Long-term survival of a child with a high-grade glioma with novel molecular features

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Accepted 1 October 2021

To cite: Adams JW, Malicki D, Levy M, *et al*. *BMJ Case Rep* 2021;**14**:e246423. doi:10.1136/bcr-2021-246423

DESCRIPTION

A 6-year-old boy presented for evaluation after a new onset focal seizure. CT demonstrated a large right hemispheric mass with midline shift (figure 1A). MRI confirmed a T2 hyperintense tumour with reduced diffusivity, minimal enhancement on post-gadolinum sequences, and linear calcifications on susceptibility-weighted sequences and pregadolinium sequences (figure 1B–F). The neuroradiographic differential diagnosis included high-grade glioma (HGG), desmoplastic infantile astrocytoma/ganglioglioma, anaplastic ependymoma, pleomorphic xanthoastrocytoma, atypical teratoid rhabdoid tumour and an unusual dysembryoplastic neuroepithelial tumour. MRI of the spine revealed no evidence of disseminated disease. The patient underwent gross total resection, and neuropathology revealed a moderately dense glial tumour with cytoarchitectural variability ranging from spindled fascicular cells with elongate, hyperchromatic nuclei and little mitotic activity to uniformly polygonal cells with perivascular pseudorosette formation and round-to-oval nuclei with open chromatin and brisk mitotic activity. Extensive necrosis and calcification were noted. Immunohistochemistry was positive for glial fibrillar acidic protein and S-100 but negative for synaptophysin; abundant Ki67 immunopositivity was detected. Following multiple external expert neuropathology opinions obtained at diagnosis, all were in agreement that the histological findings were most consistent with a diagnosis of an HGG (figure 2). Following surgical resection, the patient completed proton therapy with adjuvant temozolomide for a total of 12 cycles. He has remained recurrence-free 12 years after initial diagnosis with a normal neurological examination. Retrospective analyses were undertaken given the prolonged survival of a child with HGG, including molecular analysis of the patient's initial tumour. Next-generation sequencing (NGS) performed on the original tumour detected only three variants of unknown clinical significance in *NSD1* (c.757C>G), *IGF1R* (c.2360C>T) and *AMER1* (c.2096G>A). Microarray analysis showed a low-level gain of chromosome 1 and high copy gain (x4) in 9q21.33, encompassing *NTRK2* (exons 1–14) without evidence of a corresponding fusion on NGS.

Paediatric HGGs are rare and usually carry a poor prognosis due to a lack of effective therapeutic options.[1 2] Temozolomide with radiotherapy is standard for some adult HGGs, but the response of paediatric HGGs to this regimen has been less conclusive,[3 4] potentially because of molecular differences between these tumour types.[5 6] We report the long-term survival of a paediatric patient with HGG after tumour resection, adjuvant

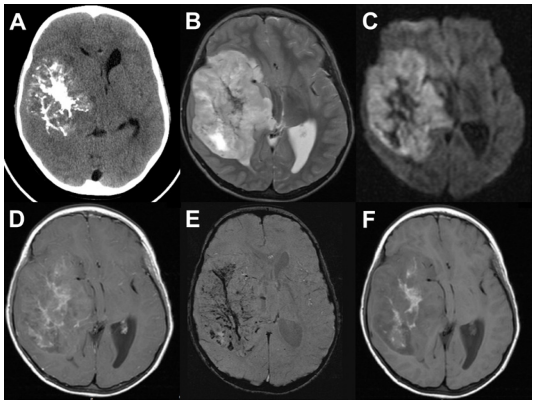

Figure 1 Neuroimaging presentation of a high-grade glioma with novel molecular features in a paediatric patient. CT reveals a large right hemispheric hyperdense mass with midline shift (A). MRI shows a T2 hyperintense tumour (B) with reduced diffusivity (C), minimal enhancement on postgadolinum sequences (D), and linear calcifications on susceptibility-weighted sequences (E) and pregadolinium sequences (F).

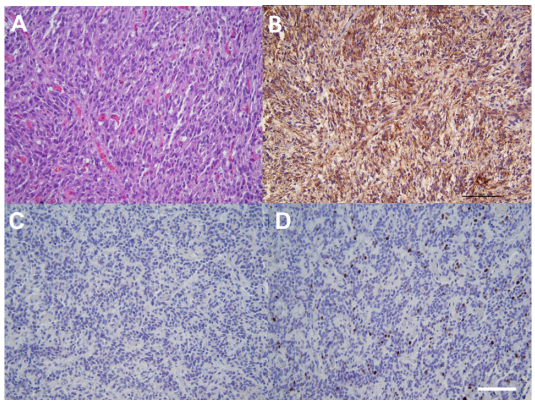

Figure 2 Neuropathological characteristics of the high-grade glioma with novel molecular features in a paediatric patient. H&E staining portrayed moderately dense cellularity with variable cytoarchitecture, including spindled fascicular cells with elongate, hyperchromatic nuclei and uniformly polygonal cells with round-to-oval nuclei (A). Immunostaining revealed positivity of glial fibrillar acidic protein (B) and the absence of synaptophysin (C). (D) Ki67 immunostaining showed an abundance of mitotically active cells. These histological features of the tumour are most consistent with a diagnosis of high-grade glioma. 200× magnification; scale bar=100 µm.

temozolomide and radiotherapy. Future investigation will be necessary to determine how the tumour's molecular profile influenced therapeutic efficacy. *NTRK2* encodes a receptor tyrosine kinase that activates the RAS-ERK, PI3K and PLCγ cascades.[7] *NTRK2* fusions constitutively activate these pathways and are putative oncogenic drivers of paediatric glioma; however, a specific NTRK fusion was not detected in this case.[8–12] Current efforts that seek to target *TRK* fusion-positive tumours with TRK inhibitors may improve the prognosis for some paediatric patients with HGG,[13–16] but tumours with non-fusion molecular alterations of *NTRK*, as may be present in this case case given the high copy gain (x4) in 9q21.33, may be less responsive to these inhibitors.[17] As molecular alterations, such as histone H3.3 variants,[18–20] become increasingly important for treatment and prognosis, classifications of paediatric and infantile HGG are rapidly evolving including the use of methylation that is still only performed in limited centres and not available in this case.[9 11 21–24] Correlating genetically diverse molecular variants with disparate clinical outcomes remains central to this endeavour. Our case highlights unique genetic features in a rare long-term survivor of paediatric HGG adding to the literature of genotypic–phenotypic correlations with survival.

Learning points

- Paediatric and adult high-grade gliomas (HGGs) have distinct molecular signatures.
- The clinical relevance of variants mutations of unknown significance detected on next-generation sequencing and copy number aberrations detected on microarray are largely unknown.
- Classifications of paediatric HGG are evolving rapidly because molecular variants are diverse and may predict clinical prognosis and treatment response.

Contributors All authors were responsible for the design and creation of the case report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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