Case report

Neuroendocrine carcinoma arising from the septum. A very rare nasal tumour

Carcinoma neuroendocrino del setto: un rarissimo tumore nasale

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SUMMARY

The case is presented of a 73-year-old male with a history of right-sided nasal obstruction, hyponasal speech and three episodes of recurrent epistaxis. On examination, there was a tumour in the right nasal cavity. Computed tomography showed a mass in the right nasal cavity extending to the right maxillary sinus, ethmoidal cells and right sphenoid sinus. The patient underwent a functional endoscopic removal of the tumour. Biopsy revealed a small cell neuroendocrine carcinoma. This is an extremely rare tumour of the nasal cavity and sinuses. Because of the aggressive behaviour of this tumour, he was also treated with combined chemotherapy and radiation. Ten months later, he remains free of disease.

KEY WORDS: Nasal cavity • Sinuses • Malignant tumours • Small cell neuroendocrine carcinoma

RIASSUNTO

Viene presentato il caso di un uomo di 73 anni con una storia di ostruzione nasale destra persistente, rinolalia chiusa, e tre episodi di epistassi ricorrente. All'esame obiettivo, era presente una neoformazione della fossa nasale destra. La tomografia computerizzata ha evidenziato la presenza di una massa della cavità nasale destra estesa al seno mascellare, alle cellule etmoidali e al seno sferoidale omolaterali. Il paziente è stato sottoposto a rimozione della massa nasale per via endoscopica. L'esame istologico ha evidenziato un carcinoma neuroendocrino a piccole cellule, che rappresenta un tumore estremamente raro delle fosse nasali. A causa del comportamento aggressivo di tale tumore, è stato necessario eseguire un trattamento combinato radio-chemioterapico. Il paziente è libero da malattia a dieci mesi dall'esordio.

PAROLE CHIAVE: *Fosse nasali • Seni paranasali • Tumori maligni • Carcinoma neuroendocrino a piccole cellule*

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Introduction

Primary small cell neuroendocrine carcinoma (SNEC) of the nasal cavity and sinuses is an extremely rare tumour and difficult to diagnose by conventional methods of histological examination. Not many cases are reported in the literature and thus analysis of the cases is not an easy procedure. Ray Chowdhuri first described SNEC as a differentiated histological entity in the paranasal sinuses in 1965 [1].

By 2000, 154 incident cases of primary SNEC (International Statistical Classification of Diseases and Related Health Problems) with histological confirmation had been identified. A crude incidence rate of 0.73 SNEC cases per 100,000 inhabitants was estimated using the 2001 Census data for the denominator (1.19 per 100,000 among men and 0.30 per 100,000 among women).

Although these tumours exhibit morphological features similar to those of anaplastic small cell carcinomas of the lung and, at first, were thought to arise from the lung, they are now considered to be completely different entities due to their behavioural differences in relation to metastasis and local spread. Also SNEC shows similar clinical and morphological features to olfactory neuroblastoma (ONB) and must also be distinguished from this tumour.

The diagnosis of SNEC of the head and neck region is based on the recognition of the typical neuroendocrine architecture and morphology and on the immunohistochemical confirmation of neuroendocrine differentiation.

In the World Health Organization (WHO) classification of endocrine tumours, SNECs are subdivided into well-differentiated tumours, well-differentiated carcinomas, and poorly differentiated carcinomas depending on their histopathological and biological characteristics.

No specific treatment exists, at present, for neuroendocrine tumours of the head and neck region, and despite the improved histological classification they are mostly treated as conventional squamous cell carcinomas or, less often, as small cell carcinomas of the lung [2].

In this article, a rare case of SNEC, arising from the nasal septum, and its management are presented.

Case report

A 73-year-old man presented at the ENT department of Hippokration General Hospital with a long-standing history of right-sided nasal obstruction, hyponasal speech and three episodes of recurrent epistaxis.

Physical examination revealed an exophytic tumour mass of the right nasal cavity. Colour of the mucosa over the growth varied from white to pink. There were no obvious, palpative lymph nodes and no distant metastasis was found.

The computed tomography (CT) scan that was carried out showed a mass of the right nasal cavity extending to the right maxillary sinus, ethmoidal cells and right sphenoid sinus.

General examination revealed that the patient was moderately built and nourished, with normal gait and satisfactory vital signs.

From his past medical history, he had hypertension and diabetes mellitus. The patient denied smoking, drinking and exposure to radiation or environmental irritants.

Functional endoscopic sinus surgery was used in order to remove the mass. Upon surgery, a large tumour of the right nasal cavity was revealed adjacent to the posterior part of the nasal septum and medial wall of the right maxillary sinus, invading the middle nasal turbinate. The tumour was translucent and polypoid in structure (Fig. 1). During the operation, repeated biopsies were taken and were found to be positive for malignancy. Debulking of the tumour carried out in order to define the site of origin, showed that the tumour arose from the posterior-superior part of the septum. Therefore, complete excision of the mass was performed and intra-operative biopsies revealed that the margins of the excision were without signs of disease.

The final histological examination showed a small cell neuroendocrine carcinoma with poor differentiation. The tumour was extremely cellular and composed of sheets or nests of small cells. The shape and size of cells were similar and regular with small amounts of cytoplasm, round nuclei, and high mitotic rate. Vascular structures and foci of necrosis were also present.

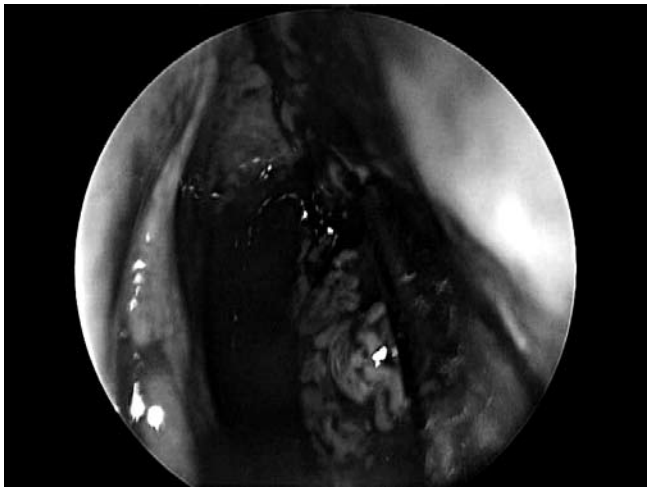

Fig. 1. Intra-operative endoscopic image of the tumour.

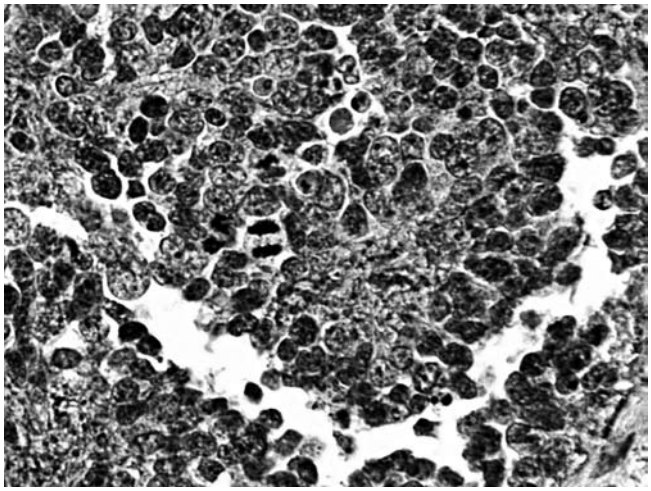

Fig. 2. Positive synaptophysin immunoreactions in neoplastic cells.

Immunophenotypic examination showed staining for synaptophysin (Fig. 2), CD56 and Ki67 (+90%) (Fig. 3), while no staining appeared for cytokeratin (CK) AE1/AE3, carcinoembryonic antigen (CEA), CK34bE12, leukocyte (LCA) or chromogranin. Immunohistochemical reaction for thyroid transcription factor-1 (TTF-1) was not necessary because of thorough examination of thyroid and lung by CT scan.

The post-operative course was uneventful. Due to the aggressive behaviour of this tumour, combined chemotherapy and radiation were also performed. Close follow-up 10 months after treatment, through endoscopic examination did not reveal any sign of local recurrence.

Discussion

Small cell carcinoma is a very rare and aggressive tumour of the sinonasal tract. Histologically, it is undistinguishable from the anaplastic small cell carcinoma of the lung. They both exhibit similar morphological features, as described by Koss et al. [3]. They are both solid tumours composed of sheets, nests and cords of small to intermediate-sized cells

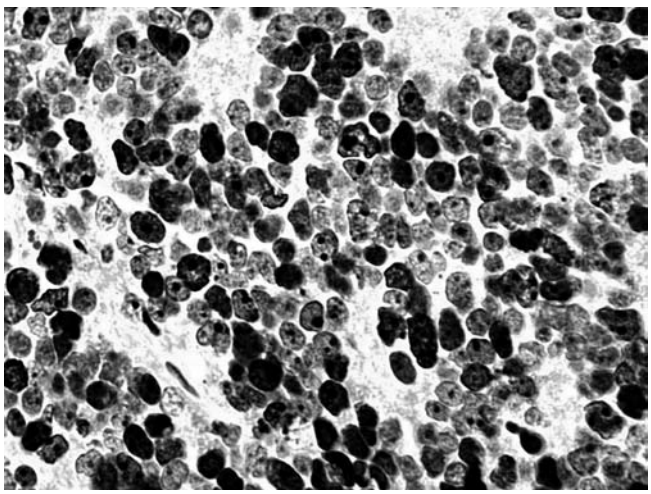

Fig. 3. Positive Ki67 immunoreaction in neoplastic cells (90%).

with high nucleo/cytoplasmic ratio, hyperchromatic nuclei with absent or occasional basophilic nucleoli. They also have a high mitotic rate with frequent abnormal mitotic figures, necrosis and haemorrhage. They are both characterized by the presence of electron-dense, membrane bound, neurosecretory granules [4]. Differential diagnosis must include other malignant tumours such as lymphoma, rhabdomyosarcoma, undifferentiated nasopharyngeal carcinoma, and undifferentiated sinonasal carcinoma.

Of great importance is to distinguish SNEC from ONB. Their relationship remains confusing and controversial. Hyams et al. [5] proposed a histological grading for ONBs based on their degree of cellular and architectural differentiation. In most cases, SNEC should be readily distinguished from low-grade ONB. Sinonasal SNEC lacks lobular architecture, fibrovascular septa, neurofibrillary stroma, and does not contain neural or olfactory rosettes. The anaplastic cells of SNEC have neglible cytoplasm, high nucleo/cytoplasmic ratio, round or oval dense hyperchromatic nuclei, numerous mitotic figures, and apoptotic cells accompanied by extensive areas of necrosis. In contrast, the cells of low-grade ONBs show moderate amounts of cytoplasm, round nuclei, low nucleo/cytoplasmic ratio, and low mitotic activity. Necrosis is uncommon in low-grade ONBs [6]. High-grade ONBs [5 6] show marked nuclear anaplasia and high mitotic activity accompanied by prominent necrosis. They also retain the lobular architecture of well-differentiated tumours, and foci of neurofibrillary stroma with rosette formation are usually identified [7]. These findings are absent in SNEC. Furthermore, prominent nucleoli are not found in SNEC.

Immunohistochemistry has not been consistently used to distinguish these two entities. SNEC lacks the S-100-positive cells seen at the periphery of the cell nests of ONB and is negative for NF [6]. SNEC usually shows staining with AE1:AE3 or Cam 5.2 antibodies, which is uncommon in ONB [6 7].

So far, no study appears to have been presented specifically investigating the immunohistochemical features of these tumours. Strong staining with synaptophysin and CD56 nerve cell adhesion molecule has been reported and weak staining with chromogranin A and CAM 5.2/AE-1 as appears also in our case [8]. Perez-Ordonez et al. showed strong staining for CAM 5.2 or AE1:AE3 in a series of 6 patients. Expression of neuroendocrine markers, such as NSE, synaptophysin, and chromogranin, although positive in all cases, was variable and may be weak with individual markers, particularly synaptophysin [9]. This pattern of staining is similar to that found in pulmonary small cell carcinoma.

Clinical manifestations and behaviour of small cell neuroendocrine carcinoma do not differ from other tumours of the sinonasal tract. It usually presents with epistaxis, nasal obstruction, followed by ophthalmic signs (exophthalmos, visual acuity trouble and limitation of eye mobility) due to orbital involvement. Less frequently, other signs suggesting loco-regional invasion have been reported, such as local pain and anosmia. Cervical node metastasis has also been described [10].

Radiographically, the tumour always involves the nasal cavity and multiple paranasal sinuses [11]. In our case, the mass of the right nasal cavity extended to the right maxillary sinus, ethmoidal cells and right sphenoid sinus. CT scan can help to diagnose the malignant nature of the tumour, as it can reveal the presence of an osteolytic lesion. Magnetic resonance imaging (MRI) with T1, T2 using i.v. gadolinium improves differentiation between inflammatory reaction, tumour and liquid retention; MRI also identifies the anatomical relationship between the tumour and the meninges.

Little is known about the management of these tumours. Different therapeutic approaches have been used over time. In the 1980s, surgery followed by radiotherapy was preferred by the Authors of the largest study [10] and has also been recommended more recently [12]. In the late 1990s, the combination of chemotherapy and radiotherapy, with or without surgery was shown to have promising results, for neuroblastoma and SNECs of the nasal and paranasal cavities. A retrospective study by E. Babin et al. [13] suggests the use of the same protocol that was proposed in the 35th Congress of the French Cervico-facial Carginological Society (November 2003) and is presented in Figure 4.

Although it has no significant effect on tumour growth, biotherapy with somatostatin analogues and/or interferon-α is recommended both for well-differentiated and functioning tumours. On the other hand, chemotherapy, usually with cisplatin and etoposide is effective in the treatment of tumours with poor differentiation grade and high pro-

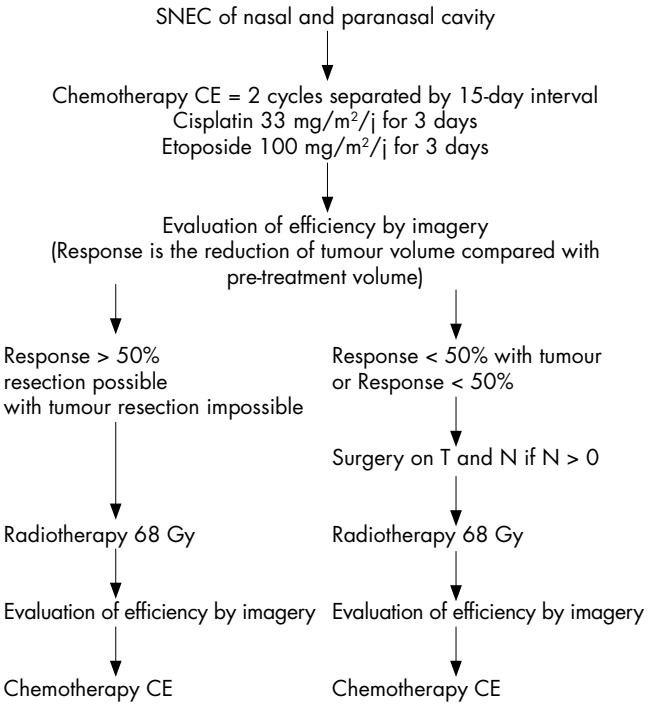

Fig. 4. Protocol of the French Cervico-facial Carcinological Society.

liferation rate. Currently, the most used therapeutic options are: surgery, radiotherapy and chemotherapy as we performed in our case, endoscopic removal of the tumour with margins free of disease followed by adjuvant radiotherapy and chemotherapy.

Novel therapies, new pharmacological formulations and more selective somatostatin analogues are now under clinical investigation for the treatment of neuroendocrine tumours [14].

Extra-pulmonary small cell carcinoma is usually a fatal disease with a 13% 5-year survival rate [15]. In the same retrospective study of 20 patients [13], recurrences and metastasis have been reported to occur after three years in 70% of the patients and 4 out of 5 patients in the combined experience of Koss et al. [3] and Weiss et al. [16] died of disease after a follow-up ranging from 8 months to 2 years. 80% of patients suffering from relapses or metastasis within the first two years. The median survival time was between two and three years. Common metastatic locations are brain, lungs, bones and skin. Four out of 6 patients, in the above-mentioned series of Perez-Ordonez et al. [9] had recurrent disease or died after a mean follow-up of 37 months**.** In a study carried out by the Mayo Clinic [15], the median overall survival of 14 patients with primary head and neck tumours was only 14.5 months. Unfavourable prognostic factors, such as invasion of the lamina cribosa, have been discussed [10]. The ectopic hormone syndrome is a predictor of bad prognosis and increased mortality of pulmonary SNEC patients because of the higher risk of cerebral metastasis. The endocrine syndrome also seems to negatively affect the prognosis in cases of head and neck SNEC [17]. Other factors, such as size of the tumour and number of mitoses, show no correlation with recurrence, metastasis or survival [10]. Because of the small number of cases in the literature, no conclusions or therapeutic recommendations can be made. However, there is the need for a multidisciplinary treatment approach combining surgery, radiotherapy and chemotherapy.

In conclusion, sinonasal small cell neuroendocrine carcinoma is a very rare neoplasm with an aggressive clinical behaviour and poor prognosis. It exhibits similar morphological and immunohistochemical features to those of anaplastic small cell carcinoma of the lung. It must be distinguished from olfactory neuroblastoma. The use of current diagnostic ancillary techniques such as, electron microscopy and immunohistochemistry can be helpful in studying the morphological and biological characteristics of the tumour. There are no treatment protocols. However, a combined therapy is advantageous.

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