Subependymal giant-cell astrocytoma in children

An unusual discrepancy between histological and clinical features


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The authors describe five cases of subependymal giant-cell astrocytoma in children in which many clinical, histological, immunohistochemical, and ultrastructural features typical of this tumor were present. However, prominent focal necrosis and mitoses, features usually associated with high-grade tumors, were seen in all cases. Despite the presence of necrosis and mitoses, clinical follow-up studies have revealed a lack of aggressive tumor behavior after surgery alone. The discrepancy between the histological and clinical features in these cases is emphasized so that excessive treatment of a basically low-grade tumor may be avoided. Mast cells were seen in all five cases, often in large numbers.

KEY WORDS • giant-cell astrocytoma • brain neoplasm • necrosis • children

SUBEPENDYMAL giant-cell astrocytoma is a tumor that typically occurs in the lateral ventricle near the foramen of Monro, and is sometimes associated with features of tuberous sclerosis. Clinically, it is a slow-growing tumor that is rarely associated with mitoses and necrosis. Five cases of subependymal giant-cell astrocytoma were seen at the Royal Children's Hospital. All tumors showed features generally associated with malignancy; however, none has behaved clinically in an aggressive fashion. The clinical and pathological features of these cases are presented.

Clinical Material and Methods

All astrocytomas in the files of the Department of Anatomical Pathology were reviewed to identify cases of subependymal giant-cell astrocytoma. The diagnosis was determined from paraffin-embedded tissue blocks stained with hematoxylin and eosin and toluidine blue. Glial fibrillary acidic protein (GFAP) was demonstrated using immunoperoxidase staining. For electron microscopy, tissue was fixed in glutaraldehyde, postfixed in osmium tetroxide, embedded in Epon, and stained with uranyl acetate and lead citrate.

The clinical features of the five patients with this disease are presented in Table 1; all five were treated with surgery only. Due to the unexpected findings on histological examination, radiotherapy and (in one case) chemotherapy were considered. However, these adjuvant treatments were rejected due to the fact that the behavior of subependymal giant-cell astrocytomas has been generally reported as relatively benign.

Results

The histological features in all five cases were similar. The tumors contained three main kinds of cells that have been previously described; namely, fibrillated spindle cells, swollen gemistocytic cells, and giant ganglion-like cells (Fig. 1 upper left). Although the nuclei showed considerable variation in size, the outlines were generally round or oval with only very occasional intranuclear cytoplasmic inclusions. Chromatin was very fine and even. The nucleoli were large, prominent, and often multiple. Mitoses were easily seen in all cases and were quite numerous focally in two cases, with at least one per high-power field. Focal areas of coagulative necrosis were present in all cases (Fig. 1 upper right), although they were rather irregularly distributed. The necrotic areas could be easily seen macroscopically as chalk-white spots in a translucent light-tan background. These foci were often surrounded by dense collections of foamy histiocytes. Mast cells were seen in all cases, varying from an occasional cell to very numerous cells.
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Fig. 1. Photomicrographs showing the histological features in cases of subependymal giant-cell astrocytoma. Upper Left: Specimen showing a mixture of fibrillated spindle cells, gemistocytic astrocytes, and large ganglion-like cells, with mitoses (arrowheads). H & E, × 175. Upper Right: Specimen demonstrating focal areas of necrosis (arrowheads), sometimes surrounded by dense collections of foamy histiocytes. H & E, × 39. Lower Left: Specimen revealing prominent mast cells between tumor cells. Toluidine blue, × 300. Lower Right: Specimen from the periphery of the tumor. Tumor cells negative for glial fibrillary acidic protein can be seen to the right side of the picture, but many positive fibers and astrocytes in surrounding gliosis are visible at the left. Immunoperoxidase stain with hematoxylin counterstain, × 125.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age (yrs)</th>
<th>Tumor Location</th>
<th>Dilated Ventricles</th>
<th>Surgery</th>
<th>Features of TS Outside CNS</th>
<th>Family History</th>
<th>Follow-Up Period &amp; Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>F, 11</td>
<td>It lateral ventricle near FM</td>
<td>both lateral</td>
<td>total excision</td>
<td>DPS</td>
<td>father with pulmonary lymphangioleiomyoma</td>
<td>7 yrs, no recurrence</td>
</tr>
<tr>
<td>2</td>
<td>F, 8</td>
<td>It lateral ventricle near FM</td>
<td>It lateral</td>
<td>subtotal excision</td>
<td>DPS, echogenic masses in kidneys</td>
<td>none</td>
<td>6 yrs 6 mos, no change</td>
</tr>
<tr>
<td>3</td>
<td>F, 5</td>
<td>rt lateral ventricle near FM</td>
<td>both lateral</td>
<td>total excision</td>
<td>DPS, infantile spasm</td>
<td>mother with epilepsy</td>
<td>5 yrs 7 mos, no recurrence</td>
</tr>
<tr>
<td>4</td>
<td>M, 7</td>
<td>It lateral ventricle near FM</td>
<td>both lateral</td>
<td>subtotal excision</td>
<td>none</td>
<td>none</td>
<td>10 mos, no change</td>
</tr>
<tr>
<td>5</td>
<td>M, 11</td>
<td>rt lateral ventricle near FM</td>
<td>both lateral</td>
<td>total excision</td>
<td>none</td>
<td>none</td>
<td>9 mos, no recurrence</td>
</tr>
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* TS = tuberous sclerosis; CNS = central nervous system; FM = foramen magnum; DPS = depigmented skin lesions.
both in the perivascular areas and between tumor cells (Fig. 1 lower left).

Immunoperoxidase staining for GFAP showed small numbers of weakly positive gemistocytic cells and very occasional positive fibers in three cases. In the other two cases the findings were negative. In contrast, the tissue adjacent to the tumors showed strongly positive astrocytes and fibers (Fig. 1 lower right); some of these fibers could be traced into the tumors for a considerable distance.

Electron microscopy revealed large tumor cells alternating with elongated cell processes. The cytoplasm contained numerous membrane-bound granules (presumably lysosomes), prominent Golgi apparatus, and mitochondria and moderate amounts of endoplasmic reticulum and ribosomes. Some cells contained dense deposits of glycogen. Occasional cell processes contained moderate numbers of microtubules and bundles of filaments, but these were generally sparse. Convincing ependymal differentiation (that is, lamina surrounded by cells with regular microvilli and joined by fascia adherentes) was not seen.

**Discussion**

All five of these cases had many of the clinical features described in other reports of subependymal giant-cell astrocytoma.\(^2\)\(^3\)\(^5\)\(^8\)\(^9\)\(^{11}\)\(^{12}\) Topographically, the tumors were situated in the lateral ventricles near the foramen of Monro. In three cases, features of tuberous sclerosis, which is well known to be associated with subependymal giant-cell astrocytoma, were noted in organs outside the central nervous system (CNS). A suggestive family history was present in two patients. The histological investigation also showed many features described in the literature, including alternation of fibrillary areas with cells containing abundant, sharply defined eosinophilic cytoplasm.\(^2\)\(^3\)\(^5\)\(^8\)\(^9\)\(^{11}\)\(^{12}\) There was marked variation in the size of the nuclei; however, the even chromatin, smooth nuclear outlines, and relative lack of intranuclear cytoplasmic inclusions differentiated this tumor from other giant-cell tumors of the CNS.\(^12\)\(^{16}\) The variable presence of GFAP was similar to that described in previous reports.\(^1\)\(^2\)\(^{14}\) Around the periphery of the tumor, the strongly positive cells and fibers were presumably reactive rather than neoplastic.

In contrast to these, occasional positive cells were seen deep inside some tumors, with nuclear and cytoplasmic features similar to the adjacent tumor cells. The positivity of these tumor cells was much weaker than that of the reactive cells.

The electron microscopic appearance was also very similar to that reported previously; that is, large cells alternating with elongated cell processes, prominent lysosomes, mitochondria, and Golgi apparatus, and a general paucity of filaments and microtubules.\(^1\)\(^5\)\(^9\)\(^{13}\)\(^{15}\) even though minor variations (such as the presence or absence of glycogen) were noted from study to study. Although an occasional cell process in the present cases did contain dense bundles of filaments, the significance of this was difficult to interpret in view of the GFAP-positive processes that were seen extending from the periphery into the tumor, raising the possibility that such processes with their numerous filaments may belong to adjacent reactive rather than neoplastic astrocytes.

The unexpected finding was the presence of focal necrosis and easily identified mitoses in all cases. The first feature has been mentioned occasionally,\(^1\) although it is generally considered extremely uncommon in subependymal giant-cell astrocytomas.\(^1\)\(^1\) Mitoses were also considered to be rare or absent in any series.\(^5\)\(^9\)\(^{11}\) However, mitoses could be easily seen in all five of our patients and were sometimes quite prominent. Even though these two features varied considerably from area to area, there was no difficulty in finding both necrosis and mitoses with adequate sampling.

As necrosis and mitoses are generally considered features of malignant gliomas,\(^10\) there was considerable concern about the management and prognosis of these cases. Radiotherapy and chemotherapy were considered but rejected. That decision was supported by the clinical course after surgery. So far, there has been no suggestion of aggressive tumor behavior in any patient. The discrepancy between the histological features and clinical features is emphasized, so that the presence of mitoses and necrosis in an otherwise typical subependymal giant-cell astrocytoma does not lead to unnecessary radiotherapy or chemotherapy. Due to the small number of cases and the relatively short follow-up period in two patients, this conclusion has to be substantiated by following large series of similar tumors in which necrosis and mitoses have been detected.

The cause of necrosis without malignant behavior is uncertain. We wondered whether this finding might be the result of mechanical factors related to the intraventricular location and associated hydrocephalus. In at least two cases, surgery showed that the tumors had a narrow base and might have been prone to torsion. We also wondered whether the prominence of mitoses might be related to the patient’s age, as is true of a few other childhood tumors such as capillary hemangioma.\(^6\) However, this does not seem to be the case, since mitoses have not been emphasized in many series containing young children.\(^1\)\(^2\)\(^{8}\)\(^9\) Nevertheless, a discrepancy between clinical behavior and morphology is a well-known phenomenon in certain childhood tumors such as infantile fibrosarcoma,\(^1\) and subependymal giant-cell astrocytoma may be yet another tumor illustrating this occurrence.

The presence of mast cells is interesting. This feature has been described in one case report\(^1\)\(^6\) but was not mentioned in several series.\(^2\)\(^3\)\(^9\) Very little information is available on mast cells in CNS tumors.\(^7\) In a separate study, we will present details of this finding. However, detection of numerous mast cells in a neoplastic tumor does seem to be distinctly unusual, and may be another feature of subependymal giant-cell astrocytoma not previously emphasized.

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Giant-cell astrocytoma in children

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11. Ibid., pp 40–42

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