Novel cavernous sinus *TSC2/JAK3* mutant hemangioendothelioma in a teenager

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DESCRIPTION

A 14-year-old girl presented with a 2-week history of right-sided facial pain and maxillary region numbness of the teeth and jaw. Neurological examination at presentation revealed right-sided V2 distribution paraesthesia. MRI demonstrated a middle cranial fossa mass abutting the dura of the right cavernous sinus residing in the area of Meckel's cave (figure 1). Differential considerations at the time included a trigeminal schwannoma, meningioma or a vascular lesion. The patient underwent subtotal resection of the mass, where pathology revealed a moderately cellular vascular lesion composed of cells with small round to oval nuclei with moderate hyperchromasia most consistent with a diagnosis of hemangioendothelioma (figure 2). A follow-up MRI performed 3 months postsurgery showed extensive regrowth of the lesion and the patient underwent a second near-total resection. Repeat pathology demonstrated similar findings, however, the Ki67 staining was upwards of 40%. A next generation DNA sequencing panel consisting of 397 cancer-related genes (table 1) performed on paraffin-embedded formalin fixed tumour of the hemangioendothelioma revealed novel *TSC2*

Figure 2 Histological features of central nervous system hemangioendothelioma. Neuropathology of the central portion of the tumour (1000×) reveals a moderately cellular vascular lesion composed of cells with small round to oval nuclei with moderate hyperchromasia most consistent with a diagnosis of hemangioendothelioma.

(V241I) and *JAK3* (R887C) mutations. Germline testing for *TSC2* mutations was negative. Given the rapid recurrence and high mitotic index, the patient underwent focal proton radiation therapy. MRI performed 5 years postsurgery and proton therapy shows no recurrent or residual disease and the patient has very minimal V2 distribution trigeminal paraesthesia.

Central nervous system (CNS) hemangioendotheliomas are an extremely rare, low grade, vascular neoplasms, occurring in less than 0.02% of all brain tumours.^{1,2} Its pathology is composed of aggregates of round-shaped cells with abundant eosinophilic cytoplasm.³ While hemangioendotheliomas are well reported outside the CNS, not much is known about the behaviour of hemangioendotheliomas within the CNS. Neuroimaging findings have been reported for only a few cases making it difficult to diagnose by preoperative imaging alone. A distinction that can be made is that hemangioendotheliomas develop intracellular

Figure 1 MRI features of central nervous system hemangioendothelioma. Initial preoperative T1-weighted images with gadolinium contrast (A, B) show right middle cranial fossa mass lesion (arrows). Postoperative contrast-enhanced T1-weighted images (C, D) show subtotal resection of the mass (arrows). Follow-up contrast-enhanced T1-weighted imaging (E, F) 3 months after initial surgery show re-expansion of the lesion (arrows). Postoperative contrast-enhanced T1-weighted images (G, H) show subtotal resection of the mass (arrows). Follow-up contrast-enhanced T1-weighted imaging (I, J) 5 years after second surgery and proton therapy reveals no evidence of disease.

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Learning points

- ▶ Central nervous system hemangioendothelioma is extremely rare neoplasm that should be included in the differential diagnosis of cavernous sinus tumours.
- ▶ The novel *TSC2* (V241I) and *JAK3* (R887C) mutations reported may provide the potential for non-invasive targeted based therapies.

Table 1 Next generation cancer gene panel

<i>Genes for which entire coding panel is interrogated</i>											
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	BTK	CT1orf30
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	FOXL2	FOXO1	FOXO1	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	KDMSA	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	MLLT3	MLLT4	MN1	MPL	MRE11A
MSH2	MSH6	MTOR	MUTYH	MYB	MYC	MYCL	MYCN	MYD88	MYH11	MYH9	NCOA1
NCOA2	NF1	NF2	NFE2L2	NFKBIA	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	TPR	TNFAIP3	TNFRSF14
TOP1	TOP2A	TP53	TPR	TRIM24	TRIM33	TRIP11	TRRAP	TSC2	TSC2	TSHR	U2AF1
VEGFA	VHL	WHSC1	WISP3	WRN	WT1	XPO1	ZBTB2	ZMYM2	ZNF217	ZNF384	ZNF521
<i>Subset of genes (28) for which potential rearrangements are evaluated</i>											
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	TPR	TPR	TPR	TPR	TPR	TPR	TPR	TPR	TPR

lumina in contrast to hemangiomas with well-formed vascular channels.¹ In summary, the presence of novel *TSC2* and *JAK3* gene mutations reported in a CNS hemangioendothelioma indicates possible implications for novel biologic based therapies as an alternative to chemotherapy or radiation in the case of tumour reoccurrence.

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