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CNS High Grade Glioma

Liam Chen

Abstract

Since the publication of the 2016 edition of the WHO Classification of CNS Tumors, advances in neuropathology have enhanced our understanding of the molecular underpinnings of CNS tumors, providing new elements to refine their classification and improve pathological diagnosis of these neoplasms. This chapter will review the highlights of the updated recommendations which provide guidance for how even in the absence of histopathological characteristics of the highest malignancy grade, molecular markers can be used to reach a diagnosis of glioblastoma, IDH–wild-type or astrocytoma, IDH-mutant, grade IV. These changes have important implications for the management of patients with CNS tumors in current neuro-oncology practice.

Keywords: astrocytoma, oligodendroglioma, glioblastoma, IDH-mutant glioma, molecular pathology

1. Introduction

The 2016 WHO classification divided the glial tumors into these categories: diffuse astrocytic and oligodendroglial tumors, other astrocytic tumors, ependymal tumors, and other gliomas [1]. It for the first time broke a nearly century-old tradition of classifying CNS tumors based merely on concepts of histogenesis and histological features by incorporating well-established molecular parameters into the classification of different gliomas. Further refinements of the classification were subsequently proposed by the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy — Not Officially WHO (cIMPACT- NOW) [2–8]. The chapter will review the highlights of the published cIMPACT-NOW updates and discusses their implications for the management of patients with CNS tumors in current neuro-oncology practice. We will focus on the adult high grade CNS glioma. Infant and pediatric high grade gliomas are beyond the scope of our discussion, but viewers can refer to some of a few excellent reviews [9, 10] published recently.

2. Grading of CNS tumors

The taxonomy and grading of neoplasms have evolved over time as clinical studies have become more sophisticated. Moreover, as the field of bioinformatics has exploded, and statistical analysis has become more powerful, pathologist, clinicians and scientists have employed these tools to better stratify nervous system tumors. In most cases, tumor classifications and grading schemes are based on

WHO Grade	Features	Prognosis*
I	• Usually circumscribed • Low proliferation • Potential for complete resection	• Good
II	• Infiltrative • Relatively low proliferation • Increased risk of recurrence or progression to higher grade	• Fair (usually >5 years)
III	• Histologic evidence of malignancy • Brisk mitotic activity • Often require adjuvant chemo and/or radiation therapy	• Poor (usually 2-3 years)
IV	• Histologic malignancy, brisk mitotic activity, and necrosis • Rapid pre- and post-surgical progression • Prone to CSF spread	• Dismal (usually 1 year)

Table 1.
WHO grading system.

retrospective studies of patients with a given tumor. Data from different pathologic features such as number of mitotic figures per 10 high powered fields (HPF) (400x magnification), nuclear anaplasia, presence or absence of necrosis, growth pattern, and specific histology are analyzed using complex multivariate analysis models to determine which factors represent statistically significant independent risk factors for aggressive behavior. In many cases, two or three of the most important features are used to determine different grades of a given tumor. For example, one criterion of the grading scheme of anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted, requires a mitotic count. Based on a series of studies, neuropathologists and physician collaborators determined that tumors with greater than 6 mitoses per 10 HPF were shown to have a worse prognosis, and were thereby designated "anaplastic" oligodendroglioma, WHO Grade 3. The current WHO grading scheme of CNS neoplasms is summarized in **Table 1**. Obviously, this is a gross oversimplification, especially considering the prognosis of tumors, given the advances in chemotherapy, radiotherapy, and diagnosis.

3. Astrocytoma, IDH-mutant

IDH-mutant astrocytoma is a diffusely infiltrating astrocytoma with a mutation in either *IDH1* or *IDH2* gene. This tumor most commonly affects young adults and occurs throughout the CNS, but is preferentially located in the frontal lobes. This is similar to the preferential localization of IDH-mutant and 1p/19q-codeleted oligodendroglioma and supports the hypothesis that these gliomas develop from a distinct population of precursor cells [11]. Seizures are common presenting symptom. MRI studies usually show T1-hypodensityh and T2-hyperintesnsity, with enlargement of the areas involved early in the evolution of the tumor. Gadolinium enhancement is not common in low-grade diffuse astrocytoma, but tends to appear during tumor progression as diffuse astrocytomas have an intrinsic capacity for malignant progression to IDH-mutant anaplastic astrocytoma and eventually to IDH-mutant glioblastoma.

Fibrillary astrocytoma is the classic type of diffuse astrocytoma. Another variant is the gemistocytic astrocytoma that is characterized by the presence of a conspicuous proportion of gemistocytic neoplastic astrocytes. The gemistocytes have plump, glassy, eosinophilic cell bodies and eccentric nuclei. Nevertheless, both types carry mutations in *IDH* genes. Glioma-associated IDH mutations impart a gain-of-function phenotype to the respective metabolic enzymes IDH1 and IDH2, which overproduce the oncometabolite 2-hydorxylutarate [12]. The physiological consequences of 2-hydroxyglutarate overproduction are widespread, including profound effects on cellular epigenomic states and gene regulation. Specifically, IDH mutations induce G-CIMP, by which widespread hypermethylation in gene promoter regions silences the expression of several important cellular differentiation factors. In this way, IDH mutation and C-CIMP are thought to maintain glioma cells of origin in stem cell-like physiological states inherently more prone to self-renewal and tumorigenesis. The vast majority of IDH-mutant diffuse astrocytomas also harbor loss-of-function mutations in *TP53* and *ATRX*. *ATRX* encodes an essential chromatin-binding protein, and its deficiency has been associated with epigenomic dysregulation and telomere dysfunction. In particular, *ATRX* mutations seem to induce an abnormal telomere maintenance mechanism known as alternative lengthening of telomeres. *ATRX* mutations and alternative lengthening of telomeres are mutually exclusive with activating mutations in the *TRET* gene, which encodes the catalytic component of telomerase. Interestingly, TERT mutations are found in the vast majority of oligodendrogliomas and IDH-wildtype glioblastomas [13]. ATRX deficiency has also been associated with generalized genomic instability, which can induce p53-dependent cell death. Therefore, *TP53* mutations in diffuse astrocytoma may enable tumor cell survival in the setting of ATRX loss.

Multiple studies have identified homozygous deletion of *CDKN2A/B* as a marker of poor prognosis in patients with IDH-mutant diffuse astrocytic gliomas [6]. Thus,
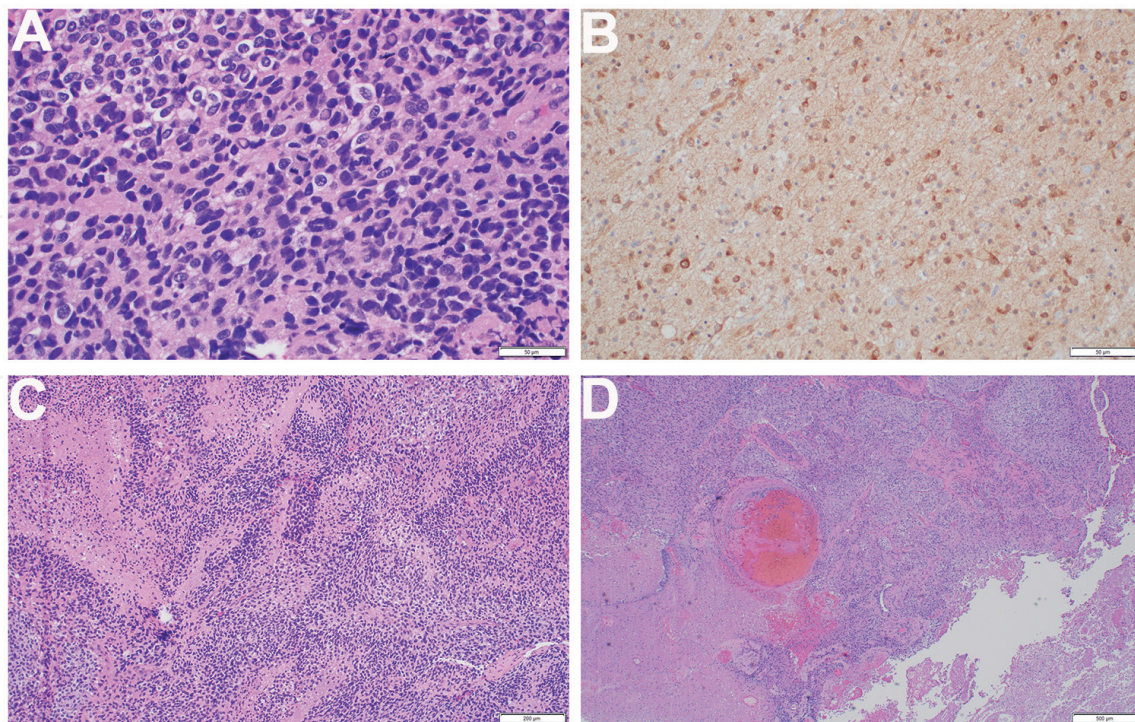

Figure 1.
Neuropathological features of high grade gliomas. Hypercellularity, nuclear pleomorphism, significant proliferative activity (A) and a mutation in IDH1 R132H as detected by immunohistochemistry (B) are essential features of astrocytoma, IDH-mutant, grade 3. A hypercellular band of cells tracing the border of necrotic zones in what is known as pseudopalisading necrosis (C) and/or microvascular proliferation (D) are required histological characteristics for diagnosis of glioblastoma, grade 4.

IDH-mutant astrocytomas that lack significant mitotic activity, histologic anaplasia, microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletion are referred to as Astrocytoma, IDH-mutant, grade 2. Patients with these tumors have a median overall survival greater than 10 years. An IDH-mutant astrocytoma that contains elevated mitotic activity and histologic anaplasia, yet lacks microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletion, currently fits into the designation of Astrocytoma, IDH-mutant, grade 3 (**Figure 1A**-**B**). Recognizing that no validated published criteria exist for mitotic count cut-off values for grading IDH-mutant astrocytomas, "significant" mitotic from grade 2 tumors. Most neuropathologists use a threshold of ≥2 mitoses within the entire specimen, or one mitosis in very small biopsies, while large specimens may require more. Lastly, IDH-mutant astrocytomas with microvascular proliferation or necrosis or CDKN2A/B homozygous deletion, or any combination of these features, correspond to WHO grade 4.

4. Glioblastoma, IDH-wildtype

By far, the most frequent malignant brain tumor in adults is glioblastoma, accounting for approximately 15% of all intracranial neoplasms and approximately 45-50% of all primary malignant brain tumors. The annual incidence of glioblastoma in the USA, adjusted to the United States Standard Population, is 3.19 cases per 100, 000 population. It preferentially affects older adults, with peak incidence occurring in patients aged 55-85 years. A series of environmental and genetic factors have been studies as potential causes of glioblastoma. To date, the only validated risk factor associations are an increased risk after ionizing radiation to the head and neck and a decreased risk among individuals with a history of allergies and atopic disease [14]. Glioblastoma is most often centered in the subcortical white matter of the cerebral hemispheres. Glioblastoma is particularly notorious for its rapid invasion of neighboring brain structures. Infiltration occurs most readily along white matter tracts, but can also involve cortical and deep gray structures. When infiltration extends through the corpus callosum, with subsequent growth in the contralateral hemisphere, the result can be a bilateral, symmetrical lesion (so called butterfly glioma). The symptoms depend largely on the tumor location, primarily manifesting as focal neurological deficits and edema with increase in intracranial pressure. As many as half of all patients are diagnosed after an inaugural seizure. On MRI, glioblastomas are irregularly shaped and have a ring-shaped zone of contrast enhancement around a dark, central area of necrosis.

Glioblastoma is typically a highly cellular glioma, usually composed of poorly differentiated, sometimes pleomorphic tumor cells with nuclear atypia and brisk mitotic activity. Tumor necrosis is a fundamental feature of glioblastoma. Palisading form, which consists of multiple, small, irregularly shaped band-like or serpiginous foci surrounded by radially oriented, densely packed glioma cells, is a histological hallmark of glioblastoma (**Figure 1C**). The other histological hallmark is microvascular proliferation (**Figure 1D**). Glioblastomas are among the most vascularized of all human tumors. Hypoxia is a major driving force of glioblastoma angiogenesis and leads to intracellular stabilization of the master regulator HIF1A [15]. HIF1A accumulation leads to transcriptional activation of over a hundred of hypoxia-regulated genes encoding proteins that control angiogenesis. Among them, VEGFA seems to be the most important mediator of glioma-associated vascular functions; it is primarily produced by perinecrotic palisading cells as a consequence of cellular stress such as hypoxia and hypoglycaemia. Therapeutic blocking of VEGFA by monoclonal antibodies is effective to target small, immature vessels and

lead to vascular normalization accompanied by improved perfusion and oxygenation [16]. On light microscopy, microvascular proliferation typically presents as so-called glomeruloid tufts of multilayered mitotically active endothelial cells together with smooth muscle cells/pericytes. Another less common form is hypertrophic proliferating endothelial cells within medium-sized vessels.

Multiple studies have concluded that a substantial subset of IDH-wildtype diffuse or anaplastic astrocytomas in adults has an aggressive clinical course, with overall patient survival time almost equal to the patients with IDH-mutant glioblastoma, WHO grade 4 [17, 18]. Thus, cIMPACT has reached a consensus that despite the WHO grade 2 or 3 histology, IDH-wildtype diffuse astrocytic tumors would follow an aggressive clinical course and considered as an entity equivalent to glioblastoma if they have the genotype of epidermal growth factor receptor (EGFR) amplification and/or combined whole chromosome seven gain and whole chromosome ten loss (+7/−10) and/or TERT promoter mutation. Although these tumors possess so-called "GBM genotypes", there has been a reluctance to designate the tumor as a glioblastoma in the absence of histological features including palisading necrosis and microvascular proliferation. cIMPACT has thus reached consensus on the designation of diffuse astrocytic glioma, IDH-wild type, with molecular features of glioblastoma, WHO grade 4 as the most appropriate terminology at this time, since this conveys the histologic, molecular and clinical features of glioblastoma that does not alter the long-standing histologic definition [4]. Glioblastoma is highly resistant to therapy, with only modest survival increases achieved in a minority of patients, even after aggressive surgical resection, external beam radiation therapy, and maximum tolerated doses of chemotherapy. MGMT promoter methylation is the only predictive biomarker for the efficacy of and response to alkylating and methylating chemotherapy agents in glioblastoma [19].

5. Oligodendroglioma

While astrocytoma represents roughly 80-90% of all gliomas, oligodendroglioma, the second most common primary CNS tumor, represents only about 5-6% of all gliomas, with peak incidence in patients aged 35-44 years [20]. Approximately two-thirds of patients present with seizures. The frontal lobe is the most common location. They are characterized by cortex and white-matter based proliferations of neoplastic cells morphologically resembling oligodendrocytes which have a characteristic "fried-egg" appearance (a delayed fixation tissue artifact seen on H&E permanent sections, and rarely observed on frozen section), delicate "chicken wire" vasculature, mucoid/cystic degeneration and microcalcifications. The current WHO classification of oligodendroglioma requires demonstration of *IDH1* or *IDH2* mutation, typically by immunohistochemistry using the mutation-specific antibody against R132H-mutant IDH1 (followed by DNA genotyping when R132H-mutant IDH1 immunostaining is negative), as well as demonstration of 1p/19q codeletion by FISH or molecular genetic testing. Mutations in the *CIC* gene on 19q13.2 and *FUBP1* gene on 1p31.1, among other genes on 1p and 19q, may contribute to the distinctive biology of 1p/19q codeletion [21]. Unlike IDH-mutant diffuse astrocytomas, oligodendroglioma usually lacks wide-spread nuclear p53 staining, a finding consistent with the mutual exclusivity of *TP53* mutation and 1p/19q deletion [22]. In addition, oligodendrogliomas lack *ATRX* mutation but virtually always carry activating mutations in the *TERT* promoter region, leading to increased expression of TERT [23]. In this manner, 1p/19q testing can be skipped if an IDH-mutant tumor appears clearly astrocytic and the ATRX/p53 immunohistochemistry results are consistent with an astrocytic genotype (*ATRX* and/or *TP53* mutations).

There is no WHO grade 1 variant of oligodendroglioma. WHO grade 2 oligodendroglioma is defined by a diffusely infiltrating, slow-growing glioma without evidence of increased mitotic activity (a few mitoses are permitted), endothelial proliferation, or necrosis. In contrast, WHO grade 3 anaplastic oligodendroglioma is defined by histological features of anaplasia. In particular, microvascular proliferation and/or increased mitotic activity (there is debate among experts, although classic studies have indicated a cutoff of ≥6 mitoses/10 HPF) have been suggested to be of important indicators of anaplasia in oligodendroglioma. Interestingly, contrast enhancement has been detected in <20% of WHO grade 2, but in >70% of grade 3 anaplastic oligodendrogliomas [24]. Thus lack of contrast enhancement does not exclude anaplastic oligodendroglioma. 1p/19q codeletion has been found to be associated with better therapeutic response and longer survival in patients treated with adjuvant radiotherapy and chemotherapy [25]. Not surprisingly, long-term follow-up data indicate higher median overall survival times (>10 years) for patients with anaplastic oligodendrogliomas who were treated with combined radiotherapy and chemotherapy.

Finally, to make matters even slight more complicated, there is a class of tumors that combines the histologic features of both astrocytomas and oligodendrogliomas. The existence of these entities is hotly contested; however, as of the 2016 iteration of the WHO classification, there is a grade II oligoastrocytoma, NOS and a grade III anaplastic oligoastrocytoma, NOS. They usually manifest in adult patients, with preferential localization in the cerebral hemispheres. Again, NOS indicates that molecular testing could not be completed or is inconclusive.

6. Diffuse midline glioma, H3 K27M-mutant

By definition, this entity is an infiltrative midline glioma with predominantly astrocytic differentiation and a K27M mutation in either *H3F3A* or *HIST1H3B/C* [3]. K27M mutations affecting H3.3 (encoded by *H3F3A*) are about three times as prevalent as the same mutation in histone variant H3.1 (occurring in *HIST1H3B* or *HIST1H3C).* Notably, these mutations are not exclusive to diffuse midline gliomas. Over the past few years, a number of tumors that are not diffuse midline gliomas have been reported with the same H3 K27M mutation, including ependymomas, pilocytic astrocytomas, pediatric diffuse astrocytomas, and gangliogliomas. Therefore these mutations cannot be used in and of themselves to define a diffuse midline glioma, H3 K27M-mutant.

It predominates in children but can also be seen in adults, with the most common locations being brain stem, thalamus, and spinal cord. Classic clinical symptoms include the triad of multiple cranial neuropathies, long tract signs, and ataxia, typically developing over a short period of time (1-2 months). The prognosis is poor, despite current therapies, with a 2-year survival rate of <10%. Correspondingly, H3 K27M-mutant diffuse midline glioma is WHO grade 4. The mere grading criterion of an entity based on a specific mutation means the histological features do not predict the outcome. Indeed, about 10% pontine examples lack mitotic figures, microvascular proliferation, and necrosis, and thus are histologically consistent with WHO grade 2. The remaining cases are histologically high grade, with 25% containing mitotic figures and the remainder containing mitotic figures as well as foci of necrosis and microvascular proliferation. The use of H3 K27M-mutant specific immunohistochemistry is useful to identify the mutation and specifically for diagnosis of diffuse midline glioma, H3 K27M-mutant. The K27M substitution results in a decrease in H3K27me3 (trimethylated), thought to be due to inhibition of PRC2 activity [26]. Antibody that has also been used to guide diagnosis of these

tumors is against H3 K27me3. H3 K27me3 immunohistochemistry, however, should only be used in conjunction with H3K27M immunohistochemistry, since loss of H3 K27me3 expression is by itself not specific.

7. Other astrocytic tumors

Pleomorphic xanthoastrocytoma is rare (constituting <1% of all astrocytic neoplasms) and most commonly affects children and young adults, with a median patient age at diagnosis of 22 years [27]. A superficial location, involving the leptomeninges and cerebrum is characteristic of this neoplasm. Approximately 98% of cases occur supratentorially, most commonly in the temporal lobe. Due to the superficial cerebral location of the lesion, many patients present with a fairly long history of seizures. On MRI, the solid portion of the tumor is hyperintense on T2 FLAIR images. Postcontrast enhancement is moderate or strong.

The adjective "pleomorphic" refers to the variable histological appearance of the tumor, in which spindled cells are intermingled with mononucleated or multinucleated giant astrocytes. The term "xanthoastrocytoma" refers to the presence of large, often multinucleated xanthomatous cells that have intracellular accumulation of lipids. Granular bodies are a nearly invariable finding. Focal collections of small lymphocytes are also frequent. The third histological hallmark of pleomorphic xanthoastrocytoma is the presence of reticulin fibers. Despite its alarming histological appearance, pleomorphic xanthoastrocytoma has relatively favorable prognosis compared with diffusely infiltrative astrocytoma, with 70.9% recurrence-free and 90.4% overall survival rates at 5 years, corresponding to WHO grade 2. Patients with anaplastic pleomorphic xanthoastrocytoma have significantly worse survival than those whose tumors show <5 mitoses per 10 HPFs. Necrosis may be present. *BRAF V600E* mutations occurs in approximately 50-78% of cases [28]. The frequency of *BRAF V600E* mutation is lower among anaplastic pleomorphic xanthoastrocytoma than among WHO grade 2 pleomorphic xanthoastrocytoma, but the prognostic significance of the mutation is unknown.

8. Ependymal tumors

Ependymomas are tumors that can arise anywhere along the ependymal-lined ventricular spaces of the neuraxis, including the brain and spinal cord. Like the other gliomas, this is a heterogeneous class of tumors that ranges from benign (subependymoma and myxopapillary ependymoma) to malignant (anaplastic ependymoma). Due to their location, even biologically benign examples can cause malignant clinical sequelae, including recurrent obstructive hydrocephalus and even death. The age of the patient seems to affect prognosis, with adults doing better than children, probably due in part to a predominant spinal cord involvement in adults. Histologically, these tumors are characterized by solid or pseudo-papillary proliferations of small to medium sized, hyperchromatic, oval to spindled cells with conspicuous pseudo-rosettes (cells palisading/lining up like a picket fence around a central capillary) and/or, less commonly, true ependymal rosettes (cells palisading around a hollow canal in an attempt to recapitulate the embryonic central canal). There are three histologic variants of WHO grade II ependymoma: papillary, clear cell (which tends to be biologically more aggressive), and tanycytic. However, the criteria for defining anaplastic ependymoma are not as well developed as those of astrocytomas as no association between grade and biological behavior or survival has been definitively established.

Advances in the understanding of the biological basis and molecular characteristics of ependymal tumors have prompted the cIMPACT-NOW group to recommend a new classification. Separation of ependymal tumors by anatomic site is an important principle of the new classification and was prompted by methylome profiling data to indicate that molecular groups of ependymal tumors in the posterior fossa and supratentorial and spinal compartments are distinct [8]. A supratentorial ependymoma characterized by a *C11orf95-RELA* fusion gene accounts for approximately 70% of all childhood supratentorial tumors and a lower proportion of such ependymomas in adult patients [29]. It forms in the context of chromothripsis, a shattering and reassembly of the genome that rearranges genes and produces oncogenic gene products. Rarely, *C11orf95* or *RELA* can be fused with other genes as a result of chromothripsis. *RELA* fusion-positive ependymomas show constitutive activation of the NF-kappaB pathway. Immunohistochemistry to assess the expression of L1CAM correlates well with the presence of a *RELA* fusion in these tumors. Importantly, *RELA* fusion-positive ependymomas have been reported to have the worst outcome among the supratentorial ependymomas [30].

9. Conclusions

Since 2016, ongoing discoveries in molecular pathology have advanced our understanding of many of the entities organized under the WHO 2016 classification. Most of these changes carry important implications for clinical practice and for the design and interpretation of clinical trials. It is almost certain that our understanding of the biology of CNS tumors will continue to expand at a rapid pace. Thus continuation of the efforts of optimal (evidence-based, balanced, rapid) and timely translation of novel insights into clinical diagnostics, is the ultimate goal to provide the best possible care to CNS tumor patients.

Conflict of interest

The author declares no conflict of interest.

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