Caso clínico

Esthesioneuroblastoma: a brief review of literature in the context of a case report

Estesioneuroblastoma: uma breve revisão da literatura no contexto de um caso clínico

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Abstract

Esthesioneuroblastoma is an uncommon neoplasia that arises from the olfactory neuroepithelium and corresponds to 3-6% of all intranasal malignant tumors. The symptoms are nonspecific and common to other pathologies of the nasal cavity. There are no guidelines regarding its treatment. The few available studies observed good outcomes with a multimodal approach.

We report the case of a young woman diagnosed with esthesioneuroblastoma, stage C of modified Kadish. The patient presented a partial response after 4 cycles of chemotherapy (cisplatin and etoposide). Then, she was proposed for radical chemoradiotherapy (66-70 Gy of radiotherapy and 3 cycles of cisplatin), with no evidence of disease at the end of treatment, remaining disease-free 1.5 years after.

The multimodal approach has good outcomes in the treatment of esthesioneuroblastoma, as observed in the reported clinical case, with complete response to combined treatment of chemotherapy and radiotherapy.

Keywords: *Esthesioneuroblastoma; Nose neoplasms; Radiotherapy; Chemotherapy.*

Resumo

O estesioneuroblastoma é uma neoplasia incomum com origem no neuroepitélio olfativo e corresponde a 3-6% de todos os tumores intranasais malignos. Os sintomas são inespecíficos e comuns a outras patologias da cavidade nasal. Não existem orientações relativamente ao seu tratamento. Os poucos estudos existentes observaram bons resultados com uma abordagem multimodal.

Reportamos o caso de uma jovem mulher diagnosticada com estesioneuroblastoma, estadio C modificado de Kadish. A paciente apresentou resposta parcial após 4 ciclos de quimioterapia (cisplatina e etoposídeo). Em seguida, foi proposta para quimioradioterapia (66-70 Gy de radioterapia e 3 ciclos de cisplatina), sem evidência de doença no final do tratamento, permanecendo livre de doença 1,5 anos depois.

A abordagem multimodal tem bons resultados no tratamento do estesioneuroblastoma, como observado no caso clínico reportado, com resposta completa ao tratamento combinado de quimioterapia e radioterapia.

Palavras-chave: Estesioneuroblastoma; Neoplasia nasal; Radioterapia; Quimioterapia.

Introduction

Esthesioneuroblastoma (ENB), also designed olfactory neuroblastoma, is a rare neuroepithelial tumor that arises from the olfactory neuroepithelium and corresponds to 3 to 6% of all intranasal malignancies.[1,2] ENB has a bimodal distribution with peaks in the second and sixth decades of life. The distribution of gender and ethnicity is roughly equal, and there is no apparent family predisposition. Also, there are no risk factors well recognized for the disease.[2] The symptoms of ENB are nonspecific and common to other pathologies of nasal cavity. The tumor can extend locally to paranasal sinuses, orbital region and anterior skull base. Around 10 to 30% of patients demonstrate cervical metastases and less than 8% present with other distant metastases.[3] The disease recurs in about 30% of patients, with locoregional recurrence in 15 to 18%.[4] ENB has no specific radiological findings, requiring biopsy of the lesion to confirm the diagnosis by histoimmunopathology. There are no generally accepted treatment recommendations, although the few available studies refer a multimodal approach, namely surgery, radiotherapy and/or chemotherapy.[5,6]

In this article we report the clinical case of a young woman with ENB from diagnosis to treatment and follow-up. It was also performed a brief review of the literature.

Clinical Case

Female patient, 21 years old, previously healthy, presented with nasal deformity associated with hyposmia, nasal obstruction and right eye ptosis. Computed tomography (CT) and magnetic resonance imaging (MRI) **(Fig. 1)** demonstrated a massive lesion in the nasal sinuses, involving the maxillary and right sphenoid sinuses, ethmoid labyrinth and ipsilateral pterygopalatine fossa, with destruction of nasal septum and walls. It was also observed right intra-orbital expression and extra-axial intracranial invasion. Positron emission tomography (PET ^{18}F-FDG) did not show regional or distant metastasis. The biopsy was compatible with ENB. The histology showed a nest of small cells within the stroma with abundant vascularization, scarce cytoplasm and rounded nuclei, with no nucleoli. The immunocytochemistry was positive for synaptophysin, neuron-specific enolase (NSE), CD56 and PS100; poor expression of pancitokeratin MNF116; and, negative for CD45, CD99, FLI1, p40, p16 and desmin.

The patient was treated with primary chemotherapy, namely 4 cycles of cisplatin (80 mg/m^2 D1) and etoposide (100 mg/m^2, D1 to D3), administered every 3 weeks. The CT after treatment showed partial response. Then, the patient was proposed for radical chemoradiotherapy. The primary tumor lesion area (pre-chemotherapy) was irradiated with 66 Gy and the residual tumor area (post-chemotherapy), with an anatomical expansion of 3 mm, with 70 Gy. The treatment was performed in 35 fractions of 2 Gy/day, 5 days a week. It was used a linear accelerator, with photons of 6 MV, resorting to VMAT technique and verification of the position with an Exactract® system. Concomitantly, the patient performed 3 cycles of cisplatin (100 mg/m^2) every 21 days. The main adverse events were mucositis, cervical dermatitis and neuropathy, G2; nausea and emesis, G3, according to CTCAE 5.0; and chronic kidney disease (stage 3, KDIGO) secondary to cisplatin nephrotoxicity. The patient remains under surveillance, with no evidence of clinical or imaging tumor recurrence 18 months after finishing the treatment.

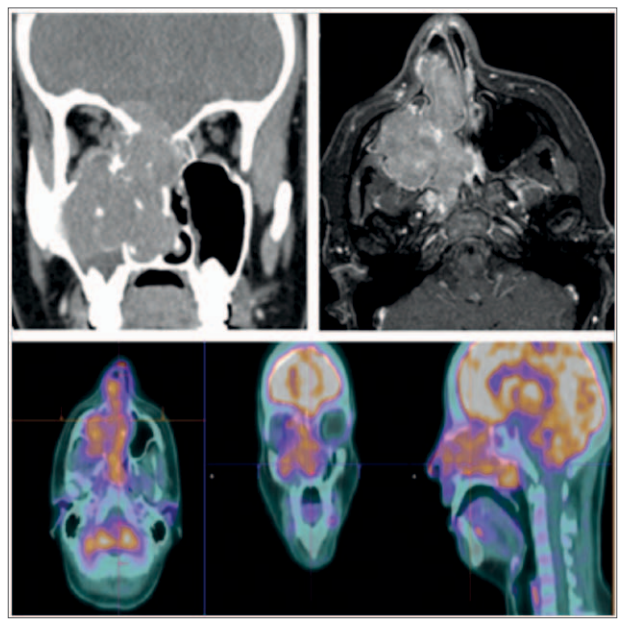

Figure 1. Tumor invading the paranasal sinuses and adjacent structures (sinuses of face, extracerebral and right orbit) objectified in CT (left), MRI (right) and PET (below).

Discussion

ENB is a rare intranasal malignant tumor, with origin in the olfactory neuroepithelium.[1,2] The symptoms are nonspecific and related to the location of invasion. The common clinical manifestations are epistaxis, unilateral nasal obstruction, hyposmia, rhinorrhea, ptosis, diplopia, visual blurring, proptosis, ocular pain, headache or focal neurological deficits.[2]

CT and MRI are normally used for the diagnosis, staging and surveillance of ENB. In CT, the tumor is presented as a homogeneous density mass, equal or denser than the surrounding soft tissues. MRI shows a tumor hypointense on T1-weighted images and iso to hyperintense on T2-weighted images. CT shows bone involvement and destruction in more detail, while MRI allows a more detailed assessment of tumor extension to adjacent structures and intracranial lesions.[7] Although ENB can be detected, delineated and its characteristics suspected by CT and MRI, it is required a biopsy of the lesion

to confirm the diagnosis. The cells are small, with a round nucleus and scarce cytoplasm, surrounded by neurofibrillar matter, with a pseudorosette or rosette arrangement in up to 50% of the samples.[8] There is no specific immunohistochemical pattern for ENB, but it has a typical profile of neuronal and neuroendocrine neoplasm which helps in the differentiation from other tumors with similar histology. The tumor is positive for PS100, CD56, chromogranin, synaptophysin, NSE and neurofilament protein; does not express cytokeratin, desmin, CD45 or CD998. In the present case, the histology and immunocytochemistry confirmed the diagnosis of ENB.

Kadish and coauthors[9] were the first to propose a system to stage the disease which continues to be widely used. In stage A, the tumor is limited to the nasal cavity; in stage B, the tumor extends into the paranasal sinuses; and, in stage C, the tumor invades beyond the nasal cavity and paranasal sinuses. Afterwards, it was added a stage D, which includes patients with distant metastasis.[10] The international TNM system[11] and the adaptation by Dulguerov *et al.*[12] are also frequently used in tumor staging. The presented case was classified as stage C for modified Kadish staging, T4N0M0 by TNM and T3N0M0 according to Dulguerov.

There are few studies regarding ENB management and most of the existing publications comprise retrospective studies of institutional experiences with small series and non-randomized samples. Therefore, it has been difficult to develop guidelines for treatment. The published data showed good outcomes with a multimodal approach, which included surgery, pre- or postoperative radiotherapy and/or (neo)adjuvant chemotherapy.[5,6,12] A meta-analysis of 26 studies with 390 patients reported an increase in survival with the combined treatment of surgery and radiotherapy (65% at 5-years) compared to only one modality of treatment (48% and 37% for surgery and radiotherapy, respectively).[12] Radiotherapy has been used alone or combined with surgery and/or chemotherapy. In the literature, preoperative doses of 45 Gy and postoperative doses of 50 to 60 Gy, according to surgical margins, were described. Doses of 65 to 70 Gy have been recommended for radical radiotherapy in patients with inoperable tumors.[2,12,13] Chemotherapy has been used mainly in the treatment of unresectable tumors, advanced stages or recurrences. The combination of cisplatin and etoposide is one of the most widely used chemotherapy regimens in the treatment of high-grade neuroendocrine carcinomas. In this sense, a few centers have used this combination in the treatment of patients with ENB,[14-16] with promising results, particularly in combination with radiotherapy.[13,16] Other agents have been used, namely doxorubicin, cyclophosphamide, vincristine and 5-fluorouracil.[2,15] In a Japanese study with 12 patients, with ENB, treated with chemotherapy and radiotherapy (with or without stem cell transplantation), they found partial response in 9 patients after 2 cycles of chemotherapy and complete response in 6 of these patients after radiotherapy.[15] Patil *et al*[14] observed effectiveness in the treatment of sinonasal tumors with cisplatin and etoposide, including ENB, with a global response to neoadjuvant chemotherapy of 80%. Bhattacharyya and colleagues16 reported remission of ENB in 8 of 9 patients treated with neoadjuvant and adjuvant chemotherapy (cisplatin and etoposide) combined with radiotherapy.

In our case, the patient presented with an unresectable tumor and was proposed for chemotherapy, presenting a partial response after 4 cycles of cisplatine and etoposide. Then, the patient completed the treatment with chemoradiotherapy, which consisted of 3 cycles of cisplatin simultaneously with radiotherapy (66-70 Gy), with no evidence of disease after treatment.

ENB recurs in about 30% of patients, with locoregional recurrence in 15 to 18%.[4] Tumor recurrence can occur in the first months after treatment, but a significant percentage metastasizes 5 to 10 years after diagnosis, so a close and long-term follow-up of these patients is recommended. Our patient remains with no evidence of clinical or imaging tumor recurrence one and half year after finishing the treatment.

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