Differentiating central neurocytoma

Case report

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In 1976 a patient underwent partial resection of an intraventricular tumor that showed central neurocytoma. No other tumor pattern was observed. In 1994 this patient underwent a second operation for removal of the tumor, at which time foci of tumor were diagnosed as central neurocytoma and ganglioglioma. This is the first reported case of differentiation of central neurocytoma into ganglioglioma, a sequence of events termed differentiating central neurocytoma.

KEY WORDS • neurocytoma • ganglioglioma • ganglion cell • differentiation • immunohistochemistry • synaptophysin

CENTRAL neurocytoma is a distinctive central nervous system tumor of neuronal lineage. It has been described as an intraventricular tumor resembling oligodendroglioma at the light microscopic level with ultrastructural and antigenic markers of neuronal lineage. This has led to the concept that this tumor consists of cells committed to granular-type neuronal lineage. We report a case in which the emergence of a component of ganglioglioma was observed 18 years after the subtotal removal of a tumor that originally showed only the characteristic features of central neurocytoma.

Case Report

This 30-year-old man had undergone surgery in 1976 at the age of 12 years following a 6-month history of partial epilepsy.

History. A computerized tomography (CT) scan obtained at the time the patient was 12 years of age revealed a right frontoparietal intraventricular tumor with evidence of calcification. A cerebral angiogram was normal. A craniotomy was performed to achieve subtotal removal of the tumor. The tumor, which was gelatinous and vascular, appeared to arise from the floor of the lateral ventricle and blocked the foramen of Monro. The tumor was characterized by histopathological analysis as a malignant glial tumor. The patient was given external-beam radiation therapy. A left-sided spastic hemiparesis persisted after surgery. A ventriculoperitoneal shunt was placed in 1977 to treat developing hydrocephalus. The patient continued to have intermittent seizures, but remained otherwise well. In 1993 a new, left frontal ventriculoperitoneal shunt was placed for progressively increasing hydrocephalus producing symptoms of raised intracranial pressure.

In November and December 1994 the patient was admitted on three separate occasions with shunt malfunction that required revision. On each admission the patient was unresponsive, had developed a fixed, dilated right-eye pupil, and required assisted ventilation. Following the third shunt dysfunction, he did not recover sufficiently to be taken off the ventilator.

Diagnostic Studies. A CT scan showed a partially calcified tumor, increased in size compared with a CT scan obtained 6 months previously (Fig. 1 left and center). A magnetic resonance image obtained in March 1994 showed an enhancing mass in the region of the right lateral ventricle, which extended into surrounding brain (Fig. 1 right). The patient’s cerebrospinal fluid protein level was 25 g/L; presumably the protein was secreted by the tumor and was responsible for the repeated shunt malfunctions.

Operation. In an attempt to reduce the patient’s cerebrospinal fluid protein level the tumor was reexplored via a right frontal craniotomy. Operative findings included a right frontal cystic cavity containing xanthochromic fluid and, at the base of this, a gray, gelatinous tumor was identified. This was partly within the lateral ventricle but mostly intraparenchymal, with poor demarcation from surrounding brain. A gross-total removal was effected with the aid of an ultrasonic aspirator.

Postoperative Course. The patient has subsequently made only a partial recovery but obeys commands and breathes and opens his eyes spontaneously. However, there is very little spontaneous activity. There have been no further episodes of shunt malfunction and he has had no seizures after tumor removal.

Pathological Examination. Eight slides stained with hematoxylin and eosin (H & E) were available from the first
resection performed in 1976. Both cortex and white matter were present; the cortex was completely uninvolved by tumor. Low-power examination of the deep white matter showed the tumor to be pallid compared to adjacent brain because of a relative lack of fibrillarity and a lack of stained cytoplasm (Fig. 2 upper left). There was a faintly nodular pattern to the involvement of brain by tumor. At higher magnification the tumor was modestly hypercellular and consisted of uniform cells with round to slightly elongated, lightly stippled nuclei of even chromaticity. In much of the tumor the cytoplasm of individual cells could not be distinguished and the background was faintly fibrillar and similar to neuropil (Fig. 2 upper right). There was some tendency for coalescence of the tumor nuclei around vessels, but these did not show the radial orientation of perivascular pseudorosettes. Foci of the tumor showed prominent optically clear cytoplasm strongly reminiscent of oligodendroglial differentiation (Fig. 2 lower left). The tumor was demonstrated to be both intraventricular and intraparenchymal by virtue of being on both sides of the ependymal lining (Fig. 2 upper left), and there was incomplete demarcation of the tumor from the surrounding brain, which suggested a limited capacity to infiltrate the brain. The tumor rarely showed focal coalescence of nuclei around cell-free, fibrillar islands of neuropil (Fig. 2 lower right). Mitoses, endothelial proliferation, and necrosis, either single cell or geographic, were not identified. No large cells indicative of ganglion cell tumor or of dysembryoblastic neuroepithelial tumor were present anywhere in this specimen. Homer Wright rosettes were not present.

The tissue from the second resection showed abundant intraoperative hemorrhage and areas of sparsely cellular hyaline fibrosis. The tissue also showed that the tumor had two relatively dissimilar histological patterns with some tendency to merge into each other (Fig. 3A). The tissue was extracted in multiple fragments that usually showed one pattern or the other. The first pattern was essentially that of the tumor from the original resection, with an accentuation of the tendency to perivascular coalescence of tumor cells (Fig. 3B). Immunohistochemical studies showed strong positivity for neuron-specific enolase and synaptophysin. The latter was strongly positive both as puncta and linear staining in the fibrillary background as well as diffuse and punctate positivity in the cytoplasm of individual tumor cells when cytoplasm was discernible (Fig. 3C). Somatic glial fibrillary acidic protein (GFAP) positivity was not demonstrated in these areas of the tumor. The second pattern was that of ganglioglioma, with an intermixtue of cells showing H & E characteristics of both astrocytes and ganglion cells (Fig. 3D). Ganglion cells were characterized by large spherical nuclei with a single prominent nucleolus and abundant pink-to-amphiphilic cytoplasm. Nissl staining provided additional morphological evidence for the presence of ganglion cells. Many ganglion cells and other not so characteristically ganglioid cells stained strongly for the presence of both neuron-specific enolase and synaptophysin (Fig. 3E). Immunohistochemical analysis for the presence of chromogranin A was negative. Other tumor cells in these areas were of astrocytic lineage, both by conventional criteria and by the immunohistochemical presence of GFAP. Complementary but overlapping areas of synaptophysin and GFAP positivity are shown in the same tissue fragment in Fig. 3 F and G. Some areas of the tumor were rather uniformly populated by bipolar-type astrocytes set in a relatively more densely fibrillar background, and Rosenthal fibers were present.

**Discussion**

Central neurocytoma is a relatively recently recognized tumor of neuronal lineage. Intraventricular location near the foramen of Munro, microscopic resemblance to oligodendrogliomas or sometimes ependymomas, consistent demonstration of neuronal differentiation as assessed either by ultrastructural or immunohistochemical methods, and a relatively benign course combine to make this a very distinctive neoplasm of children and young adults. The initial presentation, radiological and surgical findings, histological appearance, and subsequent long survival of the patient after known subtotal resection are typical of central neurocytoma. The age and mode of presentation, calcification, intraventricular location, and the
differentiating neurocytoma

Figure 2. Photomicrographs of paraffin-embedded sections obtained at the first excision in 1976. H & E. Upper Left: Tumor is present on both sides of the ventricular lining (arrows). Areas of maximum involvement of tumor show pallor compared with surrounding brain. Original magnification × 25. Upper Right: The tumor shows regular, round to slightly elongated nuclei, poorly fibrillar cytoplasm, and the tendency for tumor cells to clump around vessels. Original magnification × 250. Lower Left: Tumor cells often show round nuclei and clear cytoplasm indicative of oligodendroglioma. Original magnification × 500. Lower Right: Rare foci of coalescence of tumor nuclei around fibrillary anuclear areas are present. Original magnification × 500.

Routine histological appearance of the tumor were quite characteristic, but the last was not specific because of the similarity to oligodendroglioma. The similarity to oligodendroglioma and the faint nodularity apparent in Fig. 2 upper left raised the diagnostic possibility of dysembryoblastic neuroepithelial tumor. Dysembryoblastic neuroepithelial tumor was eliminated from consideration because of the absence of any large, dysplastic, neuronotype cells, and the deep intra- and periventricular location of the tumor without any evidence of involvement of the overlying cortex. Although it was not possible to perform specialized studies on the specimen obtained in 1976, foci of tumor with an essentially identical H & E histological appearance were present in the specimen of residual tumor obtained at the second operation, and these areas stained very strongly for the presence of both neuron-specific enolase and synaptophysin. These markers have been found to be as dependable as ultrastructural examination in characterizing this tumor.6,7 The presence of the tumor in the periventricular and intraventricular brain parenchyma constitutes the major difference between central neurocytoma as it was originally defined and the current definition; however, there are reports of tumors with basically the same characteristics as intraventricular neurocytoma in the brain parenchyma.8 Furthermore, because of the operative approach often used for intraventricularly located neurocytomas, the extent of involvement in adjacent brain may not have been well defined. For intraventricular tumors of neuronal lineage a spectrum of differentiation has been described for which the terms neuroblastoma, differentiated neuroblastoma, and neurocytoma have been used.6,7 The criteria used to make the distinction among these entities are not well defined, but convincing ultrastructural and/or immunohistochemical evidence of neuronal differentiation in a tumor that otherwise resembles an oligodendroglioma appears to warrant the use of the term neurocytoma.

The findings in the second excision are very similar to a tumor previously reported as a cerebral ganglioneurocytoma.4 In that case the tumor had both neurocytoma-like and gangliocytoma-like areas that showed evidence of advanced neuronal differentiation. This tumor was located intraventricularly and in the frontal lobe. The authors considered their case to be one of tumor cells committed to the neuronal lineage that had the potential to differentiate toward either granular or ganglion-type neurons. Although it has been suggested that the cells of neurocytomas are strictly committed to a granule-type neuronal lineage, increased experience with this entity has led to recognition of ganglion-type neurons and/or glial cells. This has resulted in the hypothesis that a stem cell from the subependymal plate is the cell of origin.2 One report
has interpreted the typical neurocytoma cell as “intermediate” in differentiation and the concomitant presence of ganglion cells as evidence of further neuronal maturation. Although it is possible that the present case was always of the ganglioneurocytoma type and that the ganglionic portion was not sampled at the time of the initial surgery, given the complete absence of large cells and the otherwise typical presentation, location, morphology and very long course, we regard the patient initially as having had a central neurocytoma. The obvious and prominent presence of gangliogliomatous elements in an excision 18 years later is regarded as the result of the emergence of these elements during that interval, suggesting a neoplasm with the capacity to differentiate along astroglial and two morphologically dissimilar neuronal lines. To our knowledge, the emergence of a ganglioglioma from a central neurocytoma has not previously been described, and we propose that this sequence of events be termed differentiating central neurocytoma.

References


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