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Angiocentric Glioma: The Infiltrative Glioma with Ependymal Differentiation

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ABSTRACT

Angiocentric glioma is an epileptogenic, infiltrative, low grade glial tumor, with ependymal and astrocytic differentiation, most commonly seen in young adults and the pediatric age group. Herein we report a case of 21-year-old male patient who presented with fever and pharmaco-resistant seizures. Computed tomography revealed an iso-dense mass lesion in the gyrus rectus of the left frontal lobe.On magnetic resonance imaging the mass was hyperintense on both T1- and T2-weighted images with no contrast enhancement. Histopathological examination revealed monomorphous tumor cells diffusely infiltrating the neuropil with circumferential, radial, or longitudinal angiocentric alignment and subpial aggregation with perpendicular alignment of the cells to the pial surface. Among central nervous system tumors with ependymal differentiation, this distinct entity is the one with an infiltrating growth pattern. In spite of the infiltrating pattern, it does not seem to have a potential for aggressive behavior.

Key Words: Central nervous system neoplasms, Glioma, Ependymal, Seizure

INTRODUCTION

Angiocentric glioma (AG) is an epileptogenic, low grade glial tumor most commonly seen in young adults and the pediatric age group (1,2). Monomorphous angiocentric glioma was first described by Wang et al. (2) in 2002. It is accepted as a Grade I, distinct entity in the current World Health Organization (WHO) classification of Central Nervous System (CNS) tumors (3). It is most commonly seen supratentorially (2,4). The tumoral cells reveal both astrocytic and ependymal differentiation shown either by immunohistochemistry or electron microscopy (EM) analysis (1,5). Since it is a rarely seen tumor, we present a case of AG (ICD-O 9431/1, WHO Grade I) with the review of the literature.

CASE REPORT

A 21-year-old male patient was admitted to the emergency room with fever. He had generalized tonic-clonic seizures during his stay at the hospital. The etiology of the fever could not be found but it disappeared soon after antipyretic injection. Unfortunately his seizures were unresponsive to pharmacotherapy. Neuro-imaging with computed tomography (CT) and magnetic resonance imaging (MRI) revealed a mass lesion with a size of 20 mm by 8 mm in the gyrus rectus of the left frontal lobe (Figure 1A-D). On CT (Figure 1D), the mass was iso-dense to the adjacent parenchyma except for the central foci of calcification. On MRI, the mass was hyperintense on both T1- and T2-weighted images (Figures 1A-C), and showed no contrast enhancement. There was no vasogenic edema or mass effect extending beyond the contours of the lesion.

Following complete resection, histopathological examination revealed monomorphous tumor cells diffusely infiltrating the neuropil with circumferential, radial, or longitudinal angiocentric alignment (Figure 2A,C) and subpial aggregation with perpendicular alignment of the cells to the pial surface.

Immunohistochemically, the tumor cells were diffusely GFAP-positive (Figure 2B) and they revealed intracytoplasmic dot-like or spherical EMA positivity (Figure 2D). The neurofilament positive axons among the tumor cells showed the infiltrative pattern of the tumor. Neuronal markers did not reveal any staining of the tumor cells. No mitosis or necrosis was seen and the KI67 labeling index was low. No recurrence is noted within 4 years of follow-up.

DISCUSSION

Angiocentric glioma (AG) has been included as a distinct entity in the 2007 WHO classification of CNS tumors based on the clinical and histopathological findings obtained in three studies of large series with 26 patients (3). The total number of reported cases in the English literature is currently still less than 50 (2,4-21). It is most commonly

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encountered in early adulthood or childhood but a few late onset cases have also been reported (12,13-21).

AGs are located superficially, most commonly in the frontoparietal cortex and temporal lobe as well as the hippocampal region. One case in the midbrain (20) and one in the thalamus (11) have also been reported. The clinical presentation is with long-standing intractable epileptic seizures (5,19,22). Seizures are completely cured by surgical excision. There are also few cases presenting only with headache (7,21) or dizziness (18).

Radiologically, an infiltrative non-contrast enhancing cortical tumor showing a high signal on both T1- and T2-weighted images represent the findings seen both in our case and in those reported previously (11,16,22). Calcification, which is a rather infrequent finding in AG, was also noted in our case. As a sensitive detector of calcification, CT would be a valuable tool in the diagnostic work up of these patients. Hyperintensity on both sequences helps radiologically differentiation from other low-grade tumors such as dysembrioplastic neuroepithelial tumors.

Histologically AG is composed of perivascularly arranged glial cells with both ependymal and astrocytic differentiation. The radial angiocentric alignment is a typical finding of this tumor. Perpendicular arrangement to the pial surface is another helpful feature (1,2,23). Vasculocentric architecture may also be prominent in smear preparations during intraoperative consultation (24). There are 6 cases in the literature with associating cortical dysplasia (6,14).

The differential diagnosis includes ependymoma, diffuse astrocytoma and pilomyxoid astrocytoma. Ependymomas have common features with AG-like pseudorosette formation resembling an angiocentric growth pattern and immunohistochemical intracytoplasmic dot-like or spherical EMA staining. However, AG is a cortical

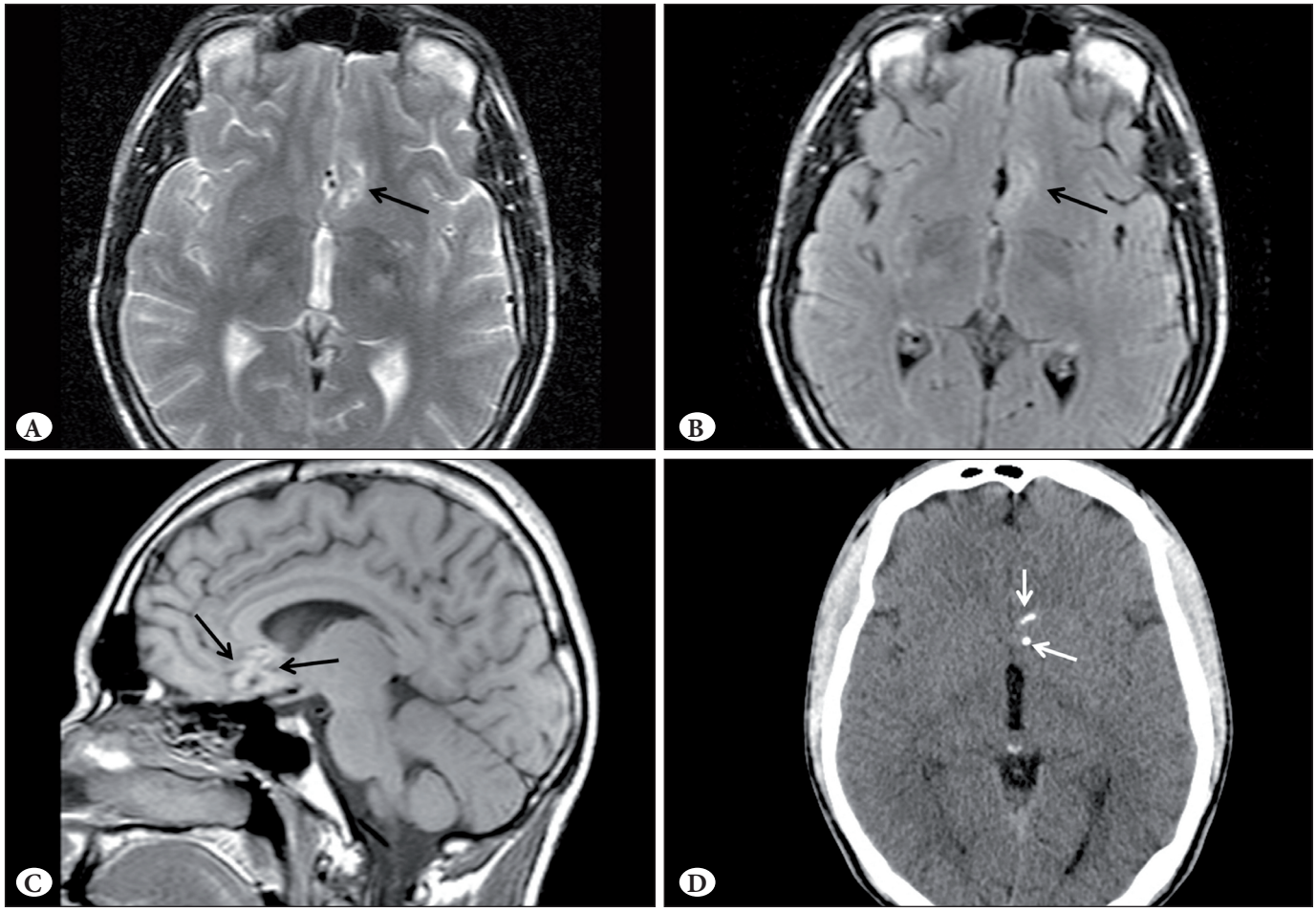

Figure 1: A,B) Transverse T2 and FLAIR weighted image shows a heterogenously hyperintense mass lesion (arrow) in the left gyrus rectus of the left frontal lobe. The abnormal signal is limited to the lesion itself with no associated vasogenic edema. **C)** Sagittal T1-weighted image shows that mass (arrows) is slightly hyperintense relative to the brain parenchyma. **D)** Foci of calcification (arrows) within the mass are noted on the plain computed tomography image.

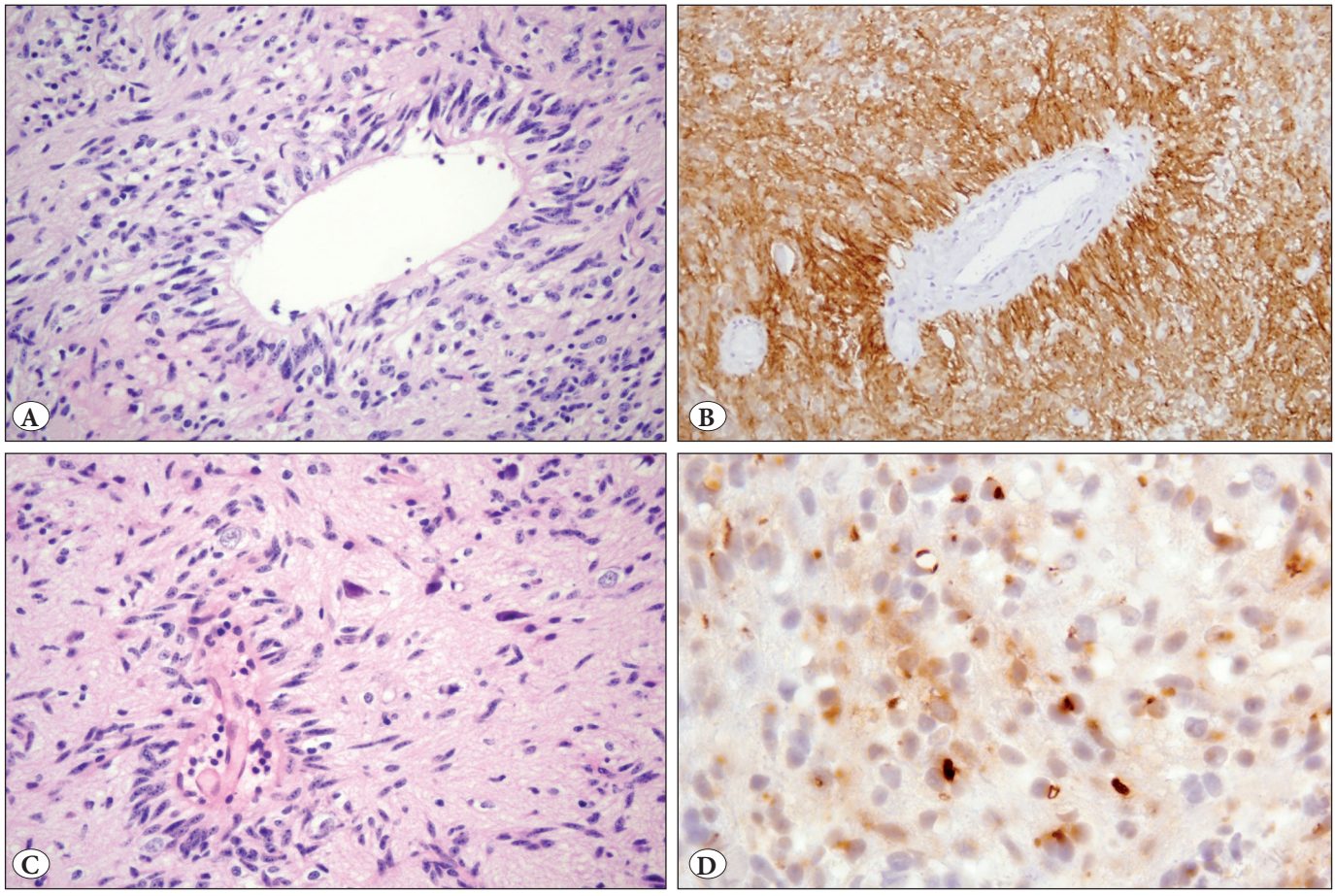

Figure 2: A) Monomorphous bipolar tumor cells make a radial arrangement around the blood vessels (H&E; x400). **B)** Tumor cells show diffuse GFAP positivity (GFAP; x400). **C)** Entrapped non-neoplastic neuronal cells, a feature supporting the infiltrative growth pattern, should not be misinterpreted as a component of the tumor (H&E; x400). **D)**Perinuclear dot-like or spherical EMA staining is an evidence of the ependymal differentiation (EMA; x1000).

lesion with infiltrative growth pattern unlike expansively growing ependymomas. Diffuse astrocytoma is in the differential due to the infiltrative pattern and diffuse GFAP immunopositivity. However, no EMA staining is expected, and no angiocentric arrangement of tumor cells is seen. Pilomyxoid astrocytomas are composed of bipolar spindled tumor cells with a vasculocentric arrangement. However, it is a non-infiltrating tumor and prominent myxoid stroma is a common feature that is not seen in AGs.

There is also one study that evaluates the presence of the IDH1 R132H mutation in AG cases (9). All of 3 cases in this study were negative for the presence of IDH1 R132H mutant protein. Spontaneous mutations of IDH1 have been detected in diffuse and anaplastic astrocytomas, oligoastrocytomas, oligodendrogliomas and secondary glioblastomas (25), but are rare in primary glioblastoma and absent in ependymoma. This finding may be helpful in distinguishing this unique neoplasm from diffuse glioma.

The immunohistochemical analysis showed both ependymal and astrocytic features of the tumor cells that was also supported by ultrastructural analysis revealing intracellular ciliated lumina with microvilli, intercellular zonula adherens contacts and/or astrocyte-like intermediate filaments in the processes and the cell body (1,2). A very similar tumor with only additional neuronal cell component was described as angiocentric neuroepithelial tumor (ANET) by Lellouch-Tubiana et al. (26). However, it is not included in the current WHO classification and the current WHO working group have reached a consensus that neoplastic cells of AG do not stain with neuronal markers.

Most of the reported cases have shown low proliferative activity. Necrosis and vascular endothelial proliferation has never been encountered. The clinical follow-up of the cases has shown indolent biological behavior except for a few cases with high mitotic count (2,13). The tumor has therefore been accepted as Grade I. The few cases exhibiting

recurrence or causing mortality were argued to have either AG with anaplastic features, anaplastic astrocytoma with angiocentric ependymal differentiation, or AG with malignant transformation. There are also some reports of AGs with high mitotic count but showing benign behavior (16). Based upon most reported cases, the overall prognosis seems to be rather benign.

Comparative genomic hybridization analysis of a few tumors demonstrated loss of chromosomal bands 6q24-q25 and gain of 11p11.2 including PTPRJ; the pathobiological relevance of these findings for this particular tumor should also be questioned (22).

Among central nervous system tumors with ependymal differentiation, this distinct entity is the one with an infiltrating growth pattern. In spite of the infiltrating pattern, it does not seem to have a potential for aggressive behavior.

The histogenesis of angiocentric glioma is a subject of debate, whether of ependymal or radial glial cell origin. A subset of angiocentric gliomas with associating cortical dysplasia may also suggest a developmental basis for their origin.

The favorable prognosis of this rare entity requires a careful evaluation of cortical epileptogenic tumors with imaging and morphological studies.

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