Evolving Insights into the Molecular Neuropathology of Diffuse Gliomas in Adults

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KEYWORDS

• Diffuse gliomas • Astrocytoma • Oligodendroglioma • IDH mutations
• 1p/19q codeletion

KEY POINTS

- Diffuse gliomas that are both IDH-mutant and 1p/19q-codeleted are classified as oligodendroglioma, whereas tumors lacking codeletion of these chromosome arms are classified as astrocytoma and are further separated based on IDH-status.
- Diffuse midline glioma, H3 K27M-mutant, was added in the WHO 2016 classification as a separate entity. These highly aggressive, diffuse infiltrative generally occur in children and are located in the midline of the CNS (brainstem, thalamus, cerebellum, and spinal cord).
- GBMs are classified into expression subtypes characteried by activation of distinct transcriptional pathways: "a mesenchymal" subtype enriched in angiogenesis and inflammatory genes, a "classical" subtype enriched in stem cell and cell cycle genes, and a "proneural" subtype enriched in neurodevelopmental genes. Recent data suggest that the previously defined "neural" subtype is not a glioma-intrinsic subtype and may reflect contamination from nontumor tissue.
- GBMs can also be classified by methylation subtypes: IDH (which carry *IDH1* mutations, display G-CIMP, and have a more favorable prognosis), RTK I (which frequently harbor *PDGFRA* amplification), mesenchymal (methylation profiles most similar to normal brain tissue despite substantial copy number changes and enriched for the mesenchymal gene expression cluster), and RTK II (characterized by high frequency of chromosome 7 gain and chromosome 10 loss).

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EVOLUTION OF THE WORLD HEALTH ORGANIZATION CLASSIFICATION OF TUMORS OF THE CENTRAL NERVOUS SYSTEM

Gliomas are tumors of the central nervous system (CNS) whose neoplastic cells microscopically resemble nontumorous glial cells. Gliomas account for most tumors originating in the brain parenchyma.[1] The term "glioma" was introduced by the German pathologist Virchow[2] in the 1850s (**Fig. 1**), and in 1925 Bailey and Cushing[3] introduced the term glioblastoma multiforme (GBM) to describe a high-grade malignant glioma showing a wide range of histologic features (hence multiforme).

Later, (neuro) pathologists Ringertz, Scherer, Broders, and Kernohan provided important next building blocks for systematic histopathologic classification of gliomas.[4–8] Especially among adults, most of these tumors are diffuse gliomas, characterized by growth of tumor cells over long distances in the surrounding brain parenchyma (diffuse infiltrative growth). Traditionally, these diffuse gliomas were classified according to their microscopic similarities with (precursors of) glial cells and then designated as astrocytomas, oligodendrogliomas, or mixed diffuse glioma/oligoastrocytoma. Additionally, a malignancy grade (ranging from low-grade to high-grade) was assigned to these gliomas based on the presence or absence of particular histologic features.

Even after publication of the first edition of the World Health Organization (WHO) classification of tumors of the CNS in 1979, different schemes for typing and grading of diffuse gliomas were used in parallel.[9] However, the second edition of the WHO classification (published in 1993) was much more universally accepted as the standard for glioma classification.[10,11] For grading of astrocytomas, this latter classification incorporated elements of the St. Anne-Mayo grading approach in which absence or presence of mitotic activity, microvascular proliferation, and necrosis were used to assign a malignancy grade.[12]

The third and fourth editions of the WHO classification of CNS tumors (published 2000 and 2007) were built on essentially the same approach of histopathology-based diagnosis of diffuse gliomas, in some situations supported by the use of immunohistochemical markers.[13–17] However, despite being the time-honored diagnostic gold standard, it was increasingly clear that histopathologic classification of diffuse gliomas suffers from considerable interobserver and intraobserver variability, even among expert neuropathologists, and that the use of molecular markers had great potential to substantially improve the unequivocal discrimination of clinically relevant diffuse glioma subgroups.[18–23]

In the 1990s, the discovery that gliomas with a combined deletion of chromosome arms 1p and 19q (1p/19q codeletion) were associated with significantly improved survival and increased sensitivity to procarbazine-lomustine (CCNU)-vincristine (PCV) chemotherapy paved the way for molecular neuropathology of CNS tumors.[24–28] Typically, 1p/19q-codeleted tumors showed oligodendroglial histology, but the codeletion was reported to occur across different types and grades of diffuse gliomas with its favorable prognostic and predictive impact.[25] Of note, the apparent chemosensitivity of oligodendrogliomas was previously reported in 1988, years before a connection was made to the 1p/19q codeletion in 1998.[29] The fact that 1p/19q-codeleted tumors responded well to PCV treatment led to introduction of 1p/19q-testing in clinical practice before this molecular marker became a part of the WHO diagnostic criteria for a subset of diffuse gliomas.[28]

Another finding with a major impact on the molecular neuropathology of diffuse gliomas is mutations of the isocitrate dehydrogenase 1 (*IDH1*) gene and the related *IDH2* gene.[30–32] IDH-mutant and IDH-wildtype astrocytomas are clinically different tumors despite overlapping histologic appearances. IDH mutations were first reported in