Rare gain of chromosome 5 in a supratentorial hemispheric paediatric pilomyxoid astrocytoma

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DESCRIPTION

A previously healthy 11-year-old boy presented with self-limited recurrent episodes of dizziness, disorientation and visual changes with a normal neurological examination. MRI revealed a well-circumscribed mixed solid/cystic left parieto-occipital mass (figure 1). He underwent a gross total resection where neuropathology demonstrated moderately cellular proliferation of bland bipolar process-forming spindle cells in a myxoid background with focal angiocentric arrangement, and absence of Rosenthal fibres, consistent with a diagnosis of pilomyxoid astrocytoma (PMA) (figure 2). DNA-based next-generation sequencing panel consisting of 397 cancer-related genes (table 1) performed on paraffin-embedded formalin-fixed tumour revealed no reportable mutations and variants of unknown significance of *PMS1* and *RB1*. However, chromosomal microarray analysis revealed a gain of chromosome 5. The patient was treated with surgery only and is currently 3 years without evidence of recurrence and a normal neurologic examination.

PMAs are currently categorised as a distinct variant of pilocytic astrocytomas (PAs). The 2016 WHO classification of tumours of the central nervous system does not assign a grade to PMAs, but these neoplasms often have a more aggressive clinical course, higher recurrence rates and shorter progression free survival than PAs.¹ As with conventional PAs, *BRAF-KIAA* fusions are the most common genetic alteration, followed by other alterations in the mitogen-activated protein kinase pathway. The majority of paediatric PAs and PMAs have normal tumour cytogenetics. Single copy number alterations, including gains of chromosome 5, have been reported previously in rare paediatric and adult cases of PA.² Gain of chromosome 5 has also been reported in one prior mixed-type PMA/PA but this case has clear delineation between the

Figure 2 H&E-stained sections showed a moderately cellular proliferation of bland bipolar process-forming spindle cells in a myxoid background with focal angiocentric arrangement consistent with a diagnosis of pilomyxoid-variant astrocytoma (200×).

pilomyxoid and non-pilomyxoid components of the tumour, and the copy number gain of chromosome 5 was only seen in the non-pilomyxoid component of tumour and was distinctly absent in the pilomyxoid component which only showed a gain of chromosome 11.³

To the best of our knowledge, this case represents the first report of single-copy number gain of chromosome 5 in a paediatric PMA. This case underscores the overlap of the genetic landscape of pilomyxoid and pure PAs. While tumour genetics may not clearly differentiate PMAs from typical PAs, tumour genomic studies are indicated in the work up of these tumours due to the high frequency of targetable molecular alterations and to gain a better understanding of the molecular drivers behind their biology. This gain of chromosome 5 in the absence

Figure 1 MRI showing T1 postcontrast and diffusion-weighted axial images of mixed solid/cystic parieto-occipital brain mass.

Learning points

- ▶ Gain of chromosome 5 can occur as a single copy number variant in paediatric pilomyxoid astrocytoma.
- ▶ There is overlap in the genomic landscape of classic paediatric pilocytic astrocytoma and the pilomyxoid variant.
- ▶ Tumour genomic testing, including next-generation sequencing and chromosomal microarray, may elucidate pharmacologically targetable mutations but also contributes to the understanding of molecular biology of these tumour types.

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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	ASPSCR1	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	BTX	C11orf30
CACNA1D	CAMTA1	CARD11	CASP8	CBFB	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	CTNNB1	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	FOXO1	FOXO2	FOXO3	FRS2
FUBP1	FUS	GABRA6	GATA1	GATA2	GATA3	GATA4	GATA6	GID4	GLI1	GMP5	GNA11
GNA13	GNAQ	GNAS	GPR124	GRIN2A	GRM3	GSK3B	H3F3A	HGF	HIP1	HNF1A	HRAS
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	MRE11A
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	SOC3	SOX10	SOX2	SOX9
SPEN	SPOP	SPTA1	SRC	SRGAP3	SS18	STAG2	STAT3	STAT4	STAT5B	STK11	SUFU
SYK	TAF1	TBX3	TCF7L2	TERC	TERT	TET2	TGFBR2	THRAP3	TMPPSS2	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	ASPSCR1	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	TMPPSS2								

of other copy number variants and clinically significant mutations identified on next-generation sequencing suggests gain of chromosome 5 as a potential genomic alteration sufficient to drive tumorigenesis.

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