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SHORT COMMUNICATION

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Diffuse infiltrating tumour with the molecular profile of an atypical teratoid rhabdoid tumour (AT/RT SHH-1B) in an adult patient

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Abstract

We describe a 46-year-old patient with an *IDH*-wildtype diffusely infiltrating atypical teratoid/rhabdoid tumour (AT/RT), SHH-1B molecular subtype. The unusual histology and subsequent diagnosis in an adult patient will be discussed.

KEYWORDS
atypical teratoid/rhabdoid tumour, methylation sequencing, molecular techniques, neuro-oncology

INTRODUCTION

Atypical teratoid/rhabdoid tumour (AT/RT) is a grade 4 malignant embryonic tumour of the central nervous system mostly occurring in infants.[1–3] Histologically, AT/RTs are heterogeneous tumours with rhabdoid cells, poorly differentiated small-round blue cells and/or components of epithelial or mesenchymal origin.[3] Molecularly, most AT/RTs are characterised by bi-allelic inactivation, including partial/complete chromosome 22q loss, of SWItch/sucrose nonfermentable (SWI/SNF) related, matrix associated, actin dependent regulator of chromatin, subfamily B1 (*SMARCB1*) (also known as *hSNF5/INI1*).[4–6] DNA methylation and transcriptome profiling have shown the existence of at least three main molecular groups of AT/RTs, called ATRT-TYR, ATRT-SHH and ATRT-MYC, each exhibiting distinct molecular and clinical characteristics.[1,3,7] A fourth and rare AT/RT group harbours *SMARCA4* variants and is *SMARCB1* wildtype.[8,9] Recently, ATRT-SHH has been further subdivided into three distinct subtypes by DNA methylation profiling: ATRT-SHH-1A and ATRT-SHH-1B, both mainly located supratentorially but differ in patient's age, and the ATRT-SHH-2 subtype, which is mainly located

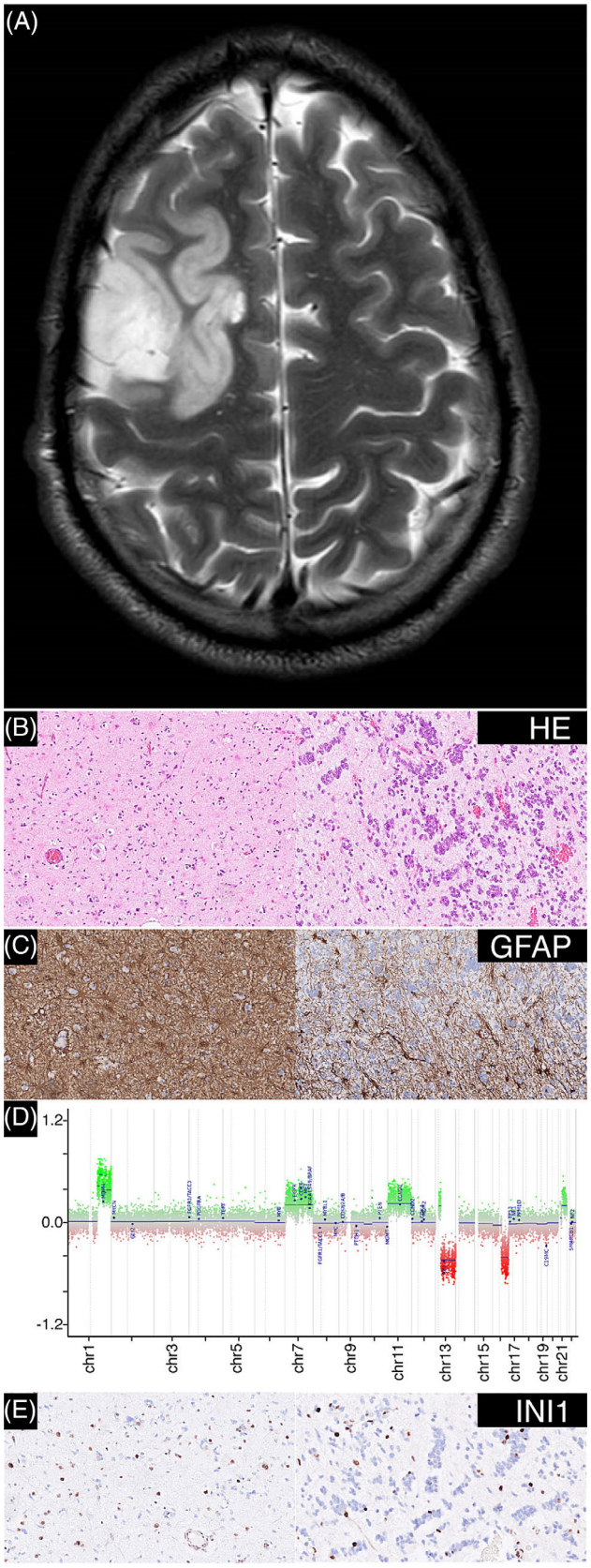

FIGURE 1 (A) Heterogenic T2-hyperintense corticosubcortical right frontal lesion (41.7 mm × 39.7 mm) with extension to the medial side. (B) Histological examination showed glial tissue with diffusely increased cellularity (left panel) and with ribbon-like growth (right panel). (C) The tumour cells are negative for GFAP in both the diffuse (left panel) and ribbon-like component (right panel). (D) Multiple copy number variants were detected but no loss of chromosome 22q was identified. (E) Tumour cells in both components were negative for INI1.

infratentorially.[1] Although ATRT-SHH-1B cases were identified in older patients, only three cases were identified in (young) adult patients with a maximum age of 28 years.[1]

Here, we discuss a 46-year-old patient who presented following a minor traumatic brain injury. A brain CT scan revealed an abnormality in the right frontal lobe with subsequent MRI imaging identifying a lesion in the right frontal lobe, primarily affecting the cortex with no obvious contrast enhancement (Figure 1A). During examination, the patient did not display any neurological abnormalities. No extracranial lesions were detected on a CT scan examination of the thorax and abdomen. Due to the suspicion that this was a diffuse glioma, a resection was planned. During awake surgical craniotomy, the resection was complicated by focal epileptic seizures affecting the patient's eye and corner of the mouth, which persisted after surgery. Therefore, only small portions of the tumour were removed.

Histological examination revealed brain tissue with increased cellularity and diffusely infiltrating atypical cells, clustering around neurons and organised in ribbon-like structures, features often observed in oligodendroglioma (Figure 1B). Atypical cells had small round to polygonal nuclei with coarse chromatin. There was no necrosis or microvascular proliferation. The tumour cells were negative for GFAP (Figure 1C), cytokeratins, IDH1 R132H, Vimentin, SMA, EMA and CD34, whereas ATRX expression was preserved. Neurofilament and synaptophysin were considered negative in atypical cells. Mitotic activity was high (12 mitoses/2 mm^2) with the Ki-67 proliferation index at 10%–15%. Targeted DNA sequencing, using a panel covering the most often altered genes in diffuse glioma, showed no alterations. CNV analysis, based on SNP distributions, revealed an imbalance of chromosome 7 and loss of 13q, but due to limited coverage, other CNVs could not be ruled out.

Subsequently, DNA methylation profiling was performed, returning a calibrated score above the 0.9 diagnostic threshold in brain tumour classifiers v11b4 and v12.5 for an AT/RT, SHH subtype. The obtained CNV profile showed multiple CNVs (Figure 1D), though no loss of 22q, which harbours *SMARCB1*, was identified. Immunohistochemical examination confirmed loss of tumour cell INI1 expression (the protein encoded by *SMARCB1*; Figure 1E).[10] Subsequent capture-based NGS using Illumina's TruSight Oncology (TSO) 500 assay revealed two variants in *SMARCB1*, respectively (NM_001362877.2) exon 2: c.157C > T; p.R53* (pathogenic, PVS1, PS4, PM2, PP5) and (NM_001362877.2) exon 9: c.1202delC; p.P401Rfs*100 (pathogenic, PVS1, PS2, PM2, PP5) compatible with INI1 loss, while maintaining 22q. The *SMARCB1* exon 2 point-variant is an often-encountered

genetic alteration in AT/RT and further supporting the findings from the brain tumour classifier are the bi-allelic point variants as this is the most frequent reason for *SMARCB1* inactivation in AT/RT, SHH subtype. In contrast to SHH-activated medulloblastoma, activating variants in the sonic hedgehog (SHH) or NOTCH pathway are generally absent in ATRT-SHH.[1] The observed variant allele frequencies (VAF) of the detected *SMARCB1* variants of 37.9% and 42.9% do not suggest a germline variant. Additional variants in *CHEK2* ((NM_007194.4) exon 4: c.470 T > C; p.I157T, VAF 51% (likely pathogenic, PM2, PM5, PP5)) and *TSC2* ((NM_000548.5) exon 30: c.3449_3450dupTG; p.G1151Wfs*41, VAF 9.8% (likely pathogenic, PVS1, PM2)) were also identified.

Since AT/RTs are highly unusual in adult patients, additional clustering analysis with selected AT/RT SHH reference cases ($n = 124$) was performed to confirm the diagnosis. Here, the tumour clustered together with the reference ATRT-SHH-1B cases (Figure 2A). SHH-1B cases stain positive for ASCL1, a proneural marker and OLIG2 (also observed in this case; Figure 2B,C).[1,11] ASCL1 and OLIG2 play a role in oligodendroglia development that could explain the similarities with the oligodendroglioma morphology.[12] MAP2, a marker often positively stained in diffuse glioma including oligodendroglioma, was negative in this case (Figure 2D).

Despite the molecular and immunohistochemical findings characteristic of AT/RT, the essential criteria for AT/RT, as defined by the WHO CNS5 classification, are not met, as no embryonic morphology is observed. Notably, the presence of ribbon-like structures could hint at an embryonal growth pattern. Furthermore, there was no distinct rhabdoid morphology (with no expression for SMA, EMA and vimentin).[10] While AT/RT typically exhibits a low frequency of copy number changes involving chromosomes other than chromosome 22, this case displays multiple CNVs. Increased numbers of CNVs have been reported in AT/RT tumours arising secondary ($n = 20$) in known primary tumours of other origins, most often pleomorphic xanthoastrocytoma or ganglioglioma.[13] However, the absence of a non-AT/RT component with uniformly retained INI1 and the lack of another distinctive genetic driver alteration (e.g., *BRAF V600E*) make the diagnosis of a secondary AT/RT very unlikely. AT/RT, SHH-1B cases do show a more complex CNV profile, compared with other molecular subtypes, with gains of whole chromosome arm 1q, loss of chromosome 10 and gains of chromosome 7.[1] While a loss of chromosome 10 was not observed in this case, additional gains and losses were identified.

The DNA methylation profile is determined by the cell of origin and can be influenced by specific variants affecting DNA methylation (e.g., *IDH1/2* point-variants), suggesting a potential role of the detected *SMARCB1* alterations in the observed methylation profile.[14,15] No other INI1-deficient tumours, except for cribriform neuroepithelial tumour *SMARCB1*-altered, are included in the v12.5 brain tumour classifier, and thus, the observed results may be reflecting a *SMARCB1*-alteration more than a true AT/RT origin. To test this, we also ran the sarcoma classifier that includes multiple tumours often containing *SMARCB1*-alterations, including epithelioid sarcoma, ossifying fibromyxoid tumour, extraskeletal myxoid chondrosarcoma,

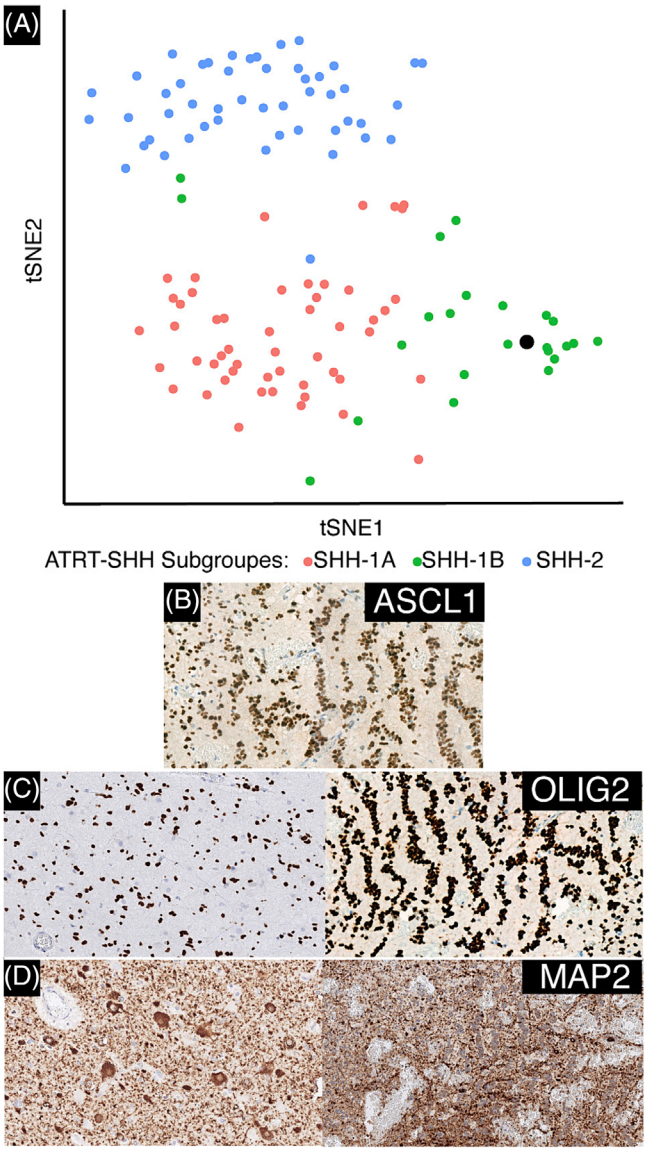

FIGURE 2 (A) In a tSNE analysis, including $n = 124$ AT/RT SHH cases from the SHH-1A, SHH-1B and SHH-2 subclasses, the case (black dot) clusters with the reference ATRT-SHH-1B cases. (B) The tumour cells stain positively for ASCL1, a proneural marker, which is often positive in ATRT-SHH-1B cases. (C) OLIG2, a marker that plays a role in oligodendroglia development, also stains positive in the tumour cells both in the diffuse infiltration component (left panel) and the ribbon-like component (right panel). (D) MAP2, often detected in diffuse gliomas including oligodendroglioma, was negative in both components of the tumour cells but did stain some stromal cells including neurons.

malignant rhabdoid tumour and dedifferentiated chordoma.[14] In this classifier, the highest score of 0.38, far below the clinically relevant threshold of 0.9, was obtained for the methylation class malignant rhabdoid tumour. This suggests that the cell of origin in our case shares a specifically close relationship with the cell of origin for paediatric AT/RT.[15]

Considering the unusual age for an AT/RT, we finally diagnosed this lesion as a 'neuroectodermal tumour with the molecular profile of

an atypical teratoid/rhabdoid tumour (AT/RT)'. This entity is not implemented in the WHO CNS5 classification and therefore "not-elsewhere classified (NEC)" was added to the diagnosis. Due to the unusual combination of clinical, histological and molecular findings, prediction of biological behaviour remains difficult. Given the high mitotic activity, diffuse infiltration pattern and molecular profile consistent with AT/RT, a more aggressive course could be suggested. However, the molecular sub-subclassification of ATRT-SHH-1B in an adult diffusely growing tumour has not been described before. It has been observed though, that AT/RT-SHH-1B cases in children over the age of 3, exhibiting positive ASCL1 staining, as was demonstrated in this case, tend to have a longer overall survival compared with other AT/RT patients.[1]

After undergoing surgery, the patient's epilepsy vanished over weeks, and 6 months post-surgery neurological impairments remain absent. Additionally, no significant change in the volume or appearance of the tumour has been detected radiologically and thus a wait-and-scan approach is followed. Broggi et al. documented 96 cases of AT/RT in adults, with 45 cases involving incomplete resection. Within this subgroup, 24 individuals (53.3%) died during observation, with the time of death spanning from the postoperative period to 2.5 years after surgery. Combined adjuvant therapy, incorporating chemotherapy and radiotherapy, significantly enhanced overall survival in this study.[16] However, no molecular subclassification of the AT/RT tumours into ATRT-TYR, ATRT-SHH and ATRT-MYC, or even subgroups of those, was reported in this study making the translation of the presented results to the current patient difficult.

This case illustrates that rarely IDH-wildtype diffuse infiltrating tumours in adults do not fulfil the criteria for glioblastoma but share the molecular characteristics of paediatric embryonic tumours. Unique features of the present case, not reported in the literature before, include the biphenotypic nature, exhibiting characteristics of a diffuse glioma alongside ribbon-like structures with INI1 loss in both components and the molecular (sub-)subclassification of ATRT-SHH-1B. When similar cases are identified that share clinical, histological and molecular findings, the true biological behaviour of diffusely infiltrating tumours with the molecular features of an AT/RT SHH-1B in adult patients can be established.

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CONFLICT OF INTEREST STATEMENT

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

ETHICS STATEMENT

Informed consent for publication of the case was obtained from the patient.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/nan.12983.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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