

*Short report*

## Astrocytic differentiation in medulloblastoma

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**SUMMARY** A case of cerebellar medulloblastoma with transitional features towards malignant fibrillary astrocytoma is described. In the cerebellum the tumour is characterised by extensive subpial infiltration with cells of undifferentiated type, and the astrocytic component could only be identified by a positive glial fibrillary acidic protein reaction. In the brainstem the character of the growth transforms to that of diffuse astrocytoma. This demonstrates the potential for differentiation existing in a "primitive" neuroepithelial neoplasm.

While it has long been assumed that the medulloblastoma of the cerebellum is composed of cells with the potential for differentiation along neuroblastic or spongioblastic lines, cases showing transition to cells of more mature astrocytic type are rare. We here describe an example of this transition in which the conventional neuropathological methods were supplemented by the peroxidase-antiperoxidase technique to demonstrate glial fibrillary acidic protein (GFAP).

### Case report

A woman aged 46 years was investigated for two weeks' right parietal headaches, with frequent falls to the left or backwards for one week, vomiting for three days and tinnitus in both ears. Two years earlier a pigmented naevus had been removed from the left arm. On examination the patient was stuporose and disoriented. She had coarse nystagmus on lateral gaze, left facial paresis, incoordination of left upper and lower limbs, and the plantar responses were extensor. Left vertebral angiography showed the presence of a large mass in the left cerebellar hemisphere extending to the superior aspect of the fourth ventricle; this was confirmed at operation when quantities of soft, grey-red necrotic tumour were removed from the centre of the hemisphere leaving a large cavity. Microscopical examination disclosed the typical appearances of medulloblastoma. Following the standard course of post-

operative radiotherapy to cranium and spinal cord the patient's initial progress was good, but six months later signs of recurrent tumour were manifest and further irradiation to the posterior fossa and a course of vincristine were given. One year from the time of presentation the patient deteriorated rapidly and died.

### Pathological findings

Post-mortem examination established the immediate cause of death to be patchy bronchopneumonia. No tumour was found, by naked-eye or microscopical examination, in any tissues outside the central nervous system. The brain weighed 1.505 kg. The leptomeninges were slightly thickened and opaque over the cerebral hemispheres; over the cerebellum they were densely adherent both to the overlying bone and to the softened cerebellar tissue; and there was marked thickening over the cervical spinal cord. The brain was sliced in the coronal plane after fixation in formalin. There was slight dilatation of the lateral ventricles, and some scattered petechial haemorrhages were present in the central grey matter, but no tumour was found above the tentorium. The left cerebellar hemisphere was largely replaced by a ragged cavity 3.5 cm in diameter bordered by a mass of soft, red-speckled pale grey tissue extending diffusely into the cerebellar white matter, middle peduncle and pons. The aqueduct and fourth ventricle were displaced from left to right. The medulla and spinal cord appeared to be normal.

**Material and methods** Sections of both cerebral hemispheres, of the cerebellum and brain stem and of spinal cord were embedded in celloidin. Smaller sections were embedded in paraffin wax. A battery of conventional neuropathological staining techniques was employed. For the demonstration of

glial fibrillary acidic protein the direct immunoperoxidase method as described by Deck *et al*<sup>1</sup> was used.

**Microscopical appearances (biopsy)** Fragments of highly cellular tumour tissue: the cells had roughly oval or rounded, darkly stained nuclei, very sparse cytoplasm and showed little variation in size (fig A). Mitotic figures were present. Rarely, rosettes of Homer Wright type were observed. Endothelial hyperplasia of blood vessels was present and sometimes the tumour cells were arranged around these vessels. Staining for reticulin showed only small amounts of connective tissue, chiefly related to blood vessels. Glial fibrils were not evident with phosphotungstic acid haematoxylin.

**Necropsy appearances** In the left cerebellar hemisphere the cavity, which contained some necrotic material and debris, was lined by tumour tissue (fig B). The tumour, which was wholly composed of small cells with oval, dark-staining nuclei, extended into the folia, forming a thick subpial coating

closely resembling the foetal granular layer. In the molecular layer a marked increase in cellularity was usual: some of the cells were astrocytes, some microglia and some appeared to be tumour cells migrating from the subpial zone. In some places a focus of intense isomorphic gliosis in the molecular layer was crowned with an aggregate of tumour cells lying superficially in the pia (fig C). In the molecular layer and white matter, where they were infiltrated by the neoplasm, it was common to see serpiginous necrotic zones bordered by small cells (fig D); here, also, the tumour cells were more pleomorphic and some had elongated nuclei. Vascular endothelial hyperplasia was less conspicuous than in the biopsy, but there were many widely dilated sinusoidal vessels, some obliterated by thrombosis. Elsewhere in the cerebellum appearances were normal apart from focal subpial gliosis and there was no persistent Obersteiner layer. Where the tumour infiltrated the cerebellar white matter, middle cerebellar peduncle and pons there was more variation in appearance.

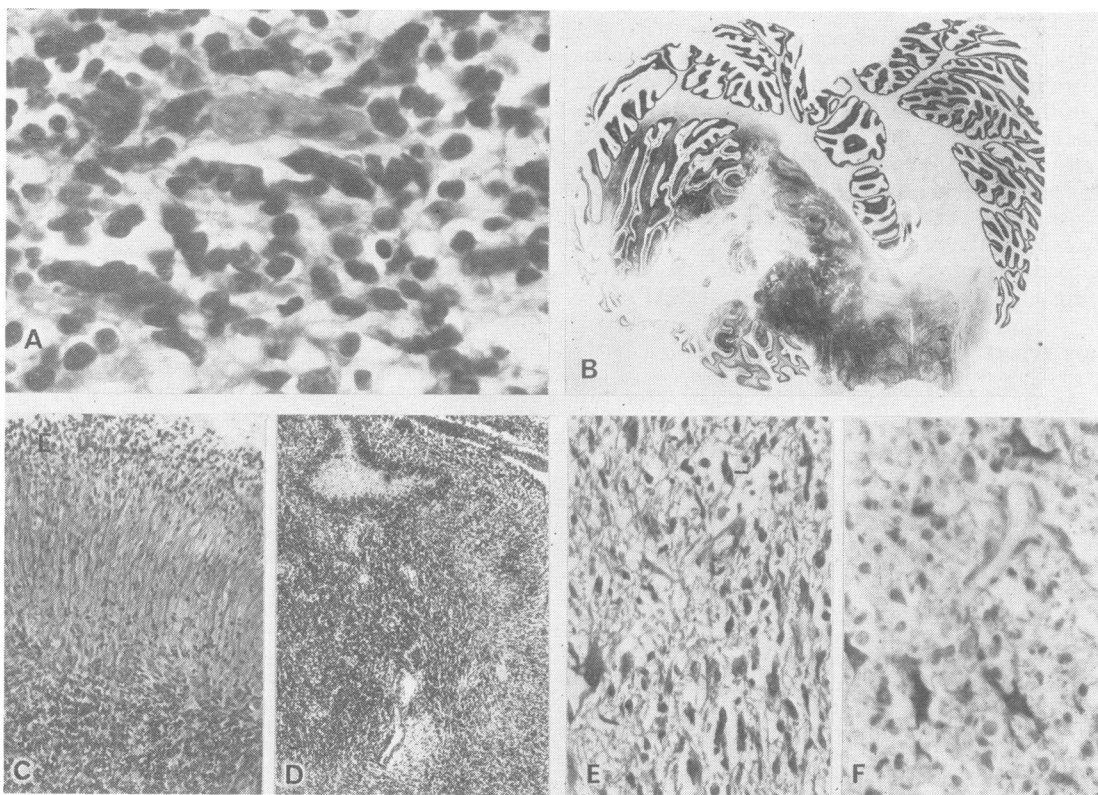


Figure (A) (Biopsy) Medulloblastoma. The tumour is highly cellular. One rosette is present. H.E.  $\times 550$ . (B) (Necropsy) The cavity in the cerebellum is lined by tumour which extends into the pons. Celloidin, Nissl  $\times 0.76$ . (C) Isomorphic gliosis of the molecular layer with a subpial 'crown' of tumour cells. Celloidin PTAH  $\times 100$  (D) Necrotic zones within the tumour in the cerebellum. Celloidin PTAH  $\times 24$ . (E) Fibrillated cells with elongated nuclei in the pons. PTAH  $\times 250$ . (F) GFAP-positive cells in the pontine tumour. GFAP  $\times 320$ .

While there were groups of cells whose morphology was typically "medulloblastoma," particularly in perivascular aggregates recalling the secondary structures of Scherer, many were elongated, with slender nuclei and short bi-polar processes (fig E). Especially in the pons, where the fibre-bundles were permeated by tumour, there were leashes of highly fibrillated cells (phosphotungstic acid-haematoxylin positive), in some fields resembling the fibrillary astrocytoma typically found in the brain stem. In addition there were small numbers of astrocytic cells of the gemistocytic type, some of which could have been "reactive" while others were abnormally large, with two or more nuclei, and a few had the bizarre appearance of the giant cells of a glioblastoma. Small haemorrhages into the tumour substance from the numerous small blood vessels were common; the vessels, in general, did not show the fibrinoid or proliferative changes associated with radiation damage, despite the presence of substantial amounts of necrosis. The cerebral hemispheres, including the basal ganglia, optic pathways and diencephalic region were tumour-free. In the spinal cord the leptomeningeal thickening was collagenous and tumour cells were not present.

*Results of GFAP reaction* Sections of a known astrocytoma were used as positive controls. Omission of incubation with anti-GFA protein served as a negative control.

In the biopsy specimen the majority of tumour cells were unstained. However, some scattered cells showing positive staining were present throughout the tumour, and around the hypertrophic blood vessels there was a heavy concentration of positive cells with processes radiating from around the vessel, giving an appearance reminiscent of astroblastoma. Review of the PTAH-stained sections did not permit identification of these cells as astrocytes (see case 6 described by Deck *et al.*<sup>1</sup>)

In the post-mortem sections the results closely paralleled those obtained with PTAH. Strong staining was chiefly among cells of elongated or fibrillated appearance in the brainstem (fig F) whereas the cells in the subpial zone and cerebellar white matter were mainly negative.

## Discussion

The concept of the cerebellar medulloblastoma as a primitive neuroepithelial neoplasm with the potential for development along neuroblastic or spongioblastic lines originated with the work of Bailey and Cushing.<sup>2</sup> This interpretation still is not universally accepted: some authors regard these tumours as sarcomas of mesenchymal origin, while others deny the possibility of a dual potential for differentiation, and believe that "medulloblastomas" can be classified into neuroblastomas, glioblastomas or oligodendrogliomas on the basis of metallic impregnation.<sup>3</sup>

While neuroblastic characteristics, expressed by the finding of Homer Wright rosettes, are common in medulloblastoma, and synaptic structures have, exceptionally, been found<sup>4</sup> differentiation towards mature astrocytes has seldom been established. Willis<sup>5</sup> considered that in the more slowly growing examples "transition to astrocyte cells can sometimes be traced." Rubenstein<sup>6</sup> illustrated a recurrent medulloblastoma in which "the tumour cells are highly reminiscent of a malignant astrocytoma," but suggested that radiation might have been responsible, following the earlier account of Oppenheimer<sup>7</sup> who described a remarkable post-irradiation change in a medulloblastoma: the tumour became highly pleomorphic with bizarre giant cells resembling those of glioblastoma. Müller and Schaefer<sup>8</sup> recorded a case of recurrent cerebellar medulloblastoma, in part having a definitely spongioblastic appearance, and electron microscopical studies showed plentiful intracytoplasmic glial filaments.

In a detailed study of a cerebellar and brain-stem tumour from a 14-year old girl, Rubinstein, Herman and Hanbury<sup>9</sup> demonstrated transitional features between medulloblastoma and diffuse astrocytoma. In the vermis cerebelli this tumour was highly cellular, and was composed of small uniform cells with no distinctive cytoplasmic features when examined electronmicroscopically. In the brainstem, however, there were wide areas of fibrillated astrocytic cells. Sequential morphological changes in tissue and organ culture systems indicated progressive differentiation from "medulloblastoma cells" to fibrillated astrocytes. The authors discussed the possible interpretation of this tumour as medulloblastoma differentiating into astrocytoma, but concluded that this was difficult to sustain because of the fairly prolonged history of clinical evolution over a two-year period and because of the absence of a demonstrable mass until the late stages. The interpretation they preferred was that this was an example of diffuse brainstem astrocytoma with focal dedifferentiation to medulloblastoma. In the present case this difficulty does not arise since the history of illness was short and the tumour was, at the time of operation, interpreted as medulloblastoma. At first sight it seemed that the pons provided conditions that were specially favourable for the cells to develop an elongated bipolar or fibrillary form and the environment was thus largely responsible for the change in morphology. But, in this context it is of interest that GFAP preparations revealed the astrocytic nature of some of the tumour cells unsuspected

at the time of the original biopsy, and therefore radiation cannot be held to be responsible for the apparent transformation to astrocytoma.

### Conclusion

A case of cerebellar medulloblastoma which shows transition toward astrocytoma emphasises the potential for divergent differentiation of this neuroepithelial neoplasm.

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