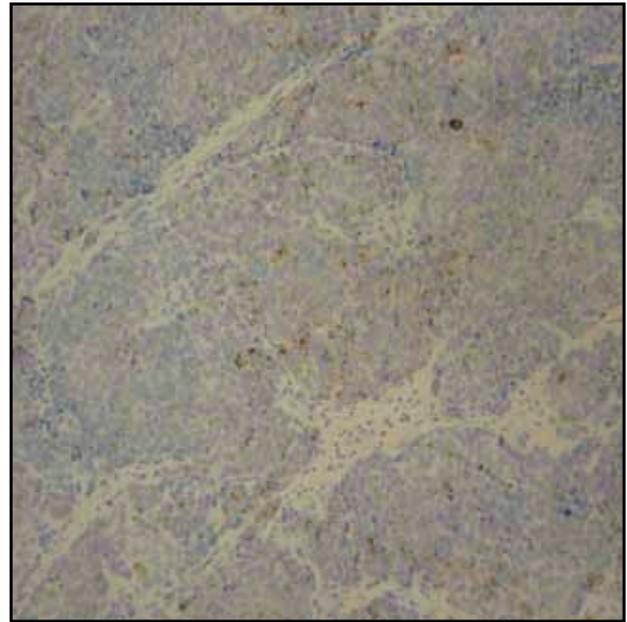
Figure 3 Perinuclear dot-like cytokeratin staining

cinoma because of the prognosis implications and different therapeutic approach. Due to their morphological and immunohistochemical similarities, SNEC is often mistaken with ENB[7]. SNEC is more cellular; it lacks the neurofibrillary background and does not display Homer-Wright rosettes. The tumor can form either solid sheets or ribbons and trabeculae. The cells are larger, with more cytoplasm, have coarse chromatin and larger nucleoli compared to ENB. Necrosis and increased mitotic figures can be seen. ENB is positive for S-100, seldom found in SNEC and, although in can be positive for cytokeratin, it has a focal disposition and it is present only in areas with Homer-Wright rosettes[8].

SNUC has questionable characteristics of neuroendocrine differentiation. SNEC is immunohistochemically distinct from SNUC. SNEC is frequently positive for chromogranin, synaptophysin, and cytokeratin expression is strong. SNUC may express evidence of neuroendocrine differentiation based on neuron specific enolase staining and, sometimes, neurosecretory granules; but, generally, synaptophysin and chromogranin staining is negative[9]. Other neuroendocrine carcinomas should also be excluded, such as: paragangliomas, which are S-100 positive, carcinoids, which are well differentiated and present low mitotic rates, and small cell carcinoma of the sinonasal tract, which presents the characteristics of its pulmonary counterpart, consisting in small-sized cells arranged in sheets, nests or cords, with moderate to scanty cytoplasm and hyperchromatic nuclei.

Although the case presented above did not manifest a strong expression of cytokeratin, it did have a strong expression of chromogranine, lacked expression of

S-100, did not present olfactory rosettes and the cells were not of small type, thus excluding the aforementioned pathologies. Based on the morphological features and immunohistochemistry, pituitary adenoma was also excluded, and so were the non-neuroendocrine lesions of the sinonasal tract, which include malignant melanoma, non-Hodgkin lymphoma, Ewing sarcoma and rhabdomyosarcoma. We note that the morphological features of the case are similar to the pulmonary large-cell carcinoma.

There is no specific recommendation regarding the management of this particular neoplasm and treatment options are extrapolated from neuroendocrine tumors of pulmonary origin. Traditionally, the treatment of sinonasal neuroendocrine tumors has been surgical resection followed by radiation for resectable tumors and chemotherapy followed by concurrent radiochemotherapy for unresectable tumors, with 5-year survival rate of 64%[10]; it has been associated with a high local recurrence rate. Fitzek et al.[11] reported good results on a series of patients treated with two initial cycles of cisplatin and etoposide. Responders underwent photon/proton radiotherapy followed by two cycles of etoposide and cisplatin. Nonresponders underwent surgical resection followed by postoperative photon/proton radiation. The reported 5-year survival rate was of 74%. When positive cervical lymph nodes are present, neck dissection is indicated and, given the retropharyngeal and parapharyngeal lymphatic drainage system, radiation of this area is indicated.

CONCLUSIONS

Sinonasal neuroendocrine carcinoma is an aggressive tumor with a high potential for local invasion, as well regional and distant metastases. Because most patients present in advanced stages, the prognosis is poor. Due to the infrequency of this pathology, overlapping features with other entities and histological heterogenicity, a delineation of this particular histological type within the group of neuroendocrine neoplasms remains to be determined. There is no recommendation regarding the treatment of the sinonasal neuroendocrine carcinoma, but the multimodal approach is favoured and generally accepted.

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