Review

Pediatric high-grade glioma: A heterogeneous group of neoplasms with different molecular drivers

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Abstract

High-grade gliomas (HGGs) in pediatric age have the same bad prognosis as those arising in adults. Approximately one-half of HGGs in children occur in the brain stem, most frequently within the pons as diffuse intrinsic pontine glioma or other midline structures. Although they have the same histological appearance of adult malignant gliomas, in recent years, the extensive use of molecular profiling techniques has demonstrated significant molecular differences between the two age groups. These data have led to a major reclassification of pediatric HGG (pHGG) based on molecular subgrouping with significant clinical correlations in terms of age at presentation, anatomical location, and prognosis. The most important molecular groups are: (1) the histone mutations related pHGG, that is, H3.K27-mutated midline and H3.G34-mutated hemispheric pHGG; (2) the rare isocitrate dehydrogenase (IDH)-mutated pHGG occurring mainly in adolescents; and (3) the H3-/IDH wild type, a heterogenous group of pHGG still object of further molecular stratification. Another important group of pHGG is that occurring in patients with cancer predisposition syndromes such as Li-Fraumeni syndrome, constitutional mismatch repair deficiency, and neurofibromatosis-1 (NF1). In this review, the different subgroups of pHGG and their major driver molecular alterations will be discussed.

Keywords: Children, histone mutations, malignant glioma, molecular drivers

Introduction

High-grade glioma (HGG) accounts for ~11% of all central nervous system tumors in children aged 0–14 years.[1] The term designates malignant, diffuse, infiltrating astrocytic tumors of both the World Health Organization (WHO) Grade III (anaplastic astrocytoma) and Grade IV (glioblastoma multiforme) gliomas. The histological appearance is the same of adult malignant gliomas, and in the past, they were grouped with their adult counterparts. However, in contrast to adults, the prognostic/biologic relevance of histologically distinguishing between Grade III and Grade IV in children is not so evident. The gliomatosis cerebri, no more a distinct entity, is considered a clinical-radiological pattern of a diffuse glioma-infiltrating multiple brain regions.[2-5] Pediatric HGG (pHGG) is a relatively rare disease occurring in approximately one in 100,000 individuals with the same bad prognosis as those that arise in adults (median survival 12–15 months).[6] Although they can occur in the cerebral hemispheres as in adults, approximately one-half of pHGG arise in the brain stem, most frequently within the ventral pons, as diffuse intrinsic pontine glioma (DIPG), in midline structures, including the thalamus (13%)[7] and spinal cord (3%),[8] as well as the cerebellum (5%).[9] In recent years, extensive use of high-throughput molecular profiling techniques has largely increased our knowledge of the origin and biological features of these childhood neoplasms. The resulting data have led to a major reclassification of pHGG based on molecular subgrouping with significant clinical correlations in terms of age at presentation, anatomical location, and prognosis.

Although DNA copy number,[10,11] gene expressions,[10,12] and even microRNA[13] profiling were known to differ in

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glioblastomas arising in children and adults, the key discovery that best illustrates the unique biology of tumors in children was the identification of somatic histone mutations. It subsequently became clear that numerous histological subtypes of HGG can harbor distinct genetic drivers and have probably more favorable clinical outcomes. The rapid advances in our understanding of pHGGs have come predominantly from the accumulation of numerous disparate retrospective collections, a reflection of the rarity of the disease. In this review, we will describe the different subgroups of pHGG based on the major driver molecular alterations.

Histone Mutations Related to Pediatric High-Grade Glioma

Two independent studies in 2012 reported the identification of somatic mutation of the H3F3A and HIST1H3B genes, which encode the histone H3 variants H3.3 and H3.1.[14,15] Such mutations result in amino acid substitutions at two key residues in the histone tail: lysine-to-methionine at position 27 (K27M) and glycine-to-arginine or -valine at position 34 (G34R/V). In addition, K27M mutation results in a global reduction of H3K27me3, leading to derepression of targets of polycomb repressive complex 2 (PRC2) [Figure 1]. Remarkably, differences in clinical (patient age, tumor location, and survival) and molecular parameters (methylation patterns and spatiotemporal expression signatures) suggest that HGG harboring H3 lysine K27 (H3K27) and G34 mutations likely arise from different cells of origin and are principally distinct diseases.[6,16]

In general, histone proteins are subjected to posttranslational modifications (PTMs) which are involved in chromatin remodeling and gene expression.[17] PTMs are under control of catalyzed enzymes that promote their addition ("writers") or removal ("erasers"). Most of them concern lysine residues, which are localized in the aminoterminal tail of histone H3 and include acetylation and methylation.

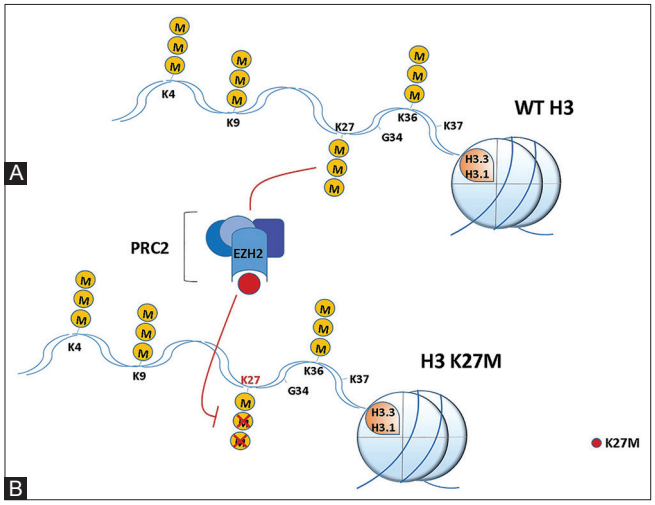

Figure 1: (A) In the absence of mutation, the aminoterminal tail of histone H3.3, H3.1, and other histone H3 proteins are subject to methylation of lysine residue 27 by PRC2. (B) K27M mutation in H3.3 and H3.1 result in a global reduction of H3K27me3

The acetylation status of the lysine residues at the N-terminus of histones is regulated by the actions of histone acetyltransferases (HATs) and the counteractivity of histone deacetylases (HDACs). Acetylation of H3K27 nucleosome is made by the HAT p300/CBP at the position where promoters or enhancers of genes are actively transcribed. The methylation of H3K27 histone protein, a process associated with gene silencing, is generated by histone-lysine N-methyltransferase EZH2, a component of the PRC2. On the other hand, demethylation process is conducted by KDM6 family including JMJD3 and UTX.[18] Moreover, the ATRX/DAXX complex deposits the histone variant H3.3 at pericentric heterochromatin and telomeres, while its deposition at euchromatin regions is carried toward the histone chaperone HIRA.[19,20]

The mutation of the DNA methylation process is more commonly involved in the oncogenesis of the H3K27-mutant tumors, where a point mutation leads to the substitution of lysine with methionine. This amino acid has a long hydrophobic side chain with minimal branching, which causes an inhibition of PCR2 activity, resulting in a global reduction of the methylated protein (H3K27me3)[21-23] and consequently an aberrant activity of activated oncogenes.

Less is known about the molecular mechanism of H3G34R/V mutation. Some studies demonstrated an elevated expression of MYCN, suggesting a possible oncogenic mechanism for these neoplasms.[24] For this reason, further studies are necessary to evaluate how H3G34 mutations regulate MYCN expression and/or other oncogenic events.

H3K27M-Mutated Pediatric High-Grade Glioma

The 2016 edition of the WHO Classification of Tumors of the Central Nervous System, which utilizes integrated diagnosis incorporating both morphologic and molecular features, has recognized a new diagnostic entity among the diffuse gliomas – "Diffuse midline glioma with histone H3K27M mutation." Studies have shown that these diffuse midline gliomas with histone H3K27M mutation are associated with aggressive clinical behavior and poor prognosis,[25,26] including those tumors which demonstrate only low-grade histologic features on biopsy.[27] On the basis of this, the WHO Grade IV has been assigned independent of the histological appearance. Midline gliomas with histone H3K27M mutation might display a wide spectrum of morphologic variation ranging from well-differentiated monomorphic astrocytes [Figure 2] to glioblastoma with giant and epithelioid cells and even undifferentiated foci [Figure 3].[28] Immunohistochemistry is useful to identify the mutation and specifically for diagnosis of diffuse midline glioma, H3K27M-mutant; K27M mutations in both the H3.3 and H3.1 histones can be detected using an anti-H3K27M antibody (clone #ABE419).[29] The possibility to detect single-cell positivity makes immunohistochemistry superior to sequencing in small biopsies with low cellularity

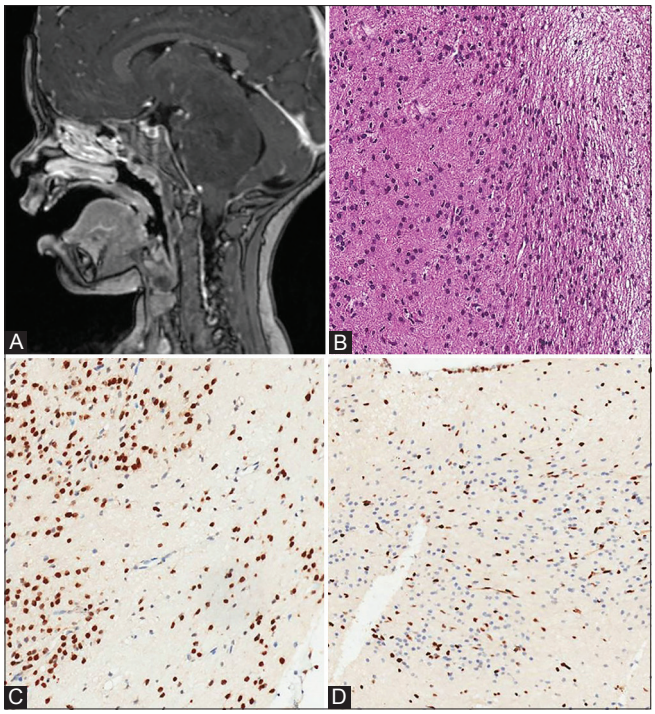

Figure 2: (A) T1W sagittal magnetic resonance imaging section of a pontine lesion (DIPG). (B) Hematoxylin and eosin low cellularity and minimal cytologic atypia (×10). (C) Nuclear expression of H3K27-mutant protein in tumor cells (×10). (D) Negative nuclear staining for H3K27me3 Ab in tumor cells (×10)

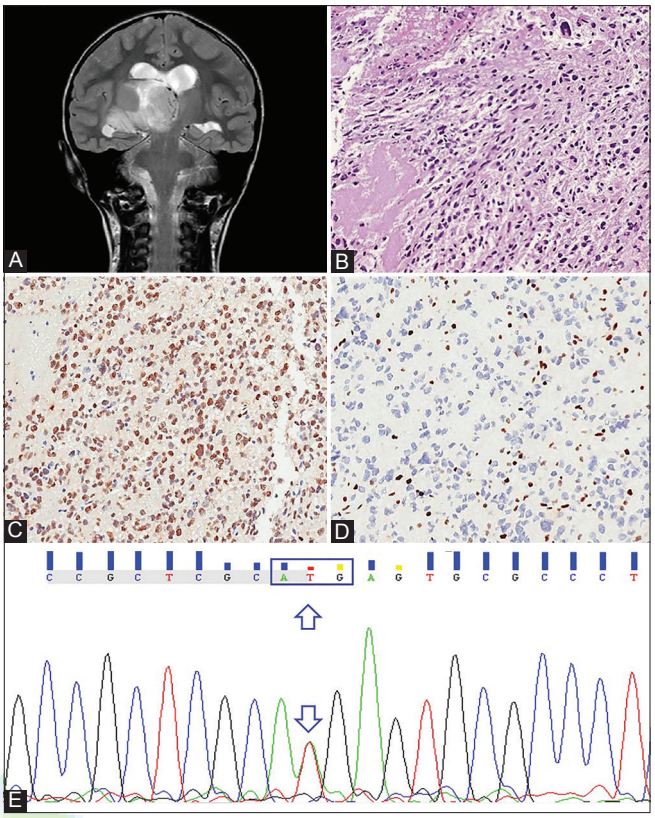

Figure 3: (A) T2W coronal magnetic resonance imaging section of a thalamic lesion. (B) Hematoxylin and eosin glioblastoma with multinucleated giant cells and foci of necrosis (×10). (C) Diffuse nuclear expression of H3K27-mutant protein (×10). (D) Loss of H3K27me3 expression (×10). (E) Electropherogram showing the mutated allele in the sequence

and containing rare neoplastic cells. The pattern of positivity is nuclear, with positivity in most of the tumor cells; nontumor cell nuclei are negative.[30] Although the specificity and sensitivity of H3K27M for K27M mutations in either H3.3 or H3.1 is 100%,[31] the H3 K27M immunohistochemistry needs to be interpreted carefully; in particular, care must be given to recognize positive nuclear staining in neoplastic cells and to avoid mistakenly calling cytoplasmic staining in macrophages and/or microglia as positive. Another antibody that has been used to guide diagnosis of these tumors is H3K27me3 (trimethylated) [Figures 2D and 3D]. H3K27me3 immunohistochemistry, however, should only be used in conjunction with H3K27M immunohistochemistry, since loss of H3K27me3 expression is by itself not specific.[23] Differences exist between the H3 histone variants in which the mutations occur. H3.3K27M tumors are found in two-thirds of DIPG and nonbrain stem midline pHGG alike, where they are associated with a shorter overall survival (OS) in both locations, as well as in the cortex, as per a small number of reported cases.[14,16,32] H3.1K27M tumors, by contrast, are restricted to the pons, patients are younger and with a slightly longer survival[33] and are largely defined at the copy number level by whole chromosomal arm gains and losses.[34-36] Adults can be affected by K27M-mutant gliomas and have been even observed in patients up to 65 years of age and even rare, in midline locations such as third ventricle, hypothalamus, pineal region, and cerebellum.[28] Moreover, thalamic gliomas in adults with H3K27M mutations might not be associated with worse prognosis than corresponding histone H3 wild-type thalamic gliomas,[37-39] suggesting heterogeneity among this molecular subgroup of diffuse midline gliomas. Genomic analysis of diffuse midline gliomas with histone H3.1K27M mutations has revealed a number of cooperating genetic alterations. In particular, these tumors often also have TP53 and ATRX mutations but do not have isocitrate dehydrogenase (IDH) 1 mutation.[40] Moreover, a subset of H3.1K27M DIPGs were found to also harbor missense mutations in the ACVR1 gene, encoding the activin A receptor type-1 transmembrane protein, that lead to activation of the BMP-TGFb signaling pathway.[34-36] Other alterations occasionally found in H3.1K27M DIPGs include PIK3CA mutation, PDGFRA mutation or amplification, PPM1D mutation, and amplification of cell cycle genes including CCND1, CDK4, and CDK6.[16,32] The cooperating genetic alterations in nonbrain stem gliomas with histone H3K27M mutation are less well defined, particularly in the spinal cord and thalamic gliomas in adult patients. Interestingly, a pattern of cosegregating mutations in relation to the location has been revealed in various studies, for example, PDGFRA alterations are predominant in pontine lesions, whereas FGFR1 variants are largely restricted to the thalamic ones.[16] Further differential amplifications have been observed such as of

CCND2 in DIPG and CDK4 in nonbrain stem midline, and most strikingly, an amplification at 17p11.2 involving TOP3A exclusively in H3.3K27M DIPG. This complex rearrangement often involves loss of more distal part of 17p involving TP53, along with intra- or inter-chromosomal translocations resulting in an increase in TOP3A copy number and gene expression. Moreover, TOP3A amplification/mutation was found to be mutually exclusive with ATRX mutation in H3.3K27M DIPG, with depletion by small interfering RNA reducing ALT cell survival,[16,41] and therefore represents a potential therapeutic target in this subgroup.

Over the past few years, a number of tumors that are not diffuse midline gliomas have been reported with the same H3K27M mutation, including ependymomas,[42] pilocytic astrocytomas, pediatric diffuse astrocytomas, and gangliogliomas.[43-45] In rare examples, such midline glial neoplasms harbor both histone H3-K27M mutation and BRAF-V600E mutation.[45,46] Noteworthy, however, these neoplasms seem to have significantly different biologic behavior indicating that in these tumors the prognostic significance of H3K27M mutations is not well defined. For these reasons, it has been strongly suggested that the term diffuse midline glioma, H3K27M-mutant should be reserved only for tumors that are diffuse (i.e., infiltrating), midline (e.g., thalamus, brain stem, spinal cord, *etc.*), and H3K27M mutant and should not be applied to other tumors that are H3K27M mutant.[47]

Based on the described molecular mechanisms, *in vivo* and *in vitro* studies have been conducted to find a specific therapeutic agent for these malignant neoplasms. Epigenetic therapies identify drugs interfering with the activity of enzymes implicated in the epigenetic alterations present in tumor cells.[48] In this regards, experiments conducted on GSKJ4 (an inhibiting agent of K27 demethylase JMJD3) show that the treatment of tumor cells harboring K27 mutation increases K27 methylation with a consequent potent antitumor activity. In particular, GSKJ4 has important consequences on cell proliferation, apoptosis, and colony formation and these effects are dose-dependent. It unveils a 50% growth inhibition, a decrease in cell cycle of tumor cells and an increased apoptotic activity. This is not true for wild-type tumor cells and for H3G34-mutated cells.[49]

Other works investigated the mechanism of inhibition of PRC2 by a direct binding with this complex, interfering with the catalytic subunit EZH2.[50] This study shows a structure − activity relationship between the entire N-terminal tail of H3 and PRC2 complex. This interaction can be inhibited by peptides containing methionine or isoleucine or norleucine (Nle) (a methionine isostere), when residues next to position 27 are alterated. PMTs, including serine 28 (S28) phosphorylation, reduce inhibition of PRC2 activity by H3K27Nle peptides. Moreover, the expression of H3K27M and phosphoserine-mimetic S28E preserves part of global reduction of K27me2 and K27me3 in cells.[50]

Furthermore, H3K27M cell lines are sensitive to HDAC inhibitors.[51] Panobinostat, an approved multi-HDAC inhibitor, makes a dose-dependent increment in both global H3 acetylation and H3K27me3, conferring a regularization of the H3K27M-induced aberrant gene expression signature.[51]

H3G34-Mutated Pediatric High-Grade Glioma

H3.3G34R/V-mutant tumors are restricted to the cerebral hemispheres with the temporal and parietal lobes being most commonly involved.[6] They occur predominately in young adults with the vast majority of patients within the age range of 11–30 years.[16,52] Histologically, these tumors display two distinct patterns, "GBM-like" and "PNET-like." The "GBM-like" tumors are highly malignant, hypercellular, astrocytic gliomas with high mitotic activity, microvascular proliferation, and palisading necrosis. Most of the tumor cells show intense expression of GFAP. In contrast, the "PNET-like tumors show features of an undifferentiated embryonal tumor composed of small and monomorphic cells with hyperchromatic nuclei and scant cytoplasm. Even Homer–Wright rosettes can be occasionally observed. Microvascular proliferation and palisading necrosis are usually absent.[52] These tumors show intense positivity for neuronal markers such as synaptophysin and Map2 [Figure 4]. Both histological variants lack expression of Olig2 protein, and in >90% of cases, strong nuclear accumulation of p53 protein and complete nuclear negativity for antibodies against ATRX protein can be seen.[52,53]

More recently, antibodies against H3.3G34R/V-mutant proteins are made available.[54] Although high specificity of these antibodies has been claimed, occasional false-negative cases have been observed raising a word of caution in their use as surrogate for detection of G34 mutations (personal observation).

The two histological variants share similar clinical and demographic data (age, gender, and tumor location), moreover, they show the same subgrouping in unsupervised clustering analysis of DNA methylation profiles.[16,26]

Beside the cosegregation with p53 and ATRX, the H3.3G34R/V tumors are also the only pediatric subgroup to harbor frequent MGMT promoter methylation.[16,52]

An intriguing aspect of H3F3A G34 mutation is the relation of specific mutations to the locations of human tumors. Thus, while G34R/V variants are highly specific for hemispheric pHGG, G34W/L mutations are specific for giant cell tumor of bones.[55,56] Moreover, the dominant-negative effect of K27M H3.3/3.1 mutations on polycomb-mediated H3K27me3 levels has been elucidated, the specific roles of H3G34 mutations on tumorigenesis are, so far, unknown.

Patients with G34-mutated HGG have poor prognosis, with a median progression-free survival of 9 months and a median OS of 22 months. Most of the patients experience local tumor regrowth as a recurrence pattern, whereas a smaller subset (8%) develops widespread leptomeningeal metastatic dissemination.[16,52]

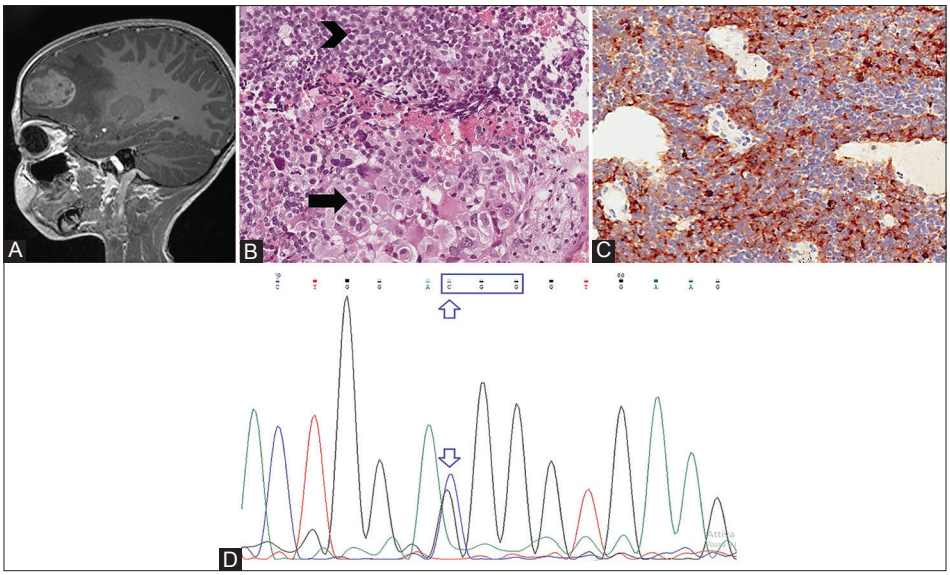

Figure 4: (A) T1W sagittal magnetic resonance imaging section of a frontoparietal lesion. (B) Hematoxylin and eosin histologic features of glioblastoma (arrow) and PNET-like components (head arrow) with small monomorphic cells, hyperchromatic nuclei and scant cytoplasm (×20). (C) Positive cytoplasm staining for synaptophysin of PNET-like component (×20). (D) Electropherogram showing the mutated allele in the sequence

The clinical course of patients with G34-mutant tumors is slightly better than that for other GBM molecular subtypes (excluding IDH1-mutant tumors). One possible explanation for this is the high frequency of MGMT promoter methylation, which could be related to enhanced responsiveness to temozolomide.[52]

Isocitrate Dehydrogenase-Mutated Pediatric High-Grade Glioma

IDH1 and IDH2 genes, which encode the IDH enzymes, are frequently mutated in adult secondary malignant gliomas. These alterations inhibit the normal function of the IDH enzyme in converting isocitrate to α-ketoglutarate, causing the conversion of α-ketoglutarate to 2-hydroxyglutarate, an oncometabolite that contributes to tumor development. IDH mutations represent an early step in tumorigenesis because such alterations are observed commonly in low-grade diffuse gliomas and precede the acquisition of other molecular alterations, such as TP53 and ATRX mutations in astrocytomas and 1p/19q codeletions in oligodendrogliomas. Various studies have demonstrated that IDH1 or IDH2 mutations, in children are restricted to a small proportion (6.25%) of tumors mostly in adolescents [Figure 5], representing the initial spectrum of a largely adult disease.[16,57-59]

H3-/Isocitrate Dehydrogenase Wild-Type Pediatric High-Grade Glioma

PHGGs lacking H3 or IDH mutations, namely H3-/IDH-wild type (wt), are a heterogeneous group of tumors, which include molecularly distinct subgroups with a variety of genomic and epigenetic profiles and different clinical behavior.[60]

The first two subgroups that have been identified, by methylation profiling analysis, are those resembling pleomorphic xanthoastrocytoma (PXA) and low-grade gliomas (LGG).[52] Patients harboring these tumors have a significantly better OS compared to molecularly confirmed GBM, suggesting distinct origin and less malignant nature. The PXA-like tumors are strongly linked with deregulation of the MAPK pathway (BRAF V600E)[53] along with CDKN2A/CDKN2B deletion.[16,61] However, although their outcome is significantly better than molecularly defined GBM, in terms of OS, the PXA-like tumors still exhibit a high rate of recurrence. On the other hand, the LGG-like neoplasms have been mainly observed in infants under 12 months of age and are associated with favorable OS. Gene fusion such as NTRKs1-NTRK3 are also common in this age group.[16]

Recent studies have further subdivided the remaining H3/IDH wt HGG into subgroups with poor outcome. The larger subtype termed "pedGBM_MYCN" shows a high frequency of MYCN amplification together with coamplification of the nearby ID2 gene on 2p.; the second designated as "pedGBM_RTK1" has an enrichment for PDGFRA amplification and the third called "pedGBM_RTK2" shows frequent amplification of EGFR. Interestingly, in all these subgroups, there is a low frequency of MGMT promoter methylation, suggesting a distinct origin of pHGG from its adult counterpart. Moreover, this high frequency of unmethylated tumors explains the low efficacy of temozolomide or other alkylating agents in treatment of these deadly neoplasms.[60]

However, further investigations of these heterogeneous subgroups are needed in order to improve integrated molecular diagnostics and patient stratification for more tailored treatment based on molecular targets.

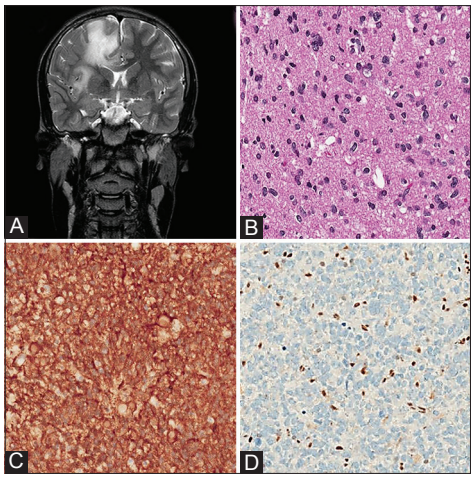

Figure 5: (A) T2W coronal magnetic resonanace imaging section of a frontoparietal lesion. (B) Hematoxylin and eosin classical features of anaplastic astrocytoma with mild cellularity and moderate nuclear atypia (×20). (C) Positive staining for IDH1 R132H mutant protein (×10). (D) Nuclear loss of ATRX expression. Positive endothelial cells as internal control (×10)

Pediatric High-Grade Glioma in Cancer Predisposition Syndromes

Numerous mutations occurring in pHGG originate in the germ line as part of cancer predisposition syndrome (CPS). The three most prominent syndromes in which pHGG can occur are LiFraumeni syndrome (LFS), constitutional mismatch repair deficiency (CMRD) and Neurofibromatosis 1 (NF1).[62]

LFS is an autosomal-dominant CPS caused by germ line mutations in TP53.[63] The spectrum of neoplasms is large and includes sarcomas, breast cancer, adrenocortical carcinoma, brain tumors, hematologic malignancies, and others. Brain tumors are the second most common malignancies in children with LFS following adrenocortical carcinoma. The median age of onset of brain tumors in LFS is 16 years compared to 57 years in the general population.[64] HGG are the most common brain tumor in LFS and tend to occur in late childhood and early adulthood. In the younger age group, choroid plexus carcinomas and medulloblastomas are more frequent.[5] The pathology and biology of pHGG in LFS is similar to sporadic tumors including rare cases with IDH1 mutations.

CMRD is a childhood cancer syndrome caused by biallelic mutations in the mismatch repair pathway (MMR). Monoallelic mutations in MMR genes results in a CPS termed Lynch syndrome, an autosomal dominant syndrome, characterized primarily by gastrointestinal and genitourinary malignancies in mid-to-late adulthood. In contrast, biallelic mutations in the MMR genes cause complete loss of MMR ability in all cells resulting in CMMRD, an autosomal recessive syndrome, associated with both extracranial and malignant brain tumors in children and/or young adults.

The most frequent mutations found in CMMRD patients (approximately 60% of cases) involve the *PMS2* gene. The spectrum of cancers reported in patients affected by CMMRD is very broad, and it includes brain/central nervous system tumors (glioblastoma and other high-grade astrocytic tumors, medulloblastoma, and supratentorial primitive neuroectodermal tumors).[65] Typically, the HGGs occurring in this CPS are characterized by an unusual number of highly pleomorphic bizarre neoplastic astrocytic cells.[66] A recent report of a CMMRD patient describes it as the concomitant occurrence of a cerebellar IDH wild-type glioblastoma and an IDH 1-mutated temporal anaplastic astrocytomas rich in pleomorphic bizarre cells.[67]

Malignant gliomas in CMMRD exhibit a hypermutator phenotype with some of the greatest mutational burdens in all human cancer. With such ultra-hypermutation profile associated with the expression of new neoantigen candidates, CMMRD-related HGG may be benefited by the treatment with immune checkpoint inhibitors.[68]

With an incidence of 1:2000–1:5000 individuals, NF1 is the most common CPS.[69] Most NF1 tumors are of benign nature. However, NF1 patients are at risk for malignant tumors including peripheral nerve sheath tumors (MPNST), HGG, and juvenile myelomonocytic leukemia among others. Pilocytic astrocytoma of the optic pathway is the most common brain tumor in NF1 that tend to arise in infancy, affecting approximately 15%–20% of NF1 patients. The incidence of HGG in NF1 is much lower. NF1-related pHGGs share the same molecular abnormalities as sporadic tumors, such as TP53 mutations and CDKN2A/p16 deletions.[70] Similarly, NF1 is one of the most frequently mutated somatic genes in both pediatric and adult sporadic H3-/IDH-wt HGG.[16,32]

Prognosis

Different mutations relate with different prognosis. Patients with IDH 1-mutant tumors have a better prognosis than patients with H3F3A and IDH 1 wt tumors.[26] G34-mutant neoplasms also showed a better OS than wt tumor types. On the other hand, patients with K27 mutations tend to have a shorter OS than patients with wt tumors. Comparing the two H3F3A mutations, patients harboring H3G34R/V mutation have a better outcome than patients with K27-mutated GBM. This relation is partially linked to more accessible surgical site of G34-mutated tumors, differing to midline K27-mutated tumors. In addition, G34-mutant tumors are associated with MGMT methylation, which results in a better prognosis while offering a further therapeutic strategy with temozolomide.[26]

Conclusions

The integrated molecular profiling has demonstrated the biological and clinicopathological heterogeneity of pHGG and their biological differences with adult malignant gliomas. Moreover, such differences emphasize the importance of conducting specific clinical trials for pHGG to assess the benefit of potential treatments.[71] While there are several distinct subgroups for which there is a strong rationale for

tailored future clinical studies, a large proportion of them continues to challenge improvements in survival. The significant molecular variability among pHGG will probably continue to evolve with the collection of larger patient cohorts and probably, further rare subsets will be detected in the near future. However, these complex molecular data are essential for patient stratification in the future clinical trials and to develop new targeted therapies for these aggressive and deadly tumors.

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Conflicts of interest

There are no conflicts of interest.

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