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Oligodendroglial tumors: diagnostic and molecular pathology

Fausto J. Rodriguez, MD, Caterina Giannini, MD, PhD

From the Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota.

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Oligodendroglial tumors, which encompass pure oligodendroglioma and mixed oligoastrocytoma, represent the second most common glioma in adults after glioblastoma. They remain controversial neoplasms in the realm of surgical neuropathology. The early recognition of their more favorable prognosis and responsiveness to treatment when compared with diffusely infiltrating astrocytomas has influenced the pathologic diagnostic interpretation, and resulted in a pervasive interobserver variability. The more recent finding of an increased frequency of 1p/19q deletion in these tumors by cytogenetic analysis, and the association of this molecular abnormality with a better prognosis has greatly impacted the field of neuro-oncology. In this review, we focus on important histopathologic aspects in the evaluation of oligodendroglial tumors, key differential diagnoses, and highlight particular clinical and molecular characteristics, as well as current diagnostic and conceptual controversies.

Oligodendroglial tumors, encompassing pure oligodendrogliomas and mixed oligoastrocytomas, have attracted a lot of attention in the past two decades in the brain tumor field. Objective diagnostic criteria for oligodendroglial tumors remain controversial and difficult to apply, particularly to mixed oligoastrocytomas. This has resulted in considerable interobserver variability and limited reproducibility in the pathologic diagnosis of these tumors.[1] Once considered rare, they have actually become the second most commonly diagnosed glioma in adults after glioblastoma, accounting for up to 25% of all infiltrating gliomas.[2]

The first and classic historical description of oligodendroglioma was that of Bailey and Cushing[3] followed by the paper of Bailey and Bucy,[4] which followed a histogenetic approach to the "cell of origin." Although the tumors owe their name to morphologic resemblance of the neoplastic cells to oligodendrocytes, the central nervous system myelin-producing cells, current evidence does not support the oligodendrocyte as the cell of origin. Furthermore, recent genetic discoveries suggest the occurrence of early tumorigenic events common to all diffuse gliomas, including diffusely infiltrating astrocytomas. Oligodendroglial tumors appear to have a relatively more favorable prognosis, and to some extent to be more responsive to treatment than pure infiltrating astrocytomas, features which to a large extent may correlate with their unique and fascinating molecular genetics.

The diagnosis of oligodendroglioma and mixed oligoastrocytoma remains one of the most controversial topics in surgical neuropathology. Although the diagnosis of oligoastrocytoma may be a frequent diagnostic category in many institutions that frequently evaluate brain tumors, some authors are skeptical about this designation in most cases, and have referred to the increase in this diagnosis in the past two decades with the colorful analogy of a "virus epidemic."[5]

Demographic, clinical, and radiographic features

Pure oligodendroglioma represents approximately 5%-6% of gliomas.[6] The true frequency of oligoastrocytomas is more difficult to estimate, given the wide variability in its

Address reprint requests and correspondence: Caterina Giannini, MD, PhD, Department of Laboratory Medicine and Pathology, Hilton 11 Bldg., 200 1st St SW, Rochester, MN 55905.
E-mail address: Giannini.caterina@mayo.edu.

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diagnosis, but may represent between 5% and 20% of gliomas in some studies.[2,7] These tumors predominantly affect middle-aged adults, between 35 and 50 years of age.[7] There is a slight predominance for males over females.

With respect to anatomical location, oligodendroglial tumors tend to occur supratentorially, with the frontal lobe being the single lobe most often involved. They typically extend to the surface of the brain, affecting the cortex, a finding that might explain why seizures are frequently the presenting symptom. Involvement of the posterior fossa or spinal cord is a distinctly unusual occurrence. Predominant leptomeningeal growth is rare and appears to occur more frequently in the pediatric population.[8]

Magnetic resonance imaging usually demonstrates a relatively well-circumscribed abnormality (Figure 1). Macroscopic cysts or hemorrhagic change may be present. Computed tomography demonstrates calcifications, which may be nodular or clumped, in 70%-90% of cases.[9] Low-grade tumors are smaller and usually do not enhance. The presence of contrast enhancement is typically associated with anaplastic histology and a poorer prognosis (Figure 1D-F). Some authors have attempted to correlate the presence of 1p/19q codeletion at the molecular level with specific imaging features. In particular, the presence of an indistinct border and mixed signal characteristics seem to be associated with 1p/19q loss.[10]

Median overall survival times after diagnosis for grade II oligodendroglioma, grade II oligoastrocytoma, grade III oligodendroglioma, and grade III oligoastrocytoma are approximately 11.6, 4-5, 6.3, and 2.8 years, respectively,[7] although these numbers depend on histologic and molecular characteristics described below. Clinical characteristics that have been associated with a better prognosis include young patient age at diagnosis, tumor size, Karnofsky (performance) scores, extent of resection, and lack of contrast enhancement on imaging. Progression-free survival in oligodendroglial tumors is variable and correlates closely with molecular characteristics of the tumors. For example, in a study of low-grade oligoastrocytomas, progression-free survival was 60 and 30 months, respectively, depending on the presence or absence of 1p/19q loss of heterozygosity.[11]

Gross and histopathologic features

Gross examination of resected specimens of oligodendroglial tumors typically shows diffuse tumor growth with extension to the cortical surface resulting often in expansion of cortical gyri and blurring of the gray–white matter junction. Calcifications may be grossly visible, producing a "crunchy" feel while cutting and occasionally a single cal-

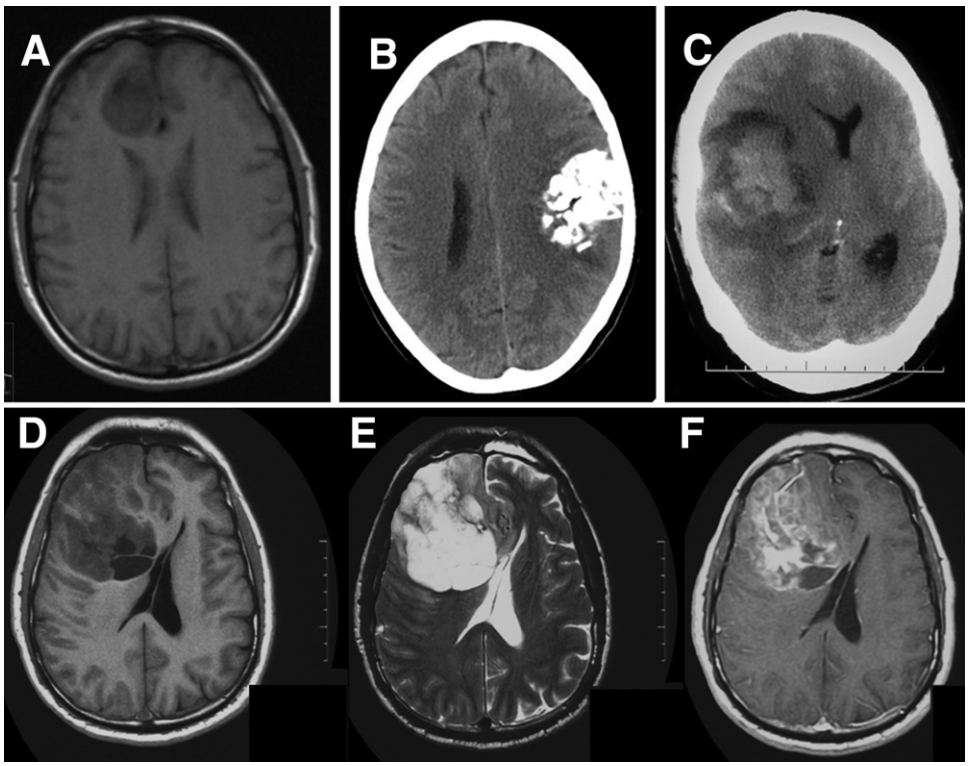

Figure 1 Radiologic characteristics of oligodendroglial tumors. Axial T1-weighted magnetic resonance imaging demonstrates a nonenhancing, relatively well-circumscribed, superficial right medial frontal lobe abnormality extending to the pial surface in a low-grade oligodendroglioma (A); axial CT demonstrates a densely calcified low-grade oligodendroglioma (B); axial CT shows a large intraparenchymal hemorrhage, which was the presenting feature of an anaplastic oligodendroglioma (C); a large anaplastic oligodendroglioma abutting the corpus callosum, with cystic change (D, E) and marked contrast enhancement (F), all features typical of high-grade gliomas.