

Case Report

Impact of the revised WHO classification of diffuse low-grade glioma on clinical decision making: A case report

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Abstract

Background: In the 2016 update of the World Health Organization Classification of Tumors of the central nervous system, phenotypic and genotypic parameters are integrated in diffuse low-grade glioma (LGG) tumor classification. Implementation of this combined phenotypic–genotypic characterization identifies prognostic relevant subgroups.

Case Description: We report a case of a 67-year-old patient with an LGG that showed molecular characteristics similar to glioblastoma multiforme (GBM). After gross total tumor resection, the patient received combination therapy (radiotherapy and chemotherapy) according to high-grade glioma treatment protocol.

Conclusion: The introduction of molecular parameters to the classification of LGG will add a level of objectivity, which will yield biological homogeneous subclasses. Consequently, this will influence patient counseling and clinical decision making regarding treatment protocols.

Key Words: Low-grade glioma, molecular characteristics, treatment, WHO classification

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INTRODUCTION

In the 2016 update of the World Health Organization Classification of Tumors of the Central Nervous System phenotypic and genotypic parameters are integrated in diffuse low-grade glioma (LGG) tumor classification. Implementation of this combined phenotypic-genotypic characterization identifies prognostic relevant subgroups

CASE REPORT

A 67-year-old male presented with transient reduced orientation and short-term memory loss. The symptoms

lasted for 24 hours during which he also suffered loss of face and object (building) recognition. The patient

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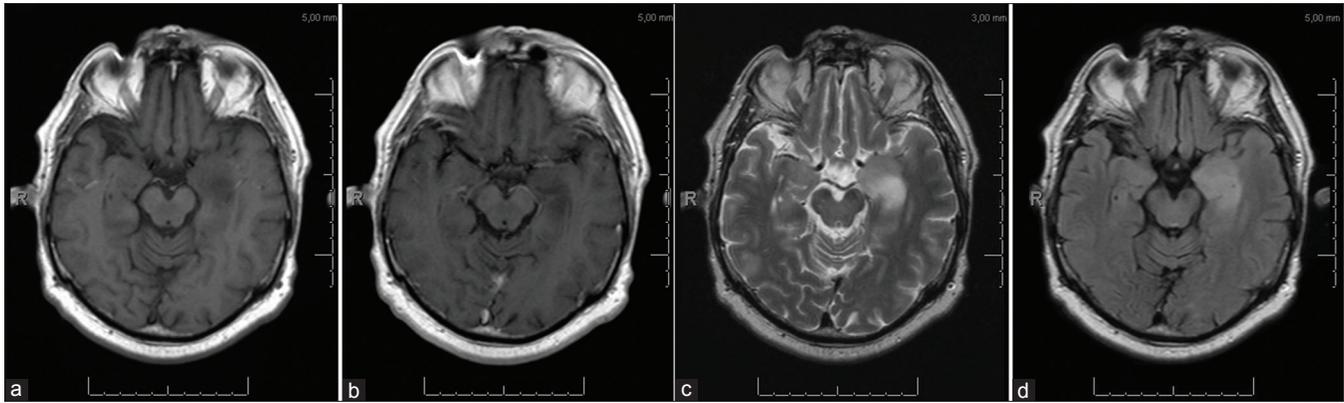


Figure 1: Preoperative MRI. (a and b) T1-weighted image without and with gadolinium. (c) T2-weighted image. (d) T2-FLAIR

reported complete amnesia for this episode. Additional amnesic evaluation revealed a period of transient global amnesia of several hours occurring one and a half years ago. His medical history stated diabetes mellitus type II and hypercholesterolemia. Neurological examination at the time of evaluation showed no abnormalities.

Electroencephalography was performed which showed a normal background activity and no signs of epileptic or epileptiform discharges. Magnetic resonance imaging (MRI) showed a nonenhancing lesion with high signal intensity on T2-weighted images and low signal intensity on T1-weighted images of the left mesial temporal lobe [Figure 1a-d]. Diffusion-weighted imaging revealed no abnormal restricted diffusion. A diffuse low-grade glioma (LGG), dysembryoplastic neuroepithelial tumor (DNET), or postictal changes were included in the radiological differential diagnosis. Subsequent MRI scan 1 month later demonstrated an essential unchanged situation, which suggested the lesion to be of glial origin rather than postictal (sub-)cortical changes.

A left-sided anterior temporal lobectomy in combination with resection of the radiologically thickened hippocampus was performed. Intraoperatively, a grayish tumorous tissue of soft consistency was removed suspicious for LGG. A gross total resection was achieved.

A postoperative MRI scan within 72 hours depicted a small area with an increased T2 signal intensity with no abnormal diffusion restrictions, suspicious for residual tumor [Figure 2a-e]. Postoperatively, the patient suffered subtle dysphasia, which showed complete remission after 3 days. The patient was discharged from the hospital on the fifth postoperative day.

Histology

The obtained tissue showed high cellularity with subpopulations of cells with enlarged nuclei and perinuclear clearing in accordance with a “fried-egg” appearance. The NeuN stain identified multiple neurons.

Glial cells stained positive with GFAP, and Ki-67-staining showed an increased proliferative activity in the enlarged atypical cells. The histological diagnosis was an LGG, WHO II, molecularly characterized by the absence of: *IDH1/2* mutation, 1p/19q codeletion, or *MGMT* promotor hypermethylation. See Figure 3 for the histology staining.

Further genomic analyses using next generation sequencing revealed no mutation in the *ATRX*, *CDKN2a*, *CIC*, *FUBP1*, *NOTCH1*, *PTEN*, and *TP53* coding genes and no mutations in the mutational hotspots of *BRAF*, *H3F3A*, *EGFR*, *IDH1/IDH2*, and *PIK3CA*. Copy number variation analyses of chromosomes 1, 7, 9, 10, 12, and 19 showed an imbalance of chromosome 7 including *EGFR*, *CD6*, and *Met* with a loss of chromosome 10.

Treatment

The patient was diagnosed according to the 2016 update of the World Health Organization classification of tumors of the central nervous system; IDH wild-type (*IDH_{wt}*), and diffuse astrocytoma.^[7] Considering the distinct high-grade molecular traits, the patient was treated postoperatively according to the Stupp protocol; concomitant temozolomide 75 mg/m²/day for 49 days and radiotherapy with a total dose up to 59.4 Gy in 33 fractions followed by 6 cycles of temozolomide.^[10]

DISCUSSION

Depending on the WHO stage (I–IV), the survival of glioma patients varies from several months to more than 20 years.^[10] The prevalence of LGG is lower when compared to the WHO IV glioblastoma multiforme; of all gliomas LGG comprise 15%.^[8] Moreover, within the spectrum of LGG, significant variation in mean overall survival is observed, ranging from 5.9 years (astrocytoma) to 11.9 for oligodendroglioma.^[8]

In May 2016, the WHO presented an update of the classification of tumors of the central nervous system.^[7] Here, for the first time, phenotypic and genotypic parameters were integrated in diffuse glial



Figure 2: Post-operative MRI. (a and b) T1-weighted image without and with gadolinium. (c) T2-weighted image, (d) T2-FLAIR, (e) Diffusion-weighted imaging

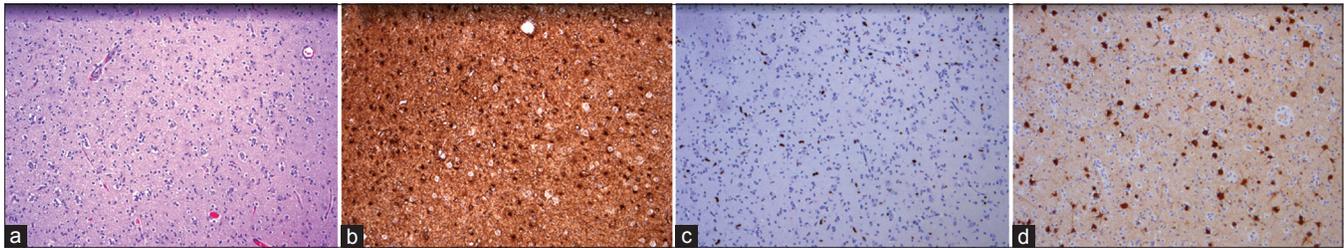


Figure 3: Histology staining. (a) Hematoxylin and eosin, $\times 100$. (b) Glial fibrillary acidic protein (GFAP), $\times 100$. (c) Ki-67 (mib1), $\times 100$. (d) Neuronal nuclei (NeuN), $\times 100$

tumor classification. Every LGG is characterized according to the presence or the absence of mutations in the isocitrate dehydrogenase 1 or 2 genes (IDH) and complete or incomplete deletion of both the short arm of chromosome 1 and of the long arm of chromosome 19 (1p/19q co-deletion). Implementation of this combined phenotypic–genotypic characterization identifies subgroups that correlate with overall survival and treatment responses. Figure 1 shows a flowchart of the classification system adapted to the molecular classification of LGG, as suggested by The Cancer Genome Atlas Research Network.^[1] Here, we will present a concise overview of several of the identified molecular markers in LGG with prognostic and biological relevance.

LGG and IDH

The first segregation of diffuse LGG is based on the presence of *IDH1/2* gene mutation [Figure 4]. These mutations occur at a single amino acid residue of *IDH1*, arginine 132, which is most commonly mutated to histidine (*R132H*).^[4] IDH is a cytosolic enzyme involved in the decarboxylation of isocitrate, producing α -ketoglutarate and CO_2 . A mutation in the *IDH1* gene (*IDH_{mut}*) allows the homodimeric enzyme to reduce α -ketoglutarate in 2-hydroxyglutarate (2-HG). Accumulation of the 2-HG metabolite is associated with the dedifferentiation of gliomas.^[4] In addition, an *IDH* gene mutation causes hypermethylation of specific DNA loci (CpG islands), resulting in a significantly different gene expression profile compared to wild type IDH LGG.^[11] Specifically, hypermethylation of the DNA-repair enzyme *O*⁶-methylguanine-DNA methyltransferase (*MGMT*) promoter gene downregulates the expression of this enzyme, and therefore increases tumor susceptibility to alkylating agents such as temozolomide.

IDH mutations are present in almost 90% of the diffuse LGG and are correlated with a favorable, therapy independent, survival compared to *IDH_{wt}* LGG: 13.1 years compared to 5.1 years.^[1,6] Furthermore, an *IDH* mutation is predictive for the response of the LGG to multimodal treatment strategies, as was recently shown that the addition of chemotherapy to radiotherapy increases progression-free and overall survival in diffuse LGG compared to radiotherapy alone.^[2]

IDH_{mut} with 1p/19q codeletion

Subsequent to *IDH_{mut}*/*IDH_{wt}* segregation, LGGs are classified according to the presence or absence of 1p/19q codeletion. A strong correlation exists between the presence an *IDH* mutation and 1p/19q codeletion with the histological oligodendroglioma with a correspondence rate of 95% for WHO II tumors. Strikingly, mutations in the coding gene for Telomerase Reverse Transcriptase (*TERT*) is found in 96% of this subclass. *TERT* gene mutations cause an activation of this enzyme.^[5] However, it is not associated with an increased telomere length in diffuse glioma, and is therefore unlikely to contribute to the maintenance of unlimited replicative potential.^[3] However *TERT* mutation status is associated with prognosis in WHO 2016 defined groups.^[9] Patients with a *IDH_{mut}*/1p/19q co-deleted LGG have significant progression-free and overall survival compared with their 1p/19q *IDH* native counterparts.^[2]

IDH_{mut} without 1p/19q codeletion

Almost all diffuse LGGs without a 1p/19q codeletion harbor mutations in the Tumor protein (TP) 53 coding gene and the majority harbor inactivating mutations in the *ATRX* gene.^[1] Dysfunction of the *TP-53* gene, as known for the Li-Fraumeni syndrome, causes a loss of tumor suppressive capabilities of *TP-53*. For LGG, it is hypothesized that, after the acquisition

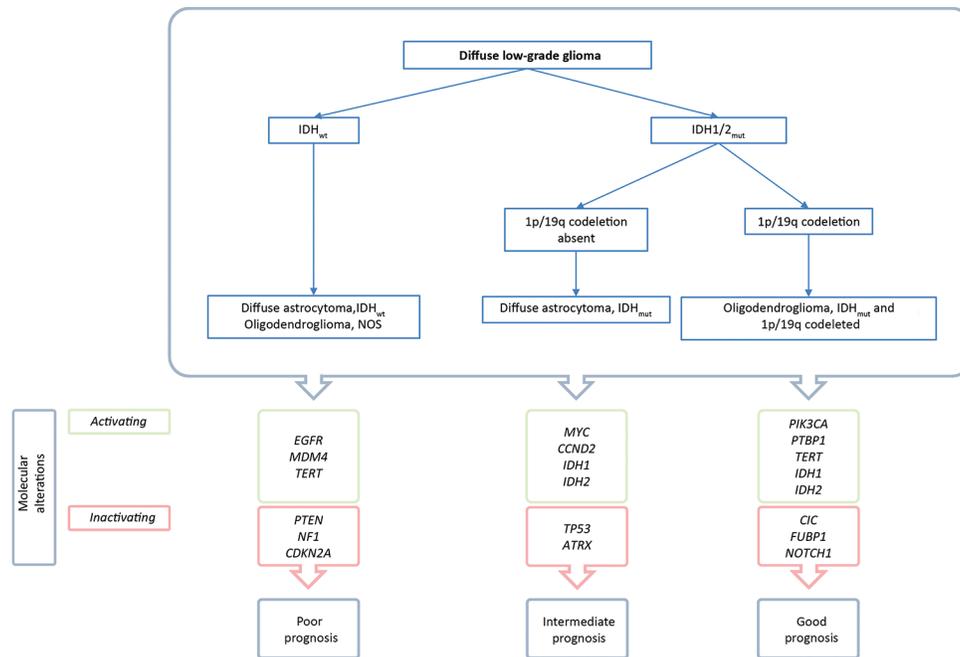


Figure 4: WHO 2016 simplified algorithm for classification of LGG, adapted to Brat et al. (2015)

of an IDH mutation, a tumor cell either acquires a 1p/19q codeletion or a mutation in TP-53. This theory is further supported by the observation that *TERT* and *ATRX* mutation are mutually exclusive and result in different subclasses: IDH_{mut} with (*TERT*) or without (*ATRX*) 1p/19q codeletion. Interestingly, not *TERT* but *ATRX* mutations were associated with increased telomere length in a pan-glioma analysis, suggesting an alternative lengthening of telomeres.^[3]

LGG-IDH^{wt}

LGG with an IDH wild type comprise 10% of all diffuse LGG WHOII tumors. Identification of LGG- IDH_{wt} is of the utmost importance as the majority of this subgroup shows molecular similarities with GBM tumors, with consequent worse prognosis and treatment response.^[1] Mutations in the genes encoding for *EGFR*, *PTEN*, and *NF1* are observed in both LGG- IDH_{wt} and GBM.^[12] Moreover, numerical and structural chromosomal abnormalities such as a trisomy of chromosome 7 and a loss of chromosome 10 are more frequently observed in high-grade glial tumors.

CONCLUSION

A subclass of diffuse LGG shows a molecular profile similar to high-grade glioma and is associated with a poor overall survival. Therefore, additional molecular characterization is necessary to identify this subgroup. The 2016 update of the WHO Classification of diffuse LGG facilitates subclass segregation and therefore formally introduces molecular diagnostic results as part of routine neuropathological practice with direct clinical consequences. The presented case illustrates that molecular characterization, beyond the scope of

the WHO classification, highly influences adjuvant treatment strategies, and is therefore an example of personalized medicine. Further research will have to show whether the identified subclass-specific genetic aberrations, such as *EGFR* amplification, will aid to the development of targeted therapy for low-grade gliomas.

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Conflicts of interest

There are no conflicts of interest.

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