Angiocentric Glioma

A Clinicopathologic Review of 5 Tumors With Identification of Associated Cortical Dysplasia

Trent Marburger, MD; Richard Prayson, MD

Context.—Angiocentric glioma is a rare, epilepsy-associated, low-grade neoplasm with a characteristic perivascular growth pattern.

Objective.—To describe the clinicopathologic features of 5 angiocentric gliomas and to evaluate for coexistent malformation of cortical development/cortical dysplasia.

Design.—Retrospective review of the clinicopathologic features of 5 angiocentric gliomas (3 males and 2 females; median age at surgery, 10 years; range, 3–19 years).

Results.—Seizures were the most common presenting symptom (n = 4); 1 patient presented with headaches. Four of the tumors were located in the parieto-occipital, parietal, or temporal cortex and 1 case arose in the thalamus. All tumors consisted of an angiocentric growth pattern of bipolar spindle cells with mild pleomorphism.

In 2005, Wang and coworkers described a report of 8 cases of a superficial cerebral tumor with elements of both ependyma and astrocytoma and marked by an angiocentric growth pattern. They coined the term “monomorphous angiocentric glioma” for this tumor. Lellouch-Tubiana et al published a report at about the same time that described 10 cases of nearly identical tumors, which they designated “angiocentric neuroepithelial tumors.” These tumors were subsequently codified as a distinct clinicopathologic entity in the 2007 World Health Organization (WHO) Classification of Tumours of the Central Nervous System and were given the name angiocentric glioma. These low-grade neoplasms (WHO grade I) typically present with chronic epilepsy and demonstrate a characteristic angiocentric growth pattern, an infiltrative border, and ultrastructural features of ependymal differentiation. A recent review of the literature by Mott et al affirmed that these cortical-based tumors are primarily found in the pediatric population with no sex predilection.

More than 90% of reported patients with angiocentric gliomas have presented with seizures. Many of the pediatric tumors that present with chronic epilepsy, such as ganglioglioma and dysembryoplastic neuroepithelial tumor, are associated with adjacent abnormal cortical architecture (malformation of cortical development [MCD] or focal cortical dysplasia). The purpose of this study is to review the clinicopathologic features of 5 angiocentric gliomas and to evaluate for adjacent coexistent MCD or focal cortical dysplasia.

MATERIALS AND METHODS

Institutional review board approval was attained prior to commencement of the study. The pathology files were searched during a 20-year period of time (1989–2009) for tumors diagnosed as angiocentric glioma or tumors with pathologic descriptions potentially representing angiocentric glioma. Five patients were identified and all available pathologic materials were reviewed; a diagnosis was confirmed in all 5 cases. These 5 patients (3 males and 2 females; median age at surgery, 10 years; range, 3–19 years) comprised the study group. Criteria used for diagnosis included those outlined by the 2007 WHO Classification of Tumours of the Central Nervous System. Histologic features evaluated included the extent of solid versus angiocentric growth pattern, cell morphology, calcifications, mitoses, necrosis, and vascular proliferation. Immunohistochemical analyses were performed using formalin-fixed, paraffin-embedded tissue sections, avidin-biotin-peroxidase methodology, and an automated immunostainer (BenchMark XT system, Ventana Medical Systems, Tucson, Arizona). Ki-67 (prediluted; Ventana) labeling indices were determined for cases in which staining had been performed. Labeling indices were determined by assessing 1000 tumor cell nuclei in the area of tumor with the most staining and expressing positive-staining tumor nuclei as a percentage.

In tumors for which there was sufficient adjacent nontumor tissue resected, an assessment for MCD/focal cortical dysplasia...
was made using the Palmini et al \(^\text{a}\) classification. Palmini et al \(^\text{a}\) focal cortical dysplasia type IA is marked by isolated architectural abnormalities (dyslamination that may or may not be accompanied by ectopically placed neurons in or adjacent to cortical layer I and/or microscopic neuronal heterotopia outside layer I). Focal cortical dysplasia type IB is additionally marked by giant or immature neurons. Type IIA focal cortical dysplasia additionally shows evidence of dysmorphic neurons, and type IIB is marked by the presence of balloon cells.

The medical record was reviewed in each case for clinical information, including patient age and sex, clinical presentation, location of tumor, extent of resection, use of adjuvant radiation or chemotherapy, and status at last known follow-up.

**RESULTS**

A summary of the clinical features of all 5 patients in the current series is contained in Table 1. The 5 patients consisted of 3 males and 2 females with a median age at surgery of 10 years (range, 3–19 years). Seizures were the most common presenting symptom (n = 4); 1 patient presented with headaches. The duration of presurgical neurologic symptoms was known for 3 patients and was 1 year, 2 years, and greater than 8 years. Four of the tumors were located in superficial cerebrotectal locations (2 parieto-occipital cortex, 1 parietal cortex, and 1 temporal cortex; Figure 1, A) and 1 case arose in the thalamus. Three patients underwent a gross total resection of the tumor and 1 patient underwent a subtotal resection of his tumor. A biopsy only of the thalamic tumor was taken. No adjuvant chemotheraphy or radiotherapy was administered following surgery. Each patient’s postoperative seizure activity was compared to his or her preoperative activity and categorized using the Engel classification\(^{10}\) to assess the efficacy of these surgical interventions. All cases with gross total resection (3 of 3) showed complete cessation of seizure symptoms (Engel class I) or only nondisabling simple partial seizures. In the single case with subtotal resection, only mild improvement in seizure symptoms with no worthwhile improvement was reported (Engel class IV). Clinical follow-up revealed a favorable prognosis, with all patients alive at last known follow-up (median follow-up of 3 years; range, <1–10 years). No tumor recurrence following gross total resection (n = 3) was observed.

**Table 1. Summary of Angiocentric Glioma Clinical Features**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Diagnosis, y/Sex</th>
<th>Presentation*</th>
<th>Location</th>
<th>Laterality</th>
<th>Surgery</th>
<th>Adjuvant Therapy</th>
<th>Time, mo</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10/F</td>
<td>Seizures (class I)</td>
<td>Parieto-occipital cortex</td>
<td>Left</td>
<td>Total resection</td>
<td>None</td>
<td>131</td>
<td>ANET, Seizure-free</td>
</tr>
<tr>
<td>2</td>
<td>15/M</td>
<td>Seizures (class IV), visual disturbance, headaches</td>
<td>Temporal cortex</td>
<td>Left</td>
<td>Subtotal resection</td>
<td>None</td>
<td>103</td>
<td>AWT, Seizures, headaches</td>
</tr>
<tr>
<td>3</td>
<td>19/M</td>
<td>Seizures (class I)</td>
<td>Parietal cortex</td>
<td>Left</td>
<td>Total resection</td>
<td>None</td>
<td>44</td>
<td>ANET, Seizure-free (when taking medications)</td>
</tr>
<tr>
<td>4</td>
<td>3/F</td>
<td>Seizures (class I)</td>
<td>Temporal cortex</td>
<td>Left</td>
<td>Total resection</td>
<td>None</td>
<td>27</td>
<td>ANET, Seizure-free (unmedicated)</td>
</tr>
<tr>
<td>5</td>
<td>15/M</td>
<td>Headache and visual disturbance</td>
<td>Thalamus</td>
<td>Right</td>
<td>Biopsy</td>
<td>None</td>
<td>17</td>
<td>AWT, Headaches, seizure-free</td>
</tr>
</tbody>
</table>

Abbreviations: ANET, alive with no evidence of tumor; AWT, alive with tumor.

* Engel classification of seizures is given in parentheses.
Figure 1. A, This T2-weighted magnetic resonance imaging of an angiocentric glioma in the left parieto-occipital region demonstrates the typical superficial nature of these predominantly cortical-based tumors. B, Angiocentric glioma with bipolar spindled cells demonstrating a characteristic perivascular pseudorosette growth pattern. C, Angiocentric glioma demonstrating a solid growth pattern with microcyst formation and perivascular rosettes. D, Angiocentric glioma (upper right corner) demonstrating an infiltrative border with adjacent cortical tissue (lower left corner). E, Area adjacent to angiocentric glioma marked by a subpial aggregation of infiltrating tumor cells. F, Ki-67 labeling of angiocentric glioma showing a paucity of reactive cells. This case demonstrated Ki-67 labeling indices of less than 1% (hematoxylin-eosin, original magnifications ×200 [B, C, and D] and ×100 [E]; Ki-67, original magnification ×400 [F]).
suggestive of a dysmorphic neuron (possible Palmini et al type IIA focal cortical dysplasia; Figure 2, D).

**COMMENT**

Angiocentric glioma is a low-grade (WHO grade I) cerebrocortical tumor of childhood with a characteristic angiocentric growth pattern. More than 90% of reported angiocentric gliomas have presented with chronic epilepsy, and excision alone has most often proved curative.

Imaging studies of these tumors demonstrate hyperintensity on T2-weighted and fluid-attenuated inversion recovery magnetic resonance imaging without contrast enhancement. Clinically, our 5 patients closely resemble those previously reported. Our identification of a thalamic angiocentric glioma and the recent report of an “Angiocentric Glioma-like Tumor of the Midbrain” by Covington et al suggest that they may less commonly arise in other locations in the brain.

<table>
<thead>
<tr>
<th>Case</th>
<th>Calcification</th>
<th>Solid Component</th>
<th>Pleomorphism</th>
<th>Ki-67 Labeling Index</th>
<th>Subpial Aggregation</th>
<th>Infiltrative Border</th>
<th>Focal Cortical Dysplasia Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−</td>
<td>+</td>
<td>Mild</td>
<td>&lt;1%</td>
<td>+</td>
<td>+</td>
<td>IB</td>
</tr>
<tr>
<td>2</td>
<td>−</td>
<td>−</td>
<td>Mild</td>
<td>0%</td>
<td>+</td>
<td>−</td>
<td>IB</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>Mild</td>
<td>&lt;1%</td>
<td>+</td>
<td>+</td>
<td>IB</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>Mild</td>
<td>4%</td>
<td>−</td>
<td>+</td>
<td>IA</td>
</tr>
<tr>
<td>5</td>
<td>−</td>
<td>−</td>
<td>Mild</td>
<td>&lt;1%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

* Mitotic activity, necrosis, vascular proliferation, and meningeal extension were not observed.

* Palmini et al classification.

Table 2. Summary of Angiocentric Glioma Pathologic Features

Figure 2. A, Section taken from the right temporal lobe of an autopsy case showing the normal layering pattern of the superficial cortex. B, Area adjacent to angiocentric glioma marked by a malformation of cortical development (Palmini et al focal cortical dysplasia type IA) characterized by an absence of cortical layer II. C, Higher-magnification appearance of B highlighting the interface between the molecular layer of the cortex and the large pyramidal-type neurons that typically make up part of cortical layer III (external pyramidal layer). D, A Bodian stain highlighting the abnormal cell processes of a large neuron situated at the deep aspect of cortical layer I, suggestive of a dysmorphic neuron (hematoxylin-eosin, original magnifications ×100 [A and B] and ×200 [C]; Bodian, original magnification ×200 [D]).
Histopathologically, angiocentric glioma exhibits a perivascular growth pattern of bipolar spindle cells with mild pleomorphism, an infiltrative border, and lack of high-grade features such as elevated mitotic activity, necrosis, vascular proliferation, and meningeal extension. All 5 tumors in the current study consisted predominantly of this characteristic angiocentric growth pattern. An infiltrative border was discernable in 3 of 4 cases with sufficient tissue for evaluation. Immunohistochemical staining of angiocentric gliomas is typically positive with antibodies to glial fibrillary acidic protein, S-100 protein, and vimentin. A dotlike pattern of immunoreactivity to epithelial membrane antigen, similar to what may be encountered in some ependymomas, has also been described. Ki-67 labeling indices were less than 4% in all 5 cases presented here, which is well within the 1% to 5% range previously reported for angiocentric glioma and in keeping with the low-grade nature of the tumor. Ultrastructurally, these tumors reportedly show evidence of ependymal differentiation, with cilia and microvilli-filled microlumens bounded by elongated intermediate junctions.

The prognosis of these stable or very slow-growing tumors is excellent, following complete surgical excision. In the 5 tumors reported here, all cases with gross total resection (3 of 3) showed complete cessation of seizure symptoms (Engel class I) or only nondisabling simple partial seizures. No tumor recurrence following gross total resection (n = 3) was observed. In the single case with subtotal resection, only mild improvement in seizure symptoms was reported (Engel class IV). Evaluation of coexistent pathology in chronic epilepsy patients with neoplasms has revealed MCD/cortical dysplasia associated with a number of tumor types. Many of the pediatric tumors that present with chronic epilepsy, such as ganglioglioma and dysembryoplastic neuroepithelial tumor, are associated with adjacent abnormal cortical architecture (MCD or focal cortical dysplasia). A recently published study found that MCD or focal cortical dysplasia was identified in 40 of 50 patients with chronic epilepsy-associated tumors and demonstrated that the majority of these displayed Palmini et al type I lesions. Evaluation for coexistent MCD/cortical dysplasia in the 5 tumors reported here revealed the presence of these abnormalities in 4 of 4 cases with sufficient tissue for evaluation; all were Palmini et al type I lesions. The nature of the relationship between angiocentric gliomas and MCD/cortical dysplasia is not known. The coexistence here, as with the gangliogliomas and dysembryoplastic neuroepithelial tumor, suggests a probable developmental basis to the origin of these tumors.

The histogenesis of angiocentric glioma is a subject of debate, with postulated ependymal or radial glial cell origin. The differentiation of these tumors appears ependymal in nature when one considers the angiocentric growth pattern, immunohistochemical profile including a dotlike pattern of immunoreactivity to epithelial membrane antigen, and ultrastructural findings. The cortical location of the great majority of these tumors, however, argues against derivation from native ependymocytes or tanyocytes. Lellouch-Tubiana et al proposed a dysembryoplastic process with a radial glial cell origin for angiocentric gliomas, citing a cytologic resemblance of radial glial cells to those of angiocentric glioma. The differential diagnosis of angiocentric glioma should include ependymoma and pilomyxoid astrocytoma. Ependymomas share a number of features with angiocentric gliomas, including a predilection for the pediatric patient population, an angiocentric growth pattern with pseudorosette formation, immunohistochemical reactivity with epithelial membrane antigen in a dotlike pattern, and ultrastructural studies demonstrating cilia and microvilli-filled microlumens bounded by elongated intermediate junctions. Angiocentric glioma differs from ependymoma by its cortical location, diffuse and infiltrative growth pattern, and prominent bipolar spindle cell morphology, not typical of ependymoma. Pilomyxoid astrocytomas arise predominantly in a pediatric patient population, most often occur in the hypothalamic/chiasmatic region, and demonstrate contrast enhancement on imaging studies. Pilomyxoid astrocytomas may histologically resemble angiocentric gliomas with a vasocentric arrangement of bipolar spindled tumor cells, but demonstrate a noninfiltrative growth pattern and prominent mucinous background, not typical of angiocentric glioma.

In summary, we report a retrospective review of 5 angiocentric gliomas that exhibit similar features to previously reported cases of this low-grade epilepsy-associated pediatric tumor. The thalamic location of 1 tumor represents an undescribed location for this typically cerebrocortical tumor. A subset of angiocentric gliomas, similar to other low-grade chronic epilepsy-related tumors of childhood, are associated with coexistent MCD/focal cortical dysplasia, suggesting a developmental basis to their origin.

References