# **Cerebral Neurocytoma**

A New Subset of Benign Neuronal Tumors of the Cerebrum

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Three cases of patients with unusual neuronal tumors in the cerebral hemisphere are reported. All were associated with long-standing epileptic seizures. Computed tomography disclosed low-density lesions without contrast enhancement, which were interpreted as either arachnoid cysts or a cerebral infarction at initial diagnosis. Magnetic resonance imaging scans, however, revealed the lesions to be solid tumors. At surgery, the tumors were found to be relatively well demarcated, soft, and gelatinous. Histologically, all tumors were composed of small uniform stellate cells, which proliferated in a loose myxoid fibrillary matrix and resembled either oligodendroglial or astrocytic tumors. Ultrastructurally, however, all tumors showed neuronal differentiation, including numerous clear and occasional dense-core vesicles, microtubules, and a number of synapses.

A review of the literature uncovered no other such cases, and therefore it was decided to classify these tumors as a distinct group of benign neuronal tumors, designated as "cerebral" neurocytoma compared with "intraventricular" neurocytoma. Related nosologic problems of neuronal tumors of the central nervous system and their possible histogenesis are also discussed. *Cancer* 1992; 70:529–537.

Key words: neurocytoma, ultrastructural study, cerebral parenchymal neoplasm, electron microscopy.

Neuronal neoplasms of the central nervous system are known to show a wide spectrum of differentiation.<sup>1–8</sup> Because of this variability, there is still considerable controversy regarding their classification and nomenclature, and various terms, such as gangliocytoma, ganglioglioma, ganglioneuroblastoma, anaplastic ganglioglioma, and neuroblastoma, have been introduced to describe this group of tumors.<sup>8,9</sup> In addition to these types of neuronal tumors, the term "supratentorial neurocytoma" was coined for two indolent neuronal tumors located in the midline of the cerebrum.<sup>10</sup> Many tumors with similar clinical features, morphology, and location have been reported as "central"<sup>11-13</sup> or "intraventricular"<sup>5</sup> neurocytomas. Recently, we studied three cerebral tumors; they were composed of small uniform indolent neuronal cells and should be classified as neurocytomas or cerebral neurocytomas. This terminology can be used as a counterpart to intraventricular neurocytoma. In this article, we describe the clinical and neuropathologic features of these cases and discuss the wide morphologic spectrum of intracranial neuronal tumors.

#### Materials and Methods

Three patients treated at Kyushu University Hospital who had cerebral tumors form the basis of this report. After the initial clinical assessment, neuroimaging investigations, consisting of computed tomographic (CT) and magnetic resonance imaging (MRI) scans of the brain, and electroencephalography (EEG) were done. These diagnostic techniques were followed by surgery.

The materials obtained at surgery were fixed in buffered formaldehyde 10% and embedded in paraffin for routine histopathologic processing and immunohistochemical study. Paraffin-embedded sections  $5-\mu$ m thick were prepared and stained with hematoxylin and eosin, Nissl stain, and Bodian's silver impregnation for neurofibrils. For the immunohistochemical study, paraffin-embedded sections were stained with primary antisera against glial fibrillary acidic protein (GFAP, Dako, Santa Fe, CA) and synaptophysin (BioGenex, Dublin, CA) according to the avidin-biotin-peroxidase complex method.<sup>14</sup> Samples for electron-microscopic study were fixed in cold glutaraldehyde 2% in cacodylate buffer,

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postfixed in osmium tetroxide 1%, dehydrated, and embedded in Epon (Oken Shoji, Tokyo, Japan). The ultrathin sections were stained with uranyl acetate and lead citrate and examined by transmission electron microscopy.

#### **Case Reports**

#### Case 1

This right-handed girl had been well until the age of 1 year 8 months when convulsive seizures in her face developed, followed by loss of consciousness. A CT scan at that time showed a round nonenhancing low-density mass in the left frontal lobe near the Sylvian fissure. Her condition was diagnosed as arachnoid cyst, and she received medication for symptomatic epilepsy. The epileptic seizures increased in frequency, and a CT scan at the age of 7 years showed that the left frontal lesion with a minute foci of calcification had increased in size (Fig. 1). There was no perifocal edema, but a mild midline shift was associated. A MRI scan showed the lesion to be of hypointensity to the brain on T1-weighted images and of hyperintensity on T2-weighted images. Because the epileptic seizures increased in frequency and she had mild headaches, she was referred to our department and admitted to the hospital on November 14, 1988.

On admission, she was found to have a normal neurologic examination. EEG showed multifocal spikes mostly in the left central area. An intracarotid injection of amobarbital (Wada's test<sup>15</sup>) found that her motor speech center was not located in the left frontal lobe. At the age of 7 years 10 months, she underwent surgery, and the tumor, which was located in the left inferior and middle frontal gyri, was removed subtotally. Her postoperative course has been uneventful during 2 years of follow-up, and no tumor recurrence has been observed on CT scan. Seizure control became easier after the operation, and the total doses of required anticonvulsants was reduced.

### Case 2

A 41-year-old man first had a generalized convulsive seizure at the age of 11 years. Since that time, he received anticonvulsant medication. At approximately age 13 years, the seizure pattern changed from generalized epilepsy to temporal lobe epilepsy. At the age of 33 years, a CT scan revealed a lowdensity lesion in the right temporal lobe. He underwent craniotomy with the preoperative diagnosis of arachnoid cyst at another hospital. A thick arachnoid membrane in the right Sylvian fissure was sampled for biopsy, and the operative notes recorded only that the texture of the surface of the anterior temporal lobe was unusual. At the age of 41 years, the epileptic seizures became uncontrollable, he was referred to us by his local physician, and he was admitted to our hospital on May 17, 1990.

On admission, he was almost normal neurologically, except for epileptic seizures that occurred several times a day. A CT scan showed a low-density lesion in the anterior medial area of the right temporal lobe with a minimal mass effect. No enhancement of the lesion after contrast administration was seen. A MRI scan demonstrated the lesion to be hypointense to the gray matter on T1-weighted images and hyperintense to the brain on T2-weighted images (Fig. 2). EEG showed multifocal spike activity in the right temporal area. During surgery, the tumor, which was located in the anteromedial part of the temporal lobe (including the amygdala) and protruded into the suprasellar and prepontine cisterns, was removed subtotally. The tumor in the hippocampal area, however was not resected. After surgery, the patient has done



Figure 1. (Left) CT scan of Patient 1 at 1.8 years of age shows a low-density lesion in the left frontal lobe. (Right) CT scan of Patient 1 at 7 years of age shows a frontal lesion to have increased in size.



Figure 2. MRI scan of Patient 2 shows a right temporal lobe tumor to be (left) hypointense to the brain on T1weighted image and (right) hyperintense on T2-weighted image.

well, and the epileptic seizure frequency has decreased. At the time of this writing, 8 months after surgery, the residual tumor has not progressed.

## Case 3

This boy had been doing well until the age of 2 years 3 months when clonic seizures occurred, beginning in his left extremities, followed by generalized convulsions with loss of

consciousness. EEG at that time showed polyspike discharges in the right central and midtemporal areas. On CT scan, a low-density lesion with minimal mass effect was seen in the right frontal lobe. No enhancement of the lesion was observed after injection of contrast material. Neither any calcification nor cystic area was apparent, and the lesion was interpreted as being a cerebral infarction at another hospital. He later had several similar seizures and received anticonvulsant medication. At the age of 3 years 4 months, the seizures in-



Figure 3. Histologic feature of tumor from Patient 1. Small uniform tumor cells proliferate in a loose mucinous fibrillary and microcystic matrix. Some astrocytic cells are also found (H & E, original magnification ×230).

creased in frequency, and a MRI scan clearly demonstrated the lesion to be located in the premotor area of the right frontal lobe. It was hypointense to the gray matter on the T1weighted images and hyperintense on T2-weighted images. The lesion was diagnosed as a low-grade glioma, and he was referred to us for surgical treatment on November 1, 1990.

The neurologic examination on admission was unremarkable. During surgery, the tumor located in the premotor area of the right frontal lobe was removed partially. His postoperative course was uneventful after 2 months of follow-up. The epileptic seizures subsided, except for one generalized seizure that occurred 2 weeks after surgery.

## Results

The morphologic features of the tumors were similar in these three patients and deserve a common description.

Macroscopically, the tumors were demarcated sharply from the adjacent brain, but they were partly unclearly demarcated. They were yellow to grayish-pale in color, gelatinous, and soft; they could be removed easily by suction. There were some dilated capillaries and arteries in the tumors, but they were generally hypovascular. Minute foci of calcification and small cystic cavities with yellowish walls were found in some areas, but no necrotic tissues were encountered.

#### Light Microscopic Findings

The tumors were composed of relatively uniform small cells with a small round nucleus, scant and poorly defined cytoplasm, and fine fibrillary processes. They usually proliferated diffusely and occasionally were



Figure 4. Histologic and immunohistochemical features of tumors. (A) The tumor is composed of small round cells and their processes. Three large ganglionic cells are found in the spongy areas (arrows) (Patient 2) (H & E, original magnification ×180). (B) Higher magnification demonstrates ganglionic neuronal cells among small stellate cells (Patient 3) (H & E, original magnification ×290). (C) Punctate immunoreactivity with synaptophysin is found in the fibrillar area (Patient 1) (Synaptophysin-ABC, original magnification ×250). (D) Scattered reactive astrocytes in the tumor are positively stained with GFAP (Patient 3) (GFAP-ABC, original magnification ×270).

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grouped into small clusters. The major part of the matrix was characterized by a fine intercellular eosinophilic fibrillar mesh, which showed less organized loose reticular and myxoid appearances (Figs. 3 and 4A). Microcystic structures, some of which contained eosinophilic fluid, frequently were present. Mitoses of the tumor cells were rare, and there was no cell pleomorphism. Bodian silver impregnation staining showed that argentaphilic fibers, which arose from the tumor cells, were found rarely. Minute calcifications were scattered in part. Reactive astrocytes were found occasionally among these small neoplastic cells. In Patients 2 and 3, ganglionic neuronal cells with a large vesicular nucleus, a single prominent nucleolus, and a relatively abundant amount of cytoplasm were seen occasionally in the mucoid matrix (Figs. 4A and 4B). These ganglionic cells varied in size and shape and showed unusual cytologic variations from normal cortical neurons. However, neither binucleate neurons nor Homer–Wright rosettes were seen.

An immunocytochemical examination revealed no evidence of staining of small tumor cells for GFAP, but



Figure 5. Ultrastructural features of the small tumor cells. (Top) Round tumor cells with a narrow cytoplasmic rim and randomly oriented cell processes are seen in the widened extracellular spaces (Patient 1) (original magnification ×7700). (Bottom) Higher magnification of a cellular process of a tumor cell showing many microtubules running longitudinally. Synapses between the cellular processes are also found (Patient 2) (original magnification ×11,000). scattered nonneoplastic reactive astrocytes were stained positively for this protein with processes observed in these tumors (Fig. 4D). Synaptophysin staining showed diffuse positivity, with a punctate and granular pattern in intercellular fibrillar areas in these tumors (Fig. 4C).

## **Electron Microscopic Findings**

The small tumor cells had either a round or ovoid configuration (Fig. 5). The nuclei of these cells were also round or ovoid, but occasionally, they had an irregular contour with clefts in the nuclear membrane. They contained clumps of chromatin beneath the nuclear envelope and throughout the nucleoplasm. Nucleoli were sometimes prominent. The cytoplasm formed a narrow rim around the nucleus and contained a number of organelles, including polysomes, mitochondria, lysosomes of various sizes and shapes, and microtubules. The Golgi apparatus occasionally was prominent, and some neoplastic cells had abundant dilated rough endoplasmic reticulum (Fig. 6). In the perikarya of the tumor cells, and more frequently in the cytoplasmic processes, several small clear vesicles were identified. Dense-core vesicles also were found occasionally in the perikarya of the tumor cells and cytoplasmic processes. During the electron microscopic observation, ganglionic cells occasionally were encountered (Fig. 7). The cytoplasm of these cells was larger than that of the usual small ones, and the nucleus had clear finely dispersed chromatin and a neat nucleolus. The organelles were essentially similar to those of the small tumor cells.

Among tumor cells, many randomly oriented cytoplasmic processes, containing bundles of microtubules running parallel to the long axis, were interspersed in the widened extracellular spaces in most areas and were arranged compactly in areas (Figs. 5 and 8). Wellformed synaptic structures, consisting of an aggregation of clear vesicle, dense-core vesicle, and thickening of the presynaptolemma and postsynaptolemma, frequently were present between the cytoplasmic processes of tumor cells and occasionally between the process and the perikaryon of the tumor cells (Figs. 5 to 8). In addition, astrocytes containing intermediate fila-



Figure 6. (Left) Some tumor cells have many dilated rough endoplasmic reticula. Two synaptic devices are found (arrows) (Patient 2) (×8800). (Right) Higher magnification of an axosomatic synaptic structure, which contains numerous small clear and some dense-core vesicles (Patient 2) (×20,000)

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Figure 7. Ultrastructure of ganglionic cells. (Top) The tumor cell has a neat nucleolus. Neither oligodendrocytes nor astrocytes are found around the ganglionic cell (Patient 2) (original magnification ×6200). (Bottom) A cellular process of the ganglionic cell contains many microtubules and mitochondria (Patient 3) (×5400).

ments and myelinated nerve fibers were found, although this was rare.

### Discussion

These three unusual cases had similar clinical and neuropathologic features and are interesting from a diagnostic, therapeutic, and histopathologic point of view. Clinically, disease occurred in young people with a history of epileptic seizures. In Patients 1 and 2, the initial symptoms occurred more than 5 and 30 years previously, respectively. After our experience with Patients 1 and 2, the diagnosis was made relatively early (13 months after the onset of the initial seizure) in Patient 3. CT scans of these three patients also showed similar feature of a well-demarcated nonenhancing low-den-

sity lesion with minimal mass effect, all of which had been interpreted as being either arachnoid cysts or cerebral infarction. Serial observations with CT scans on Patients 1 and 2, however, showed a slight but definite increase in the size of the lesions, and MRI scans revealed these lesions to be a solid mass of hypointensity to the brain on T1-weighted images and of hyperintensity on T2-weighted images. All patients underwent tumor removal and did well postoperatively without adjuvant therapy. Although the postoperative follow-up period was limited, it appears that these tumors are of low-grade malignancy, judging from the long clinical history in two patients and the neuropathologic features discussed subsequently.

Anatomopathologically, these lesions showed both similar macroscopic characteristics and microscopic patterns. They were yellow to grayish-pale in color, relatively well demarcated, hypovascular, gelatinous, and soft. Histologically, they were composed of small uniform cells and lacked light microscopic evidence of malignancy, such as cellular pleomorphism and necrosis. Some of the histologic features, such as small cell population with fibrillary matrix, minute calcifications, and mucoid degeneration, suggest the diagnosis of oligodendroglioma or astrocytoma, but none of the tumorconstituting cells stained positively for GFAP. Alternatively, positive staining for synaptophysin was observed in the tumors, and ultrastructurally, clear and dense-core vesicles, microtubules, and synapses between the processes or between the process and the perikaryon of a tumor cell were observed frequently. The presence of these organelles and structures, which are identical to those seen in the normal peripheral, central, and autonomic nervous systems and in various kinds of neuronal tumors,<sup>4,5,6,8,16-19</sup> indicated an obvious and a greater degree of neuronal differentiation in the studied lesions.<sup>5,16,20,21</sup>

Although neuronal tumors of the central nervous system are known to show wide morphologic variability,<sup>1-8</sup> these tumors did not correspond to the histologic and ultrastructural criteria for diagnosis of previously described neuronal tumors. Although dysembryonic neuroepithelial tumors<sup>22</sup> were found to be composed of "oligodendrocytes," astrocytes, and neuronal cells, there were some similar clinical and histologic features to these three tumors. Because immunohistochemical staining for synaptophysin and electron microscopic studies were not done on these earlier tumors, it is possible that small tumor cells considered to be "oligodendrocytes" were actually small neuronal cells. As in the tumors we studied, the diagnosis of neuronal tumors of the central nervous system by light microscopy alone is sometimes difficult.<sup>10</sup> Many neuronal tumors, which are composed of small round or stellate cells, might have been confused with and classified as a certain kind



Figure 8. Ultrastructure of cellular processes of tumor cells in a compactly arranged area. Many synapses of various shapes are found (Patient 3) (original magnification  $\times$ 17,000).

of glial tumor, such as oligodendroglioma, ependymoma, or astrocytoma.<sup>5,23-25</sup>

Recently, intraventricular tumors composed of small neuronal cells have been diagnosed using the term "neurocytoma." The characteristics of these tumors are indolent clinical behavior, benign histologic features, and ultrastructural features of neuronal differentiation. Although our tumors also have these characteristics, they are different from intraventricular neurocytomas in several aspects. The tumors we studied were located in the cerebral hemisphere not the midline structures, and light microscopically, small neuronal cells of our lesions proliferated in a loose reticular pattern. Those of intraventricular neurocytomas proliferated compactly in sheets. There was also no patchy fibrillary matrix in the tumors we studied; this is normally characteristic of intraventricular neurocytomas.<sup>5,10</sup> In addition, ultrastructurally, we found synapses and clear vesicles were frequently in our specimens; these rarely were identified in intraventricular neurocytomas.<sup>5</sup> Numerous neuritic cellular processes, which were arranged compactly and formed a back-toback appearance in intraventricular neurocytomas, were interspersed in the widened extracellular spaces in the tumors we studied. Despite these differences, we consider that these tumors also can be classified as neurocytomas or cerebral neurocytomas because there may be a range of cell differentiation in this kind of tumor. Neurocyte is a general term, which collectively represents various kinds of mature neuronal cells, and

neurocytoma is also a term that collectively represents tumors composed of bland neuronal cells or neurocytes.

In 1990, 11 intraventricular neurocytomas were examined; both histologic and immunohistochemical diversities were reported.<sup>13</sup> In this series, a tumor composed, not only of small isomorphous cells, but also of ganglionic cells was included. These authors believed that these neoplastic ganglionic cells were in an advanced stage of neuronal differentiation and that the small neuronal cells were intermediate between those immature cells of the neuroblastoma and the mature cells of the gangliocytoma. Two of three specimens in our series also contained ganglionic neuronal cells, although it is uncertain whether they were neoplastic or an inclusion of preexisting neurons engulfed by the neoplasm. If these ganglionic neuronal cells were neoplastic, then should the small stellate neuronal cell in these tumors be considered an intermediate stage of neuronal maturation from a neuroblast to a ganglionic cell? Do they have the potential to differentiate further into "mature" neurons, such as ganglionic cells, as suggested previously? In a cytogenetic scheme, we believe the tumors we studied should be viewed in another way.

It is well known that there are various types of mature neurons, and ganglionic cell formation is not considered to be the sole feature of end-stage neuronal maturation. Ultrastructurally, the small stellate cells in our tumors resemble small neurons because of their frequent synapse formation, and they may be mature cells

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that resemble small granular neurons rather than large pyramidal or ganglionic cells. The precursor cells for neuronal tumors may be multipotential and simultaneously evolve along several pathways of neuronal differentiation toward various kinds of mature neurons.<sup>2,4,26–28</sup> The presence of ganglionic cells in two specimens we studied, if they are neoplastic, also may be explained as an example of the spectrum of differentiation of tumor cells that arises from a mitotically active neuroblastic cell and progresses to two kinds of mature neurons: small stellate and ganglionic neuronal cells.

In summary, we believe that these three cases represent a variant of neuronal tumors of the cerebral parenchyma, which, to our knowledge, has not been described previously. This new subset of neuronal tumors (for which we propose the term cerebral neurocytoma as a counterpart of intraventricular neurocytoma) deserves special attention because of its benign clinical and biologic behavior. Epileptic seizures, characteristic neuroimaging features, histologic resemblance to glial neoplasms, and ultrastructural neuronal features were found. Reports of central nervous system small cell neuronal tumors have increased over the past 10 years. From these cases, it is apparent that central nervous system neuronal tumors have a wider variety of forms than previously described, both clinically and pathologically.<sup>3</sup> Additional study is needed to determine the precise biologic behavior of the tumors we studied and their proper place in the spectrum of neuronal tumors of the central nervous system.

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