Cerebral Primitive Neuro-Ectodermal Tumour Following Treatment of a Unilateral Retinoblastoma

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Summary

Cerebral primitive neuro-ectodermal tumour (PNET) occurring as a second primary malignancy in childhood is exceedingly rare. We present a 7-year-old boy who developed a proven supratentorial PNET five years after enucleation and radio-/chemotherapy for a sporadic, unilateral retinoblastoma with optic nerve invasion. The association with this malignant eye disease as well as the effect of irradiation and multi-agent chemotherapy on second tumour induction are evaluated.

Keywords: Retinoblastoma; primitive neuro-ectodermal tumour; radio-/chemotherapy; second primary malignancy.

Introduction

Retinoblastoma is the most common intra-ocular malignancy of childhood, with 90% of cases diagnosed within the first three years of life. The tumour occurs in two distinct forms, hereditary and non-hereditary. Approximately 30%-40% of patients with retinoblastoma, including all bilateral and familial cases, have an autosomal dominant inheritance pattern. The responsible germline mutation affects the RB 1 tumour suppressor gene which is located at the long arm of chromosome 13q14 [20]. The majority of cases, all of whom have a unilateral manifestation, belong to the sporadic, non-hereditary form and result from two somatic mutations in a single retinal cell [19]. Hereditary retinoblastoma has been linked to an increased incidence of second primary malignancies in long-term survivors, the most frequent being osteosarcoma [1, 11–13, 28, 29, 35].

The occurrence of a cerebral primitive neuro-ectodermal tumour (PNET) more than four years after treatment of a sporadic unilateral retinoblastoma in a 27-month-old boy in this case report presents, to the best of our knowledge, for the first time this embryonal tumour as a second primary malignancy in a non-hereditary retinoblastoma patient. The possible link to both the prior treatment modality and a genetic predisposition are discussed.

Case Report

A 7-year-old boy was diagnosed with a cerebral PNET after he had been treated for a unilateral retinoblastoma 5 years previously. In January 1991, at age 27 months, a retinoblastoma of the right eye with vitreous seeding and optic nerve invasion was diagnosed. Ophthalmoscopic examination and magnetic resonance imaging (MRI) showed no tumour involvement of the contralateral eye or the intracranial space. Bone scintigraphy, cerebrospinal fluid cytology and bone marrow aspiration were performed, without evidence of tumour metastasis. There was no family history of eye tumours, the paternal grandmother had died from a brain tumour in old age.

Enucleation of the involved eye was performed and revealed intravitreal tumour extension as well as infiltration into the prelamellar optic nerve near the resectional margin (Fig. 1). Since patients with tumour invasion at the site of optic nerve transection are at increased risk to develop retinoblastoma metastasis, a secondary optic nerve-stump resection was performed. According to the stage-related treatment recommendations of a previously introduced clinico-pathological classification system [17] and in accordance with the Austrian Neuroblastoma Protocol (NB-A-89), the child received systemic multi-agent chemotherapy with two alternating blocks over a period of 9 months (dacarbazine, doxorubicin, mechlorethamine and vincristine versus mechlorethamine, VM-26, dacarbazine, vincristine and cyclophosphamide). In addition, whole brain irradiation with a total dose of 27.6 Gy was delivered via right and left lateral parallel-opposed fields with an average dose per fraction of 1.5 Gy. Concomitantly, intrathecal methotrexate, prednisolone and cytosine arabinoside were administered. The whole treatment was well tolerated and completed in November...
1991, and the young boy did not present any neurologic deficit or impairment of mental function.

Regular MRI follow-up examinations disclosed several non-enhancing high-intensity lesions on T2-weighted images in the temporo-occipital deep white matter and periventricular region over both hemispheres as early as January 1992, i.e., eight months after radiotherapy/intrathecal methotrexate, and two months after the completion of systemic chemotherapy. In addition to these high-intensity alterations, subsequent examinations showed several small, non-enhancing cystic lesions in the subcortical and deep white matter over both hemispheres, resembling lacunar defects (Fig. 2). Six months before the PNET was diagnosed, MRI demonstrated, in addition to the unaltered pre-existing foci, a new, high-intensity lesion on T2-weighted images with partial gadolinium enhancement on T1-weighted images involving the right frontoparietal subcortical white matter. The differing MR characteristics were pointing to an acute focal radiation necrosis.

In January 1996, the now 7-year-old boy began to complain of increased fatigue and headaches, accompanied by nausea. Following a transient weakness with hypaesthesia of his left arm, he was admitted to the hospital. An emergency MRI revealed multiple heterogeneous, partially contrast-enhancing lesions in the right fronto-parietal region, with areas of necrosis, calcification, focal haemorrhage and cyst formation. There was marked perifocal oedema with midline shift (Fig. 3).

Following the initiation of anti-oedematous treatment, open