CASE REPORT

Recurrent Pineoblastoma Responsive to Chemotherapy

P Kulshrestha, P Aggrawal, S Kumar, S Arora, K Singh, AK Bahadur, AK Rathi, PK Mohanta
Department of Radiotherapy, Maulana Azad Medical College, New Delhi, India

ABSTRACT
Pineoblastomas are malignant embryonal tumours that are classified as suprasellar primitive neuro-ectodermal tumours. Incidence of pineoblastoma is approximately 0.1% to 0.3% of histologically verified primary malignant brain tumours. This case report concerns a 19-year-old male with a mass lesion in an area posterior to third ventricle, which was diagnosed as pineoblastoma. He achieved complete response after post-operative radiotherapy and chemotherapy. Disease recurred after 8 months in the form of drop metastasis at the level of C2-C4 in the spinal cord. He achieved complete response again following salvage chemotherapy. This report is submitted in view of rarity of this disease and its good response to chemotherapy after recurrence.

Key Words: Antineoplastic combined chemotherapy protocols, Cisplatin, Neoplasm metastasis, Pinealoma

INTRODUCTION
The pineal body is a small reddish grey body lying in the depression between the superior colliculi attached to the roof of the third ventricle in the brain. This gland is host to a spectrum of neoplasms. Most of the tumours arising from the pineal body are malignant germ cell tumours. Pineal parenchymal cell neoplasms are rare.1 From 1993 to 2000, the World Health Organization (WHO) classification of pineal parenchymal tumours recognized pineocytoma, pineoblastoma and mixed pineocytoma/pineoblastoma, and more recently pineal parenchyma tumours, with intermediate differentiation.2 Pineocytomas and pineoblastomas are now recognized as a spectrum of the same disease.3 Pineocytomas are well defined and complete excision alone usually yields long-term control. In contrast, pineoblastomas are extremely rare in adults and literature regarding their natural history is scarce. Pineocytomas are composed of differentiated cells resembling those of normal pineal parenchyma, and lie at the best differentiated end of the spectrum or continuum, followed by a mixed tumour/intermediate differentiation group in the middle, and pineoblastoma situated at the malignant end. The duration of response after recurrence in pineoblastoma is short and deterioration is fast.

We present this case report because of the rarity of: (i) recurrent pineoblastoma and (ii) a good response to chemotherapy in this neoplasm.

CASE REPORT
A 19-year-old male patient came to our hospital in April 2003 with chief complaints of headache for one and a half years and difficulty in walking for two and a half months. On examination, his Karnofsky performance status was 70, and there was decreased power in the lower limbs, diplopia, right upper gaze palsy, nystagmus, and sixth nerve palsy. Magnetic resonance imaging (MRI) showed a solid cystic calcified mass lesion posterior to the third ventricle with obstructive hydrocephalus (Figure 1). Cerebrospinal fluid cytology was negative.

Figure 1. Pineoblastoma at diagnosis.
for malignant cells. The patient was referred to the neurosurgery department of G.B. Pant Hospital (one of our associated hospitals) for consideration of surgical intervention. He underwent right ventriculo-peritoneal shunt followed by decompressive surgery. Histopathology revealed a highly cellular round cell tumour presented in patternless sheets. Tumour cells were round to oval in shape, possessing scanty cytoplasm and vesicular nuclei with inconspicuous nucleoli. The background was finely fibrillar, with scattered tumour rosettes. There were many thin capsules interspersed in between tumour cells. Focal areas of necrosis were also seen. The tumour cells were negative for the immunohistochemical stain of glial fibrillary acidic protein. The final pathological diagnosis was pineoblastoma. The postoperative computed tomography (CT) scan still showed a large residual mass in the original tumour bed.

The patient underwent cranio-spinal irradiation — phase 1 (whole brain and spine) 36 Gy in 20 fractions in 4 weeks and phase 2 (primary tumour) 20 Gy in 10 fractions in 2 weeks from 5 May to 16 June, 2003 along with supportive treatment. No complication of radiotherapy was encountered. There was good response to radiotherapy; the only problem remaining after completion of treatment was diplopia. Follow-up CT scan revealed marked regression of the tumour. Subsequently, the patient was started on combination chemotherapy from 14 July 2003 onwards, 4 weeks after completion of radiotherapy. The chemotherapy consisted of intravenous cisplatin 30 mg/m² on days 1 to 3, intravenous vincristine 1.4 mg/m² on days 1, 8, 15 every 4 weeks and oral 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine, CCNU) 100 mg/m² on day 1 every 6 weeks. He had received a total of 4 cycles of chemotherapy when it was completed on 17 November 2003. He showed complete response clinically and radiologically, but was subsequently lost to follow-up.

The patient again presented on 7 July 2004 with main complaints of decreased power in the left upper limb and weakness in the right hemi-body. MRI of the spine showed multiple drop lesions at C2-C4 level with compression of spinal cord (Figure 2). To relieve the compression, C2 laminectomy was done in G.B. Pant Hospital. During the operation, a 3 x 2 x 2 cm intradural and extramedullary mass compressing the spinal cord at C2/C3 level was observed. Histopathology of the mass revealed pineoblastoma. He was started on ICE chemotherapy from 2 August 2004, consisting of intravenous ifosfamide 1 g/m² with mesna 200 mg/m² on days 1 to 3, intravenous cisplatin 30 mg /m² days 1 to 3 and intravenous etoposide 100 mg/m² on days 1 to 3. All drugs were repeated every 4 weeks with antiemetic support and steroids. Toxicities encountered included WHO grade 3 nausea/vomiting and grade 2 myelosuppression (haemoglobin 8 g/100 mL, total leukocyte count 2200 x 10^6 /L and absolute neutrophil count 1000 x 10^6 /L). The patient was given prophylactic granulocyte colony-stimulating factor starting on day 5 from the second cycle onwards. All symptoms had improved by the end of the second cycle.

Up until 20 December 2004, a total of 6 cycles of the chemotherapy were given to which the patient responded extremely well. The only remaining symptom was weakness in the right half of the body (power of grade 4 over 5). MRI of the spine after 8 weeks of completion of chemotherapy (in January 2005) showed no residual disease (Figure 3). He was scheduled for regular follow-up and was last seen in May 2005, 4 months from the end of the salvage chemotherapy, when there was no sign or symptom of recurrence.

**DISCUSSION**

Tumours of the pineal region pose an interesting challenge to clinicians due to their rarity. Pineoblastomas are malignant embryonic tumours that arise from the pineal parenchyma and are classified under the group of supratentorial primitive neuroectodermal tumours. Malignant pineoblastoma is very rare in adults. Few
clinical data are available in the literature regarding adults with malignant pineoblastoma. Stage, histological characteristics and response to therapy are independent risk factors in adults with pineal parenchyma tumours. In the last 5 years, we have seen just 1 patient with pineoblastoma.

Radiation therapy has been the standard therapy after surgical excision for more than 50 years. Barlas et al published a study describing non-surgical management of pineoblastoma, comprising stereotactic biopsy, cerebrospinal fluid diversion, and fractionated radiotherapy. The results of 6 patients treated over a period of 6 years were presented. Recurrence was treated with interstitial irradiation with iodine-125 seeds. The results of this study suggested that radiotherapy was an acceptable initial treatment alternative to radical surgical resection for pineoblastoma.

The use of systemic chemotherapy in pineal tumour is worthy of a short historical description. In 1977, De Tribolet and Barrelet described what they believed to be the first report of the successful use of chemotherapy (doxorubicin, vincristine, bleomycin) for an uncharacterized pineal tumour in a 27-year-old man relapsing after radiotherapy. They described a favourable response. In the last decade, several groups reported the efficacy of systemic platinum-based chemotherapy for recurrent central nervous system tumours of neuroectodermal lineage in young people. Walker and Allen reported the favourable chemo-responsiveness of pinealoblastoma to platinum-based chemotherapy.

Gururangan et al used high-dose chemotherapy regimens of cyclophosphamide plus melphalan or busulfan plus melphalan, followed by autologous stem cell rescue in children and adults with newly diagnosed pineoblastoma. Twelve patients were enrolled and were initially treated with surgery and induction chemotherapy. All but 2 patients underwent radiotherapy. These authors concluded that the use of high-dose chemotherapy in addition to radiotherapy could be an effective treatment for patients with newly diagnosed pineoblastoma. Two Japanese publications, which included patients with pineoblastoma and pineocytoma, have also reported good results with chemotherapy.

On the basis of these encouraging reports of successful outcomes in patients with recurrent pineoblastoma treated by standard chemotherapy, we decided to use the regimen of ifosfamide, cisplatin and etoposide to salvage the spinal recurrence in the current report. There was significant clinical and radiological response to chemotherapy in our patient, leading to symptom relief for at least a few months with modest toxicities that were fairly predictable and successfully managed with supportive care. Longer period of follow-up is required to assess the durability of response and hence the value of salvage chemotherapy for pineoblastoma recurrence.

To conclude, pineoblastomas are rare central nervous system tumours with less well-defined management guidelines. Review of the available literature suggests that the use of combination chemotherapy in the treatment of both primary tumour and recurrences can produce encouraging results. However, studies of more patients are needed in order to optimally define the choice, dose and administration of chemotherapeutic agents.

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