CASE REPORT

Esthesioneuroblastoma treated with external radiotherapy. Case report

Un caso di estesioneuroblastoma trattato con radioterapia esterna

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SUMMARY

Esthesioneuroblastoma is a rare tumour arising from the olfactory epithelium of the nasal vault which frequently invades the cranial base and orbit. Esthesioneuroblastoma has a bimodal age distribution between 11 and 20 years and between 51 and 60 years. Esthesioneuroblastoma accounts for approximately 1-5% of intranasal cancers. The case is reported of a 79-year-old female patient with a Kadish stage C tumour with a one-year history of headache, nasal obstruction, anosmia, rhinorrhoea and epistaxis. Aim of this study is to analyse the natural history, treatment and prognosis of this tumour, based on a review of the literature.

KEY WORDS: Nose • Malignant tumours • Esthesioneuroblastoma • Radiotherapy alone

RIASSUNTO

L'estesioneuroblatoma è un raro tumore che origina dall'epitelio olfattorio delle cavità nasali, frequentemente invade la base cranica e l'orbita. L'estesioneuroblatoma ha una distribuzione bimodale dell'età tra gli 11 ed i 20 anni e tra i 51 ed i 60 anni; è collocato approssimativamente tra l'1 e il 5% dei tumori intranasali. In questo articolo viene riportato un caso di una donna di 79 anni con un tumore stadio C di Kadish con anamnesi positiva di cefalea, ostruzione nasale, anosmia, rinorrea ed epistassi. Lo scopo di questo studio è analizzare la storia naturale, il trattamento radioterapico e la prognosi di questi tumori sulla base dei dati presenti in letteratura.

PAROLE CHIAVE: *Naso • Tumori maligni • Estesioneuroblastoma • Radioterapia esclusiva*

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Introduction

Esthesioneuroblastoma (ENB) or olfactory neuroblastoma is a rare neuroepithelial tumour arising from the olfactory epithelium in the cribriform area or nasal cavity [1]. First described in 1924 by Berger and Luc [2], it has a histological pattern similar to that of sympathetic ganglia, retina, and adrenal medulla [2] and only recently [3] has it become recognized as a distinct pathological entity probably as a result of immunohistochemistry and by means of electron microscopy techniques. Both have contributed to differentiating ENB from similar undifferentiated nasal cavity tumours [3]. No uniform criteria for the correct diagnosis of ENB exist. A tumour was considered to be an ENB if it had the characteristic morphology on haematoxylin-eosin (H&E)-stained slides, i.e., lobular architecture with a neurofibrillary background and tumour cells forming pseudorosettes and presenting small uniform nuclei, as well as a demonstrated neuro-endocrine immunophenotype. ENB accounts for 1 to 5% of malignant neoplasms of the nasal cavity. Fewer than 945 cases of ENB have been reported in the world literature [4]. Unlike most other neuroectodermal tumours, occurring in childhood, ENB, has a bimodal age distribution between 11-20 years and 51-60 years [5].

Aim of this report is to describe the case of a patient with ENB and compare findings with data appearing in the literature.

Case

A 79-year-old female with a one-year history of headache, nasal obstruction, anosmia, rhinorrhoea, and epistaxis was referred to our Radiotherapy Department, in 2003, from the Othorinolaryngology Department with pathological diagnosis of ENB. According to the pathological service, at another hospital, physical examination revealed a left nasal mass that, following endonasal endoscopy with biopsy, was found to be an ENB. Computed tomography (CT) demonstrated that the tumour filled the entire left nasal cavity, left maxillary sinus, invasion to nasal septum, ethmoid sinuses, and hypo-pneumatization frontal sinus. This case of ENB was classified, according to the Kadish system, as stage C. Due to invasion of the adjacent structures patient's age and presence of heart disorders, craniofacial resection was con-

sidered unadvisable. For the diagnosis we have considered the characteristic morphology on Gomori, PAS, and some special technique such as: CK = ----; S100 = ++++; CD34 = +---; GFAP = +---; NSE = +++-. The linear accelerator used, in this case, was VARIAN CLINAC 2100 equipped with a multi-leaf collimator, 6 MV X-ray beams. The patient received a total dose of 70 Gy in 35 fractions of 2 Gy a day for 5 fractions/week. Total treatment period lasted 7 weeks. The course of treatment was never interrupted. A three-field technique was used.

The acute and chronic tolerance of treatment was good with the patient presenting only symptoms of a dry mouth for 2-3 months.

During follow-up – 6 months after radiotherapy – CT scan showed a considerable reduction of the neoformation tissue and cervical lateral left lymph node < 1 cm near the submandibular gland. Biopsy was collected and a metastatic lymph node was revealed.

Discussion

In 1966, Skolnik et al. [6] reviewed 97 cases reported in the literature from 1924 (date of the first description of ENB) to 1966. For the 50 patients, followed for 5 or more years, he found an advantage, in 5-year survival, for patients treated with surgery compared with those undergoing radiotherapy (64 *vs*. 38%).

Kadish et al. [7], in a review of 17 patients, suggested limited surgery, followed by radiation therapy, in stage A ENB. For lesions limited to the nasal cavity and paranasal sinuses (stage B), Kadish suggested pre-operative radiation therapy and limited surgery, and for stage C ENB, high-dose radiation therapy of 60-65 Gy for 7 weeks followed by surgical resection of residual disease, if operable. Of the 17 patients in this series, 13 (76%) were alive without disease. The local control rates were 7/7 patients with stage A ENB (100%), 4/5 patients (80%) with stage B ENB, and 2/5 patients (49%) with stage C ENB.

The staging system, based on tumour extension, presented by Kadish et al. [7] in 1976, and applied to 563 cases, has been widely accepted. This system includes three stages:

Table I. Analysis of literature: treatment and survival status of esthesioneuroblastoma.

References	N. cases	Treatment	5-year survival %
Skolnik 1966 [6]	97	S, RT	S = 64 RT = 38
Kadish 1976 [7]	17	S, RT, S + RT	A = 100 B = 80 C = 40 S = 100 RT = 25 S + RT = 80
Chao 2001 [14]	25	S, RT, CHT	66
Gruber 2002 [16]	28	S, RT	70
Theilgaard 2003 [17]	40	S, RT, CHT	A = 75 B = 67 C = 32

S = Surgery; RT = Radiotherapy; CHT = Chemotherapy; A, B, C = Kadish Stage

Table II. Kadish system.

A	Disease confined to nasal cavity
B	Disease confined to nasal cavity and one or more paranasal sinuses
C	Disease extending beyond nasal cavity or paranasal sinuses; including involvement of orbit, base of skull or intra-cranial cavity, cervical lymph nodes, or distant metastatic sites

A) disease confined to the nasal cavity; B) disease confined to the nasal cavity and one or more paranasal sinuses; C) disease extending beyond the nasal cavity or paranasal sinuses; it includes involvement of the orbit, base of skull or intracranial cavity, cervical lymph nodes, or distant metastatic sites [6] (Table II). Recently, Morita et al. [8] suggested a modified classification by inserting stage D tumours, presenting metastases in cervical lymph nodes or at a distance. Two other staging methods, the Biller method [9] and the Dulguerov method [10], have also been described and used. The tumour may spread to the opposite ethmoid bone superiorly to the frontal sinus and anterior cranial fossa, posteriorly to the sphenoid sinus, nasopharynx, and base of skull; laterally to the orbits, forward to the frontonasal angle, or inferiorly to the nasal cavity and antrum. Lymphatic spread may be to the subdigastric, posterior cervical, submaxillary, or preauricular nodes, as well as to the nodes of Rouviere. The exact incidence of distant metastases is uncertain; it has been quoted to be as high as 50%, but this rate is influenced by the use of chemotherapy in high-risk patients. The symptoms are related to sites and invasion of the tumour. The most common clinical symptoms are epistaxis and nasal blockage. Patients may also have local pain or headache, visual disturbances, rhinorrhoea, tearing, proptosis, or swelling in the cheek [7 11].

The treatment of ENB, reported in the literature, includes primary surgical treatment [11 12], primary radiation therapy [11 13] or combined radiation and surgery. Recently, some Authors suggested the use of planned pre-operative radiation followed by surgery. Patients with locally advanced disease or high-grade tumours should receive aggressive treatment with combined modalities, such as surgery (S), radiation therapy (RT) and chemotherapy (CHT).

Chao et al. [14] reported findings on 25 patients with ENB, age ranging from 16 to 73 years (median, 37 years). The tumours were Kadish stage A in 3 patients, stage B in 13, stage C in 8, and modified D in one (cervical nodal metastasis). A total of 17 patients were treated with surgery and RT, 6 with RT alone, and 2 with surgery only, while 8 patients received neo-adjuvant chemotherapy. Median follow-up was 8 years (range, 2-24 years). The 5-year actuarial overall survival, disease-free survival, and local tumour control rates were 66.3%, 56.3%, and 73%, respectively.

Gruber et al. [16] reported on 28 patients with histologically confirmed ENB who underwent RT, with a median dose of 60 Gy (range 38-73). According to the Kadish classification, 4 patients had stage A, 8 stage B, and 16 stage C tumours. Radical resection was performed in 13 cases, in 9 before RT and in 4 after RT because of stable or progressive disease. After a mean follow-up of 68 months, 54% of patients were free from tumour progression. The 5- and 10-year local progression-free survival rates were 81% and 51%, respectively, and the disease-free survival rates were

70% and 25%, respectively. Four of the ten deaths were intercurrent, resulting in a cause-specific survival of 77% and 69% at 5 and 10 years, respectively. Radical resection offered significantly better local progression-free survival and disease-free survival ($p < 0.02$).
Theilgaard et al. [17] reported on a Danish demographic study comprising 40 patients, registered between 1978 and 2000. The 40 cases represent an incidence rate of 0.4 cases/million inhabitants per year. The following therapeutic guidelines have been suggested: Kadish stage A patients, surgical tumour resection and RT; Kadish stage B, surgical tumour resection and RT; Kadish stage C, surgical tumour resection via a craniofacial resection and RT combined with CHT. The disease-free survival, at 5 years, was 75% for Kadish stage A patients, 67% for stage B, and 32% for stage C.

Conclusions

On the basis of data reported in the literature, it is clearly evident that patient survival is increased thanks to a combination of different treatment approaches (surgery, RT, CHT) and use of new technologies. Surgery, RT and CHT increase patients' life expectation but a prompt and early diagnosis is always a determinant prerequisite in the prognosis of the disease.
The Kadish system is useful in the diagnosis of this disease being the optimal technique for stage A but not very effective in the identification of stages C and D.

Three-dimensional conformal RT (CRT 3D) permits a dose increase to the tumour thus sparing the surrounding and critical areas. After undergoing RT, our patient did not complain of epistaxis or headache. Three months after the end of RT the mass was reduced by approximately 50%. The patients did not suffer from nasal obstruction. During follow-up – 6 months after RT-CT showed a mass reduction of about 80%, modest thickening of the left maxillary sinus and, unfortunately, a thickened latero-cervical lymph node, found to be metastatic.
Magnetic resonance imaging (MRI) was performed which confirmed the considerable reduction in the tumour so that the surgeon could re-assess it for possible resection and the oncologist for possible CHT. 14 months after RT, the patient died on account of evolution of the systemic disease.
EBN is a very uncommon malignant tumour arising from the olfactory epithelium, that has a long natural history characterized by frequent local or regional recurrence. Surgery combined with adjuvant RT, is probably the most suitable treatment. The role of systemic CHT in the treatment of distant metastasis should be further evaluated [18]. RT alone can control local tumour and the correlated symptoms.

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