Primary neuroendocrine carcinomas (NEC) of the sinonasal cavities are exceedingly uncommon and difficult to diagnose by conventional histologic examination. NEC are small cell neoplasms that show positive immunoreaction to neuroendocrine markers and lack of olfactory maturation. The English-language literature consists of small series and isolated case reports, many of which are poorly documented, therefore retrospective analysis of published cases is difficult. In addition, a critical review of these reports indicates that some of the lesions described exhibited clinical or pathological features consistent with other diagnosis, and in particular with olfactory neuroblastoma (ON). In this article, we describe a single case of NEC of the sinonasal cavities that clinically presented as a tumor of the nasopharynx.

CASE REPORT

A 48-year-old white female presented to the ENT clinic at Virgen Macarena University Hospital with a long-standing history of hyponasal speech, pharyngeal paresthesias, and right-sided nasal obstruction. The patient denied smoking and exposure to radiation or environmental irritants. Physical examination revealed an exophytic tumor mass of the nasopharynx protruding anteriorly into the right nasal fossae. A CT and MRI scan showed a well-defined and homogenous large tumor of the entire nasopharynx that extended anteriorly to the right maxillary and ethmoidal sinuses, and posteriorly to the sphenoid sinus with infiltration of the clivus (Fig 1).

The patient underwent rhinoscopy and biopsy on 3 different occasions in order to obtain a sufficient specimen. Histologic examination found that the tumor was extremely cellular and composed of sheets or nests of small cells with high mitotic rate and extensive necrosis. The tumor cells showed positive immunoreaction to cytokeratin, neuron specific enolase (NSE), synaptophysin and chromogranin, and no immunostaining for protein S-100 and neurofibrilar protein (NFP). On electron microscopy, the tumor cells showed cytoplasmic processes, numerous dense core granules, and few microtubules. Based on these findings, the patient’s definitive diagnosis was of locally advanced NEC.

After discussing treatment options with the patient and the Medical Oncology and Radiation Oncology Services, to try to control this unresectable tumor, combined therapy was planned. The patient underwent local radiation therapy completing a total of 59.4 Gy fractionated into 33 sessions, and 4 cycles of chemotherapy (cisplatin 100 mg/m² + etoposide 50 mg/m²) with an intercycle interval of 2 weeks. Follow-up showed poor response to treatment with progression of disease; the patient died within 4 months after completion of therapy.

DISCUSSION

NEC is a distinctive neoplasm with an aggressive clinical behavior and similar immunohistochemical features to those of anaplastic small cell carcinoma of the lung. The tumors of the sinonasal cavities are uncommon and consequently some published reports group together various histologic types, such as NEC, ON, and undifferentiated carcinoma and melanoma without making a clear distinction between some of them. Thus, lesions within the morphological spectrum of ON have been classified as neuroendocrine carcinomas. Furthermore ON as well as NEC have been included under the vague denomination of sinonasal undifferentiated carcinoma. However, a short series (6 cases) of true NEC has been recently published; the authors pointed out that the histologic differential diagnosis with ON, of a more indolent clinical course, should be essentially established.

In the present case, the morphologic study with ancillary methods reproduces the profile of the small cell NEC of any location: hyperchromatic small cells, high mitotic rate, extensive necrosis, immunohistochemical (NSE, synaptophysin, and chromogranin) and ultrastructural neuroendocrine markers expression, and negative immunoreaction for S-100 and neurofibrilar...
protein. On the other hand, the key pathologic feature of ON can be easily recognized with light microscopy, even in high grade cases and is based on the presence of a fibrillary background, corresponding to large and numerous neural cell processes; less commonly Flexner or Homer Wright rosettes may be found, and ganglion cells are seen rarely but, when present, are also diagnostic. With electron microscopy, it is usually difficult to distinguish both tumors, but the presence of neurofilaments, in addition to abundant neurotubules, dense core granules, and cytoplasmic processes, may help in the diagnosis of ON. Immunohistochemistry has not been consistently used in separating these tumor entities. However, the tumor cells of ON are positive for neurofibrillar protein, and the S-100 positive cells seen probably represent Schwann-like sustentacular cells. About 30% of ON have patchy areas labeling for cytokeratin; in contrast, NEC shows a strong and diffuse staining.

Patients with NEC usually have sinonasal symptoms of relatively short duration, attributable to nasal, orbital, or cranial nerve involvement. Radiographically, the tumor always involves the nasal cavity and multiple paranasal sinuses. This case is a good example of a clinical presentation simulating a nasopharyngeal undifferentiated carcinoma, but with radiographic features of extensive invasion that were compatible with a more aggressive neoplasm. Three different biopsy specimens were necessary in order to establish a definitive diagnosis of NEC, which may be extremely difficult or impossible to distinguish from other sinonasal neoplasms when only small, mechanically distorted, biopsy specimens are available. So, the differential diagnosis of the NEC with the undifferentiated nasopharyngeal carcinoma required immunohistochemical findings that showed positive reaction to the neuroendocrine markers in the first one and negative in the second.

The best therapeutic results in locally advanced NEC have been obtained using a small cell lung cancer treatment regimen, consisting of a combination of chemotherapy (cisplatin + etoposide) and radiation therapy. All patients included in study by Perez-Ordoñez et al. died of the disease with about a 20% 5-year survival rate. The most common cause of death is failure to control local disease. In the present case, the tumor was locally advanced and invaded adjacent structures (skull base), making itself therefore unresectable according to accepted surgical criteria. In spite of treatment based on successful reported experience, the clinical course was unfavorable; this indicates that at this juncture there is not enough clinical experience with advanced stage disease to follow specific treatment guidelines and confirms the intrinsic aggressiveness of this fortunately uncommon tumor.

REFERENCES