Histopathology and Classification of Glioma: Review Article

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Abstract

Neoplastic transformation occurs in all glial cell types of the human nervous system, producing a wide variety of clinico-pathological entities and morphological variants. Astrocytomas are most common and span an unusually wide spectrum, ranging from the slowly growing juvenile pilocytic astrocytoma to the highly malignant glioblastoma multiform. Diffusely infiltrating astrocytomas of the cerebral hemispheres show an inherent tendency for progression towards a more malignant phenotype. This change is morphologically categorized in histologic grading schemes (e.g., WHO Grade II to IV) and is associated with the sequential acquisition of genetic alteration, including mutation in the p53 and homozygous deletion of the p16 tumor suppressor genes. Loss of heterozygosity on chromosomes 10 and 19q as well as amplification of the EGF receptor are largely restricted to malignant gliomas and thus considered late events in astrocytoma progression. Gliomas often show phenotypic expression of different glial cell lineages (e.g., oligoastrocytoma). Recent studies suggest that the occurrence of mixed gliomas is not indicative of a polyclonal origin but rather reflects altered gene expression leading to a charge in the balance of growth factors influencing glioma differentiation.

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Introduction:

Brain tumors are characterized by high morbidity and mortality owing to their localization and often locally invasive growth. Most neoplastic brain lesions are metastases arising from cancers outside the central nervous system (CNS) (which are 5–10 times more common than primary brain tumors) (1).

A glioma is a type of tumor that starts in the glial cells of the brain or the spinal cord. Gliomas comprise about 30 percent of all CNS tumors, and 80 percent of all malignant brain tumors. Gliomas do not usually metastasize by the bloodstream, but they can spread via the cerebrospinal fluid and cause "drop metastases" to the spinal cord. Complex visual hallucinations have been described as a symptom of low-grade glioma (2).

Symptoms accompanying gliomas depend on affected part of CNS, a brain glioma can cause headache, vomiting, seizures, and cranial nerve disorders as a result of increased intracranial pressure. A glioma of the optic nerve can cause visual loss. Spinal cord gliomas can cause pain, weakness, or numbness in the extremities (3).

A child who has a subacute disorder of CNS that produces cranial nerve abnormalities (especially of cranial nerve VII and the lower bulbar nerves), long-tract signs, unsteady gait secondary to spasticity, and some behavioral changes is most likely to have a pontine glioma (4).

Pathogenesis of glioma :

Recent advances made through multidisciplinary molecular research on cancers using large-scale DNA methylation profiling and next-generation sequencing approaches have enabled the molecular stratification of diffuse gliomas by the combination of genetic aberrations rather than assessing the status of individual markers (5).

Importantly, the identification of distinct genetic profiles in each glioma has culminated in novel glioma classifications with diagnostic, prognostic and predictive molecular biomarkers (Figure 1)(6). Metabolic reprogramming is an emerging core hallmark of cancer, and genetic aberrations, in combination with intrinsic and extrinsic molecular signaling, shift intracellular metabolism to support

the demands of rapidly proliferating cancer cells, in order to facilitate energy production, biosynthesis of macromolecules, and maintenance of reduction– oxidation (redox) reactions(7).The hallmark of this reprogramming is highlighted by aerobic glycolysis, termed "the Warburg effect", as well as other critical metabolic circuits including amino acid metabolism such as glutaminolysis, lipid and nucleotide synthesis, and reactive oxygen species (ROS) management. Furthermore, metabolic reprogramming could dynamically shift the epigenetic landscape, as exemplified by DNA and histone modifications, through the production of intermediary metabolites (8).

Recent studies have clearly demonstrated that cancer metabolism is activated by dynamic changes in signaling and transcriptional networks that is induced by activated oncogenes (e.g. epidermal growth factor receptor (EGFR, RAS, MYC) and deregulated tumor suppressor proteins (e.g. TP53, Rb) which are hallmark genetic aberrations for diffuse gliomas, including glioblastoma multiforme (GBM)(9).

Additionally, mutations in intracellular metabolic enzymes are also involved in carcinogenesis, as is highlighted by the discovery of the gene for isocitrate dehydrogenase 1 (IDH1), or less commonly IDH2, gene mutations that are detected in more than 70%of World Health Organization (WHO) grade II and grade III diffuse astrocytic and oligodendroglial tumors, as well as in a small fraction of GBMs that progress from lower-grade gliomas (LGGs) **Figure (1).** (10)

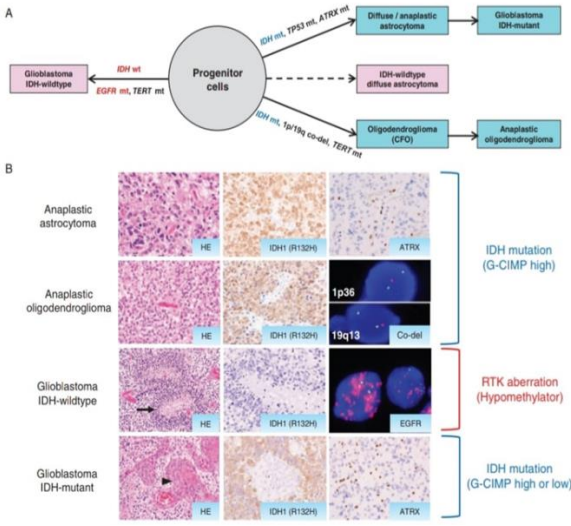

Figure (1) Genetic aberrations for gliomagenesis in adults. (A) Shown are major genetic mutations for each glioma entity. (B) Immunohistochemistry for IDH1 (R132H) and ATRX is useful for the molecular classification of diffuse gliomas in adults. The presence of IDH mutation significantly affects the status of methylation phenotypes in gliomas. 1p/19q-codeletion and EGFR amplification can be detected by FISH: green, probes for centromere regions; red, probes for targeted regions. Arrow, palisading necrosis; arrowhead, microvasucular proliferation. ATRX, alpha thalassemia/mental retardation syndrome X-linked; CFO, classic for oligodendroglioma; codel, codeletion; EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization; G-CIMP, glioma with a CpG island methylator phenotype; IDH, isocitrate dehydrogenase; IDH1, isocitrate dehydrogenase 1; mt, mutant; RTK, receptor tyrosine kinase; TERT, telomerase reverse transcriptase; wt, wild-type. (10)

WHO classification of gliomas (2016):

The WHO classification of gliomas is used to guide glioma treatment. As indicated in the classification, most patients require surgical intervention via gross total resection or biopsy (4).

Diffuse astrocytic and oligodendroglial tumors:

- Diffuse astrocytoma, IDH-mutant (Grade II).
- Anaplastic astrocytoma, IDH- mutant (Grade III).
- Glioblastoma, IDH wild-type (Grade IV).
- Oligodendroglioma, IDH-mutant, and 1p/19q-co-deleted (Grade II).
- Anaplastic Oligodendroglioma, IDH-mutant, and 1p/19q-co-deleted (Grade III).

Other astrocytic tumors:

- Pilocytic astrocytoma (Grade I).
- Subependymal giant cell astrocytoma (Grade I).
- Pleomorphic xanthoastrocytoma (Grade II).
- Anaplastic pleomorphic xanthoastrocytoma (III).

Ependymal tumors:

- Subependymoma (Grade I).
- Myxopapillary ependymoma (Grade I).
- Ependymoma (Grade II).
- Ependymoma, RELA fusion-positive (Grade II or III).
- Anaplastic ependymoma (Grade III).

Other gliomas:

- Angiocentric glioma (Grade I).
- Chordoid glioma of the third ventricle (Grade II) (4).

WHO classification of gliomas (2021)

The fifth edition of the WHO Classification of Tumors of the Central Nervous System (WHO CNS5) is the sixth version of the international standard for the classification of brain and spinal cord. WHO CNS5 features substantial changes by moving further to advance the role of molecular diagnostics in CNS tumor classification .(11)

Table (1): WHO classification of CNS tumors 2021. (11)

Table (1) 2021 WHO Classification of Tumors of the Central Nervous System. Provisional Entities are in Italics

World Health Organization Classification of Tumors of the Central Nervous System, fifth edition
Gliomas, glioneuronal tumors, and neuronal tumors
Adult-type diffuse gliomas
Astrocytoma, IDH-mutant
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
Glioblastoma, IDH-wildtype
Pediatric-type diffuse low-grade gliomas
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Angiocentric glioma
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Pediatric-type diffuse high-grade gliomas
Diffuse midline glioma, H3 K27-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
Circumscribed astrocytic gliomas
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Chordoid glioma
Astroblastoma, *MN1*-altered
Glioneuronal and neuronal tumors
Ganglioglioma
Desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma
Dysembryoplastic neuroepithelial tumor
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
Papillary glioneuronal tumor
Rosette-forming glioneuronal tumor
Myxoid glioneuronal tumor
Diffuse leptomeningeal glioneuronal tumor
Gangliocytoma
Multinodular and vacuolating neuronal tumor
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma
Ependymal tumors
Supratentorial ependymoma
Supratentorial ependymoma, *ZFTA* fusion-positive
Supratentorial ependymoma, *YAP1* fusion-positive
Posterior fossa ependymoma
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma
Spinal ependymoma, *MYCN*-amplified
Myxopapillary ependymoma
Subependymoma

Gene and Protein Nomenclature for CNS Tumor Classification

The fifth edition of the WHO Classification of Tumours uses the HUGO Gene Nomenclature Committee (HGNC) system for gene symbols and gene names (https://www.genenames.org/),(12) the Human Genome Variation Society (HGVS) recommendations for sequence variants (http://varnomen.hgvs.org/),(13)and the reporting guidelines for chromosomal alterations of the International System for Human Cytogenetic Nomenclature 2020.

CNS Tumor Grading

CNS tumor grading has for many decades differed from the grading of other, non-CNS neoplasms, since brain and spinal cord tumors have had grades applied across different entities.(14) WHO CNS5 has moved CNS tumor grading closer to how grading is done for non-CNS neoplasms but has retained some key aspects of tradi- tional CNS tumor grading because of how embedded such grading has been in neuro-oncology practice. Two specific aspects of CNS tumor grading have changed for WHO CNS5: Arabic numerals are employed (rather than Roman numerals) and neoplasms are graded within types (rather than across different tumor types). (15) Nonetheless, because CNS tumor grading still differs from other tumor grading systems, WHO CNS5 endorses use of the term “CNS WHO grade” when assigning grade .

Arabic vs Roman numerals. —Traditionally, CNS WHO tumor grades were written as Roman numerals. However, the fifth-edition WHO Blue Books have emphasized more uniform approaches to tumor classification and grading and have favored the use of Arabic numerals for grading, as is currently done for all the other organ sys- tems. Furthermore, a danger of using Roman numerals in a within-tumor grading system is that a “II” and a “III” or a “III” and a “IV” can be mistaken for one another and an uncaught typographical error could have clinical con- sequences. This was less likely when each tumor type had a different name, eg, “anaplastic” was present in addition to grade “III.” Given these considerations, WHO CNS5 has changed all CNS WHO tumor grades to Arabic numerals .

Grading within types.—As outlined above, CNS tumors have traditionally had a grade assigned to each entity, and grades were applied across different entities.(14)

Table (2)CNS WHO Grades of Selected Types, Covering Entities for Which There Is a New Approach to Grading, an Updated Grade, or a Newly Recognized Tumor That Hasan Accepted Grade

CNS WHO Grades of Selected Types	
Astrocytoma, IDH-mutant	2,3,4
Oligodendroglioma, IDH-mutant, and1p/19q-codeleted	2,3
Glioblastoma, IDH-wildtype	4
Diffuseastrocytoma, *MYB*-or*MYBL1*-altered	1
Polymorphous low-grade neuroepithelial tumor of the young	1
Diffusehemisphericglioma, H3G34-mutant	4
Pleomorphic xanthoastrocytoma	2,3
Multinodular and vacuolating neuronal tumor	1
Supratentorial ependymoma	2,3
Posterior fossa ependymoma	2,3
Myxopapillary ependymoma	2
Meningioma	99999 1,2,3
Solitary fibrous tumor	1,2,3

This entity-specific and clinical approach to tumor grading was different from the grading used in other, non- CNS tumor types.(14) Most tumors in other organ systems are graded within tumor types, eg, a breast or prostate cancer is graded according to its particular grading system. In the 2016 CNS WHO classification, solitary fibrous tumor/ hemangiopericytoma was graded in this manner, using a single name but with the option of 3 grades. In WHO CNS5, the shift to within-tumor-type grading has been extended to many categories (eg, see Tables (2). This change was done for several reasons: to provide more flexibility in using grade relative to the tumor type, to emphasize biological similarities within tumor types rather than ap- proximate clinical behavior, and to conform with WHO grading in non-CNS tumor types.(14)

Combined histological and molecular grading.—

Traditionally, CNS tumor grading has been based exclusively on histological features, but certain molecular markers can now provide powerful prognostic information. For this reason, molecular parameters have now been added as biomarkers of grading and for further estimating prognosis within multiple tumor types. Examples in WHO CNS5 include CDKN2A/B homozygous deletion in IDH-mutant astrocytomas, as well as TERT promoter mutation, EGFR amplification, and +7/−10 copy number changes in IDH-wildtype diffuse astrocytomas (allowing a glioblastoma , IDH-wildtype CNS WHO grade 4 designation even in cases that otherwise appear histologically lower grade). In other words, a molecular parameter can sometimes add value to histological findings in assigning a grade. Specific instances are discussed for the relevant tumor types . It is also important to note that CNS WHO grade is therefore no longer restricted to being a histological grade, as was previously recommended.(16)

NOS (Not Otherwise Specified) and NEC (Not Elsewhere Classified) Diagnoses

The use of the suffixes NOS and NEC allow the ready separation of standard, well-characterized WHO diagnoses from those diagnoses that result from either (1) a lack of necessary diagnostic (e g, molecular) in- formation or (2) non diagnostic (ie, for a WHO diagnosis) or negative results. Adding an NOS suffix indicates that the diagnostic information (histological or molecular) necessary to assign a specific WHO diagnosis is not available, providing an alert to the oncologist that a molecular work-up has not been undertaken or failed technically. An NEC suffix, on the other hand, indicates that the necessary diagnostic testing has been successfully performed but that the results do not readily allow for a WHO diagnosis; for ex- ample, if there is a mismatch between clinical, histological, immunohistochemical, and/or genetic features. NEC diag- noses are what pathologists have termed “descriptive diag- noses,” in which the pathologist uses a non-WHO diagnosis to categorize the tumor. (17)(18)

Novel Diagnostic Technologies

Over the past century, many novel technologies have im- pacted tumor classification. These have included light microscopy, histochemical stains, electron microscopy, immunohistochemistry, molecular genetics, and most recently, a variety of broad molecular profiling approaches. Each burst on the scene as a method that promised to change classification completely and each then eventually found a specific niche alongside the others, rather than replacing them. Over the past couple of decades, nucleic acid-based methodologies (eg, DNA and RNA sequencing, DNA fluorescence in situ hybridization, RNA expression profiling) have clearly shown their abilities to contribute to tumor diagnosis and classification, as evidenced by the changes in the updated fourth edition (2016) and in WHO CNS5. The availability of such technologies was increasing throughout the world as the 2016 classification was being prepared,(19)(20) and the last few years have witnessed further expansion of availability as well as skillful ways to adapt to molecular classification recommendations.(21)(22) WHO CNS5 thus incorporates more molecular approaches for the classification of CNS tumors.

Integrated and Layered Diagnoses

Because of the growing importance of molecular information in CNS tumor classification, diagnoses

and diagnostic reports need to combine different data types into a single, "integrated" diagnosis. Such integrated diagnoses are im- plicit in the use of WHO CNS5. Even diagnostic terms that do not incorporate a molecular term may require a molecular characteristic for diagnosis (eg, AT/RT). Thus, to display the full range of diagnostic information available, the use of layered (or tiered) diagnostic reports is strongly encouraged, as endorsed by the International Society of

Neuropathology—Haarlem consensus guidelines (16) and the International Collaboration on Cancer Reporting.(23) Such re- ports feature an integrated diagnosis at the top, followed by layers that display histological, molecular, and other key types of information Table (3).

Table (3) Layered Report Structure

Integrated diagnosis (combined tissue-based histological and moleculardiagnosis)
Histologicaldiagnosis
CNSWHOgrade
Molecularinformation (listed)

For some tumor types in WHO CNS5, the listed diagnostic terms are general ones (eg, Diffuse high-grade pediatric-type glioma, H3-wildtype and IDH-wildtype and Diffuse low-grade glioma, MAPK pathway-altered); for these types, a combination of diagnostic features drawn from a matrix of relevant histological and molecular abnormalities is necessary to arrive at a specific integrated di- agnosis. These approaches are described for each of these tumor groups and are similar to how the 2016 CNS WHO classified medulloblastomas(16) and what cIMPACT-NOW Update 4 recommended for pediatric low-grade diffuse gliomas(24)

Gliomas, Glioneuronal Tumors, and Neuronal Tumors

WHO CNS5 has taken a new approach to classify the Gliomas, Glioneuronal Tumors, and Neuronal Tumors,and dividing them into 6 different families: Adult-type diffuse gliomas (the majority of primary brain tumors in neuro-oncology practice of adults, eg, glioblastoma, IDH- wildtype); Pediatric-type diffuse low-grade gliomas (expected to have good prognoses); Pediatric-type diffuse high-grade gliomas (expected to behave aggres- sively); Circumscribed astrocytic gliomas ("circum- scribed" referring to their more solid growth pattern, as opposed to the inherently "diffuse" tumors in groups 1, 2, and 3);Glioneuronal and neuronal tumors (a diverse group of tumors, featuring neuronal differentiation); and Ependymomas (now classified by site as well as histological and molecular features). Choroid Plexus Tumors, with their marked epithelial characteristics, are separated from the category of Gliomas, Glioneuronal Tumors, and Neuronal Tumors (16)

Adult-type diffuse gliomas:

UAdult-type diffuse gliomas are the most common malignant tumors of the central nervous system (25) Histopathological categories (e.g., astrocytoma, oligodendroglioma, and glioblastoma) were conceptually based on presumed cell of origin. However, in recent years these tumors have been subjected to significant molecular characterization and it has become clear that molecular markers yield more uniform disease entities and better predict clinical behavior (26) WHO 2021 expands upon the trend started in 2016, using key molecular biomarkers to define neoplastic entities and greatly reducing the dependency on morphologic features for tumor classification. Terminology around tumor grading has also been simplified, with molecular features dictating classification and joint histopathologic and molecular analysis determining grade. The classification of diffuse gliomas under the 2021 update is dependent largely on isocitrate dehydrogenase (IDH1/2) mutation status and 1p/19q codeletion status, resulting in 3 primary disease groups: IDH-mutant, 1p/19q codeleted oligodendroglioma; IDH-mutant, noncodeleted astrocytoma; and IDH-wildtype glioblastoma.This revision further demarcates IDH-mutant from IDH-wildtype disease, a necessity given the wide gap in survival between IDH-mutant and IDH-wildtype tumors, even those bearing the same histopathologic classification (27)

1 | ASTROCYTOMA, IDH MUTANT

Astrocytoma, IDH-mutant is now the preferred designation for all adult-type gliomas that are IDH1- or IDH2-mutant with absence of 1p/19q codeletion. These diffusely infiltrating gliomas frequently harbor inactivating mutations in TP53 and ATRX and can be defined as either CNS WHO grade 2, grade 3, or grade 4. Designations such as diffuse astrocytoma, IDH-mutant; anaplastic astrocytoma, IDH-mutant; and glioblastoma, IDH-mutant are no longer preferred, having been replaced with astrocytoma, IDH-mutant grade 2, grade 3, and grade 4, respectively .(Figure 2) The association of multiple possible WHO grade designations with a specific diagnostic entity

represents a departure from earlier CNS tumor classifications, which linked all named diagnoses with specific WHO grades, whether 1, 2, 3, or 4. Finally, disease entities such as diffuse astrocytoma, IDH-wild type, and anaplastic astrocytoma, IDH-wildtype are now encompassed by other entities not bearing the astrocytoma designation, most notably glioblastoma, IDH-wildtype .The histologic appearance of astrocytoma can vary greatly, from well-differentiated, and minimally mitotic (CNS WHO grade 2) to overtly anaplastic, hypercellular, and proliferative (CNS WHO grades 3–4). Broadly astrocytomas are highly infiltrative, with hypercellular regions intermixed with and entrapping normal brain. Nuclear morphology is key in identifying neoplastic cells, which commonly exhibit angular nuclei with uneven chromatin and hyperchromasia (28). While the WHO does not define a firm threshold for proliferative activity, grade 3 designation is dependent on an elevated mitotic rate, while WHO grade 2 tumors are comparatively inert (Figure 3). Generally, grade 3 tumors have greater cellular crowding and nuclear atypia; abnormal mitoses and multinucleated tumor cells may also be present. Grade 4 IDH-mutant astrocytomas possess, by definition, microvascular proliferation, necrosis, and/or homozygous deletion of cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) (29). Large foci of ischemic and pseudopalisading necrosis, typically associated with IDH-wild type glioblastoma, are not infrequent (30).

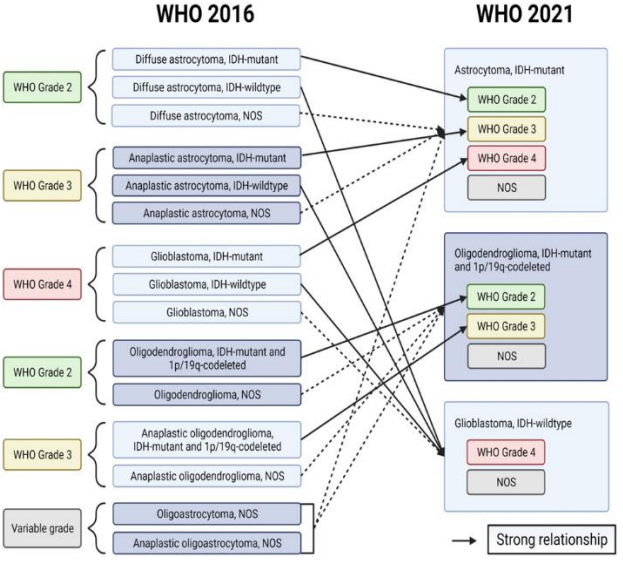

Figure (2) Schematic showing how the disease entities from WHO 2016 is now defined in WHO 2021. Solid lines denote strong correlations between the two classifications, while dotted lines denote how a WHO 2016 disease entity would likely, but not definitively, be defined (31)

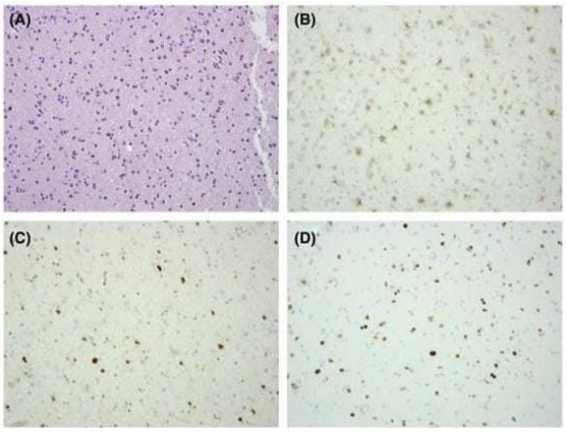

Figure (3) Astrocytoma, IDHmutant, WHO grade 2. H & E-stained sections reveal an infiltrating glial neoplasm composed of pleomorphic tumor cells (A). Microvascular proliferation, necrosis, and mitotic activity are inapparent. Immunohistochemical stains reveal that the tumor cells express IDH1 R132H (B), while exhibiting loss of nuclear ATRX expression (C; note retained expression in background normal cellular constituents). p53 immunostaining is positive in tumor cells (D). (200X magnification) (31)

2| OLIGODENDROGLIOMA, IDHMUTANT, AND 1P/19Q CODELETED

Oligodendroglioma is defined on a molecular level by co-occurrence of IDH mutation and complete deletion of the 1p and 19q chromosomal arms. Histologically oligodendrogliomas consist of closely packed tumor cells with round-to-oval, monotonous nuclei . The presence of perinuclear clearing is frequently described as giving the cells a “fried egg” appearance. Dense, branching capillary networks within the tumors lead to a “chicken wire” appearance, and microcalcifications are frequently present (32). Much like IDH-mutant astrocytomas in WHO 2021, IDH-mutant and 1p/19q-codeleted oligodendrogliomas are now associated with multiple possible CNS WHO grades, either grade 2 or grade 3, reflecting significant differences in overall survival (33).Histopathologically, Grade 3 tumors display some number of the following features: increased cellularity, marked atypia, greater mitotic activity, microvascular proliferation, and necrosis with or without palisading (Figure 4). Although ≥2.5 mitoses/mm2 has been identified as a cutoff of prognostic significance, there is no set proliferative standard differentiating grade 2 and grade 3

oligodendrogliomas (34) Accordingly, Ki-67 immunostaining and clinical features (e.g., rapid symptomatic progression) can be informative in borderline cases. Homozygous CDKN2A and/or CDKN2B deletion is present in a relatively small proportion of oligodendrogliomas; however, its association with poor prognosis independent of histologic features has prompted its designation as a molecular marker for grade 3 oligodendroglioma (35)

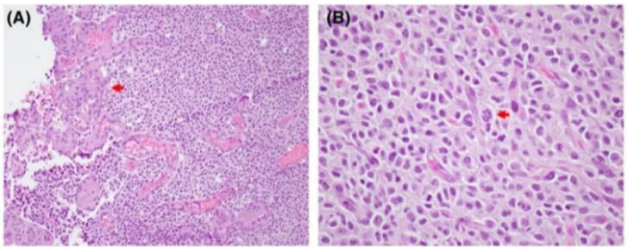

Figure (4) Oligodendroglioma, IDH-mutant, and 1p/19q codeleted, WHO grade 3. H & E-stained sections reveal a densely cellular oligodendroglial neoplasm with obvious glomeruloid microvascular proliferation (A; arrow; 200X magnification). Mitotic activity is readilyapparent (B; arrow; 400X magnification) (31)

4 | GLIOBLASTOMA, IDHWILDTYPE

WHO 2021 reserves the term glioblastoma specifically for IDH-wildtype tumors, with IDH-mutant glioblastoma having been effectively renamed astrocytoma, WHO grade 4. Mutations to histone variant 3 (H3) are also common in IDH-wildtype diffuse glioma, particularly in pediatric and young adult populations, but these tumor variants are designated separately. IDH-wildtype glioblastomas are generally high grade and rapidly proliferating, with very poor prognosis (36) Historically these tumors have been identified based on the histologic presence of florid microvascular proliferation and/or necrosis with or without pseudopalisading (Figure 5). Glioblastomas also tend to be poorly differentiated with brisk mitotic activity. Microvascular proliferation and/or necrosis are both sufficient to establish a diagnosis of glioblastoma in an IDH-wildtype, H3-wildtype diffuse glioma. However, WHO 2021 also delineates multiple defining molecular features for IDH-wildtype glioblastoma, namely TERT promoter mutation, epidermal growth factor receptor (EGFR) amplification, and combined chromosome 7 gain/chromosome 10 loss (+7/−10) (37)

Promoter methylation of the MGMT gene has been shown to play a significant role in the glioblastoma prognosis and therapeutic response (38)MGMT encodes an enzyme responsible for removal of alkyl groups from the O6 position on guanine, which reduces the efficacy of alkylating agents. Promoter methylation impairs MGMT transcription, resulting in decreased enzymatic activity and mitigated therapeutic resistance. Assessment of MGMT promoter methylation yields the only validated predictive biomarker routinely employed in the management of IDH-wildtype glioblastoma. Additionalmolecular alterations have been associated with prognostic relevance in glioblastoma, although results are less than unanimous. CDKN2A/B loss has been linked with reduced overall survival; however, some studies have found this to be true only in tumors without MGMT methylation (39)Recent work has also demonstrated variable associations between TERT mutation and unfavorable clinical course (40)

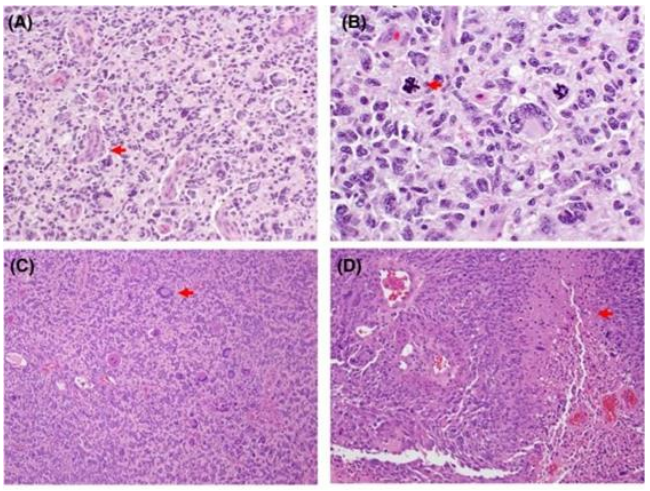

FIGURE (5) Glioblastoma, IDHwild type, WHO grade 4. H & E-stained sections reveal a cellular, pleomorphic, glial neoplasm with glomeruloid microvascular proliferation (A; arrow; 200X magnification). Atypical mitotic figures (B; arrow; 400X magnification) are prominent. H & E-stained sections of another case demonstrating notable nuclear pleomorphism and giant cell features (C; arrow; 100X magnification), along with pseudopalisading necrosis (D; arrow; 200X magnification) (31).

Pediatric-type low-grade and high-grade diffuse gliomas:

Two new families of tumor types have been added to the classification to reflect the practical and conceptual importance of separating pediatric-type gliomas from other diffuse gliomas: one for Pediatric-type diffuse low-grade gliomas and one

for Pediatric-type diffuse high-grade gliomas. The low-grade group includes 4 entities that feature

diffuse growth in the brain but with sometimes overlapping and less specific histological features; in all, molecular work-up helps to characterize the lesion as one type or the other. For CNS5, the 4 types are Diffuse astrocytoma, MYB- or MYBL1-altered; Angiocentric glioma; Polymorphous low-grade neuroepithelial tumor of the young (often abbreviated as PLNTY); and Diffuse low-grade glioma, MAPK pathway-altered. The last of these diagnoses encompass tumors with an astrocytic or oligodendroglial morphology. For these tumors (as for most other glioma types), precise classification requires molecular characterization and the integration of histopathological and molecular information in a tiered diag- nosticformat.(16) Clear delineation of the specific molecular features, in turn, sets the stage for targeted therapies of such tumors.

The high-grade family also comprises 4 types: Diffuse midline glioma, H3 K27-altered; Diffuse hemispheric glioma, H3 G34-mutant ; Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype; and Infant-type hemispheric glioma. Diffuse midline glioma, H3 K27-altered had been in the 2016 classification, but as mentioned above, its name has been changed to reflect the fact that other changes (eg, EZHIP protein overexpression) candefine this entity in addition to the previously recognized H3 K27 mutations. The other 3 are newly recognized types. Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype is specified as being wildtype for both H3 and IDH gene families and, like many other CNS tumor types, requires molecular characterization and integration of histopathological and molecular data for diagnostic pur- poses. Infant-type hemispheric glioma is a novel type of high-grade glioma that occurs in newborns and infants and that has a distinct molecular profile, with fusion genes involving ALK, ROS1, NTRK1/2/3, or MET.(41,42) Of note, the term “glioblastoma” is no longer used in the setting of a pediatric-type neoplasm.

Neuronal and glioneuronal tumors:

All tumors with a neuronal component have remained grouped together in WHO CNS5. Three new types have been added, although the first is provisional (ie, will likely become a fully recognized type in a future classification but currently awaits further published characterizations): DGONC (provisional); Myxoid glioneuronal tumor; and Multinodular and vacuolating neuronal tumor (16)

Ependymomas.

Ependymomas should now be classified according to a combination of histopathological and molecular features as well as anatomic site,(43)thus dividing them into molecular groups across the supratentorial, posterior fossa (PF), and spinal compartments WHO CNS5 also now lists 2 molecularly defined types of supratentorial ependymoma: one with ZFTA (the new designation for C11orf95, which is considered more repre- sentative of the tumor type than RELA because it may be fused with partners more than RELA) fusion and another with YAP1 fusion. It also now includes 2 molecularly de- fined types of PF ependymoma, group PFA and group PFB, as well as a spinal tumor defined by the presenceof MYCN amplification. Also listed are ependymomas defined by anatomic location but not by a molecular alteration; these can be used either when molecular anal- ysis finds a different molecular alteration to one used to define ependymomas at a particular site or when molec- ular analysis fails or is unavailable. As described above, the former situation utilizes the NEC suffix and the latter utilizes the NOS suffix. Myxopapillary ependymoma and Subependymoma remain tumor types; currently, although these can be identified with methylome studies, molecular classification does not provide added clinicopathological utility for these 2 tumors.(43) In contrast to previous WHO classifications, the myxopapillary ependymoma is now considered CNS WHO grade 2 rather than 1, since its like- lihood of recurrence is now understood to be similar to conventional spinal ependymoma. Papillary, clear cell, and tanycytic morphological variants are no longer listed as subtypes of ependymoma, being included instead as pat- terns in the histopathological description of ependymoma. Longstanding controversy surrounds the reproduci- bility and clinicopathological utility of grading ependymal tumors (44) although use of WHO grade in the thera- peutic stratification of adult patients with supratentorial ependymoma remains established practice(45) while the full clinical associations of molecular alterations in this patient population are being evaluated. WHO CNS5 allows only a histologically defined diagnosis of Ependymoma to be made at any of the 3 anatomic sites; the term “anaplastic ependymoma” is no longer listed. .(43)

Nonetheless, as for other tumors in WHO CNS5, a pathologist can still choose to assign either CNS WHO grade 2 or grade 3 to an ependymoma, according to its histopathological features. In an integrated diagnosis, CNS WHO grade can be presented in a specific tier (22)

REFERENCES

1. Pellerino, A., Caccese, M., Padovan, M., Cerretti, G., & Lombardi, G. (2022). Epidemiology, risk factors, and prognostic factors of gliomas. Clinical and Translational Imaging, 1-9.
2. Chen, R., Smith-Cohn, M., Cohen, A. L., & Colman, H. (2017). Glioma subclassifications and their clinical significance. Neurotherapeutics, 14(2), 284-297.
3. Weller, M., Wick, W., Aldape, K., Brada, M., Berger, M., Pfister, S. M., ... &Reifenberger, G. (2015). Glioma. Nature reviews Disease primers, 1(1), 1-18.
4. Mesfin, F. B., & Al-Dhahir, M. A. (2022). Gliomas in StatPearls.
5. Capper D, Stichel D, Sahm F et al. Practical implementation of DNA methylation and copy-numberbased CNS tumor diagnostics: The Heidelberg experience. Acta Neuropathol 2018; 136: 181–210.
6. Louis, D. N., Perry, A., Reifenberger, G., Von Deimling, A., Figarella-Branger, D., Cavenee, W. K., ... & Ellison, D. W. (2016). The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta neuropathologica, 131(6), 803-820.
7. Pavlova NN, Thompson CB (2016). The emerging hallmarks of cancer metabolism. Cell Metab 2016; 23: 27–47.
8. Kaelin WG, McKnight SL (2013). Influence of metabolism on epigenetics and disease. Cell 2013; 153: 56–69.
9. Agnihotri S, Zadeh G (2016). Metabolic reprogramming in glioblastoma: The influence of cancer metabolism on epigenetics and unanswered questions. Neuro Oncol 2016; 18: 160–172. 10.
10. Yan H, Parsons DW, Jin G et al. (2009). IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009; 360: 765–773.
11. Louis, D. N., Perry, A., Wesseling, P., Brat, D. J., Cree, I. A., Figarella-Branger, D., ... & Ellison, D. W. (2021). The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro-oncology, 23(8), 1231-1251.
12. Bruford EA, Braschi B, Denny P, Jones TEM, Seal RL, Tweedie S. Guidelines for human gene nomenclature. Nature genetics. 2020;52(8):754–758.
13. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS recommendations for the description of sequence variants: 2016 update. Hum Mutat. 2016;37(6):564–569.
14. Louis DN, von Deimling A. Grading of diffuse astrocytic gliomas: Broders, Kernohan, Zülch, the WHO… and Shakespeare. Acta Neuropathol. 2017;134(4):517–520
15. Louis DN, Wesseling P, Aldape K, et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACTUtrecht meeting on future CNS tumor classification and grading. Brain Pathol. 2020;30(4):844–856.
16. Louis DN, Perry A, Burger P, et al. International Society of Neuropathology--Haarlem consensus guidelines for nervous system tumor classification and grading. Brain Pathol. 2014;24(5):429–435
17. Louis DN, Wesseling P, Paulus W, et al. cIMPACT-NOW update 1: Not Otherwise Specified (NOS) and Not Elsewhere Classified (NEC). Acta Neuropathol. 2018;135(3):481–484
18. Louis DN, Ellison DW, Brat DJ, et al. cIMPACT-NOW: a practical summary of diagnostic points from Round 1 updates. Brain Pathol. 2019;29(4):469–472.
19. Aldape K, Nejad R, Louis DN, Zadeh G. Integrating molecular markers into the World Health Organization classification of CNS tumors: a survey of the neuro-oncology community. Neuro Oncol. 2017;19(3):336–34
20. Andreiuolo F, Mazeraud A, Chrétien F, Pietsch T. A global view on the availability of methods and information in the neuropathological diagnostics of CNS tumors: results of an international survey among neuropathological units. Brain Pathol. 2016;26(4):551–554.
21. Santosh V, Sravya P, Gupta T, et al. ISNO consensus guidelines for practical adaptation of the WHO 2016 classification of adult diffuse gliomas. Neurol India. 2019;67(1):173–182.
22. Sonoda Y, Yokoo H, Tanaka S, et al. Practical procedures for the integrated diagnosis of astrocytic and oligodendroglial tumors. Brain Tumor Pathol. 2019;36(2):56–62.
23. Louis DN, Wesseling P, Brandner S, et al. Data sets for the reporting of tumors of the central nervous system: Recommendations from the International Collaboration on Cancer Reporting. Arch Pathol Lab Med. 2019;144(2):196–206
24. Ellison DW, Hawkins C, Jones DTW, et al. cIMPACT-NOW update 4: diffuse gliomas characterized by MYB, MYBL1, or FGFR1 alterations or BRAFV600E mutation. Acta Neuropathol. 2019;137(4):683–687.
25. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. Neuro-Oncol. 2019;21(Supplement_5):v1–100
26. Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, et al. NOA-04 randomized phase iii trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol. 2009;27(35):5874–80.
27. Hartmann C, Hentschel B, Simon M, Westphal M, Schackert G, Tonn JC, et al. Long-term survival in primary glioblastoma with versus without isocitrate dehydrogenase mutations. Clin Cancer Res Off J Am Assoc Cancer Res. 2013;19(18):5146–57
28. Ichimura K, Narita Y, Hawkins CE. Diffusely infiltrating astrocytomas: pathology, molecular mechanisms and markers. Acta Neuropathol (Berl). 2015;129(6):789–808.
29. Brat DJ, Aldape K, Colman H, Figrarella-Branger D, Fuller GN, Giannini C, et al. cIMPACT-NOW Update 5: Recommended Grading Criteria And Terminologies for IDH-mutant astrocytomas. Acta Neuropathol (Berl). 2020;139(3):603–8.
30. Brat DJ, Aldape K, Colman H, Figrarella-Branger D, Fuller GN, Giannini C, et al. cIMPACT-NOW Update 5: Recommended Grading Criteria And Terminologies for IDH-mutant astrocytomas. Acta Neuropathol (Berl). 2020;139(3):603–8.
31. Whitfield, B. T., &Huse, J. T. (2022). Classification of adult-type diffuse gliomas: Impact of the World Health Organization 2021 update. Brain Pathology, 32(4), e13062.
32. Figarella-Branger D, Mokhtari K, Dehais C, Jouvet A, UroCoste E, Colin C, et al. Mitotic index, microvascular proliferation, and necrosis define 3 groups of 1p/19q codeleted anaplastic oligodendrogliomas associated with different genomic alterations. Neuro-Oncol. 2014;16(9):1244–54.
33. Cimino PJ, Zager M, McFerrin L, Wirsching H-G, Bolouri H, Hentschel B, et al. Multidimensional scaling of diffuse gliomas: application to the 2016 World Health Organization classification system with prognostically relevant molecular subtype discovery. Acta NeuropatholCommun. 2017;5:39.
34. Giannini C, Scheithauer BW, Weaver AL, Burger PC, Kros JM, Mork S, et al. Oligodendrogliomas: reproducibility and prognostic value of histologic diagnosis and grading. J Neuropathol Exp Neurol. 2001;60(3):248–62.
35. Appay R, Dehais C, Maurage C-A, Alentorn A, Carpentier C, Colin C, et al. CDKN2A homozygous deletion is a strong adverse prognosis factor in diffuse malignant IDH-mutant gliomas. Neuro-Oncol. 2019;21(12):1519–28.
36. Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro-Oncol. 2014;16(Suppl 4):iv1–63.
37. Brat DJ, Aldape K, Colman H, Figrarella-Branger D, Fuller GN, Giannini C, et al. cIMPACT-NOW Update 5: Recommended Grading Criteria And Terminologies for IDH-mutant astrocytomas. Acta Neuropathol (Berl). 2020;139(3):603–8.
38. Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. N Engl J Med. 2000;343(19):1350–4
39. Funakoshi Y, Hata N, Takigawa K, Arita H, Kuga D, Hatae R, et al. Clinical significance of CDKN2A homozygous deletion in combination with methylated MGMT status for IDH-wildtype glioblastoma. Cancer Med. 2021;10(10):3177–87.
40. Ma S, Rudra S, Campian JL, Dahiya S, Dunn GP, Johanns T, et al. Prognostic impact of CDKN2A/B deletion, TERT mutation, and EGFR amplification on histological and molecular IDHwildtype glioblastoma. Neuro-Oncol Adv. 2020;2(1):vdaa126.
41. Clarke M, Mackay A, Ismer B, et al. Infant high-grade gliomas comprise multiple subgroups characterized by novel targetable gene fusions and favorable outcomes. Cancer Discov. 2020;10(7):942–963
42. GuerreiroStucklin AS, Ryall S, Fukuoka K, et al. Alterations in ALK/ ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. Nat Commun. 2019;10(1):4343
43. Ellison DW, Aldape KD, Capper D, et al. cIMPACT-NOW update 7: advancing the molecular classification of ependymal tumors. Brain Pathol. 2020;30(5):863–866.
44. Ellison DW, Kocak M, Figarella-Branger D, et al. Histopathological grading of pediatric ependymoma: reproducibility and clinical relevance in European trial cohorts. J Negat Results Biomed. 2011;10:7
45. Vera-Bolanos E, Aldape K, Yuan Y, et al. Clinical course and progressionfree survival of adult intracranial and spinal ependymoma patients. Neuro Oncol. 2015;17(3):440–447.