Congenital astroblastoma: an immunohistochemical study

Case report

BARRY L. PIZER, M.R.C.P., PH.D, TIMOTHY MOSS, M.R.C.PATH, PH.D.,
ANTHONY OAKHILL, F.R.C.P., DAVID WEBB, M.R.C.P, M.D.,
AND HUGH B. COAKHAM, F.R.C.P., F.R.C.S.

Imperial Cancer Research Fund, Paediatric and Neuro-Oncology Laboratory, and Departments of
Neuropathology and Neurosurgery, Frenchay Hospital, Bristol, United Kingdom; Department of
Paediatric Oncology, Royal Hospital for Sick Children, Bristol, United Kingdom; and Department of
Neurosurgery, University of Bristol, Bristol, United Kingdom

Astroblastomas are a rare type of glial tumor, usually occurring in older children and young adults. It has a distinctive histological appearance that is characterized by a radiating arrangement of tumor cells that form perivascular pseudorosettes. The authors report only the second case of astroblastoma presenting in congenital form. Following subtotal tumor resection, the infant received 10 courses of chemotherapy consisting of vincristine, etoposide, and carboplatinum. Evidence is presented for a tumor response to chemotherapy, a previously unreported observation. The child is alive 2.5 years after diagnosis with satisfactory functional status. Immunohistological and ultrastructural features of this tumor are presented. The discussion focuses on the biology, natural history, and management of this unusual neoplasm.

KEY WORDS • astroblastoma • immunohistochemistry • chemotherapy • histological study

Astroblastoma is a rare type of glial tumor, accounting for between 0.45%\(^1\) and 2.8%\(^2\) of gliomas in various series. Its first description in 1924\(^3\) was supported by a series of 25 patients reported by Bailey and Bucy in 1930.\(^4\) Since then, there has only been occasional reference to this tumor, although Bonnin and Rubinstein\(^5\) published a pathological study of 23 cases. The existence of astroblastoma as a pure nosological entity has been questioned,\(^6\) but most recent reports have concluded that it should be regarded as distinct from other types of astrocytic glioma.\(^6,7\) It was distinguished from other gliomas in the most recent International Classification of Tumors of the Central Nervous System proposed by the World Health Organization.\(^8\)

Astroblastomas have a distinctive histological appearance characterized by a radiating arrangement of tumor cells with broad footplates forming perivascular pseudorosettes.\(^9\) Although astroblastoma may occur in a patient of any age, it usually presents as a tumor in older children or young adults: its occurrence in children of less than 5 years is most unusual.\(^6\) We report, to the best of our knowledge, only the second case of congenital astroblastoma and perhaps the first in the English literature. Following radical but subtotal tumor resection, our patient received chemotherapy, radiation therapy being considered too hazardous for an infant. Evidence is presented for a possible response to chemotherapy, a benefit which has not previously been reported. The histological, ultrastructural, and immunohistochemical features of this tumor are also described.

Case Report

This male infant, weighing 2.5 kg (third percentile), was born at 39 weeks gestation to unrelated Caucasian parents following a normal pregnancy and delivery. At birth he appeared normal with a head circumference of 34.0 cm (25th percentile).

Examination. He presented at 17 days of age with a 5-day history of vomiting, poor feeding, and irritability. On examination, there was obvious hydrocephalus with splayed cranial sutures, distended scalp veins, and a tense,
bulging anterior fontanelle. His head circumference was 38.5 cm (90–97th percentile); examination of the central nervous system (CNS) was otherwise normal. Computerized tomography (CT) scanning of the head revealed a large cystic mass occupying the whole of the left frontal lobe (Fig. 1). The margin was thick, irregular, and slightly contrast enhancing. Considerable mass effect was seen with complete effacement of the cortical sulci.

**Operation.** The patient was treated with a course of dexamethasone and underwent craniotomy via left coronal incision. On opening the dura, pinkish-grey tumor extruded, which was sent for intraoperative histological examination. The tumor cyst, containing large amounts of old blood, was entered, and a radical but subtotal resection of the tumor was performed using microsurgical technique with bipolar diathermy and suction.

**Postoperative Course.** Postoperative progress was straightforward apart from three episodes of raised intracranial pressure requiring aspiration of cerebrospinal fluid. Shunt insertion, however, was not necessary, and steroid therapy was discontinued 10 days after surgery. At discharge 6 days later, he was well, tolerating oral feedings, and gaining weight. His head circumference was 40.8 cm (97th percentile).

A repeat CT scan of head at 74 days of age revealed no cyst reaccumulation, but a large left subdural effusion was detected. In addition, a contrast-enhancing area was noted at the genu of the corpus callosum, which was believed to be indicative of residual tumor (Fig. 2) An enhancing area was also seen in the region of the left caudate nucleus, which was possibly representative of residual disease. At that time he was well with no gross neurological deficit. Further therapy with external beam radiation was precluded by the child’s age. He was instead treated with 10 courses of chemotherapy at 3-week intervals, consisting of vincristine (1.5 mg/m²), etoposide (VP16; 120 mg/m² administered intravenously for 3 days) and carboplatinum (250 mg/m²). Apart from two episodes of staphylococcal septicemia following long line infections and the need for two blood transfusions, treatment was well tolerated.

Additional CT scans of head after both two and 10 (Fig. 3) courses of chemotherapy were similar, revealing persistence of a large left subdural effusion together with dilation of both lateral ventricles. Both scans demonstrated a considerable loss of the left frontal and parietal cortex. The previously enhancing areas in the genu of the corpus callosum and in the region of the caudate nucleus were much less evident, and an area of encephalomalacia was seen to occupy the site of the previous lesion in the left caudate nucleus.

Now aged 2 years and 8 months, he suffers from a right-sided hemiplegia but can walk well with a broad gait and is starting to run. He is able to use both hands in a two-handed activity but with marked left-sided dominance. His general developmental skills fall within the 18-month to 2-year range. He is thriving, and full hearing and visu-
al assessments show normal function. A recent CT scan shows no evidence of tumor recurrence.

Pathological Examination

Light Microscopy. Tissue taken at operation was divided into two parts. The tissue for light microscopy was fixed by immersion in 10% neutral formalin, processed by normal methods, and embedded in paraffin wax. Sections, 7 μm thick, were stained with hematoxylin and eosin, Mallory’s phosphotungstic acid–hematoxylin (PTAH), and a reticulin impregnation.

Staining of the sections with hematoxylin and eosin revealed a tumor of very uniform architectural and cytological appearance. Most tumor cells had large rounded nuclei and coarsely clumped chromatin, together with eccentrically oriented broad cytoplasmic processes. These tumor cells were arranged in numerous pseudorosettes around very numerous, thin-walled, capillary-like vessels, which appeared as palisades of cells oriented along vessels when cut in longitudinal sections (Fig. 4). Between perivascular pseudorosettes, stellate or spindle cells were sparsely arranged with very fine cytoplasmic processes. Mitotic figures were present but not numerous. There was one focal area of necrosis, but no vascular endothelial proliferation. Staining for reticulin confirmed the pattern of fine, thin-walled vessels and lack of vascular endothelial proliferation. Only sparse gliofibrillary processes were stained using PTAH.

Electron Microscopy. The biopsy tissue for electron microscopy was fixed by immediate immersion in 2.5% glutaraldehyde in 0.1 M cacodylate buffer and then divided into blocks no more than 1 mm across. These were postfixed in 1% osmium tetroxide in 0.1 M veronal-acetate buffer and then prepared for electron microscopy using normal methods. Areas for ultramicrotomy were selected using 1-μm resin sections stained with 1% toluidine blue. Ultrathin sections were cut on an ultramicrotome and examined using an electron microscope.

Electron microscopy revealed cells with ovoid nuclei situated distant from the vessels and displaying prominent nucleoli (Fig. 5). Cells were radially oriented with broad lobes of cytoplasm closely applied to the vascular basement. Higher magnifications clearly demonstrated glial-type intermediate filaments in the tumor cytoplasm.

Immunohistochemistry. Immunohistochemical analysis was performed with the antibodies listed in Table 1, using either an immunoperoxidase technique or by indirect immunofluorescence. For immunoperoxidase staining, 7-μm-thick sections were mounted on gelatin-coated slides and stained using the antibody as the first layer and a rabbit anti–mouse peroxidase (Dako, Copenhagen, Denmark) as the second layer. Both layers were incubated at room temperature for 30 minutes. Enzyme pretreatment was only used with the cytokeratin antibody, when the sections were preincubated with protease enzyme (Sigma Chemical Co., St. Louis, MO). Following the second layer, the reaction product was precipitated with diaminobenzidine and 1% hydrogen peroxide and lightly counterstained with Harris’s hematoxylin for 12 seconds.

Sections, 7 μm thick, were stained by immunofluorescence using antibody as the first layer and fluorescein-isothiocyanate conjugated rabbit anti–mouse F(ab')2 fragment (Dako, Copenhagen, Denmark) as the second layer. Both layers were incubated at room temperature for 15 minutes. Sections were visualized using a photomicroscope. Both techniques were monitored on every staining run by, including both negative control sections stained only with nonreactive serum as first layer, and positive control sections from tissue known to be positive for a given antibody.

On staining for surface-expressed antigens, the tumor was found to express the adhesion molecules: CD44 and the neural cell adhesion molecule. There was no determinable expression of Thy-1, epidermal growth factor receptor, or epithelial membrane antigen.

With regard to cytoplasmic antigens, glial fibrillary acidic protein (GFAP) was expressed but in a patchy distribution, positive staining mainly being found in the cytoplasmic lobes of tumor cells. The tumor cells exhibited diffuse positive expression of vimentin, neuron specific

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<th>Antibody</th>
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* Abbreviations: EMA = epithelial membrane antigen; EGFR = epidermal growth factor receptor; GFAP = glial fibrillary acidic protein; NCAM = neural cell adhesion molecule; NSE = neuron specific enolase; ICRF = Imperial Cancer Research Fund.
FIG. 5. Electron micrograph of a perivascular pseudorosette, showing tumor cells with broad lobes of lucent cytoplasm radially arranged around the central blood vessel (B). Bar = 5 μm. *Inset:* The tumor cell cytoplasm (C) contains glial-type intermediate filaments and is closely applied to the vascular endothelial cells (E) and their enveloping basal lamina. Bar = 1 μm.
enolase, and S-100 protein, whereas immunostaining for low-molecular-weight cytokeratin (CAM 5.2) was negative.

Discussion

As in this case, astroblastomas typically present as circumscribed spherical tumors occurring deep within the cerebral hemispheres. Other reported sites include the corpus callosum, the cerebellum, the brainstem, optic nerve, and cauda equina. The cell of origin of this tumor remains unknown. The astroblast postulated by Bailey and Bucy is unlikely to exist in light of current knowledge about glial progenitor cells. However, Rubinstein and Herman extensively studied two astroblastomas growing in long-term tissue culture. They observed a close ultrastructural and immunohistochemical similarity between the tumor cells and the tanycyte, which is a cell integral to the ependyma of submammalian species with features transitional between the astrocyte and ependymal cell. It has been suggested that a similar cell may also occur transiently during normal human embryogenesis and that astroblastoma may derive from abnormally persisting examples of such embryonal precursor cells. To the best of our knowledge, this is only the second report of this tumor occurring congenitally, as the first was described in 1982 by Nakajima and colleagues. These two cases tend to lend weight to the embryological hypothesis of Rubinstein and Herman, although, if this is correct, it seems odd that so few tumors occurring congenitally or in early childhood have been described to date.

From the point of view of differential pathological diagnosis, an astroblastoma is most likely to be confused with an ependymoma, especially when well differentiated. However, the histological organization of these two gliomas is quite different, with astroblastoma exhibiting rarified spaces between the pseudorosettes. This is in contrast to the typically compact intravascular architecture of the ependymoma. Further differentiating features between these tumors include differences in the nuclear characteristics of the tumor cells and the thickness of the perivascular cytoplasmic processes, with astroblastomas exhibiting broad footplates as opposed to the tapering processes seen in ependymoma. Although small areas of tumor with astroblastoma-like features may occasionally be found in some otherwise typical anaplastic astrocytomas, the case described here characteristic features of astrocytoma were found throughout the tumor, and we have no hesitation in describing this as an astroblastoma of pure type.

The immunohistochemical profile in this case is similar to that previously described. The distinction between this and nonglial papillary tumors was aided by immunohistochemistry, which demonstrated positive staining with glial markers such as GFAP and S-100. The interesting finding of a patchy distribution of GFAP, despite the presence of abundant intermediate-type filaments, has been noted by others. In addition, Cabello, et al., noted, as in the present case, intense positivity for vimentin. They hypothesized that the filaments seen were vimentin rather than typical glial-associated filaments. This may underlie the primitive nature of the astrocytoma, as vimentin filaments tend to precede their glial counterparts in neuroepithelial cell development.

The ultrastructural features conform to those of the very few previous reports, with typical cell architecture and the presence of abundant intermediate-type filaments and occasional microtubules. As described by Husain and Leestma, tumor cells were very closely opposed with no visible junctional complexes.

The natural history and prognosis of astroblastoma remain uncertain. In their report of 1930, Bailey and Bucy noted that the prognosis for astroblastoma appeared to be intermediate between that of glioblastoma and astrocytoma, a view widely held in the literature. The prognosis, however, is complicated by the recognized propensity of this tumor to transform into a more malignant type of glioma. In a study of 23 tumors, Bonnin and Rubinstein found that two distinct histological types of astroblastoma could clearly be discerned: a low-grade type, which showed features of a well-differentiated glioma with little evidence of anaplasia, and a high-grade type with a more anaplastic appearance. Of eight patients evaluated with low-grade tumors, five had survived from 3 to 20 years after therapy. Three of four patients evaluated with tumors of high-grade died within 2.5 years. In two of these patients, the tumor converted into a gliosarcoma and a glioblastoma, respectively. One patient in this group, however, was alive 11.5 years after surgical excision of the tumor and radiotherapy, having relapsed at 8.5 years with a tumor of low-grade histological features. The tumor reported here appears to fall most easily into the well-differentiated group. This may be borne out by the good clinical course thus far, but it appears that clinicopathological correlation in terms of prognosis is not reliable.

The optimum management of this tumor remains in doubt. It appears that most neurosurgeons would attempt tumor clearance and administer postoperative radiotherapy. In the series by Bonnin and Rubinstein, complete surgical excision was achieved in 12 of 13 patients. Eleven patients received radiotherapy and five chemotherapy. It is of note that the only patient to have radiotherapy following a diagnostic biopsy was alive 12 years after diagnosis, suggesting a benefit for radiation therapy. In the present case the morbidity likely to occur after irradiation of such an immature brain was thought to preclude this treatment. Despite a lack of evidence as to the efficacy of chemotherapy for astroblastoma, we elected to treat our patient with a combination of three agents known to be effective against other CNS malignancies. The treatment regimen appeared to be well tolerated. Radiological evidence of a tumor response to chemotherapy was noted, a previously unreported observation. Following two courses of chemotherapy, CT scanning showed the disappearance of an area of contrast-enhancing tissue, probably residual tumor, at the genu of the corpus callosum, with a possible reduction in size of a high attenuation area in the region of the left caudate nucleus.

Nearly 3 years after diagnosis, this child appears to be making satisfactory progress considering the extent of tumor and his age at presentation. Despite no evidence of disease at present, the prognosis must still remain guarded.
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due to the uncertain natural history of this tumor as described above.

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References


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Address reprint requests to: Barry L. Pizer, M.R.C.P., Department of Paediatric Oncology, Royal Hospital for Sick Children, St. Michael’s Hill, Bristol BS2 8BJ, United Kingdom.