



## SHORT COMMUNICATION

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

Fleur Cordier<sup>1,2</sup>  | Joost W. Schouten<sup>3</sup> | Marjolein Geurts<sup>4</sup> | Johan M. Kros<sup>1</sup> | Hendrikus J. Dubbink<sup>1</sup> | Vincent Verlinden<sup>5</sup> | Aniello Federico<sup>6,7</sup> | Marcel Kool<sup>6,7,8,9</sup> | Sybren L. N. Maas<sup>1,10</sup> 

<sup>1</sup>Department of Pathology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

<sup>2</sup>Department of Pathology, University Hospital Ghent, Ghent, Belgium

<sup>3</sup>Department of Neurosurgery, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

<sup>4</sup>Department of Neurology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

<sup>5</sup>Department of Radiology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

<sup>6</sup>Hopp Childrens Cancer Center (KITZ), Heidelberg, Germany

<sup>7</sup>German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany

<sup>8</sup>Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

<sup>9</sup>University Medical Center Utrecht, Utrecht, The Netherlands

<sup>10</sup>Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

## Correspondence

Sybren L. N. Maas, Department of Pathology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Postbox 2040, 3000 CA Rotterdam, The Netherlands.  
Email: [s.maas@erasmusmc.nl](mailto:s.maas@erasmusmc.nl)

## Funding information

The authors received no financial support for the research, authorship and/or publication of this article

## 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

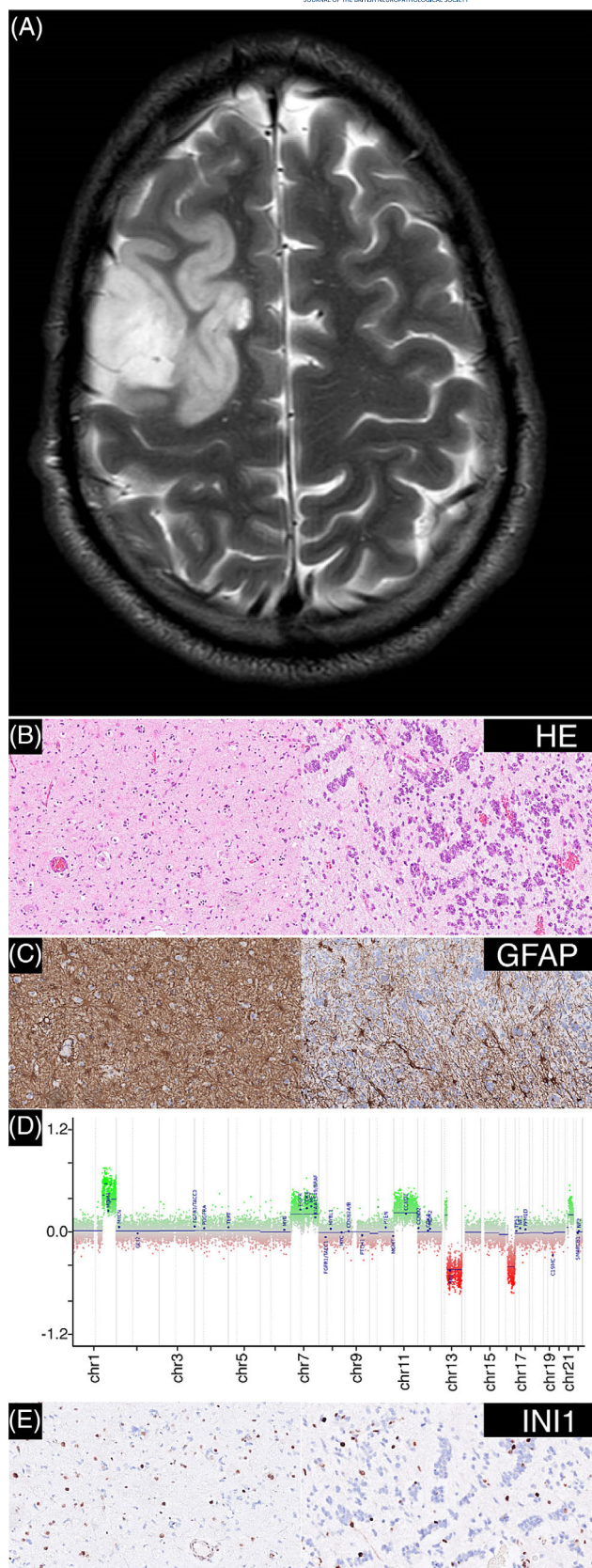
## INTRODUCTION

Atypical teratoid/rhabdoid tumour (AT/RT) is a grade 4 malignant embryonic tumour of the central nervous system mostly occurring in infants.<sup>1-3</sup> Histologically, AT/RTs are heterogeneous tumours with rhabdoid cells, poorly differentiated small-round blue cells and/or components of epithelial or mesenchymal origin.<sup>3</sup> Molecularly, most AT/RTs are characterised by bi-allelic inactivation, including partial/complete chromosome 22q loss, of SWI/tch/sucrose nonfermentable (SWI/SNF) related, matrix associated, actin dependent regulator of

chromatin, subfamily B1 (*SMARCB1*) (also known as *hSNF5/INI1*).<sup>4-6</sup> 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.<sup>1,3,7</sup> A fourth and rare AT/RT group harbours *SMARCA4* variants and is *SMARCB1* wildtype.<sup>8,9</sup> 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

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Authors. *Neuropathology and Applied Neurobiology* published by John Wiley & Sons Ltd on behalf of British Neuropathological Society.



**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.<sup>1</sup> 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.<sup>1</sup>

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<sup>2</sup>) 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.

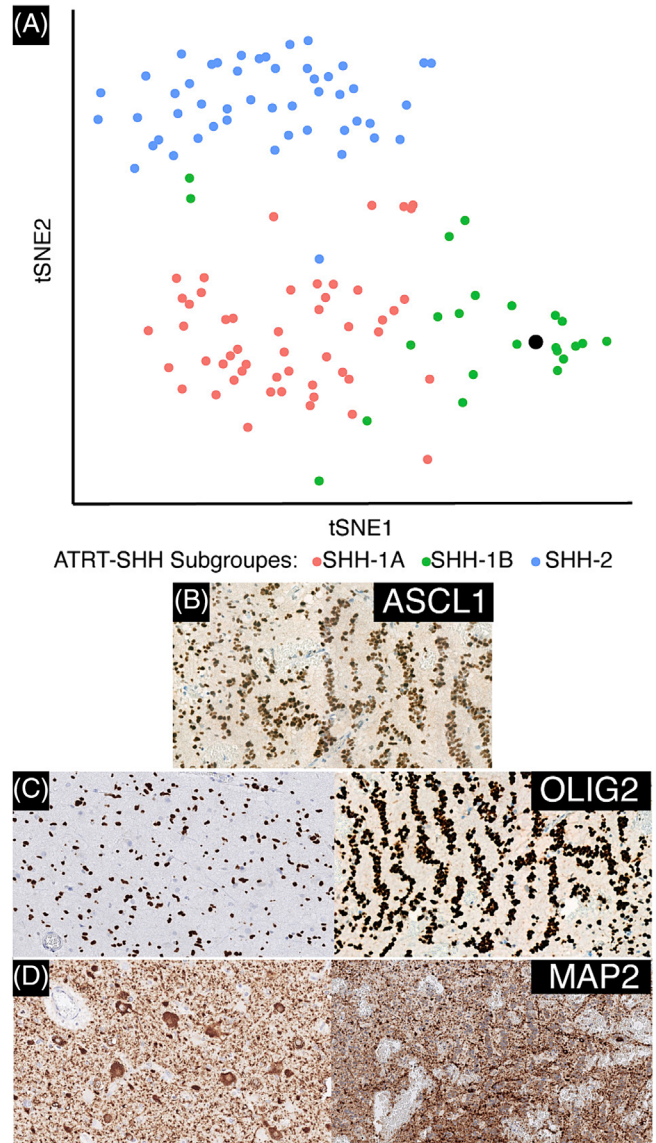
Subsequently, DNA methylation profiling was performed, returning a calibrated score above the 0.9 diagnostic threshold in brain tumour classifiers v11b4 and v12.5 for an AT/RT, SHH subtype. The obtained CNV profile showed multiple CNVs (Figure 1D), though no loss of 22q, which harbours *SMARCB1*, was identified. Immunohistochemical examination confirmed loss of tumour cell INI1 expression (the protein encoded by *SMARCB1*; Figure 1E).<sup>10</sup> 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.<sup>1</sup> 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).<sup>11</sup> ASCL1 and OLIG2 play a role in oligodendroglia development that could explain the similarities with the oligodendroglioma morphology.<sup>12</sup> 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).<sup>10</sup> 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.<sup>13</sup> 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.<sup>1</sup> 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.<sup>14,15</sup> 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, extraskelatal 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.<sup>14</sup> 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.<sup>15</sup>

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.<sup>1</sup>

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.<sup>16</sup> 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.

## ACKNOWLEDGEMENTS

We acknowledge the assistance by Thierry van den Bosch of the Pathology Research and Trial Service (PARTS) in the Erasmus Medical Center for the help with the immunohistochemical stains included in the manuscript.

## 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.

## ORCID

Fleur Cordier  <https://orcid.org/0000-0003-0876-3398>

Sybre N. L. Maas  <https://orcid.org/0000-0002-8745-4405>

## REFERENCES

1. Federico A, Thomas C, Miskiewicz K, et al. ATRT-SHH comprises three molecular subgroups with characteristic clinical and histopathological features and prognostic significance. *Acta Neuropathol.* 2022;143(6):697-711. doi:10.1007/s00401-022-02424-5
2. Rorke LB, Packer R, Biegel J. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood. *J Neurooncol.* 1995;24(1):21-28. doi:10.1007/BF01052653
3. Zin F, Cotter JA, Haberler C, et al. Histopathological patterns in atypical teratoid/rhabdoid tumors are related to molecular subgroup. *Brain Pathol (Zurich, Switzerland).* 2021;31(5):e12967. doi:10.1111/bpa.12967
4. Biegel JA, Zhou JY, Rorke LB, Stenstrom C, Wainwright LM, Fogelgren B. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. *Cancer Res.* 1999;59(1):74-79.
5. Fruhwald MC, Biegel JA, Bourdeaut F, Roberts CW, Chi SN. Atypical teratoid/rhabdoid tumors-current concepts, advances in biology, and potential future therapies. *Neuro Oncol.* 2016;18(6):764-778. doi:10.1093/neuonc/nov264
6. Jackson EM, Sievert AJ, Gai X, et al. Genomic analysis using high-density single nucleotide polymorphism-based oligonucleotide arrays and multiplex ligation-dependent probe amplification provides a comprehensive analysis of INI1/SMARCB1 in malignant rhabdoid tumors. *Clin Cancer Res: an Official J am Assoc Cancer Res.* 2009;15(6):1923-1930. doi:10.1158/1078-0432.CCR-08-2091
7. Ho B, Johann PD, Grabovska Y, et al. Molecular subgrouping of atypical teratoid/rhabdoid tumors-a reinvestigation and current consensus. *Neuro Oncol.* 2020;22(5):613-624. doi:10.1093/neuonc/noz235
8. Hasselblatt M, Nagel I, Oyen F, et al. SMARCA4-mutated atypical teratoid/rhabdoid tumors are associated with inherited germline alterations and poor prognosis. *Acta Neuropathol.* 2014;128(3):453-456. doi:10.1007/s00401-014-1323-x
9. Schneppenheim R, Fruhwald MC, Gesk S, et al. Germline nonsense mutation and somatic inactivation of SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome. *Am J Hum Genet.* 2010;86(2):279-284. doi:10.1016/j.ajhg.2010.01.013
10. Judkins AR, Mauger J, Ht A, Rorke LB, Biegel JA. Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. *Am J Surg Pathol.* 2004;28(5):644-650. doi:10.1097/0000478-200405000-00013
11. Aydin B, Kakumanu A, Rossillo M, et al. Proneural factors Ascl1 and Neurog2 contribute to neuronal subtype identities by establishing distinct chromatin landscapes. *Nat Neurosci.* 2019;22(6):897-908. doi:10.1038/s41593-019-0399-y
12. Sugimori M, Nagao M, Parras CM, et al. Ascl1 is required for oligodendrocyte development in the spinal cord. *Development.* 2008;135(7):1271-1281. doi:10.1242/dev.015370

13. Nobusawa S, Nakata S, Yoshida Y, et al. Secondary INI1-deficient rhabdoid tumors of the central nervous system: analysis of four cases and literature review. *Virchows Archiv: An Int J Pathol*. 2020;476(5):763-772. doi:[10.1007/s00428-019-02686-7](https://doi.org/10.1007/s00428-019-02686-7)
14. Koelsche C, Schrimpf D, Stichel D, et al. Sarcoma classification by DNA methylation profiling. *Nat Commun*. 2021;12(1):498. doi:[10.1038/s41467-020-20603-4](https://doi.org/10.1038/s41467-020-20603-4)
15. Schweizer Y, Meszaros Z, Jones DTW, Koelsche C, Boudalil M, Fiesel P, Schrimpf D, Piro RM, Brehmer S, von Deimling A et al (2017) Molecular transition of an adult low-grade brain tumor to an atypical Teratoid/Rhabdoid tumor over a time-course of 14 years. *J Neuropathol Exp Neurol* 76: 655–664 [10.1093/jnen/nlx044](https://doi.org/10.1093/jnen/nlx044), 8
16. Broggi G, Gianno F, Shemy DT, et al. Atypical teratoid/rhabdoid tumor in adults: a systematic review of the literature with meta-

analysis and additional reports of 4 cases. *J Neurooncol*. 2022;157(1):1-14. doi:[10.1007/s11060-022-03959-z](https://doi.org/10.1007/s11060-022-03959-z)

**How to cite this article:** Cordier F, Schouten JW, Geurts M, et al. Diffuse infiltrating tumour with the molecular profile of an atypical teratoid rhabdoid tumour (AT/RT SHH-1B) in an adult patient. *Neuropathol Appl Neurobiol*. 2024;50(3):e12983. doi:[10.1111/nan.12983](https://doi.org/10.1111/nan.12983)