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CASE REPORT

Successful treatment of metastatic esthesioneuroblastoma

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ABSTRACT

This case report describes a patient with a metastasised olfactorial esthesioneuroblastoma Hyams grade 4 who has been treated with debulking surgery and radiotherapy. After relapse in lymph node, lung and brain, he received additional irradiation and six cycles of carboplatin, vincristine and cyclophosphamide intravenously every three weeks. The patient has now been disease free for 7.8 years. Our data suggest that metastatic esthesioneuroblastoma is sensitive to platinum-based chemotherapy. This patient illustrates that this tumour is very sensitive to platinum-based chemotherapy and that durable complete response can be achieved, even in a metastatic ENB.

INTRODUCTION

Olfactorial neuroblastoma is a rare tumour, arising from the olfactory epithelium. It comprises about 3% of all nasal tumours and usually occurs in the third and fourth decade of life. The incidence in males and females seems to be similar. There are over 300 case reports of patients with localised disease to be found in the literature. The tumour frequently presents with unilateral nasal obstruction and epistaxis. Less frequent are proptosis and retrobulbar pain. At radiology, a unilateral intranasal soft tissue mass, opacity of the paranasal sinuses and destruction of the nasoantral and orbital walls, or extension to the skull base are usually observed. Pathological interpretation can be difficult due to the poor differentiation of tumour cells. Although a number of histochemical tumour markers are available such as neurofilament, neurospecific enolase, synaptophysine or S100, no specific marker has emerged. There are two kinds of classification systems:

1. The Hyams grading system, which is a pathologically based system with emphasis on the lobular architecture, mitotic activity and presence of necrosis.[1]
2. The Kadish staging system which, in the absence of a TNM classification, describes the local extent of the tumour and the possible presence of metastases necrosis.[1]

Metastases can be found in the cervical nodes, meninges, bone, parotid gland, lungs, spinal cord and prostate. In patients with haemotogenous metastases, several cytostatic agents, single and in combination, have been used. In this case report, we describe a patient who has been treated with combination chemotherapy because of distal metastases.

CASE REPORT

A 28-year-old man, presenting with a short history of proptosis, blurred vision of the right eye and diplopia, was found to have an esthesioneuroblastoma (ENB) of the lamina cribrosa in February 1992. Besides the presence of necrosis, histology showed a high mitotic index and the tumour was classified histologically as Hyams grade 4. Clinically it proved to be a Kadish stage C, due to involvement of the lamina cribrosa, as seen on the CT scan.[2]

Debulking surgery, comprising a right lateral rhinotomy and excentration of the right orbita, was followed by radiotherapy from March to May 1992: 50 Gy to a bi-directional field

with an additional booster dose of 16 Gy to the involved lamina cribrosa to a total of 66 Gy, in 33 fractions over 49 days, including the right orbita and right ethmoid in the target field. In May 1992, a CT scan of head and neck revealed a previously unknown enlargement of a right subdigastric lymph node and a bilateral supraomohyoidal cervical node dissection was performed. Histology showed one lymph node metastasis with extranodular tumour extension, and simultaneously headache pointed to a 2 cm diameter subdural metastasis laterally of the frontal lobe without a clear relationship to the primary site, as revealed by MRI. A chest X-ray in May 1992, before the supraomohyoidal cervical node dissection, showed no pathology. In July 1992, however, at the discovery of the subdural frontal metastasis, two lung metastases adjacent to the right hilus were found. From July to August 1992 radiotherapy (30 Gy in 10 fractions) was administered to the subdural frontal metastasis. After the radiation therapy, chemotherapy was initiated (carboplatin 300 mg/m^2, vincristine 1 mg/m^2, cyclophosphamide 750 mg/m^2 per cycle, COC) administrated intravenously every three weeks for six cycles. This resulted in a complete response of the lung metastases. In May 1995, he presented with pain between the scapulae. A bone scan and X-ray showed metastases in the corpus of the thoracic vertebrae Th4, Th5 and Th8. In June 1995 30 Gy radiation was given in ten fractions directed to Th3 - Th9. In November 1996 he experienced a seizure, but there were no new lesions found on the CT of the brain.[3]

Thereafter he received phenytoin 2 x 100 mg orally daily and no further seizures occurred. At this moment, the patient is 134 months post-diagnosis and is currently free of disease.

DISCUSSION

Primary treatment of an esthesioneuroblastoma consists of radical craniofacial resection, frequently combined with elective radiotherapy. This combination is based on whether or not the tumour is confined to the nasal cavity (Kadish stage A) or beyond (Kadish stage B and C). Standard radiotherapy consists of 50 Gy given as 25 fractions of 2 Gy.

A booster dose between 10 and 20 Gy can be given depending on the extent of invasion. Our patient relapsed within two months after radiotherapy. Based on a study of 13 patients this indicates a poor prognosis.[1] If invasion of the primary tumour site includes involvement of the cribriform plate, base of the skull, orbit or intracranial cavity (Kadish stage C) or if metastases to cervical lymph nodes or distant sites occur, chemotherapy has been added to surgery and radiotherapy. Active agents are: vincristine, cyclophosphamide, cisplatin, doxorubicin, etoposide and methotrexate.[4-7] The sequence of therapy modalities still needs to be clarified. Although two papers suggest a survival benefit with neo-adjuvant treatment, the patient population in both studies is too small to be conclusive.[4,7] A review of thirteen patients with metastatic ENB describes an objective response after cisplatin and etoposide in eight patients (61.5%).[8] These studies are based on the morphological, immunophenotypic and ultrastructural resemblance of ENB with the primitive peripheral neuroectodermal tumour-Ewing lineage (PNET). However, the typical absence of trisomy 8 and translocation t(11;22)(q24;q12) exclude ENB as a member of PNET.[9] The use of the Packer chemotherapy protocol, based on its efficacy in medulloblastoma as an example of another primitive small round cell tumour, is not supported by these specific chromosomal findings.[10,11] Eventually we preferred a combination of vincristine, carboplatin and cyclophosphamide because of less toxicity in the outpatient setting.

Recently, a 36-year-old woman presented with prolonged headache, loss of smell and vomiting and ENB was diagnosed in August 2002. She had an emergency bifrontal craniotomy and incomplete debulking surgery, followed by cranial irradiation. In April 2003 she became dyspnoeic and bedridden because she had developed large lymph node metastases in the right neck and multiple lung metastases (*figure 1*), but no liver or bone metastases. She was treated with the same chemotherapy regimen as the first patient (similar dosages of COC for six cycles). Even after three cycles of COC, the chest X-ray showed a complete remission (*figures 2* and *3*) and the masses in the neck had disappeared. She is now in follow-up.

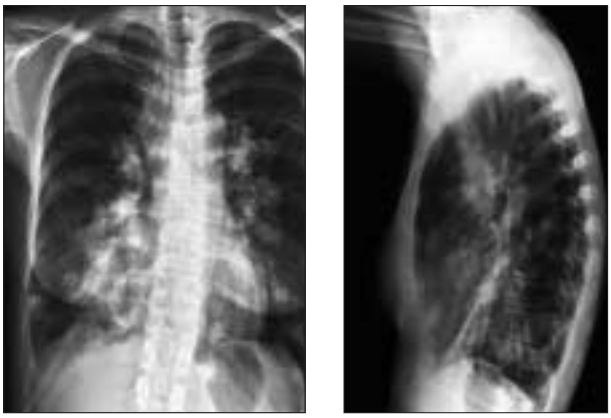

Figure 1
Lung metastases at diagnosis

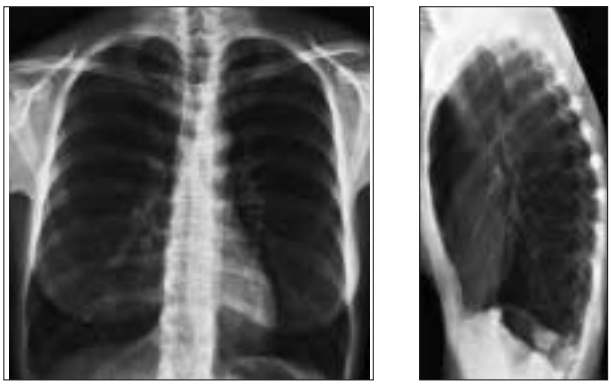

Figure 2
Complete response of lung metastases after three cycles of COC

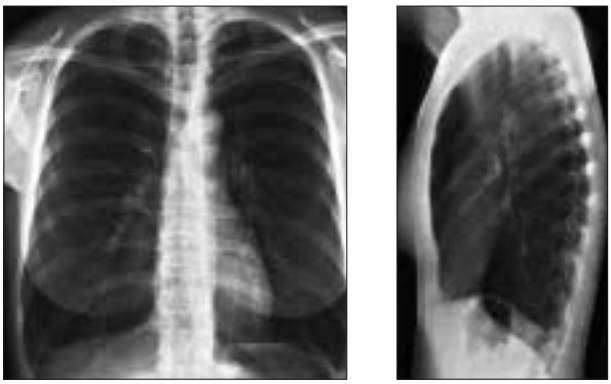

Figure 3
Complete response of lung metastases after discontinuation treatment

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