State-of-the-Art Pathology: New WHO Classification, Implications, and New Developments

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To keep up with advances in central nervous system (CNS) tumor diagnosis and discovery of new entities, the classification of these tumors requires periodic review and revision. Since the initial 1979 publication from the World Health Organization (WHO) of *Histological Typing of Tumours of the Central Nervous System,* 3 further editions have been published, cataloging the advances in CNS tumor classification and diagnosis over the past 3 decades. The second edition, published in 1993, incorporated advances in tumor classification resulting from the use of immunohistochemical techniques in diagnosis. Subsequently, the third edition, published in 2000, elaborated on the use of genetic techniques as an aid to tumor diagnosis, as well as describing associated clinical and radiologic findings and prognostic factors. The current 2007 edition includes several new entities, variants, and patterns of differentiation, and expands on the use of molecular techniques in diagnosis and prognostication. In this article, we discuss select new additions to the current classification, including new diagnostic tools, differential diagnoses, and management implications.

ANGIOCENTRIC GLIOMA, WHO GRADE 1

Angiocentric glioma is a low-grade indolent cortically based tumor of the cerebrum usually presenting in children with a history of seizures.[1–6] The tumor was first recognized in as a new entity in 2005.[1,2] The name originates from the presence of perivascular tumor cells, which are mostly bipolar, and are arranged in a circumferential, longitudinal, or perpendicular orientation to blood vessels.[1,2]

A total of 26 cases had been described at the time of publication of the 2007 WHO *Classification of Tumours of the Central Nervous System*, with a mean age of 17 years.[7] However, all but 2 of the 26 presented with seizures in childhood.[1–3] Five cases, all 13 years of age or younger,[4–6] have been described since. One additional cortical tumor in a 5-year-old presenting with headaches has been reported, with features described as

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ependymoma or angiocentric glioma.[8] Most of the patients had a preceding history of either refractory epilepsy or childhood seizures,[1–6] but one case presented with headache, loss of visual acuity, and no seizure history.[5]

Radiographically, the tumor appears as an ill-defined cortical lesion that is hyperintense on T2-weighted magnetic resonance images, and noncontrast enhancing on T1-weighed images, with superficial extension into the associated subjacent white matter.[1,2,4,5] Diffusion tensor imaging tractography has revealed tumor displacement of fibers.[6] One case has been reported to contain microcalcifications not detected radiographically.[2] The presence of a T2/FLAIR (fluid attenuated inversion recovery) "stalk-like" extension of the cortical tumor extending to the ventricle was described in a case series by Lellouch-Tubiana and colleagues.[2]

Histologically, the tumor is composed of a monomorphic population of cells, most with bipolar or fusiform cell processes, infiltrating the cortex as a single cell population with associated entrapped cortical neurons[1] or as masses of fusiform cells.[1,2] In less cellular areas, the tumor cells can have a circumferential and longitudinal orientation to blood vessels including capillaries (**Fig. 1**A).[1] In more densely cellular areas, the tumor cells are more radially oriented, forming perivascular pseudorosettes[1,4] and nodules of compact tumor cells.[1] The tumor is also reported to have subpial spread, with the tumor cells oriented perpendicular to the pial surface.[1] The cells are variably glial fibrillary acidic protein (GFAP) and EMA immunopositive and typically vimentin immunopositive (see **Fig. 1**B, C).[1–4] When positive, EMA usually has a dotlike immunopositive staining pattern similar to ependymomas,[1,3] but unlike ependymomas, angiocentric glioma tumor cells are CD99 immunonegative.[1] The tumor is variably immunopositive for neuronal markers, such as synaptophysin, NeuN, and chromogranin.[1,2,4]

Electron microscopy of some cases has revealed focal microlumina with associated microvilli and "zipper-like" intracellular junctions,[1,3] suggesting an ependymal phenotype. Preusser and colleagues[3] postulate an origin from radial glia, the basis for this theory being the radial orientation of tumor cells within the cortex, and the immunopositivity of the tumor for GFAP, vimentin, and S100. Chromosomal comparative genomic hybridization analysis of tumor DNA has revealed a loss of chromosomal bands 6q24-q25 and gain of chromosomal band 11p11.2.[3]

In one patient, placement of depth electrodes within the tumor revealed ictal activity centered

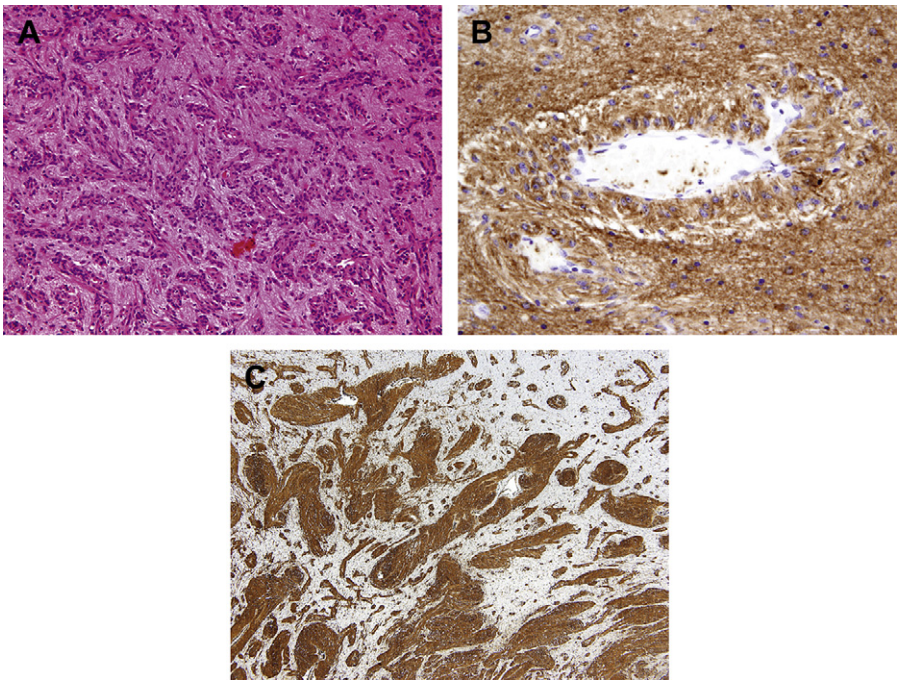

Fig. 1. Angiocentric gliomas: 13-year-old child with medically refractory epilepsy. (*A*) Circumferential and longitudinal arrangement of perivascular tumor cells around small blood vessels (hematoxylin-eosin, original magnification ×200). The perivascular radial orientation of tumor cells is highlighted by immunostains for (*B*) GFAP (original magnification ×400) and (*C*) vimentin (original magnification ×40).