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BRIEF COMMUNICATION

Neuroendocrine carcinomas in otolaryngology: A difficult diagnosis

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KEYWORDS
Neuroendocrine tumours of the head and neck;
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Abstract Neuroendocrine carcinomas of the head and neck are infrequent. They appear as original tumours in this area, or more frequently as lymph node metastasis, while some of them are of unknown origin. We describe four cases diagnosed by pathological study of neuroendocrine carcinomas in the head and neck area since 2002. All of the cases were male, with a mean age of 59 years. In the two primary cases, the tumours were located inside the maxillary sinus and larynx; the other two were cases of cervical metastasis originating outside of the head and neck area. Three of them died in less than 18 months. We emphasise the wide distribution this kind of tumours has and the varying forms of associating; these factors make it difficult to join the symptomatology into a single group, as well as to arrive at the diagnosis and to carry out treatment.

PALABRAS CLAVE
Tumores neuroendocrinos de cabeza y cuello;
Laringe;
Senos paranasales;
Metástasis cervicales

Carcinomas neuroendocrinos en ORL: Un diagnóstico difícil

Resumen Los carcinomas neuroendocrinos de cabeza y cuello son poco frecuentes. Se presentan como foco primario en esta área, o más frecuentemente como metástasis ganglionar cervical, pudiendo, en muchos casos, formar parte de los tumores de origen desconocido.

Presentamos 4 casos diagnosticados por estudio anatomopatológico de carcinomas neuroendocrinos pobremente diferenciados desde el año 2002, en área ORL, todos ellos varones con una edad promedio de 59 años. En 2, el foco primario se localiza en el seno maxilar y en la laringe; los otros 2 como metástasis cervicales de focos fuera de área ORL. Tres fallecieron en menos de 18 meses.

Hacemos hincapié en la amplia distribución y diversas formas de agruparse, lo que hace difícil reunir en un solo conjunto la sintomatología, así como llegar al diagnóstico y efectuar su tratamiento.

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Introduction

Neuroendocrine carcinomas (NEC) are the least differentiated tumours of the diffuse neuroendocrine system (DNES). The DNES consists of cells with different embryological origins; hence the difficulty in diagnosing certain tumours that develop in this system.

In practice, there are 2 groups of tumours from DNES elements. Those of *endodermal origin*, from the anterior intestine, are the "gastroenteropancreatic" tumours. This group includes laryngotracheal tumours and NECs are of this nature. The second group encompasses those of *ectodermal origin* (neural crest), including paragangliomas, phaeochromocytomas, parathyroid adenomas, medullary carcinoma of the thyroid gland, neuroblastomas and melanomas.[1]

We have deemed it interesting to present this work, due to the complexity of their classification and the difficulty in obtaining an accurate diagnosis for well-directed treatment, which requires a multidisciplinary management, including otolaryngology (ENT) services, endocrinology, oncologists and anatomopathologists. In addition, due to their complexity, NECs are sometimes labelled as tumours of unknown origin. If they were borne in mind, the number of tumours of unknown origin would decrease significantly.

Clinical cases

We present 4 male patients diagnosed with poorly differentiated NEC, whose diagnosis was confirmed by anatomopathological examination. All the subjects were males, with an average age of 59 years. Two presented a primary focus, one in the maxillary sinus and the other in the larynx; the other 2 were expressed as cervical metastasis of foci outside the ORL area. Three of them died within less than 18 months. Table shows the characteristics of the 4 patients.

Discussion

Head and neck tissues give rise to a variety of neuroectodermal tumours, some of which present epithelial differentiation (the NEC) and some of which do not (olfactory neuroblastoma, melanoma, Ewing sarcoma).[1] In its classification of neuroendocrine tumours of the larynx from 2005, the World Health Organization described 4 types: carcinoid tumour, atypical carcinoid tumour, small cell neuroendocrine tumour and combined neuroendocrine small cell carcinoma (these are neuroendocrine small cell carcinomas with another additional carcinoma, almost always squamous or adenocarcinoma). They are very rare and only 14 cases had been described until 2004.[2]

Authors such as Mills[3] prefer to consider them as well differentiated, moderately differentiated, and poorly differentiated NEC, of small cells and large cells. This classification would avoid confusing terms such as "atypical carcinoid" and its overlap with large cell NEC. In addition, it would also allow adequate clinical and pathological correlation.

The WHO does not yet consider large cell tumours to be part of the ENT area, as it does with lung carcinomas.

Table Monitoring of the 4 patients

Patient no., gender, age, situation	Tumoral lesion	Other lesions	Immunohistochemistry	Imaging studies	Treatment
1, M, 54 Died at 18 months	Large cell NEC (mixed), of the left NF and left maxillary and ethmoid sinuses	Metastasis in lung, thalamus, hepatic and bones	Positive cells to Ch, En, Sy, CEA and partially for Cy and S-100	CT	Cx: (left maxilloethmoidectomy) and Rt+Cx (5Fu, Adriamycin, Cyclophosphamide and Platinum)
2, M, 56 Died 6 months after diagnosis	Large cell NEC of right hemilarynx	Carcinoma in right eye. Metastasis in cerebellum and bones	Positive for Cy, Sy, Ch, CEA, and En. Negative for S-100, Vimentin	CT, MRI	Cx (laryngectomy and FCLND, Rt and concomitant Cx (Carboplatin, Etoposide)
3, M, 70 Died after one year	Large cell NEC, gangliar. Pulmonary?	Sarcoidosis stage II	Positive for Ch and Sy	Thoracic-abdominal CT	Ct
4, M, 62 Alive, 3 years after diagnosis	Small cell NEC, of cervical lymph nodes. Undetermined primary T		Positive for Ch and Sy and negative for CD20	CT	Cx (panendoscopy, amygdalectomy and left FCLND), Cx

5fu indicates 5 fluorouracil; CEA, carcinoembryonic antigen; Ch, chromogranin; CT, computed tomography; Cx, chemotherapy; Cy, cytokeratin; En, enolase; FCLND, functional cervical lymph node dissection; M, male; MRI, magnetic resonance imaging; NEC, neuroendocrine carcinoma; NF, nasal fossae; Ox, surgery; Rt, radiotherapy; Sy, synaptophysin; T, tumour.

Our sample includes 4 patients: 2 with a primary tumour, one large cell tumour of the larynx and another sinonasal. The other 2 were large cell cervical metastasis from a primary with pulmonary suspicion and a small cell tumour of undetermined origin. In cases of cervical metastasis of unknown origin, it should be noted that this type of tumour may comprise up to 5%[4]

Primary NEC in ENT areas are rare, the most common being moderately differentiated in the larynx and in second place, poorly differentiated small cell tumours of the salivary glands. The poorly differentiated large cell types may include sinonasal undifferentiated carcinoma as a prototype,[3] as is the case with our patient No. 1.

They are more common in males. In our series, all 4 cases were male and aged over 50 years. Except for the well differentiated, they were closely related to tobacco; our patients were heavy smokers. Their morphology displays characteristics of both endocrine and neural cells with a common phenotype translating the expression of protein markers (neuroendocrine). From the histological standpoint, their growth pattern is usually organoid, solid, glandular (tubular-acinar), banded and may also form pseudorosettes.

One feature of this type of tumour is a very abundant vascularisation, consisting of capillaries outlining small cell islets. Poorly differentiated tumours exhibit very atypical cells, with a high nucleus to cytoplasm ratio and lacking a precise architecture[1] (Figures 1A, 1B, 1C, and 1D). They present a very high mitotic index and also, frequently, tumour necrosis.

Presentation symptoms do not differ from those of other carcinomas, and will depend on the location of the lesion. If the larynx is affected, as in Case No. 2, symptoms will include dysphonia, dysphagia and foreign body sensation. If the tumour is sinonasal (patient No. 1) it will manifest through initially banal symptoms, such as mild respiratory distress, rhinorrhea and epistaxis. If it is metastatic, the cervical mass will alert of the disease (Cases 3 and 4).

The difficulty of its diagnosis is variable. In the well differentiated with a characteristic topography, the standard histological examination is usually sufficient to establish the diagnosis. When a predominant metastasis is observed, the examination is complemented by immunodetection of the secretion product markers, to guide the investigation of the primary tumour. However, diagnosis is limited when it comes to very poorly differentiated or undifferentiated NEC, with very few neurosecretory granules. A differential diagnosis is required between undifferentiated carcinoma, malignant lymphoma and even a sarcomatous process. In this context, all clinical grounds and a thorough examination are important, along with the histopathological study (cytokeratin, anti-chromogranin A and B antibodies and anti-synaptophysin antibodies).[1,5,6] The patients listed in the table, all due to being undifferentiated, required an

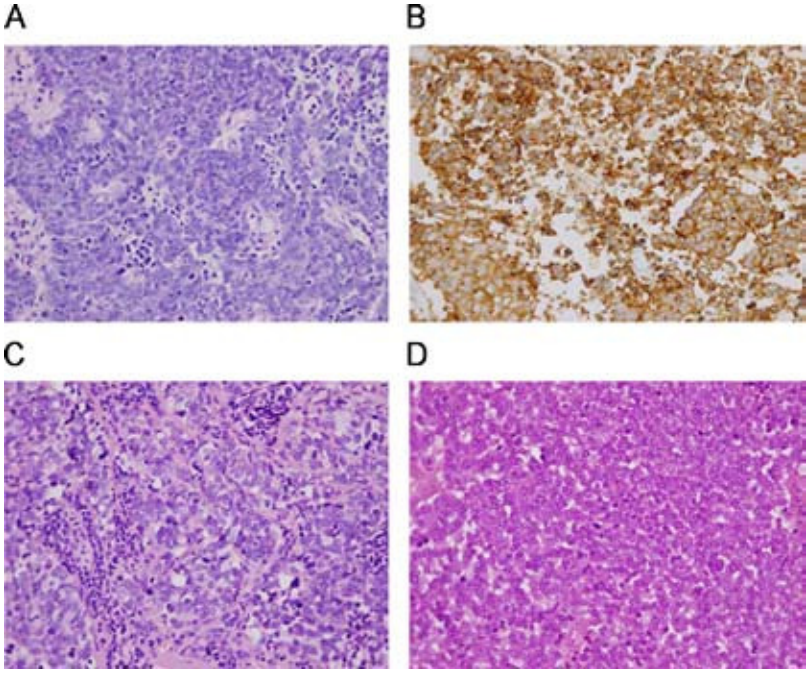

Figure 1 A) Poorly differentiated large cell sinonasal NEC. Architectural pattern in cords, nests or trabeculae, with organoid arrangement and rich intermediate fibrovascular stroma. Atypical high mitotic rate. B) Large cell laryngeal NEC. Polymorphic pattern with organoid features in solid nests, anastomosed cords or cribriform structures. Cells with marked anisokaryosis, vesicular nuclei with granular chromatin and prominent nucleoli. High mitotic index. The immunohistochemical study showed tumour cells with expression of cytokeratin AE1-AE3, EMA, synaptophysin, chromogranin, CEA, neuron-specific enolase. C) Metastasis of large cell NEC, consisting of medium sized cells, large, with irregular vesicular nuclei, with scarce nucleoli. Arranged in the form of nests. The cells were strongly positive for neuroendocrine markers (chromogranin and synaptophysin). D) Metastasis of small cell NEC: numerous small, atypical cells with hyperchromatic spheroidal nuclei, with slight anisokaryosis and mitosis and imperceptible cytoplasm. Arranged in isolated rows with nuclear facets and in small groups. Stained with hematoxylin and eosin. Magnification: x40.

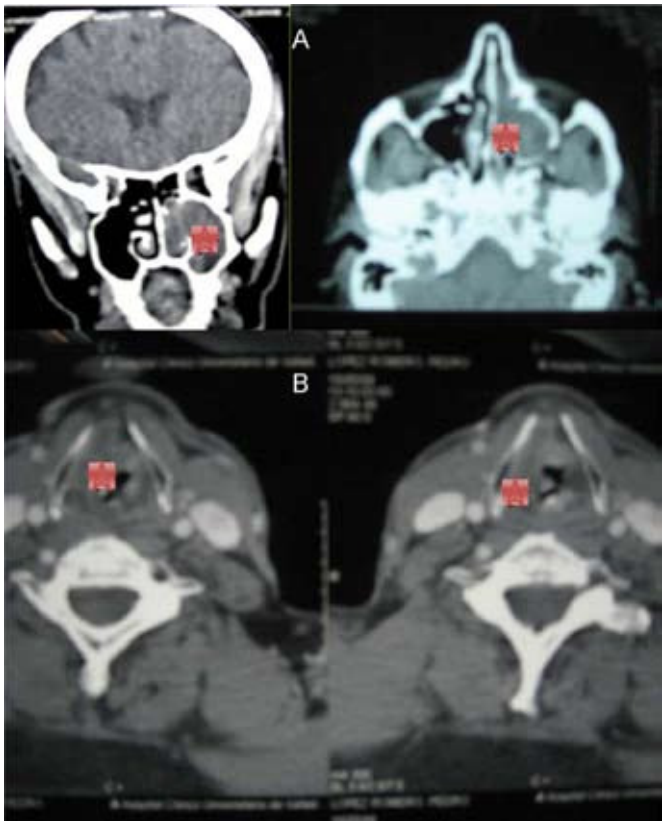

Figure 2 Imaging study of Cases 1 and 2. A) Sinonasal CT: there is mass in the left nostril, left maxillary and ethmoid sinuses from a large cell neuroendocrine carcinoma. B) Cervical CT: the stars indicate a mass in the right hemilarynx from a large cell neuroendocrine carcinoma.

immunohistochemical study as well as CT and MRI imaging to assess their extension (Figures 2A and 2B).

It is crucial for the diagnosis to be precise because the treatment and prognosis differ according to the entity involved. A differential diagnosis must be carried out with tumours of other families that appear with the same morphology, but whose treatment and prognosis differ from NEC, such as paragangliomas, thyroid medullary carcinoma metastasis, malignant melanoma and basaloid squamous cell carcinoma, among others.

With regard to tumour spread, metastases occasionally appear in well differentiated tumours, frequently in moderately differentiated and always in high-grade. Our cases were consistent with this description.

These tumours are generally treated by removal of the lesion in well differentiated and moderately differentiated cases. In the other 2 types, chemotherapy and radiotherapy are the initial treatments.[4,7,8] In our study, 3 of the 4 patients underwent surgery; 2 of them also received radiotherapy and chemotherapy. Only one was treated exclusively with chemotherapy.

The histological type of injury significantly influences the prognosis of these tumours. In the well differentiated, survival at 5 years can be of 100%, dropping to half in the moderately differentiated and to a low of 5% in the undifferentiated.[7,9] In the case of our patients, all diagnosed with poorly differentiated NEC, 3 of them died before 18 months, presenting locoregional and distant invasion. The patient with small cell NEC, whose primary tumour is yet to be determined, is currently alive.

Conflict of interest

The authors declare no conflict of interest.

References

1. Thomassin JM, Deveze A, Chrestian MA. Sistema Neuroendocrino difuso y patología cervicofacial. Encyclopédie Médico-Chirurgicale - E-20-945-A-10. 2002.
2. Ereño Zárate C. The updated WHO Head and Neck Tumours Classification (2005). Epithelial precursor lesions and tumours of the larynx, hypopharynx and trachea. Rev Esp Patol. 2007;40: 3-10.
3. Mills SE. Neruoectodermal neoplasms of the Head and Neck with Emphasis or Neuroendocrine Cacinomas. Mod Pathol. 2002;15:264-78.
4. Hainsworth JD, Greco FA. Neuroendocrine carcinoma of unknown primary site. HU http://www.utdol.com/online/content/topic.do?topicKey=misc tum/2316UH. This topic last updated: 2007 Feb 8.

5. Jumah MD, Fleiner F, Wendt S, Pavel M, Schwabe M, Göktas O. Poorly differentiated neuroendocrine carcinoma of the larynx. Diagnostic features, treatment strategy, and prognosis. HNO. 2009;57:135-41.
6. Carbone A, Gloghini A, Rinaldo A, Devaney KO, Tubbs R, Ferlito A. True identity by immunohistochemistry and molecular morphology of undifferentiated malignancies of the head and neck. HUHead Neck UH. 2009.
7. Dhingra M, Agarwal A, Kaushik S, Singh SN. Small-cell neuroendocrine tumor of larynx: a rare presentation. Indian J Pathol Microbiol. 2008;51:63-4.
8. Babin E, Rouleau V, Vedrine PO, Toussaint B, De Raucourt D, Malard O, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. J Laryngol Otol. 2006;120:289-97.
9. Ezcurra P, Albertí A, Blázquez S, Mur E, Risco J. Carcinoide atípico de aritenoides. A propósito de um caso. ORL-DIPSsoor, 31:162-4.