CNS Oncology

Dural-based atypical teratoid/rhabdoid tumor in an adult: DNA methylation profiling as a tool for the diagnosis

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Atypical teratoid/rhabdoid tumor (ATRT) is a malignant CNS embryonal tumor that mostly occurs in childhood, adult cases are rare. We report a case of a 23-year-old male with an extra-axial dura-based lesion in the left frontal area, previously diagnosed as gliosarcoma. After 6 years, the patient had a recurrence and the previous slides were reviewed. Tumor was positive for vimentin and negative for INI1. The differential diagnosis for this extra-axial tumor with long survival was rhabdoid meningioma with INI1 loss or ATRT. DNA methylation profiling was performed to reach the final and the most definitive diagnosis; the result was ATRT. Our case suggests the usefulness of DNA methylation profiling for diagnosing challenging CNS tumors.

Atypical teratoid/rhabdoid tumor (ATRT) is a malignant CNS embryonal tumor composed of poorly differentiated elements, including rhabdoid cells, with inactivation of SMARCB1 (INI1) or rarely of SMARCA4 (BRG1) [1].

ATRT is the most common malignant brain tumor in children below the age of 6 months [2], it can be located in either supratentorial or infratentorial locations [1] and may occasionally develop in adolescents and adults [3]. In adults, ATRT affects predominantly females and is mostly located in the sellar region [4–6].

SMARCB1/INI1 is one of the core subunit proteins of the ATP-dependent-*SWI*/*SNF* chromatin remodeling complex [7,8]. SMARCB1/INI1 protein loss has been reported in various tumors in many organs [7,9]. The aberrant expression could be either complete, mosaic or reduced. Many tumors have a complete loss of INI1 in addition to ATRT of the brain, including malignant peripheral nerve sheath tumors and epithelioid sarcoma [7].

DNA methylation profiling is a highly robust and reproducible approach for the classification of CNS tumors. This technique exploits the concept that cancer methylome is a combination of somatically acquired DNA methylation changes and characteristics reflecting cell of origin and events contributing to transformation [10].

DNA methylation profiling of ATRT identified three molecular subgroups with specific transcriptional signatures: ATRT-*SHH*, ATRT-*TYR* and ATRT-*MYC* [11]. These subgroups are different in regard to the age of onset, the location of the tumor, *SMARCB1* mutational pattern and radiological features [11,12]. We report the case of a dural-based frontal tumor in an adult male with histological and clinical features that suggest a diagnosis of rhabdoid meningioma with INI1 loss or ATRT. This led us to order DNA methylation profiling to reach the final and the most definitive diagnosis and the tumor was classified as ATRT.

Our case highlights the importance of DNA methylation profiling as a tool for diagnosis in selected adult cases that do not fulfill all the specific criteria for a specific tumor histotype.
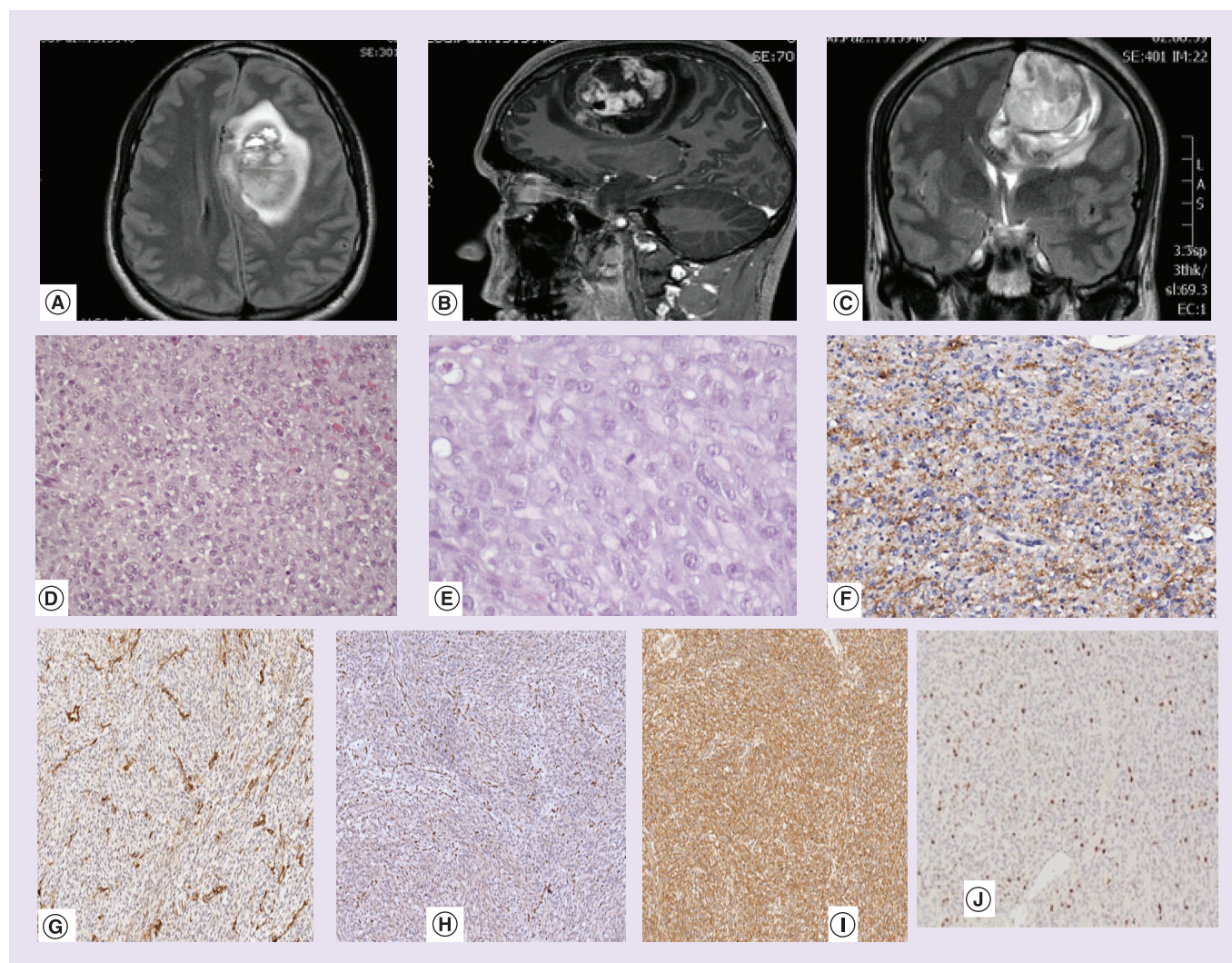
Future Medicine

Figure 1.   Radiological, histopathological and immunohistochemical features of the tumor. (A) FLAIR sequence MRI of the head showing hyperdense large tumor with midline shift and mass effect. **(B)** T1 sequence postcontrast and **(C)** and T2 sequence show a large lobulated heterogeneously enhancing extra-axial tumor, attached to dura. Histopathological examination shows **(D)** Highly cellular tumor composed of rhabdoid cells (H&E ×100). **(E)** Rhabdoid cells show eccentric nuclei, prominent nucleoli and eosinophilic cytoplasm (H&E 400). Immunohistochemical stains show **(F)** Focal positivity for synaptophysin (×200) and **(G)** Smooth muscle actin (×200), **(H)** Loss of INI1 (×200), **(I)** Diffuse positivity for vimentin (×200) and **(J)** Ki67 (×100). Negative markers including CK, GFAP and EMA (Not shown).
FLAIR: Fluid attenuation inversion recovery; H&E: Hematoxylin and eosin stain; T1: Longitudinal relaxation time; T2: Transverse relaxation time.

Case description

A 23-year-old male presented with headache, cognitive-motor slowing and right motor hemi syndrome in 2013. MRI showed a large extra-axial dura-based lesion in the left frontal area with altered signal and focal contrast enhancement (Figure 1 A–C). The mass was diagnosed as gliosarcoma (WHO Grade IV). The patient was treated with adjuvant radio- and chemotherapy for 3 months and temozolomide for six cycles. In 2018 there was a suspected recurrence of the tumor, and MRI showed an altered signal area around the surgical cavity with a contrast enhancement nodule. In consideration of the long clinical history of a gliosarcoma, the original slides were reviewed.

Methylation profiling

DNA methylation profiling was performed according to protocols approved by the institutional review board after obtaining written consent from the patient. Tumor areas with the highest tumor cell content (≥70%) were selected for DNA extraction. Samples were analyzed using Infinium-Human Methylation EPIC Bead Chip (Illumina, CA,
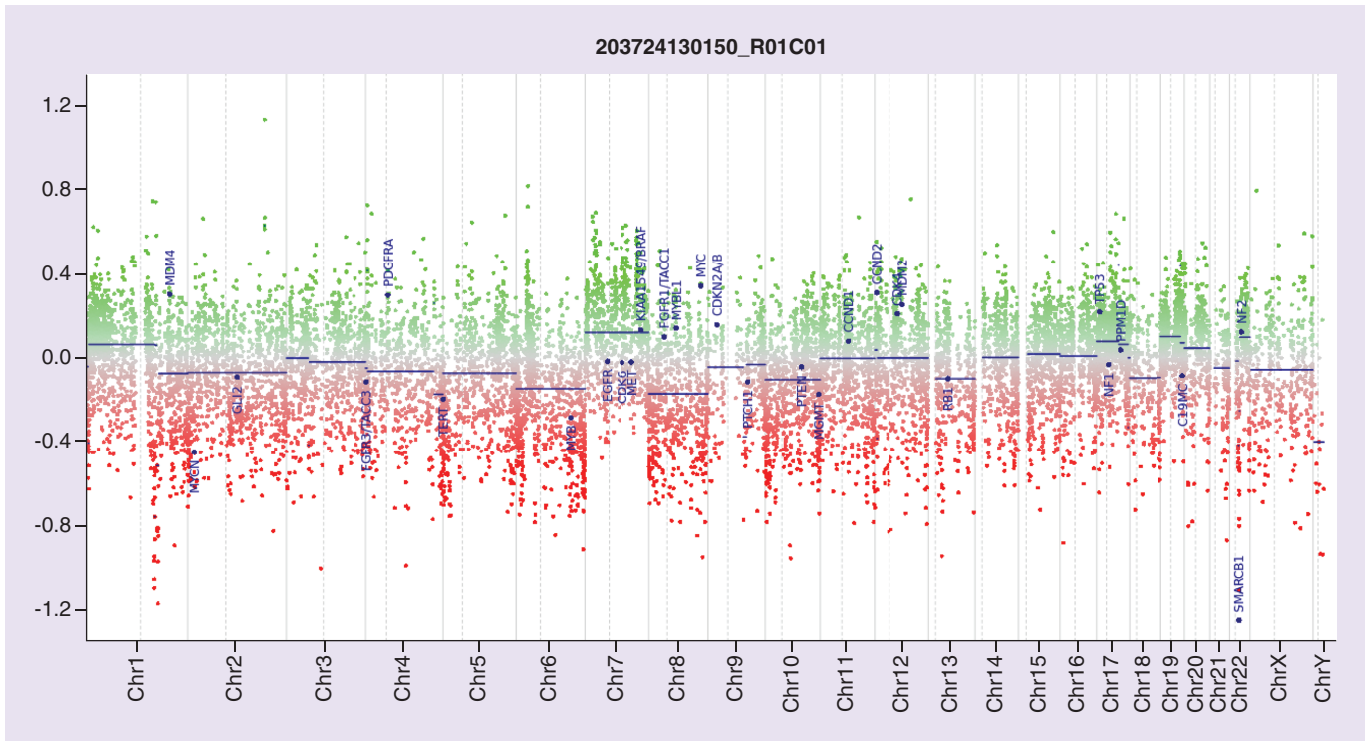
Figure 2.   Copy number variation profile analysis – depiction of structural rearrangements involving autosomes and X/Y chromosomes. Gains/amplifications represent positive (green), losses negative (red) deviations from the baseline. 29 tumor relevant genomic regions are highlighted. The red arrow indicates *SMARCB1* focal deletion.

USA) arrays according to the manufacturer's instructions, as previously reported [13–15]. Generated methylation data were compared with the Heidelberg brain tumor classifier to assign a subgroup score for the tumor compared with 91 different brain tumor entities [10].

Pathology & molecular findings

The tumor showed a highly cellular tumor composed of rhabdoid cells with an eccentric nucleus, prominent nucleolus and eosinophilic cytoplasm. The tumor was mitotically active 5–9 mitosis/10 high power field (HPF) but without necrosis or vascular proliferation. No meningothelial whorls or pseudoinclusions were seen. The tumor infiltrated the adjacent brain parenchyma (Figure 1D & E).

The tumor cells were diffusely positive for vimentin (Figure 1I), focally positive for synaptophysin and SMA (Figure 1F & G) and negative for CK, GFAP and EMA. All tumor cells showed a loss of nuclear SMARCB1/INI1 protein expression with retained immunoreactivity in vascular endothelial cells (Figure 1H). Ki67 index was variable between different areas ranging between 5 and 15% (Figure 1J).

Based on the radiological and clinical information the differential diagnosis was rhabdoid meningioma with *INI1* loss or ATRT. DNA methylation profiling was performed to reach the final and the most definitive diagnosis. The tumor had a score of 0.98 in the methylation class ATRT, subclass *MYC*. Copy number variation analysis showed a loss of *SMARCB1* (Figure 2).

Discussion

The first adult case of ATRT was reported in 1992 [16], and since then many cases have been reported in the literature [3]. Females are more commonly affected than males and the intracranial location is more common than the spine [3]. The most common intracranial location is suprasellar (46%) followed by cerebral hemispheres (32%) [3]. In our case, the tumor is located in the extra-axial meningeal location, a location rarely reported in the literature [17,18].

ATRT of the brain is a *SMARCB1*-deficient tumor. *SMARCB1* (*SWI/SNF*-related, matrix-associated, an independent regulator of chromatin, subfamily B, member 1), located at 22q11.23, also known as *INI1*, is a tumor

suppressor gene, that encodes a core subunit of the *SWI/SNF* chromatin-remodeling complex [19]. Inactivation of both copies of *SMARCB1* leads to the loss of nuclear expression of SMARCB1 protein in tumors cells, which can be easily identified by using immunohistochemistry [20]. *SMARCB1*-deficient tumors can be divided into two groups according to intracranial or extracranial location. The extracranial *SMARCB1*-deficient tumors mostly comprise soft tissue tumors, such as epithelioid sarcoma, some extra skeletal myxoid chondrosarcomas and some myoepithelial tumors [21]. The intracranial *SMARCB1*-deficient tumors include ATRTs, cribriform neuroepithelial tumor [21,22] and rare, poorly differentiated chordomas [23]. These intracranial *SMARCB1*-deficient tumors are rarely reported in meningeal locations [1,17,18,23–27].

The diagnosis of ATRT is easily suspected in infants, but the differential diagnosis is wider in adults as it is in our case. The differential diagnosis of rhabdoid morphology could be epithelioid/rhabdoid glioblastoma, composite rhabdoid tumors, including carcinomas, melanomas, sarcomas and desmoplastic small round cell tumors which have secondary rhabdoid phenotype [28], germinomas, embryonal tumors and rhabdoid meningiomas. Although these mentioned and the parent tumors in composite ones are characterized by retained *INI1* expression [28], there are two reported cases about *SMARCB1*-deficient meningeal tumors [21]. This was our reference toward our main differential diagnosis of rhabdoid meningioma, in addition to extra-axial location, rhabdoid morphology and long survival, but the tumor was negative for EMA which has suboptimal sensitivity and specificity and vary according to the grades or subtypes of meningioma and it can be negative in high-grade meningioma [29]. In addition, a high Ki67 index, increased mitotic activity and absence of meningothelial whorls can happen in some high-grade rhabdoid meningioma [29].

DNA methylation profiling is a powerful tool that aids in the diagnosis of challenging CNS tumors. The integration of methylation-based CNS tumor classification into the diagnosis has significant clinical benefit for patients with ambiguous CNS tumors and can directly affect patients' management, avoid unnecessary or unwanted treatment in some cases, allow us to offer the best care for the patients and avoid unnecessary health costs [10,30,31]. Pathologists rarely use it for ATRT diagnosis because they depend mainly on INI1 loss; however, in our case, the presence of these two reported cases of *SMARCB1*-deficient meningeal tumors [21], the unique location of the tumor, the long term survival of 6-years after diagnosis, the absence of EMA staining and the positivity for SMA and synaptophysin led us to order methylation profile to reach the final and the most definitive diagnosis and for further epigenetic subgrouping [11], especially that this patient was previously misdiagnosed with gliosarcoma.

DNA methylation profile for pediatric ATRT brain tumors, enhancer landscape and subgroup-specific transcriptional networks separate ATRT into three molecular subgroups: ATRT-*SHH*, ATRT-*TYR* and ATRT-*MYC* [11] – and these subgroups are different in regard to the age of onset, the location of the tumor, *SMARCB1* mutational pattern and radiological features [11,12]. The ATRT-*TYR* subgroup is strongly associated with an infratentorial location and ATRT-*MYC* with supratentorial location, while ATRT-*SHH* appears in both locations. The methylation profile for our case fits with methylation class ATRT, with epigenetic similarities to pediatric ATRTs of the ATRT-*MYC* subgroup and a similar profile to the other reported adult ATRT case in the sellar region [4].

ATRTs in adults generally have a poor prognosis, but long-term survival is possible after surgery and adjuvant chemotherapy and radiotherapy [32,33]. In a systematic review of literature, the overall survival was 23 months and the median time to progression was 5 months [34]. However, in addition to our case, three reported cases of adult ATRT did show survival of more than 3 years [34–36]. Interestingly, two of the three reported cases were initially misdiagnosed as high-grade glioma [35,36].

We report for the first time a case of an adult meningeal frontal tumor with histological features of rhabdoid meningioma but further classified by DNA-methylation profiling as ATRT. This molecular approach allows us to better define tumors with peculiar histopathological characteristics.

Author contributions

Acknowledgments

Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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Summary points

- SMARCB1/INI1 protein loss has been reported in various tumors in many organs and is an important marker for the diagnosis of these tumors.
- Rhabdoid morphology and INI1 loss should be taken seriously, even in abnormal locations and different age groups.
- DNA methylation profiling is a highly robust and reproducible approach for the classification of CNS tumors.
- DNA methylation profiling can be used as a tool for diagnosis in selected adult cases.
- The integration of methylation-based CNS tumor classification into the diagnosis has a significant clinical benefit for patients with ambiguous CNS tumors.
- The integration of methylation-based CNS tumor classification into the diagnosis can directly affect patients' management.

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