Central neurocytoma is a rare, well-differentiated neuronal tumor seen predominantly in young adults. The tumor usually arises from the septum pellucidum or the walls of the lateral ventricle. The patients’ prognoses are generally good because these tumors are believed to be at the benign end of the range of neuronal tumors. More than 145 cases of central neurocytoma have been reported since 1982, but only seven recurrences, all of which were local, have been reported.

We present two cases of recurrent central neurocytoma with dissemination throughout the ventricular system and spine. Such widespread dissemination has not been previously reported and suggests that central neurocytoma occasionally may have a more malignant course.

Case Reports

Case 1

This 22-year-old right-handed woman initially presented with a 1-month history of headache, nausea, vomiting, and double vision. She had undergone surgery at another institution for an intraventricular tumor that arose from the septum pellucidum and extended into the third and lateral ventricles (Fig. 1A). The pathology was initially reported as that of an ependymoma. After a total resection, which was confirmed by postoperative computerized tomography scanning, she received no further therapy. She was well until 3 years after surgery when routine postoperative imaging showed tumor recurrence in the third ventricle.

Review of the initial pathological specimen revealed the tumor to be a central neurocytoma (Fig. 1B and C). The neurological examination was normal. A magnetic resonance (MR) image of the brain showed recurrent tumor in the third ventricle and seeding along the walls of the lateral and fourth ventricles (Fig. 1D and E). An MR image of the spine (Fig. 1F) revealed an intradural enhancing lesion at the level of T-8. Repeated MR imaging of the brain obtained 4 months later demonstrated an increase in the size of the ventricular lesions. The patient is currently receiving chemotherapy with etoposide (60 mg/m² three times per day), cisplatin (30 mg/m² per day for 3 days), and cyclophosphamide (1 g on Day 3).

Case 2

The second patient, also a 22-year-old right-handed woman, presented with persistent increasing headaches. An MR image revealed a tumor in the right lateral ventricle with extension into the third ventricle. The patient underwent a craniotomy and most of the tumor was removed except for a small residual tumor in the third ventricle. Pathological examination revealed the tumor to be a central neurocytoma. Seven months after the initial surgery, the patient underwent ventriculoperitoneal shunt placement to treat her hydrocephalus. Twenty months after her initial craniotomy, MR imaging showed tumor...
recurrence in the lateral ventricles (Fig. 2A). The patient again underwent surgery, and although the surgeon believed a total resection was achieved, postoperative MR imaging indicated possible residual tumor in the most anterior portion of the third ventricle. Fourteen months later, MR imaging revealed a tumor recurrence in her third and lateral ventricles (Fig. 2B). Her neurological examination at this time was normal. An MR image of the spine was also obtained at this time and showed abnormal leptomeningeal enhancement (Fig. 2C). A lumbar puncture was positive for cytology consistent with central neurocytoma. The patient is currently receiving chemotherapy consisting of the same regimen as the patient in Case 1.

Pathological Analysis

Case 1. Analysis of tissue sections revealed a benign neoplasm composed of nests and cords of small tumor cells with rounded nuclei surrounded by prominent perinuclear halos (Fig. 1B). The sections also showed a con-
spicuous fibrillary network that occasionally surrounded blood vessels, giving the tumor a superficial resemblance to ependymoma (Fig. 1B). Immunostaining showed that the neoplasm was strongly positive for the neuronal marker synaptophysin (Fig. 1C) and immunonegative for glial fibrillary acidic protein (GFAP) and for S-100 protein, confirming the diagnosis of a central neurocytoma. Mitotic figures were rare (<1/10 high-power fields). The MIB-1 (Ki-67 antigen) tumor labeling index was 3.3%. Immunostaining for the p53 tumor suppressor gene was negative.

Case 2. Tissue sections from the initial biopsy specimen showed the typical morphological features of central neurocytoma: round tumor cells with perinuclear halos mimicking the appearance of oligodendroglioma cells (Fig. 2D). The diagnosis was also confirmed by immunostaining. The neoplasm was positive for synaptophysin and negative for GFAP and S-100 protein. Mitotic figures were rare (<1/10 high-power fields) in both the initial resection and the recurrent tumor. The 5-bromodeoxyuridine tumor labeling index determined on tissue from the initial resection was 0.8% and the MIB-1 (Ki-67 antigen) labeling index for the same specimen was 1.8%. The MIB-1 labeling index for the tumor removed at the first recurrence was 4.1%. The minute amount of tissue available from the second recurrence was insufficient to obtain an accurate labeling index. Immunostaining for the p53 tumor suppressor gene was negative on both the initial resection and the first recurrence. Cytological analysis of the cerebrospinal fluid obtained after MR studies revealed that spinal leptomeningeal enhancement showed clusters of tumor cells exhibiting the morphological features of neurocytoma (Fig. 2E).

Discussion

General Clinical Features

Central neurocytoma was first described in 1982 by Hassoun, et al.13 A well-differentiated tumor of neuronal origin, it is usually diagnosed during the second and third decades of life, but two 60-year-old patients have been reported.13 The tumor is usually intraventricular in origin, arising from the septum pellucidum, fornix, or the walls of the lateral ventricles. In a review of 127 cases, Hassoun, et al.,14 found that 98 tumors were located in the lateral ven-
tricles. Tumors were twice as common in the left ventricle as in the right. Third ventricular involvement was seen in 33 cases, of which 27 also showed lateral ventricular involvement, leaving only six cases (<5% of the total number) in which the neurocytoma was exclusively confined to the third ventricle. Two exceptional cases with massive tetraventricular extension have been reported. No examples of central neurocytoma arising from and confined to the fourth ventricle have been reported. Although several instances of intraparenchymal neurocytomas have been described, the relationship of these tumors to intraventricular neurocytomas and other low grade entities, such as dysembryoplastic neuroepithelial tumors, is uncertain and requires further study.

Histological Characteristics

The typical characteristics of neurocytoma—small tumor cells with rounded nuclei surrounded by prominent perinuclear halos—were seen in the tumors in both patients. As mentioned before, the perivascular fibrillary network and often prominent perinuclear halos seen in central neurocytoma may cause these tumors to be confused with ependymoma or oligodendroglioma. Therefore, it is not unusual for patients to be diagnosed initially as having an oligodendroglioma or an ependymoma, as was the case in the first patient. Central neurocytoma is easily distinguished from both of these glial neoplasms by demonstration of immunopositivity for the neuronal marker synaptophysin and negativity for GFAP. In the very small minority of tumors that fail to show synaptophysin positivity (usually for technical reasons), electron microscopy may be performed to identify characteristic neuronal ultrastructural features, including elongated cell processes with parallel arrays of microtubules and scattered neurosecretory vesicles. The distinction of neurocytoma from the other class of small cell neuronal tumors, neuroblastomas, is not generally a problem. Neuroblastoma is a malignant small cell neoplasm characterized by densely packed anaplastic cells with hyperchromatic nuclei, very scant cytoplasm, a high mitotic rate, and an intraparenchymal location. These features contrast sharply with the perinuclear halos, low mitotic index, and intraventricular location of neurocytomas.

Besides synaptophysin, a wide variety of neuron-associated proteins have been demonstrated to be present in neurocytomas, including synapsin, calcineurin, microtubule-associated proteins (MAP2, γ), neuron-associated Class III β-tubulin, neurofilament proteins, neuronal L1 adhesion molecule, and several neural cell adhesion molecule isoforms. Given the tendency for histological misdiagnoses, the actual number of central neurocytomas has almost certainly been historically underreported.

Recurrence of Neurocytoma

Tumor recurrence with ventricular and subarachnoid dissemination, as seen in our two patients, has not been previously reported in the literature. Of the seven reported cases of recurrence, none has been noted to have ventricular or spinal dissemination (Table 1). Yaşargil, et al., reported three cases of recurrence after total resection. One patient’s tumor recurred 3 years after initial surgery and was treated with a second excision followed by radiation therapy (50 Gy). The second operation revealed the same benign pathology as the original tumor, and the patient was still tumor-free 37 months later. The two other patients in the report by Yaşargil, et al., had recurrences 3 and 6 years, respectively, after the initial surgeries and were being followed expectantly because they were asymptomatic. Sgouros, et al., reported one case of a recurrent tumor in a 19-year-old woman 1 year after a subtotal resection. This patient underwent a second operation followed by radiation treatment. There was no further report on the patient.

Robbins, et al., reported a cystic recurrence in a patient who, 8 months earlier, had a 90% tumor resection followed by radiation treatment. This patient underwent a second operation but died 3 years after his initial presentation. Kim, et al., reported one case of a recurrent tumor after total resection. The patient’s original pathological examination indicated a benign tumor and the patient received only radiation therapy after the recurrence. In a subsequent report, Kim, et al., reported another patient who developed a recurrence 26 months after a subtotal resection followed by radiation treatment. This patient died of the tumor recurrence.

The report of our two patients is unique in that the recurrences included dissemination throughout the ventricular system and into the spinal column (Figs. 1D–F and 2B, C, and E). In our cases, as in those of Yaşargil, et al., and Kim, et al., histological examination indicated benign tumors without signs of high mitotic activity, microvascular proliferation, or necrosis.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Case</th>
<th>Initial Treatment</th>
<th>Time to Recurrence</th>
<th>Treatment at Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sgouros, et al., 1994</td>
<td>5</td>
<td>STR</td>
<td>56 Gy</td>
<td>8 mos</td>
</tr>
<tr>
<td>Robbins, et al., 1995</td>
<td>6</td>
<td>GTR</td>
<td>no</td>
<td>18 mos</td>
</tr>
<tr>
<td>Kim, et al., 1996</td>
<td>7</td>
<td>STR</td>
<td>54 Gy</td>
<td>26 mos</td>
</tr>
</tbody>
</table>

* AWD = alive with disease; DOD = died of disease; GTR = gross-total resection; NED = no evidence of disease; STR = subtotal resection; XRT = radiation therapy; — = not known.
Craniospinal dissemination of central neurocytoma

Proliferation Markers and Molecular Biology

The proliferation potential of central neurocytomas has been assessed in a very limited number of cases using various markers, including Ki-67, MIB-1, proliferating cell nuclear antigen, and silver-staining nucleolar organizer regions. All studies to date show central neurocytoma to be a slowly proliferating neoplasm. The reported MIB-1 labeling indices range from 0.3 to 8%. Although extrapolation of labeling indices from one laboratory to another are problematic because of a variety of technical reasons, the MIB-1 labeling indices observed in our two cases, 3.3% in Case 1 and 1.8 to 4.1% in Case 2, are well within the reported range for otherwise unremarkable central neurocytomas. Therefore, central neurocytoma can have a histologically benign appearance with a low proliferative index and yet be characterized by recurrence and even dissemination as seen in our cases. Both Kim, et al., and Robbins, et al., have also reported recurrences in patients with tumors of benign histology and low proliferative index.

Few cytogenetic or molecular biology studies have been reported for central neurocytoma. Cerdá-Nicolás, et al., reported a case of neurocytoma with loss of chromosome 17, which suggested the possibility of involvement of the p53 tumor suppressor gene. In our two cases immunohistochemistry failed to reveal alteration of the p53 protein in both primary and recurrent tumor. This finding is corroborated by preliminary data of Gyure, et al., who found no p53 alterations using immunohistochemical analysis in eight patients.

Conclusions

The natural history of central neurocytoma remains undefined. For newly diagnosed central neurocytoma, complete resection has been shown to provide the best long-term prognosis in most cases. Although it has been suggested that central neurocytomas are benign, the caveat is that they do recur. In the majority of recurrences, the event is local, and the patient seems to do well after a second resection followed by radiation therapy. However, ventricular and spinal dissemination does occur, even in cases in which the original pathology is without indication of malignant characteristics. Consequently, one should be aware of this possible sequela when treating and following these patients. Follow-up reports of our two cases and reports of other cases will help illuminate the best treatment for patients with these tumors.

References


J. Neurosurg. / Volume 86 / March, 1997

551