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CASE REPORT

Atypical anaplastic astrocytoma with unique molecular features and diffuse leptomeningeal spread in a child with long-term survival

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SUMMARY

Paediatric high-grade gliomas, including glioblastoma and anaplastic astrocytoma, make up 8%–12% of paediatric central nervous system tumours¹ and have poor prognosis, with 2-year survival less than 30%² and overall survival less than 10%. The only known prognostic factors in this population include extent of resection and tumour histological grade. We present the case of a 9-year-old boy with disseminated anaplastic astrocytoma treated with subtotal resection, craniospinal radiation and temozolomide, with 8-year survival despite metastatic disease at presentation and subtotal resection. Next generation cancer gene panel sequencing revealed an usual pattern of 12 amplifications and four mutations not previously described.

BACKGROUND

Despite overall advances in paediatric cancer treatment, the treatment options and prognosis remain poor in paediatric high-grade gliomas (HGG). However, the increasing availability of tumour molecular genetic analysis may provide insight on which tumours will preferentially respond to treatment. Recent molecular genetics analyses of adult and paediatric HGG suggest that they are different entities.^{1,2} In addition, the role of temozolomide, an alkylating agent, in paediatric HGG is not well understood.

Figure 1 Sagittal fluid-attenuated inversion recovery (FLAIR) sequence MRI of the brain showing ill-defined, heterogeneous infiltrative cerebellar mass (A) with mild multifocal enhancement (B). Post gadolinium MRI spine reveals extensive leptomeningeal disease (arrow) (C).

Figure 2 Histopathology demonstrates a moderately cellular proliferation of glial cells with elongate, pleomorphic, hyperchromatic nuclei and mitotic activity infiltrating cerebellar cortex including the molecular layer (x600 magnification).

CASE PRESENTATION

A 9-year-old previously healthy boy presented with 6 weeks of intermittent vomiting and imbalance. Neurological exam was notable for decreased visual acuity, bilateral papilloedema and wide-based ataxic gait.

INVESTIGATIONS

MRI of the brain revealed an ill-defined, heterogeneous, mildly enhancing 5.7 cm mass centred in the midline cerebellum between the superior vermis and right inferior cerebellar tonsil with mild non-communicating hydrocephalus (figure 1A–B). MRI of the spine showed extensive diffuse leptomeningeal metastatic disease involving the entire cervical and thoracic spinal cord (figure 1C). He underwent sub-total resection of the mass, which could not be fully resected due to invasion of the entire inferior cerebellum. Pathology revealed moderately cellular proliferation of glial cells with elongate, pleomorphic, hyperchromatic nuclei and mitotic activity infiltrating cerebellar cortex including the molecular layer (figure 2) consistent with an anaplastic astrocytoma.

Based on the unique neuroimaging features and aggressive pathology, a next generation sequencing analysis of 397 cancer-related genes was performed to help guide therapeutic decisions (table 1). The genetic analysis revealed amplification of *MYC*,

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Table 1 Next generation cancer gene panel

Genes for which entire coding panel is interrogated:

ABL1	ABL2	ACVR1B	AKAP9	AKT1	AKT2	AKT3	ALK	AMER1	APC	AR	ARAF
ARFRP1	ARID1A	ARID1B	ARID2	ASPSR1	ASXL1	ATF6	ATM	ATP1A1	ATP2B3	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL11A	BCL11B	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BLM	BMPR1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTB	C11orf30
CACNA1D	CAMTA1	CARD11	CASP8	C8orf72	CBL	CBLB	CCND1	CCND2	CCND3	CCNE1	CD274
CD79A	CD79B	CDC73	CDH1	CDH11	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A
CDKN2B	CDKN2C	CEBPA	CHD2	CHD4	CHEK1	CHEK2	CIC	CLTCL1	COL1A1	CREBBP	CRKL
CRLF2	CSF1R	CSF3R	CTCF	CTNNA1	CTNNA2	CUL3	CYLD	DAXX	DDIT3	DDR2	DICER1
DNM2	DNMT3A	DOT1L	EBF1	EGFR	EIF1AX	EP300	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2
ERBB3	ERBB4	ERCC3	ERCC4	ERCC5	ERG	ERRF1	ESR1	ETV1	ETV4	ETV5	ETV6
EWSR1	EXT1	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FAS
FAT1	FBXO11	FBXW7	FGF10	FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2
FGFR3	FGFR4	FH	FLCN	FLT1	FLT3	FLT4	FOXA1	FOXL2	FOXO1	FOXP1	FRS2
FUBP1	FUS	GABRA6	GATA1	GATA2	GATA3	GATA4	GATA6	GID4	GLI1	GMPS	GNA11
GNA13	GNAQ	GNAS	GPR124	GRIN2A	GRM3	GSK3B	H3F3A	HGF	HIP1	HNF1A	HRA5
HSD3B1	HSP90AA1	IDH1	IDH2	IGF1R	IGF2	IKBKE	IKZF1	IL7R	INHBA	INPP4B	IRF2
IRF4	IRS2	ITK	JAK1	JAK2	JAK3	JUN	KAT6A	KAT6B	KDM5A	KDM5C	KDM6A
KDR	KEAP1	KEL	KIF5B	KIT	KLHL6	KMT2A	KMT2D	KRAS	LCP1	LIFR	LMO1
LRIG3	LRP1B	LYN	LZTR1	MAGI2	MAML2	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MCL1	MDM2
MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MLL2	MLL3	MLL4	MN1	MPL
MSH2	MSH6	MTOR	MUTYH	MYB	MYC	MYCL	MYCN	MYD88	MYH11	MYH9	NCOA1
NCOA2	NF1	NF2	NFE2L2	NFKB1A	NIN	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NR4A3
NRAS	NSD1	NTRK1	NTRK2	NTRK3	NUMA1	NUP214	NUP93	NUP98	PAK3	PALB2	PARK2
PAX3	PAX5	PAX7	PBRM1	PCM1	PDCD1LG2	PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3CA	PIK3CB
PIK3CG	PIK3R1	PIK3R2	PLCG2	PMS1	PMS2	POLD1	POLE	PPARG	PPP2R1A	PRDM1	PRDM16
PREX2	PRKAR1A	PRKCI	PRKDC	PRSS8	PTCH1	PTEN	PTPN11	PTPRC	QKI	RAC1	RAD21
RAD50	RAD51	RAF1	RALGDS	RANBP17	RANBP2	RARA	RB1	RBM10	RET	RICTOR	RNF43
ROS1	RPTOR	RUNX1	RUNX1T1	SDHA	SDHB	SDHC	SDHD	SETBP1	SETD2	SF3B1	SLC34A2
SLIT2	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP	SOC1	SOX10	SOX2	SOX9
SPEN	SPOP	SPTA1	SRC	SRGAP3	SS18	STAG2	STAT3	STAT4	STAT5B	STK11	SUFU
SYK	TAF1	TBX3	TCF7L2	TERC	TERT	TET2	TGFBR2	THRAP3	TMPSR2	TNFAIP3	TNFRSF14
TOP1	TOP2A	TP53	TPR	TRIM24	TRIM33	TRIP11	TRRAP	TSC1	TSC2	TSHR	U2AF1
VEGFA	VHL	WHSC1	WISP3	WRN	WT1	XPO1	ZBTB2	ZMYM2	ZNF217	ZNF384	ZNF521

Subset of genes (28) for which potential rearrangements are evaluated:

ALK	ASPSR1	BRAF	BRD4	DDIT3	EGFR	ETV1	ETV4	ETV5	ETV6	EWSR1	FGFR1
FGFR2	FGFR3	FOXO1	FUS	MYB	NOTCH2	NR4A3	NTRK1	NTRK2	PDGFRA	PPARG	RAF1
RET	ROS1	SS18	TMPSR2								

CDK6, CDKN1B, EZH2, FH, GATA6, GRM3, HGF, MAG12, RAC1, SMAD2 and SMAD4. Novel mutations were identified in four genes: MLL (A53V), MTOR (T1834M), NUP93 (A470V) and RAD50 (R725W). Specifically, there were no gene mutations reported in those genes associated with HGG pathogenesis including EGFR, IDH1, IDH2, TP53, ATRX, H3K27M and BRAF V600E. Methylguanine DNA methyltransferase (MGMT) methylation analysis was negative.

TREATMENT

The patient had a ventriculo-peritoneal shunt placement at the time of subtotal resection. Following surgery, he was treated with high-dose craniospinal photon radiation (3600 cGy) with posterior fossa boost (5400 cGy) along with concomitant temozolomide (90 mg/m²) daily during radiation. After completion of radiation, he was treated with monthly temozolomide (200 mg/m² daily on days 1–5 of 28-day cycles) that was discontinued after seven cycles due to persistent thrombocytopenia.

OUTCOME AND FOLLOW-UP

The patient has had no evidence of recurrent disease at 8-year post-therapy and a normal neurological exam.

DISCUSSION

HGG, including glioblastomas and anaplastic astrocytomas, make up 8%–12% of paediatric central nervous system tumours¹ and have very poor prognosis, with 2-year survival rates between 10% and 30%.² Treating young patients is challenging, as radiation therapy can impair neurocognition and quality of life. The only known prognostic factor in paediatric HGG is extent of resection and histological grade.¹

Temozolomide with radiation has been studied in adult HGG, with 26% increase in 2-year survival rate compared with 10% with radiation alone,³ and the greatest benefit was seen in adults whose tumours had methylation of MGMT. However, this correlation has not been replicated in paediatric HGG.¹ Temozolomide has been used in children with estimated response rates of 12%–20%⁴ but with increased side effects,

thrombocytopaenia being the most common. Retrospective analyses of temozolomide in paediatric HGG have not shown definite benefit, although randomised trials are lacking.^{2,4}

The increased information of tumour molecular genetics in recent years has suggested that paediatric HGG and adult HGG are different entities with minimal overlap¹²; thus, further studies on genetic prognostic factors and chemotherapies in paediatric HGG are warranted. Amplification of MYC has been reported in one adult patient with multifocal anaplastic astrocytoma.⁵

In conclusion, we present a case of a disseminated paediatric HGG with multiple cancer gene mutations and duplications, not previously reported, treated with subtotal resection, craniospinal radiation and temozolomide with 8-year survival and no neurological disability, which represents a rare but excellent outcome. To the best of our knowledge, this is the first reported case of a paediatric multifocal anaplastic astrocytoma with this particular pattern

of cancer gene amplifications including MYC to be reported in the literature. Although it is unclear which, if any, of the amplified or mutated genes reported represent the molecular drivers of the disease. Given the atypical long-term survival with standard therapy, the authors feel that this unusual HGG is worthy of reporting and may represent a distinct molecular tumour entity.

Contributors Dr YA was responsible for the design and writing of the case report. Dr DM was responsible for the design and writing of the case report. Dr ML was responsible for the design and writing of the case report. Dr JC was responsible for the design and writing of the case report. All authors approved of the submitted manuscript. All authors report no reported conflicts of interest.

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Learning points

- Paediatric high-grade gliomas (HGG) generally have poor prognosis; however, long-term survivors have been reported.
- Next generation sequencing may be helpful in the categorisation of paediatric brain tumours.
- Further studies are needed to establish prognostic factors in paediatric HGG, especially as more genetic information and biologically targeted agents become available to treat tumours.

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