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CORRESPONDENCE

Cribriform neuroepithelial tumour: novel clinicopathological, ultrastructural and cytogenetic findings

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Cribriform neuroepithelial tumour (CRINET) is a recently described tumour of neuroectodermal origin with distinct cribriform non-rhabdoid histological features and loss of INI1 protein expression [2]. The INI protein is encoded by the *hSNF/INI1/BAF47* (*SMARCB1*) tumour suppressor gene, which is located on chromosome 22q.11.2 [4]. The gene product is a subunit of the adenosine triphosphate (ATP)-dependent SWI/SNF chromatin-remodelling complex, which normally regulates cell proliferation [7, 8]. Biallelic loss of *SMARCB1* is seen in peripheral rhabdoid tumours, atypical teratoid/rhabdoid tumours (AT/RTs) of the central nervous system as well as familial schwannomatosis [1, 3, 10]. In contrast to AT/RTs, CRINETs lack rhabdoid tumour cells, and may be associated with a more favourable prognosis [2]. Here, we present a third case of CRINET with complete clinicopathological, ultrastructural and cytogenetic features.

A 21-month-old boy presented with a 1-week history of imbalance, discoordination, recurrent falls and torticollis, as well as progressive nausea, vomiting and irritability. The family history was significant for possible ependymomas in the maternal great uncle and two maternal second cousins. Computed tomography (CT) and magnetic resonance (MR) imaging demonstrated a large heterogeneously enhancing mass within the fourth ventricle extending into the left cerebellopontine angle and associated with mild hydrocephalus and brainstem compression (Fig. 1a).

The patient experienced an acute neurological deterioration and an urgent CT scan demonstrated haemorrhage into the tumour causing obliteration of the fourth ventricle and acute obstructive hydrocephalus (Fig. 1b). The patient underwent an urgent posterior fossa decompression and gross total tumour resection. Post-operatively, he underwent chemotherapy according to the Children's Oncology Group (COG) 99703 protocol, which includes cisplatin, cyclophosphamide, etoposide and vincristine with stem cell rescue followed by the maintenance chemotherapy with tamoxifen and *cis*-retinoic acid. Fourteen months following the presentation, he remains in remission.

On histology, the specimen showed a cellular neoplasm, in which mitotic activity was scattered and MIB-1 index was high. Cells were found to have oval nuclei with occasional notable nucleoli (Fig. 2a). Cuboidal to polygonal cells were arranged in sheets and chords occasionally forming tubule-like or rosette-like structures. The specimen contained punched out foci of necrosis. Typical rhabdoid cells were not appreciated.

Immunohistochemistry showed neoplastic cells to be non-reactive for BAF47 (Fig. 2b). These cells were reactive for Vimentin, S100, beta-catenin (nucleus and cytoplasm), c-erbB2 and MAP2. Isolated cells reacted for p53, GFAP, cytokeratin (rare), EMA (scattered foci) and SMA (usually vasocentric). Studies for synaptophysin were negative. A summary of the current and previous immunohistochemical findings is presented in Table 1. Electron

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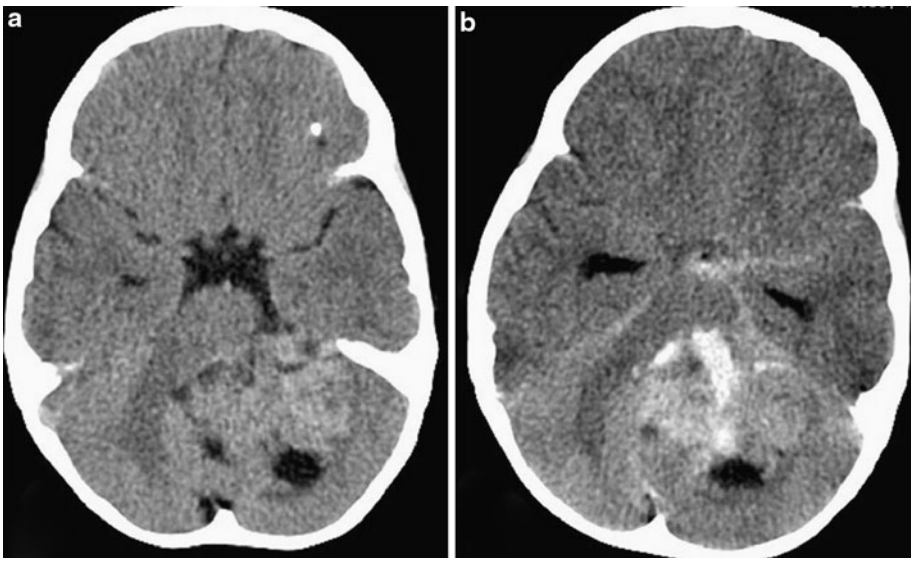

Fig. 1 **a** Initial non-contrast axial CT showing fourth ventricular tumour extending to the left cerebellopontine angle. **b** Interval intra-tumoral haemorrhage with notable intraventricular and subarachnoid extension and hydrocephalus

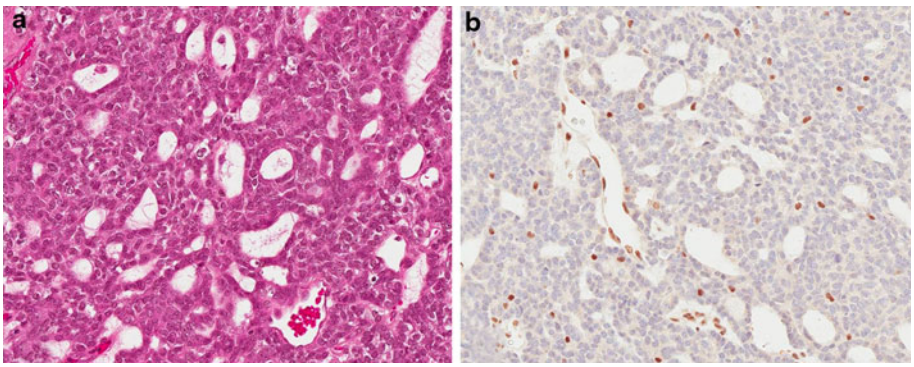

Fig. 2 **a** H&E (20×) showing cuboidal to polygonal cells arranged in sheets and cords. **b** BAF47 (20×) immunohistochemistry showing non-reactivity of neoplastic cells

microscopy (Fig. 3) demonstrated cells with prominent, coiled nucleoli and scattered tight junctions suggestive of a primitive tumour with lack of differentiation.

Karyotypic and fluorescence in situ hybridisation (FISH) analysis of the tumour showed monosomy 22 (Fig. 4). The patient also underwent genetic testing on the tumour tissue as well as on DNA extracted from peripheral blood lymphocytes, using bidirectional cycle sequencing of exons 1–9 followed by multiple-ligation probe assay (MLPA) to detect copy number changes in the coding and promoter regions of the *INI1/SMARCB1* gene. Two heterozygous mutations were discovered; a duplication of exon 6 and a total *INI1/SMARCB1* gene deletion encompassing the gene promoter and flanking genes. Only the exon 6 duplication was found in DNA extracted from blood lymphocytes.

The current case of CRINET further characterizes this recently described neoplasm. First, we document intra-tumoural haemorrhage necessitating urgent surgical decompression. While intra-tumoural haemorrhage has not been previously described in the published cases of CRINET, it is well documented in AT/RTs [5, 6].

Constitutional *INI1/SMARCB1* mutations may result in an inherited predisposition to rhabdoid tumours in general and AT/RTs in the CNS. Mechanisms of INI1 inactivation in rhabdoid tumours include homozygous deletions and mitotic recombination leading to isodisomy and non-disjunction/duplication [9]. At present, it remains unclear why individuals with *INI1/SMARCB1* loss may present with tumours with starkly different biologies ranging from schwannomatosis to CRINET and AT/RT. In the two prior cases of CRINET, duplication within exon 4 and no mutation were identified, respectively. The current report is the first to describe a germline mutation associated with CRINET. The current patient harboured two heterozygous mutations, one of which was constitutionally expressed in peripheral lymphocytes, suggesting a 'two-hit' mechanism for tumourigenesis. This additionally underlines the importance of the identification of specific genetic alternations of INI1 [1].

Table 1 Clinicopathological features of documented Cribriform Neuroepithelial Tumors

Clinicopathological features	Case 1 (2)	Case 2 (2)	Current study
Age at presentation	26 months	10 months	21 months
Gender	F	M	M
Location	Third ventricle	Fourth ventricle	Fourth ventricle
Maximum diameter	25 mm	56 mm	53 mm
Contrast enhancement	+++	+++	+++
Intra-tumoural haemorrhage	No	No	Yes
Treatment	CPT-SIOP-2000; RT	HIT-SKK-2000	COG99703; SSR
Outcome at last follow-up	Remission at 72 months	Remission at 85 months	Remission at 14 months
Immunohistochemistry			
BAF47/INI1	−	−	−
Vimentin	+++	++	+++
S100	+ (Focal)	−	+++ (Focal)
MAP2	+++	+++	+++
GFAP	−	−	+ (Focal)
Cytokeratin	++ (Focal)	++ (Focal)	+ (Rare)
Synaptophysin	++ (Focal)	++	–
EMA	+++ (Surfaces)	+++ (Surfaces)	+ (Scattered foci)
Beta-catenin	Not reported	Not reported	+++ (Nucleus and cytoplasm)
c-erbB2	Not reported	Not reported	++
p53	Not reported	Not reported	+ (Focal)
SMA	Not reported	Not reported	+ (Vasocentric)
Ki76/MIBI labelling index	30%	28%	30%
Genetic testing			
Karyotype	Not reported	Not reported	45, XY, −22
SMARCB1	No genetic alterations	Exon 4 duplication	Two heterozygous abnormalities[a]

CPT-SIOP-2000 etoposide, cyclophosphamide, and vincristine; *HIT-SKK-2000* methotrexate, cyclophosphamide and vincristine; *COG99703* cisplatin, cyclophosphamide, etoposide and vincristine; *RT* radiation therapy; *SSR* stem cell rescue; −, absent; +, weak; ++, distinct; +++ strong immunostaining; *EMA* epithelial membrane antigen; *GFAP* glial fibrillary acidic protein; *MAP2* microtubule-associated protein; *SMA* smooth muscle actin

[a] Duplication of exon 6 (in tumour and peripheral lymphocytes) and total INI1/SMARCB1 gene deletion encompassing gene promoter and flanking genes

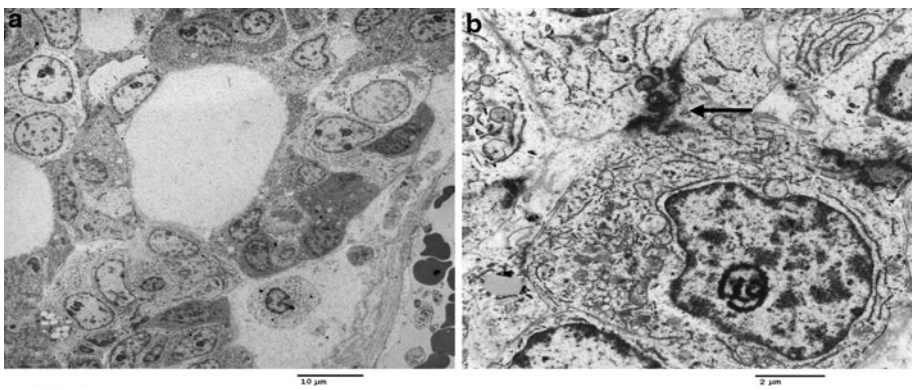

Fig. 3 Electron microscopy showing **a** cells arranged in cord-like structures, and **b** cytoplasm with rough endoplasmic reticulum in short linear profiles admixed with mitochondria, nucleus with rope-like nucleolus and scattered cell-to-cell (tight) junctions of variable length (see *arrow*)

The present case highlights the importance of not only testing immunohistochemical reactivity for BAF47 in embryonal CNS tumours, but also the molecular genetic alterations in the *INI1/SMARCB1* gene. We furthermore characterize previously unreported clinicopathological and genetic features of CRINET, which along with AT/RTs likely form a spectrum of INI1-negative tumours.

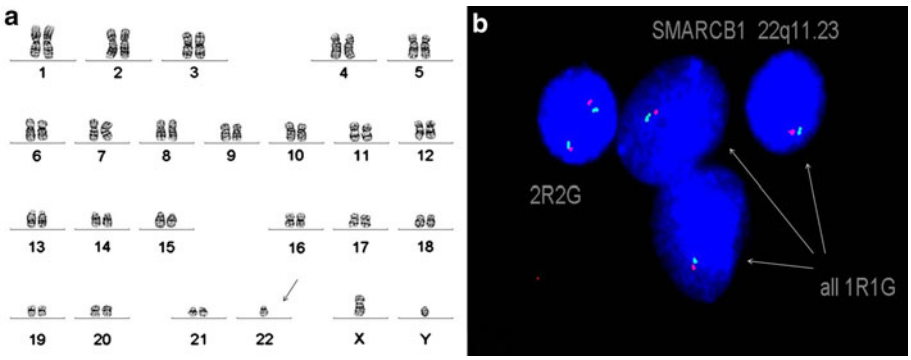

Fig. 4 **a** Karyotype showing monosomy 22, and **b** FISH analysis with red probe containing *SMARCB1/INI1* gene (22q.11.23) and control green probe (*EWSR1*; 22q12). All neoplastic cells contain only one green and one red signal

Conflict of interest The authors declare they have no conflicts of interest.

References

1. Biegel JA, Zhou JY, Rorke LB et al (1999) Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res 59:74–79
2. Hasselblatt M, Oyen F, Gesk S et al (2009) Cribriform neuroepithelial tumor (CRINET): a nonrhabdoid ventricular tumor with INI1 loss and relatively favorable prognosis. J Neuropathol Exp Neurol 68:1249–1255
3. Hulsebos TJ, Plomp AS, Wolterman RA et al (2007) Germline mutation of INI1/SMARCB1 in familial schwannomatosis. Am J Hum Genet 80:805–810
4. Kalpana GV, Marmon S, Wang W et al (1994) Binding and stimulation of HIV-1 integrase by a human homolog of yeast transcription factor SNF5. Science 266:2002–2006
5. Meyers SP, Khademian ZP, Biegel JA et al (2006) Primary intracranial atypical teratoid/rhabdoid tumors of infancy and childhood: MRI features and patient outcomes. AJNR Am J Neuroradiol 27:962–971
6. Parwani AV, Stelow EB, Pambuccian SE et al (2005) Atypical teratoid/rhabdoid tumor of the brain: cytopathologic characteristics and differential diagnosis. Cancer 105:65–70
7. Pfister SM, Korshunov A, Kool M et al (2010) Molecular diagnostics of CNS embryonal tumors. Acta Neuropathol 120:553–566
8. Roberts CW, Biegel JA (2009) The role of SMARCB1/INI1 in development of rhabdoid tumor. Cancer Biol Ther 8:412–416
9. Rousseau-Merck MF, Versteege I, Legrand I et al (1999) hSNF5/INI1 inactivation is mainly associated with homozygous deletions and mitotic recombinations in rhabdoid tumors. Cancer Res 59:3152–3156
10. Versteege I, Sevenet N, Lange J et al (1998) Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature 394:203–206