Central neurocytoma: histopathological variants and therapeutic approaches

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The central neurocytoma has recently been added to the differential diagnosis of intraventricular tumors. Histopathologically, this tumor is characterized by a uniform neoplastic cell population with features of neuronal differentiation. Central neurocytomas occur in young adults, develop in the area of the foramen of Monro, and are usually associated with the septum pellucidum. Initial reports appeared to indicate that these tumors are benign lesions with a favorable postoperative prognosis. The authors present clinical and neuropathological findings in a series of eight patients with central neurocytoma. An anterior transcicallosal micro-neurosurgical approach yielded good outcomes. Postoperative radiation therapy was restricted to two patients with a malignant variant of central neurocytoma and one patient with a recurrent tumor. Observations of anaplastic variants of this neoplasm in two cases and local tumor recurrences in three indicate that the biological behavior and postoperative prognosis of central neurocytoma may not always be as favorable as previously assumed.

KEY WORDS • neurocytoma • malignancy • anaplastic variant • radiation therapy • tumor recurrence

INTRAVENTRICULAR tumors usually present with signs of occlusive hydrocephalus such as headache, nausea, and visual and mental disturbances. The differential diagnoses of these tumors include choroid plexus papilloma, ependymoma, subependymal giant-cell astrocytoma, intraventricular meningioma, astrocytoma, and oligodendroglioma. Recently, the central neurocytoma has been added to the family of ventricular neoplasms. Central neurocytomas were first described by Hassoun, et al., in 1982. They are characterized by morphological features of neuronal differentiation and have been regarded as benign lesions with a favorable postoperative prognosis. In a series of 11 central neurocytomas, we have recently observed two malignant cases characterized by an increased mitotic activity, vascular endothelial proliferation, and tumor necroses. In this paper we present clinical, neuroradiological, surgical, and neuropathological findings in eight patients with central neurocytoma who were treated surgically at our institution. The data indicate that some of these tumors carry a significant risk for postoperative recurrence.

Clinical Material and Methods

Patient Population

Eight patients with intraventricular neurocytoma were treated between 1978 and 1990 by the senior author (M.G.Y.). The age of the patients at the time of surgery ranged from 19 to 47 years (average 27 years); there were five women and three men. The clinical records, computerized tomography (CT) scans, magnetic resonance (MR) images, angiograms, and histological slides were reviewed retrospectively. All patients presented with signs of raised intracranial pressure, including headache and nausea. Papillary edema was observed in six, visual impairment in six, olfactory dysfunction in two, and mental disturbances in all eight patients. One patient with a 3-year history of headache developed sensorimotor hemiparesis before admission.
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**FIG. 1.** Magnetic resonance T1-weighted images in Case 6. *Left* and *Center:* Preoperative gadolinium-diethylenetriamine penta-acetic acid-enhanced images showing a giant central neurocytoma with extension into the fourth ventricle. *Right:* Postoperative image demonstrating residual tumor in the fourth ventricle.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>CT Angio Surgery</th>
<th>RT</th>
<th>Follow-Up</th>
<th>Grading</th>
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<tr>
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<td>6</td>
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<td>39, M</td>
<td>- + + total</td>
<td>54 G</td>
<td>5 mos</td>
<td>malignant</td>
</tr>
</tbody>
</table>

* Abbreviations: CT = computerized tomography; MR = magnetic resonance imaging; angio = cerebral angiography; RT = postoperative radiation therapy dose; + = study performed; - = study not performed; total = total removal of the tumor.
† This patient had tumor recurrence after a 38-month postoperative period. The follow-up period for the recurrent tumor was 37 months.

TABLE 1
Clinical, neuroradiological, neurosurgical, and neuropathological findings in eight patients with central neurocytoma

- Neuroimaging Findings
  All tumors were localized in the lateral ventricles and showed a strong preference for the area of the septum pellucidum. Signs of obstructive hydrocephalus were detectable in all patients. A giant neurocytoma with extension into both the third and fourth ventricles was found in one patient (Case 6, Fig. 1). In another patient (Case 8), tumor infiltration into the frontal lobe had occurred (Fig. 2).
  On CT scans, the tumors generally presented as well-circumscribed lesions with irregular density. Moderate enhancement was achieved by administration of contrast medium. Tumor diameters varied between 33 and 70 mm. Multiple small calcifications were observed in four patients (Cases 1, 3, 5, and 6) and there was a large calcified mass in one patient (Case 8). Only the latter was visible on plain skull x-ray films.
  On MR imaging, the tumors generally had a signal intensity similar to that of the cerebral cortex. Intravenous application of contrast medium (gadolinium-diethylenetriamine penta-acetic acid, 0.1 mmol/kg body

- Immunocytochemical reactions. Regular stains included hematoxylin and eosin and reticulin impregnation. For immunohistochemistry, sections were incubated with monoclonal antibodies to synaptophysin (dilution 1:30) or neurofilament protein (dilution 1:10), and with polyclonal rabbit antiserum to neuron-specific enolase (dilution 1:150) and to glial fibrillary acidic protein (dilution 1:150). Primary antibodies were visualized with an avidin-biotin staining kit for mouse immunoglobulin G (IgG) and with a peroxidase-antiperoxidase sandwich to rabbit IgG.
  Five tumors were examined by electron microscopy. The specimens were fixed in 2% glutaraldehyde, 0.1 M phosphate buffer, pH 7.4, embedded in Epon, and analyzed. Osmium tetroxide (2%) and uranyl acetate (4%) were used as contrast media.

- Results

Diagnosis and Surgical Approach
The neuroradiological diagnosis was established by CT in four patients and by MR imaging in four. In addition, cerebral angiography was performed in two cases.
An anterior transcallosal microneurosurgical approach was chosen for all tumors. A detailed description of the operative procedure is given below.

Neuropathological Techniques
For histopathological analysis, surgical biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, and processed for light microscopy and immunocytochemical reactions. Regular stains included hematoxylin and eosin and reticulin impregnation. For immunohistochemistry, sections were incubated with monoclonal antibodies to synaptophysin (dilution 1:30) or neurofilament protein (dilution 1:10), and with polyclonal rabbit antiserum to neuron-specific enolase (dilution 1:150) and to glial fibrillary acidic protein (dilution 1:150). Primary antibodies were visualized with an avidin-biotin staining kit for mouse immunoglobulin G (IgG) and with a peroxidase-antiperoxidase sandwich to rabbit IgG.
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weight) resulted in moderate enhancement. Most of the tumors appeared to be attached either to the septum or to the lateral wall of the ventricle.

Surgical Findings

An anterior transcallosal microneurosurgical interhemispheric approach was used for all neurocytomas. Depending on the major extension of the tumor within the lateral ventricles, paramedian osteoplastic craniotomy was performed on the right side in four patients and on the left side in four. A small segment of the interhemispheric fissure between two bridging veins was exposed under the operating microscope. This allowed sufficient access to the central corpus callosum. Following careful dissection of pericallosal arteries and local application of papaverine to prevent vasospasm, a paramedian incision of 12 to 15 mm was made into the anterior corpus callosum. Cerebrospinal fluid was aspirated from the ipsilateral ventricle, the septum was focally incised, and the contralateral ventricle was also drained. Intraoperatively, the tumors were generally well circumscribed with the main portion located in the lateral ventricle. The tumor tissue was attached to the wall of the lateral ventricles. Four tumors appeared to originate from the septum pellucidum and two from the corpus callosum. In Case 4, no definite site of adhesion could be determined. One neurocytoma (Case 8) was broadly attached to and infiltrated the frontal lobe.

Several neurocytomas were extensively vascularized and their resection required meticulous neurosurgical technique. Complete macroscopic removal of the tumor was achieved in seven patients. One patient (Case 6) presented with a large central neurocytoma extending into the third and fourth ventricles. The portion of tumor in the aqueduct and fourth ventricle could not be excised (Fig. 1 right).

Three patients exhibited persistent or progressive hydrocephalus and required implantation of a ventriculoperitoneal shunt system. In two patients (Cases 2 and 6), the shunt was placed 1 and 2 months, respectively, after removal of the tumor. One patient with recurrent neurocytoma (Case 3) developed obstructive hydrocephalus 1 year after tumor resection and received a ventriculoperitoneal shunt at that time. Postoperatively, seven of the eight patients exhibited a good physical and mental status.

Follow-Up Examination

Regular clinical examinations were performed annually. The patients included in this report were followed for postoperative periods of between 5 months and 12 years (average 5 years) (Table I). Good postoperative results were achieved in all cases with the exception of one patient (Case 6) with incomplete tumor removal who had residual right-sided hemiparesis. The remaining seven patients were able to return to work.

Computerized tomography scans obtained during the first postoperative week revealed residual tumor in only one patient (Case 6). At different postoperative intervals, four patients were examined by CT and two pa-
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In three cases, there was no evidence of a recurrent lesion; however, the other three patients showed recurrent tumors without exhibiting clinical symptoms. One of these patients (Case 3) presented with a tumor mass 45 mm in diameter 3 years after surgery (Fig. 3). This tumor was treated surgically and subsequently irradiated (50 Gy). Histopathological analysis of this tumor showed a central neurocytoma indistinguishable from the original neoplasm. There was no evidence of anaplastic tumor progression in this case. This patient has now been followed for an additional 37 months without evidence of residual or recurrent tumor tissue. The recurrence in Case 4 was detected after 3 years and had a diameter of 20 mm. Magnetic resonance imaging in Case 2 revealed a recurrent tumor 8 mm in diameter 6 years after surgery. These two patients have so far been asymptomatic.

In Cases 7 and 8, a malignant variant of central neurocytoma was diagnosed histopathologically. Therefore, these patients received postoperative radiation therapy. During brief observation periods of 12 and 5 months, respectively, these two patients have not developed a recurrent neurocytoma (Fig. 2 right).

Histopathology

All central neurocytomas included in this study were thoroughly examined with histopathological and immunocytochemical techniques. A feature common to all of these tumors was the isomorphous neoplastic cell population. Honeycomb architecture reminiscent of oligodendroglioma was a prominent feature in three of the neoplasms. Other distinct patterns included perivascular pseudorosettes in five cases, cell-free neuropil islands in four, and "Indian files" in one (Case 8). Several neurocytomas showed a mixture of various histopathological architectures. Calcification was observed in four cases. Generally, the tumors were well demarcated from the adjacent brain. The mitotic activity varied and ranged from 1 to 14 mitoses/20 high-power fields. Two patients with a large number of mitotic figures (Cases 7 and 8) exhibited areas of necrosis and vascular endothelial proliferation, and were therefore considered malignant. Representative photomicrographs of a benign and a malignant central neurocytoma are shown in Fig. 4.

Immunohistochemical examinations revealed a consistent and uniform expression of the neuronal marker proteins neuron-specific enolase and synaptophysin in all neurocytomas. Electron microscopy was performed in five of the tumors and demonstrated neurosecretory granules, synapses, microtubules, or neuritic processes. These findings confirmed the neuronal origin and differentiation potential of this tumor.

Discussion

Historical Perspectives and Clinical Presentation

Following the original description of central neurocytoma in 1982 by Hassoun, et al.,4 several clinical and histopathological reports on this neural tumor have been published.1,6,17 Common features include intraventricular localization, predominant occurrence in young adults, and a generally benign postoperative course. Recent evidence from our own institution suggests that central neurocytoma represents approximately 0.1% of all primary central nervous system (CNS) tumors. All patients included in this report presented with nonspecific signs of intracranial hypertension due to obstructive hydrocephalus. Only one patient with tumor infiltration in the frontal lobe (Case 8) developed a focal neurological deficit. Computerized tomography revealed a circumscribed tumor mass in the lateral ventricles with moderate enhancement. Calcifications were found in four of the eight cases. Therefore, central neurocytoma cannot be unequivocally distinguished from oligodendroglioma, ependymoma, and intraventricular meningioma. The higher resolution of MR imaging allows better definition of the topographical relationship of tumor and adjacent brain tissue. A combination of intraventricular localization, good demarcation, and attachment to the septum pellucidum are features suggestive of central neurocytoma.4

Fig. 4. Photomicrographs showing the histopathological appearance of the benign and malignant variants of central neurocytoma. A: Central neurocytoma with perinuclear halos and honeycomb architecture (Case 6). This feature mimics oligodendroglioma. H & E, x 133. B: Formation of perivascular rosettes, reminiscent of ependymoma (Case 6). H & E, x 133. C: Malignant central neurocytoma with increased mitotic activity (arrow) and necrosis (asterisk) (Case 8). H & E, x 266.
Histopathological Features and Differential Diagnosis

In the past, central neurocytoma was frequently misdiagnosed because it mimics histopathological features of other CNS neoplasms, such as oligodendroglioma and ependymoma. The neuropathological diagnosis of this tumor requires electron microscopic or immunocytochemical techniques, which demonstrate the neuronal origin of the tumor. Several of our cases had originally been classified as ependymoma of the foramen of Monro, a tumor entity proposed by Zülch and Schmid. Immunohistochemical analysis of ependymomas of the foramen of Monro at our institution revealed expression of the neuronal marker protein synaptophysin, indicating that these tumors in fact represent central neurocytomas. Intraventricular oligodendrogliomas frequently share features of central neurocytoma, including age at presentation, localization, and histopathological appearance.

The principal neurosurgical approaches to intraventricular lesions include transcallosal or transventricular routes. For our patients with central neurocytoma, we invariably chose the anterior transcallosal microneurosurgical approach. The main consideration was minimization of surgical damage to the adjacent brain. It was possible to remove all tumors totally, with the exception of one central neurocytoma (Case 6) which had extended into the fourth ventricle. The latter patient developed a persistent right-sided hemiparesis. In the remaining seven patients, good postoperative results were achieved.

Prognosis

The central neurocytoma has generally been viewed as a highly differentiated, benign neoplasm with a favorable prognosis. However, two of the tumors included in this series showed high mitotic activity, vascular endothelial proliferation, and areas of intratumoral necrosis. These neuropathological features indicated an increased proliferative potential. The cyto-logical appearance and immunocytochemical expression patterns were, however, indistinguishable from those of the remaining tumors. In particular, none of these tumors contained a poorly differentiated neuroblastic cell population, the hallmark of neuroblastoma or other primitive neuroectodermal tumors. Both patients with potentially malignant neurocytomas received postoperative radiation therapy, and their tumors had not recurred after periods of 5 and 12 months. In a histopathological survey of 12 central neurocytomas, we have recently encountered three additional cases with similar features. However, postoperative follow-up data were not available for these patients. It remains to be determined if these anaplastic variants are associated with a poor clinical prognosis and to what extent the malignant neurocytoma responds to radiation therapy. Two cases of residual central neurocytoma with a documented response to radiation therapy have been reported in the literature.

The surprising observation of recurrent neurocytomas within 3 years of surgical treatment indicates that the general prognosis may not always be as favorable as previously believed. To our knowledge, recurrences of central neurocytomas have not yet been reported. Only one of our recurrent neurocytomas underwent repeat surgery. On histopathological evaluation, this neoplasm did not show features of anaplasia. Therefore, the possibility that standard histopathological analysis underestimates the potential for regrowth of central neurocytomas cannot be excluded. Long postoperative intervals without relapse have also been documented. One patient included in this study (Case 1) remains tumor-free 12 years after surgery. A patient reported by Nishio, et al., who underwent incomplete removal of a central neurocytoma and received postoperative radiation therapy did not develop a recurrence during a follow-up period of 18 years. Morphological and biological factors accounting for these differences in the postoperative course are unknown at the present time.

Postoperative Radiation Therapy

An important aspect of clinical management concerns the sensitivity of this tumor to radiation therapy. The histopathological features of prototype neurocytomas, such as advanced neuronal differentiation, low mitotic activity, absence of vascular endothelial pro-
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liferations, and tumor necrosis, suggest a relative resistance to ionizing radiation. We therefore propose complete microsurgical removal of the tumor as the treatment of choice for central neurocytomas without histopathological evidence of malignancy. Patients with anaplastic variants receive postoperative radiation therapy at a dose of 50 to 55 Gy at our institution. Radiation therapy should also be considered for residual and recurrent neurocytomas. However, further studies are required to determine the susceptibility of central neurocytomas to irradiation.

Conclusions

Our findings demonstrate that central neurocytomas represent a tumor entity with characteristic clinical, neuroradiological, and histopathological properties. The central neurocytoma should be included in the differential diagnosis of intraventricular neoplasms in young adults. So far, these tumors have been associated with an excellent postoperative prognosis. However, variants with morphological features of malignancy and the observation of recurrent neurocytomas in three of our eight patients indicate that the prognosis of these neoplasms may not always be as favorable as previously assumed. An anterior transcallosal microsurgical approach is the treatment of choice. Until the radiation sensitivity of central neurocytomas has been established, postoperative radiation therapy should be restricted to histopathologically confirmed variants with an increased proliferative potential.

References


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