

Diffuse Pontine Astrocytoma With Lipocytic Differentiation

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ABSTRACT

A 7-year-old boy was treated with radiation and chemotherapy for a diffuse pontine glioma. At autopsy, 8 months after diagnosis, the tumor was a diffuse grade II fibrillary astrocytoma with prominent lipocytic differentiation. Literature review suggests that lipocytic differentiation in low-grade astrocytomas occurs in a variety of patient ages, anatomic sites, grades, and astrocytic subtypes. Although the majority of low-grade lipoastrocytomas have behaved benignly, this child's lipoastrocytoma was the underlying cause of death. This outcome suggests that the outcomes of low-grade lipoastrocytic tumors may be expected to be the same as the underlying tumor subtype.

INTRODUCTION

Mesenchymal differentiation in primary brain neoplasms, although unusual, is well documented. Lipocytic differentiation with the coalition of fat droplets forming a single vacuole that displaces the nucleus to the cytoplasmic margin—as opposed to lipidization or xanthomatous change with small vacuoles scattered throughout the cytoplasm without nuclear peripheralization—can occur in a variety of primary brain tumors. Differentiation may present via identified tumor types such as cerebellar neuro-lipocytomas¹ or as variants of established tumor types such as central neurocytomas, medulloblasto-

mas, ependymomas, mixed glial neuronal tumors,^{2,3} glioblastomas,⁴ and gliosarcomas.³ Lipocytic differentiation in lower grade astrocytic lesions is beginning to be recognized as lipoastrocytomas.² Whether lipoastrocytoma is a distinct tumor or only a variant pattern encountered in a variety of astrocytomas has yet to be established.

We report a 7-year-old boy with a diffusely infiltrating pontine astrocytoma with lipocytic differentiation. We review the current literature on lipoastrocytomas to determine the different sites and underlying astrocytoma subtypes exhibited by these reported lipoastrocytomas. Based on this review, we discuss whether these lipoastrocytomas should be considered a distinct tumor type or represent only a pattern encountered in different subtypes of astrocytomas.

CASE REPORT

At 6 years of age, an otherwise normally developed African-American boy presented with ataxia, slurred speech, and internal deviation of the left eye. Magnetic resonance imaging (MRI) showed pontine enlargement with diffuse signal abnormality, decreased signal on T1-weighted images, and increased signal on T2-weighted images (Figure 1). No cystic component was demonstrated at this time. We diagnosed diffuse pontine glioma based on the MRI findings without biopsy confirmation.

Radiation consisted of 5400 Gy in 30 fractions. Chemotherapy included temozolomide 100 mg (90 mg/m²/d) for 42 days. Five weeks later, he received temozolomide 200 mg (160 mg/m²/d) for 5 days and oral lomustine 100 mg (90 mg/m²/d) × 1 day every 42 days for 2 cycles. He did well for 5 months and then suddenly lost the use of his left arm and developed a wide-based gait, slurred speech, and cranial nerve palsies. He was started on valproic acid 10 mg/kg/d, increasing to 17 mg/kg/d, with oral etoposide 50 mg/kg/d as palliation therapy. The patient entered hospice, where he developed *Streptococcus pneumoniae* sepsis. Further treatment was refused, and he died at age 7, 8 months after diagnosis.

Autopsy revealed meningoencephalitis with positive blood cultures for *S pneumoniae*. The pons was expanded more on the right than the left. Sectioning

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Figure 1. T1- (A) and T2- (B) weighted axial images demonstrate diffuse enlargement of the pons with decreased signal on the T1-weighted image and increased signal on the T2-weighted image, consistent with a pontine glioma.

revealed a well-defined 1.4×1.6 cm discrete pale white nodule on the right side of the pons; the tumor expanded the pons and extended into the right cerebral peduncle and right midbrain (Figure 2). Inferiorly, at the pontine-medullary junction, was a $1.6 \times 1.4 \times 1.2$ cm cyst with a rust-colored lining. Autopsy also showed occasional punctate hemorrhages in the tumor.

Microscopically, the tumor epicenter was the pons, with extension into the midbrain, cerebellar peduncle, medulla, and meninges over the medulla. Although there was a discrete nodule, the tumor



Figure 2. Section through the pons demonstrates a 1.6×1.4 cm well-circumscribed tumor in the right pons, with diffuse enlargement of the surrounding pontine tissue.

diffusely infiltrated the surrounding tissue. The tumor nodule was moderately cellular and composed of predominately fibrillary astrocytes with a gemistocytic component, and the infiltrating component was predominately neoplastic fibrillary astrocytes. Nuclei were oval to spindle and hyperchromatic with irregular outlines, but without prominent nucleoli or mitoses. Frequently admixed within the nodule—and to a lesser extent the diffusely infiltrating tumor—were large fat vacuoles, usually single, pushing the nucleus to the margin of the cytoplasm (Figure 3). The necrosis present was bland, cystic in the center, represented the grossly identified cyst, and was not surrounded by palisading tumor cells. No vascular proliferation was present. No Rosenthal fibers, microcystic components, or eosinophilic granular bodies were found. Glial fibrillary acidic protein was positive in the fibrillary and gemistocytic astrocytes of the tumor but was uninterrupted in the cells with fatty vacuoles. Synaptophysin and NeuN demonstrated entrapped neurons within the nodule, as well as normal neurons within the infiltrating portion of the tumor. MiB-1 stained only rare nuclei (<1%). TP53 demonstrated no nuclear staining. Isocitrate dehydrogenase 1 (IDH1) stained the fibrillary processes of the astrocytic tumor cells.

Electron microscopy for the tumor nodule that was fixed initially in formalin showed single, large membrane-bound vacuoles and occasional collections of smaller vacuoles, representing fat, that distended the tumor cell cytoplasm. Elsewhere were numerous cytoplasmic processes filled with intermediate filaments (astrocytic tumor processes) and numerous myelinated axonal processes.

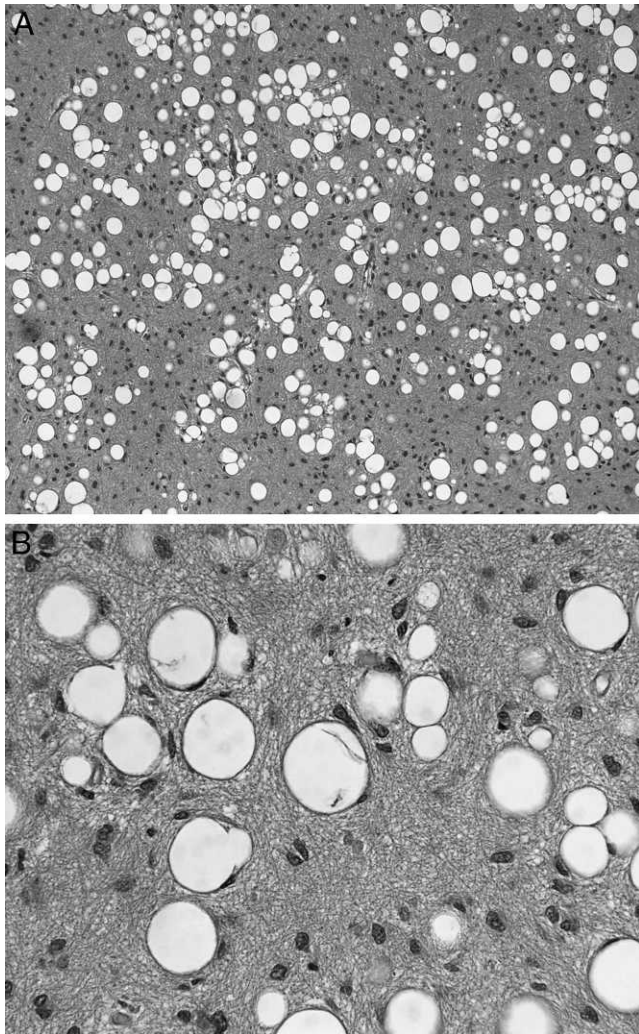


Figure 3. A. Section through the pontine nodule demonstrates only a mixture of astrocytes and mature adipocytes (hematoxylin-eosin stain, $\times 100$). B. Higher power view demonstrates the adipocytes with peripheral displacement of the nucleus. The background is composed of fibrillary astrocytic processes (hematoxylin-eosin stain, $\times 400$).

DISCUSSION

Although most diffuse pontine gliomas in children are high-grade gliomas—either glioblastoma multiforme (GBM) or anaplastic astrocytoma—33% are low-grade gliomas.⁵ Our patient's tumor had bland necrosis in the paucicellular areas of the tumor without palisading of the tumor nuclei; the necrosis could be attributed to therapy. Other features supporting a lower grade included a moderate but not high cellularity, a lack of mitosis, a low proliferative index (GBM reported as 20.4%, low-grade glioma as 3%),⁶ vascular proliferation, and no TP53 staining. Although the disease was progressive and we consider the infiltrative tumor to be the underlying cause of death, the immediate cause of death was

sepsis/meningoencephalitis rather than the direct compromise of vital structures by the tumor.

The table summarizes the 10 low-grade lipoastrocytomas reported in the literature, including the present report. Although none was called pilocytic astrocytoma, pilocytic features were described in 6 of the tumors; all were circumscribed (except in the patient with multifocal tumors, some of which were unencapsulated, while others were encapsulated).⁸ Three tumors were fibrillary, including ours, and one was only described as low grade. Patient 5's tumor was called fibrillary, but from the description was probably pilocytic. Four tumors involved the cerebral cortex, 2 the cerebellum, 2 the spinal cord, 1 the 4th ventricle, and ours the pons. Seven patients underwent gross total resection, 2 subtotal resection, and 1 no resection; the last was our patient, in which the tumor was not resected because of its location. Only one tumor recurred and was resected again.⁹ Nine patients were alive at last follow-up, 2 with stable disease. Our patient, who received chemotherapy and radiation, was the only patient who died from the disease. Like many other diffuse astrocytomas, the tumor in our patient demonstrated IDH1 cytoplasmic staining, indicative of an IDH1 mutation.¹⁵

Fat appears bright on T1-weighted images and is isointense to subcutaneous fat. No signal characteristics were consistent with fat in this child's imaging studies. Magnetic resonance spectroscopy—which was not performed in this case—is the most sensitive imaging tool to detect small amounts of fat and may have demonstrated a lipid peak. When routine imaging detects a fat signal, other diagnoses, such as a teratoma or dermoid cyst, may be considered.

Adipocytic differentiation is not restricted to any one tumor variant type and does not predominate in any certain anatomical site. Adipocytic differentiation does not increase the aggressiveness of the tumor; the only tumor death in the identified cases related to the tumor's location in the pons, which usually carries a dismal prognosis. However, whether adipocytic differentiation improves survival is unclear because it tends to occur in tumors with pilocytic features, and pilocytic astrocytomas are usually grade 1 lesions. Also, the presence of adipocytic differentiation alone cannot imply a less aggressive tumor because glioblastomas may contain adipocytic differentiation. Only 2 of the lipoastrocytoma patients underwent radiation or chemotherapy, so the adipocytic differentiation does not appear to be related to therapy.

CONCLUSION

The adipocytic differentiation in these tumors is a type of tumor metaplasia, the cause of which at present is unknown. Until more is known about these

Table. Summary of Low-Grade Lipoastrocytomas

Reference	Patient	Age (years)/ Sex	Site	Characteristics	Therapy	Survival After Diagnosis
Walter et al ⁷	1	77/F	Right cerebellar hemisphere	5 cm, localized, NOS, pilocytic features	Subtotal resection	9 months, stable disease
Roda and Gutiérrez-Molina ⁸	2	48/F	Spinal cord, multifocal, intramedullary	Encapsulated and unencapsulated, pilocytic features	Gross total resection	2 years, NED
Giangaspero et al ⁹	3	2/F	Left temporal-occipital	Circumscribed, pilocytic features	Gross total resection, reexcised at 28 months	3 years, NED
Giangaspero et al ⁹	4	12/M	Left frontal lobe	Circumscribed, cystic, mural nodule, pilocytic features	Gross total resection	7 years, NED
Aryan et al ¹⁰	5	36/F	T9-11 spinal cord, intramedullary	Circumscribed, biphasic, fibrillary (pilocytic) ^a	Gross total resection	1 year, NED
Ramirez-Aguilar et al ¹¹	6	24/M	Right temporal	Circumscribed, fibrillary	Gross total resection	5 years, NED
Lee et al ¹²	7	32/M	Intraventricular, 4th	Circumscribed, NOS, pilocytic features	Gross total resection	<1 year, NED
Gheri et al ¹³	8	39/M	Cerebellar-pontine, extra-axial	Exophytic, fibrillary	Subtotal resection	10 months, residual disease
Massimi et al ¹⁴	9	12/M	Left frontal	Circumscribed, low grade	Radiation, chemotherapy, gross total resection	2 years, NED
Craver et al	10	7/M	Pontine	Diffuse, fibrillary	Radiation, chemotherapy	DOD, 8 months after diagnosis

NOS, not otherwise specified; NED, no evidence of disease; DOD, dead of disease.

^a The report does not mention pilocytic astrocytoma, but the description includes features often associated with pilocytic astrocytoma—a biphasic pattern, Rosenthal bodies, and eosinophilic microgranular bodies.

tumors, little justification exists for prognostically separating lipoastrocytomas from the underlying variants from which they arise.

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