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TITLE: Molecular Glioblastoma: high-grade malignancy with low-grade histomorphology

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Abstract

Glioblastoma is a highly aggressive primary malignancy of the central nervous system. Classically, the histology is that of a diffusely infiltrative astrocytic glioma with one or more high-grade features, these being microvascular proliferation and necrosis;

prominent mitotic activity is also a common feature. However, since the 2021 edition of the WHO Classification of Tumours of the Central Nervous System (CNS WHO 2021), it is recognised that in rare cases these high-grade features may be absent entirely, with specific molecular alterations being sufficient to support the diagnosis.

The case presented here is an example of such a lesion, with low-grade histomorphology, but high-grade molecular features. Such cases highlight the importance of molecular testing and integrated diagnosis in neuropathology, as well as careful evaluation of the diagnostic criteria as presented in CNS WHO 2021.

Keywords

Glioma; methylation profiling; next generation sequencing; integrated diagnosis

Case Report

A man in his 6th decade presented with new onset generalised tonic-clonic seizures. He had no other past medical history of note.

A Magnetic Resonance Imaging (MRI) scan of the brain at presentation showed an area of T2 signal change involving the right temporal lobe and thalamus. This showed no contrast enhancement and appeared hypocellular. The initial radiological differential diagnosis was low-grade glioma vs. encephalitis. A computed tomography (CT) scan of the body showed no primary malignancy elsewhere. Two short interval MRI scans performed over the following three months showed sequential increases in the area of signal change near the right thalamus, but this remained non-enhancing (Figure 1A).

Surgical debulking of the right temporal aspect of the lesion was performed. The surgery was uneventful, though recovery was complicated by left sided weakness; postoperative MRI demonstrated a small ischaemic focus in the right internal capsule. Following step down from the Intensive Care Unit, he was discharged to specialist rehabilitation services.

Histology of the lesion showed a diffusely infiltrative glioma; the neoplastic nuclei were round to oval with fine granular chromatin, and the cytoplasm was fibrillary and eosinophilic (Figure 1B,C). Some areas showed prominent satellitosis (Figure 1D) There were no histological high-grade features evident; there was no necrosis, no microvascular proliferation, and no mitoses were seen. The provisional histological diagnosis was that of low-grade diffuse glioma.

A methylation array (MethylationEPIC, Illumina, San Diego, USA) showed gain of chromosome 7 and loss of chromosome 10, along with loss of 14 and a segmental loss of 13q (Figure 1E). The methylation classifier (Epignostix, Heidelberg, Germany) returned no match, with the highest calibrated score being 0.43453 for the superfamily of low-grade glial/glioneuronal/neuroepithelial tumours. For comparison, the raw data was also submitted to the NIH Bethesda brain tumour classifier (Laboratory of Pathology, National Cancer Institute, Bethesda, Maryland, USA); this returned a classification of ganglioglioma (class mean score 0.991), also matching for the low grade glial/glioneuronal superfamily (superfamily mean score 0.923). The MGMT promoter methylation estimation gave an uninformative result, but this was subsequently confirmed to be unmethylated by methylation-specific polymerase chain reaction (MS-PCR).

Next generation sequencing (TruSight Oncology 500, Illumina, San Diego, USA) revealed a pathogenic variant in the TERT promoter (NM_198253.3:c.-146C>T), but no other variants were detected in the panel; importantly, this confirmed the IDH1, IDH2, and H3 status to be wildtype.

When determining the integrated diagnosis, the diagnostic criteria as presented in CNS WHO 2021 were considered [1, Table #20370]. The histology of this case is that of a diffuse glioma, with sequencing confirming it to be H3-wildtype and IDH-wildtype. Beyond this, the essential criteria for a glioblastoma are one or more of microvascular proliferation, necrosis, TERT promoter mutation, EGFR amplification, and a chromosome copy number alteration pattern of +7/-10 [1]. In our case, even in the absence of traditional histological high-grade features, the lesion showed both a pathogenic TERT variant and +7/-10 copy number pattern; this therefore satisfies the criteria for Glioblastoma, IDH-wild type, CNS WHO Grade 4.

Discussion

This was a challenging case with discordant radiological, histological and molecular features; as such, it highlights the importance of evaluating all the evidence together, within the context of the CNS WHO diagnostic criteria. Given the diagnostic complexity, the case was reviewed at local molecular meetings in addition to routine multidisciplinary team (MDT) discussion. The Bethesda classification of ganglioglioma was deemed not to fit the clinicopathological picture due to the diffusely infiltrative nature of the lesion, and absence of dysplastic ganglion cells; the finding of a TERT promoter variant would also be highly unusual in ganglioglioma. Considering the high-grade molecular features, the lesion was treated as glioblastoma once the patient's performance status allowed. Two serial MRI scans over the subsequent 6 months showed progressive T2 signal change and mass effect within the right thalamus and

midbrain with irregular rim enhancement, in keeping with disease progression (Figure 1F).

The diagnosis of glioblastoma underwent significant revisions with the updates provided in CNS WHO 2021 [2]. High grade diffuse gliomas with pathogenic IDH1 or IDH2 variants, previously considered to be Glioblastoma, IDH-mutant, were reclassified as Astrocytoma, IDH-mutant, CNS WHO grade 4. Conversely, IDH-wildtype lesions with low grade histology, formerly considered to be Astrocytoma, IDH-wildtype under CNS WHO 2016, have also been reclassified; lesions of this type that also carry specific molecular alterations, namely +7/-10 CNV, TERT promoter mutation, or EGFR amplification are now diagnosed molecular glioblastoma (molGB), a subset of Glioblastoma, IDH-wildtype, CNS WHO grade 4. This illustrates how molecular investigations improve prognostic accuracy; while these IDH-wildtype lesions with low-grade histology were recognised to carry a worse prognosis than IDH-variant low-grade lesions, they were not considered inherently high-grade. Recent analyses have shown that molGB has a prognosis not significantly different to that of glioblastoma with high grade histological features [3]. It is therefore crucial that such cases are identified, to facilitate appropriate prognostication, treatment, and care planning.

Practice Points

- Molecular glioblastoma is an IDH-wildtype diffuse glioma with low-grade histology, but at least one molecular high-grade feature; these include pathogenic TERT promoter variants, EGFR amplifications, and +7/-10 copy number variation.
- The discordance between histological appearances and biological behaviour can make molecular glioblastoma a challenging diagnosis.
- Local molecular pathology protocols for CNS tumours need to be sufficient to capture the requisite information needed to make accurate diagnoses according to the CNS WHO 2021 diagnostic guidelines.

Figure 1: A Preoperative axial T2 FLAIR MRI scan, with signal change in the right thalamus; this extended to the right temporal lobe. **B** 50X and **C** 200X magnification of a representative area of the lesion; this section is that on which subsequent molecular studies were performed. **D** 200X magnification of a second area with pronounced satellitosis. **E** Copy number plot derived from methylation array; the +7/-10 CNV pattern can be readily observed. **F** 6-month postoperative coronal T1 weighted MRI scan with contrast, showing new expansion of right thalamic signal change with enhancement.

Questions:

1. What pattern of chromosome copy number variation is associated with glioblastoma?
   A) -7/-10
   B) +7/+10
   C) +7/-10
   D) -7/+10
   E) +7/-22q

Answer: C

2. Which pathogenic IDH variant is most common in low grade diffuse gliomas?
   A) IDH1 R132H
   B) IDH1 R140Q
   C) IDH2 R132H
   D) IDH2 R140Q
   E) IDH2 R172K

Answer: A

3. MGMT promoter methylation status predicts response to which family of chemotherapy drugs?
   A) Alkylating agents
   B) Anthracyclines
   C) Antimetabolites
   D) Microtubule inhibitors
   E) Topoisomerase inhibitors

Answer: A

References

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