Pineal malignant neoplasm in association with hereditary retinoblastoma

CLARE STANNARD,¹ B K KNIGHT,² AND R SEALY¹

From the Department of ¹Radiotherapy and ²Pathology, Groote Schuur Hospital and University of Cape Town, South Africa

SUMMARY A patient with unilateral hereditary retinoblastoma who was successfully treated at the age of 7 weeks developed a tumour in the pineal region two and a half years later. The initial response to radiation treatment of the latter lesion was not maintained. Subsequent necropsy findings are described. Clinically and pathologically this case represents an example of the recently described trilateral retinoblastoma. The response to treatment after early recognition was disappointing.

Several reports have described the occurrence of second malignancies in patients treated for bilateral retinoblastoma.¹⁻¹² One report³ included three patients with intracranial malignancies, of which one was clinically a pinealoma. In 1977, Jakobiec *et al.*¹³ described two neuroblastic intracranial tumours in patients with retinoblastoma, one of which was a pineal tumour. More recently the association of a pineal tumour with bilateral retinoblastoma has been described and the concept of trilateral retinoblastoma suggested.¹⁴⁻¹⁸

The following case report illustrates the occurrence of a pineal neoplasm in a patient with hereditary unilateral retinoblastoma.

Case report

The patient was a boy whose mother and sister had both been treated for bilateral retinoblastoma. The pregnancy and delivery were normal. The eyes were examined under anaesthetic (EUA) at the age of 7 weeks because of the strong family history of retinoblastoma. A white fluffy lesion measuring 10.5×9 mm was seen in the posterior pole of the left eye. It was situated over the macula and was close to but did not encroach on the optic disc. There were no other lesions of the left eye and there were no tumours in the right eye. There were no other

physical abnormalities. A diagnosis of retinoblastoma was made.

The patient was treated with dibromodulcitol 3.5 mg/kg body weight and procarbazine 75 mg/m²; both drugs were given daily for 33 days. EUA after 11 days showed that the tumour had regressed from the optic disc. After a further 10 days radiation treatment was started with 250kV x-rays, 3.5 mm copper half value layer, and a tumour dose of 3095 cGy given. This treatment was given in 17 fractions over a period of 23 days through planned fields to the posterior pole of the left eye. The time dose fraction factor (TDF) was 60 allowing for a relative biological effect of 1.175 compared with cobalt rays.

Five weeks after completion of radiotherapy EUA showed further regression and calcification of the tumour. It measured 7.5×6 mm, and the medial edge was 3 mm lateral to the optic disc. Chemotherapy was resumed in the same dosages as previously and was given three times a week for a further three months.

Subsequent EUAs revealed that the tumour in the left eye remained static, and no tumour was ever detected in the right eye.

At the age of 2 years and 8 months the child developed headaches, episodes of vomiting, and became irritable and lethargic. On examination there was meningism but no other neurological sign. EUA showed that the fundi were unchanged. Computerised tomographic (CT) scan confirmed the presence of a calcified area in the left posterior fundus lateral to the optic disc (Fig. 1). It also showed a 15×22 mm enhancing lesion in the region of the pineal gland

Correspondence to Dr Clare Stannard, Radiotherapy Department, Groote Schuur Hospital, Observatory, 7925 Cape Town, Republic of South Africa.

Fig. 1 CT scan showing calcified tumour in the posterior fundus of the left eye.

(Fig. 2). There was mild dilatation of the lateral ventricles but no shift of the midline structures. Cytological examination of the cerebrospinal fluid (CSF) showed small malignant cells with pyknotic nuclei (Fig. 3). No tissue was taken for histological examination.

The patient was treated with dexamethasone

Fig. 2 CT scan showing an enhancing lesion in the region of the pineal gland and mild ventricular dilatation.

Fig. 3 Malignant cells in the cerebrospinal fluid showing moulded, small, dark pleomorphic nuclei and rosette formation. (Papanicolaou stain, $\times 400$).

1.5 mg six hourly initially, and this dose was gradually reduced over the following three weeks. The cranio-spinal axis was irradiated with cobalt-60. The head received 4000 cGy in daily fractions of 120 cGy followed by a further 500 cGy to the pineal area. The spinal cord received 3800–4100 cGy also in daily fractions of 120 cGy. The radiotherapy was protracted over a period of three months because of myelosuppression and intercurrent infections.

A CT scan performed seven weeks after the start of the irradiation showed reduction in the size of the pineal lesion to 10×10 mm and resolution of the hydrocephalus. Cytological examination of the CSF revealed many undifferentiated cells, most of which were degenerate.

The patient remained well for one month after the completion of irradiation, when the headaches, vomiting, and lethargy recurred. A further CT scan showed moderate dilatation of the ventricles, enlargement of the pineal lesion to 24×14 mm, and a second 20×20 mm lesion in the region of the right caudate nucleus. The CSF contained numerous anaplastic tumour cells. Bone marrow biopsy was normal, and there was no evidence of other metastases. The patient was not given any further active treatment and died two months later.

POST-MORTEM FINDINGS

The post-mortem interval was approximately six hours. The body weighed 10.5 kg and showed alopecia. The scalp and skull were otherwise unremarkable. The central nervous system (brain and spinal cord) and the posterior half of each eye together with attached optic nerves were fixed for six weeks in 10% formol saline prior to examination.

The external surface of the brain and spinal cord showed extensive superficial spread of tumour (Fig. 4a). Deposits of tumour were found on the surface of both optic nerves. A large haemorrhagic mass of tumour was present over the cribriform plate. It measured approximately 3 cm in diameter and involved the adjacent cerebral cortex on the inferior aspect of the frontal lobes. The optic chiasm was covered by a thick cake of tumour which extended into the third ventricle. Further deposits of tumour covered many of the cranial nerve roots. The neoplasm gave rise to a malignant meningitis involving much of the inferior aspect of the mid-brain, hind-brain and cerebellar hemispheres. Obstruction of the foramina of Luschka and Magendie was seen.

Similar subarachnoid spread of tumour gave rise to

widespread involvement of the spinal cord and peripheral nerve roots. This process extended from the cervical region to the cauda equina. In the cervical and lumbar region, tumour was seen to invade the adjacent spinal cord.

The ventricular system was dilated owing to obstruction of the outlets of the fourth ventricle by tumour. Numerous subependymal deposits of tumour were present in the walls of the third ventricle. The pineal gland was largely destroyed by a mass of tumour measuring approximately 6 cm in diameter which protruded into the third ventricle and extended into the lateral walls of the thalamus and cerebral peduncles (Fig. 4b).

Histological examination of the tumour deposits showed a similar appearance in all lesions sectioned. The features were those of a poorly differentiated neuroectodermal tumour. The cells were poorly preserved. They had small dark basophilic nuclei and scant eosinophilic cytoplasm. Ill defined rosettes of tumour cells were seen. Perivascular growth of malignant cells was noted and much of the tumour was necrotic. Tumour was present within residual pineal tissue and possibly arose from this site.

Fig. 4 A: The inferior surface of the brain showing a large haemorrhagic mass of tumour in the region of the olfactory nerves. Diffuse spread of tumour over the surface of cranial nerves and basal meninges was present. B: The coronal section of brain showing large tumour (arrow) in the region of the pineal gland which extended into the cerebral peduncles. Note the dilatation of the ventricular system. C: The small calcified retinoblastoma found at necropsy in the left retina (arrow).

A small focus of involuted calcified retinoblastoma was present in the lateral aspect of the left retina (Fig. 4c), but no residual viable tumour was present in the left eye. Although there was spread of tumour between the dura and the perineureum of the left optic nerve, the neoplasm was not seen to invade the lamina cribrosa. Tumour was not found in the right eye, but similar spread was present along the right optic nerve as far anteriorly as the lamina cribrosa.

Other post-mortem findings included a horseshoe kidney and bronchopneumonia, which was the immediate cause of death.

Discussion

In 1977 'the occurrence of independent brain tumours in two patients with retinoblastoma' was reported.¹³ The lesions were both neuroblastic: one was sited in the pineal organ, the other in a retrochiasmal position. Subsequently an association has been reported between bilateral retinoblastoma and secondary primary putative retinoblastomas of the pineal.¹⁴ These workers proposed the concept of trilateral retinoblastoma and suggested that retinoblastoma may arise in vestigial photoreceptors in the pineal. This thesis has been reiterated subsequently.^{15 16} The entity is considered to be clinicopathologically distinct from the more common case of retinoblastoma with a second primary sarcoma.¹⁻¹²

In lower vertebrates the pineal organ is photoreceptor,¹⁹ comprises cells very similar to the rods and cones, and is derived from a similar neuroepithelial cell line.²⁰ The mammalian pineal organ has lost its direct photoreceptor function but retains its sensitivity to photic stimuli through the inferior accessory optic tract mediated via the superior cervical autonomic ganglion.²⁰ A similar situation is thought to pertain in humans.^{21 22} While the occurrence of residual photoreceptor cells in the normal human pineal organ has not been documented,²³⁻³¹ pinealoblastomas have been reported to show occasional features usually associated with retinoblastoma.³² In this context the review³³ emphasising the similar appearance of primitive neuroepithelial tumours arising from different sites is of importance.

The common embryological origin of retinoblasts and pinealoblasts²⁴ may well account for the susceptibility of both organs to the oncogenic factors operative in individuals carrying the retinoblastoma gene.

The present case may represent an example of this entity. The patient had a strong family history of hereditary retinoblastoma. He presented at the age of 7 weeks with a lesion of the left retina which had the appearance of a retinoblastoma and was treated accordingly. Subsequent post-mortem examination showed the presence of a calcified retinoblastoma

restricted to the left retina, confirming the clinical diagnosis. Although the patient did not develop a tumour in the right eye, it is certain that he carried the retinoblastoma gene. All 11 patients in Bader and colleagues' series¹⁵ had bilateral tumours, and seven of them had a positive family history. They presented at an average age of 6 months compared with the range of 8-22 months in several series of bilateral retinoblastomas and 24-43 months for unilateral retinoblastomas.^{9 34-43}

The sequence of clinical events in the case reported here is suggestive of the development of a second primary lesion rather than a metastatic lesion. The neoplasm of the retina was treated successfully by local radiotherapy, did not recur, and at necropsy was calcified and limited to the retina. Two and a half years later the patient developed symptoms of an intracranial lesion. Although the histological appearance of this second lesion was not known until after death (and a full course of radiotherapy), CT scan localised the neoplasm to the region of the pineal organ. Despite the therapy the child developed numerous intracranial and spinal metastases and died.

At necropsy extensive disease in the central nervous system made assessment difficult. However, tumour was found only in the perineural subarachnoid space and not in the substance of either optic nerve. Viable tumour was not found in either retina nor crossing the lamina cribrosa of either eye. It was considered that the neoplastic cells in the subarachnoid space had metastasised from the intracranial site. The capacity of the lesion to spread in the subarachnoid space was evident by the extensive metastases covering spinal nerve roots.

At necropsy the second tumour showed the microscopic features of a poorly differentiated neuroepithelial neoplasm. In accordance with the view of Jakobiec and colleagues¹³ and Becker and Hinton³³ only certain knowledge of the site of origin of the lesion could have separated retinoblastoma from pinealoblastoma. The early CT scan suggested that the lesion arose in the pineal organ, and at necropsy tumour was intimately part of residual pineal tissue. These factors favour the opinion that the second lesion was a new and distinct neuroepithelial neoplasm—a component of the so-called trilateral retinoblastoma.

The results of treatment, where it has been instituted, have been unsuccessful.^{13 17 18} All patients have died except for two who were said to be alive with disease at one and 10 months respectively.¹⁵ In this case the response to aggressive treatment after early recognition of the entity was disappointing. However, the prolonged overall time of treatment, three months instead of six weeks, could have allowed

tumour regrowth between treatments. The use of prior chemotherapy, therefore, with possible myelosuppression, is to be avoided. Alternatively these tumours may have a hypoxic element and be radio-resistant.

This tumour had an initial volume of 2.4 cm³ and thus might be expected to have a cell volume of 2.4×10^9 . A dose for 37% cell survival of 130 cGy might therefore be expected to allow tumour eradication with a dose of 2860 cGy if all cells were to be oxygenated. The failure of a dose 1.5 times larger than this would suggest the presence of hypoxic cells and thus strategies for improved therapy.

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