

Two Cases of Atypical Teratoid/Rhabdoid Tumor in the Spinal Cord: Loss of SMARCB1 in a Child and Loss of SMARCA4 in an Adult

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Abstract

We compare two cases of primary spinal atypical teratoid/rhabdoid tumor (AT/RT), which rarely occurs in adults marked by *SMARCA4* inactivation, and *SMARCB1* inactivation for pediatric cases. AT/RT represents a highly malignant neoplasm comprising poorly differentiated constituents and rhabdoid cells, with *SMARCB1* (INI1) or infrequently *SMARCA4* (BRG1) inactivation. These tumors are predominantly found in children but are rare in adults. While AT/RT can arise anywhere in the central nervous system, spinal cord localization is comparatively scarce. Despite mutation or loss of *SMARCB1* at the 22q11.2 locus serving as the genetic hallmark of AT/RTs, infrequent cases of *SMARCA4* inactivation with intact *SMARCB1* protein expression are significant. We present each case of primary spinal tumors in a child and an adult, showing loss of the *SMARCB1* and *SMARCA4* proteins, respectively. Both tumors met the AT/RT diagnostic criteria. The histopathology demonstrated the presence of rhabdoid cells in both cases. Diagnosing primary spinal AT/RT with *SMARCB1* protein loss remains a challenge. Nevertheless, the presence of *SMARCB1* positivity alone must be noted to be insufficient to exclude the possibility of AT/RT diagnosis. In cases in which the diagnosis of AT/RT is highly suspected clinically, additional testing is warranted, including *SMARCA4* analysis.

Keywords: spinal tumor, AT/RT, spine, INI-1, BRG-1

Introduction

Atypical teratoid/rhabdoid tumor (AT/RT) is a highly malignant tumor comprising poorly differentiated constituents, which often includes rhabdoid cells, with inactivation of SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1; *SMARCB1* (integrase interactor 1; INI1) or rarely SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4; *SMARCA4* (Brahma-related gene 1; BRG1).¹ These cases often occur in children under five

years²) but rarely in adults.³ Although AT/RT typically has been reported in all central nervous system (CNS) regions,⁴ pediatric primary spinal AT/RTs cases are below 60, while adult primary spinal AT/RTs are even more scarce, with reported cases below 10.⁵ The extreme rarity of primary spinal AT/RT presents a diagnostic challenge, especially for adult patients.

The genetic hallmark of AT/RTs is the mutation or loss of the *SMARCB1* locus at 22q11.2 in most cases,^{6,7} resulting in the complete abrogation of the *SMARCB1* protein expression. Hence, the assessment through immunohisto-

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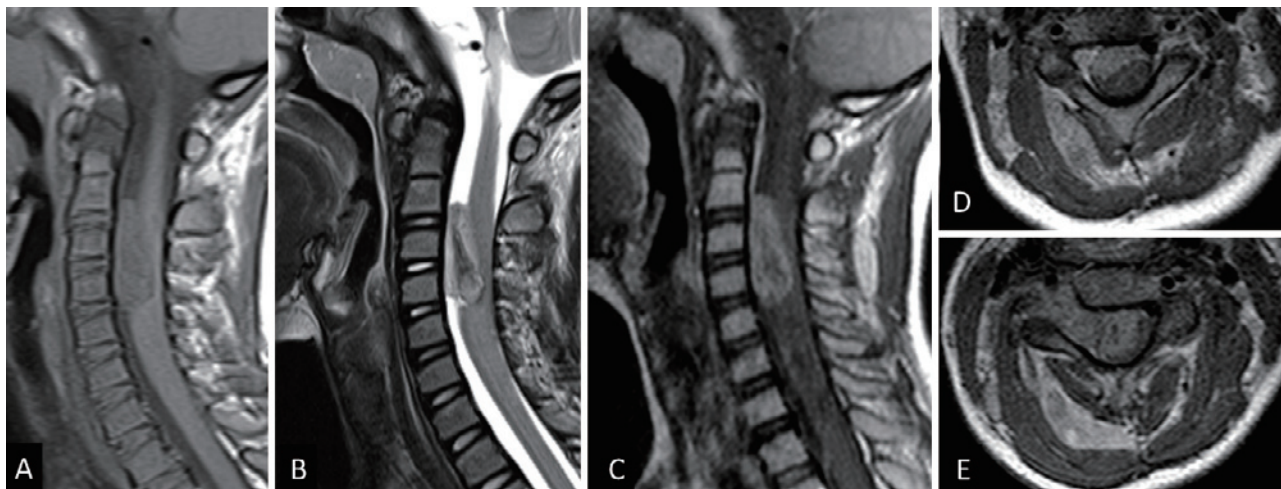


Fig. 1 Magnetic resonance imaging of the spine showing a dumbbell tumor of Eden type II, with heterogeneous enhancement at the vertebral body level between C2 and C5. The tumor has spread from the intradural extramedullary to the intramuscular and compressed the cervical cord. (A) T1-weighted sagittal image, (B) T2-weighted sagittal image, (C) gadolinium-enhanced T1-weighted sagittal image, (D) gadolinium-enhanced T1-weighted C2/3 axial image, (E) gadolinium-enhanced T1-weighted C3/4 axial image.

chemistry for SMARCB1(INI1) protein loss serves as a specific diagnostic clue.⁸⁾ In rare cases, *SMARCA4* mutations are reported, characterizing the loss of SMARCA4 expression while retaining SMARCB1 protein expression.⁹⁾

We report pediatric and adult spinal AT/RT cases. In the adult case, the diagnosis was challenging due to the atypical nature of the primary spinal AT/RT and the harbored *SMARCA4* mutation.

Case Report

Case 1

A 5-year-old female presented with neck pain and difficulty in using her right hand. Clinical examination revealed right upper-limb weakness and cervical rotatory disorder. Magnetic resonance imaging (MRI) showed a dumbbell tumor of Eden type II, with heterogeneous enhancement, located within the intradural extramedullary space and paraspinal muscles between the C2 and C5 vertebral bodies. The tumor had compressed the cervical cord (Fig. 1). Furthermore, the tumor had encroached upon the extraforaminal paravertebral space, thus necessitating combining the anterior and posterior approaches to achieve gross total resection.

Subtotal removal of the spinal tumor was scheduled to decompress the spinal cord. The surgical procedure was conducted with the patient in the prone position, and a skin incision was made from the C1 to C5 spinous processes. Grayish cyst-like tumor tissue was discerned in the right paraspinal muscle, extending into the right C4/5 intervertebral foramen. The tumor was also detected in the right side of the spinal canal. Though dissected from the spinal cord and surrounding tissue, the tumor seemed to

invade the right C5 dorsal and anterior roots. Furthermore, it had extended to the contralateral extramedullary space via the ventral aspect of the spinal cord, which was difficult to remove. Therefore, the right C5 dorsal root was amputated, while the right C5 anterior root was preserved with the residual tumor. Subtotal removal of the foraminal and the paravertebral tumor was subsequently accomplished via a posterior approach (Fig. 2A and B). The foraminal tumor was removed extensively from posterior foraminotomy with medial 1/3 of lateral mass resection. The paravertebral tumor connecting to the foraminal lesion was also removed, including the surrounding tumor-invasive muscle without any surgical margin, and was amputated just on the surface of the lateral edge of the lateral mass.

Pathological investigation of the excised tumoral tissues revealed a malignant neoplasm comprising rhabdoid cells, endothelial proliferation, and necrosis (Fig. 2C). Immunohistochemical examination confirmed positive vimentin and pan-CKAE1/AE3 expression. Tumorous cells were partly positive for synaptophysin, smooth-muscle actin, and CD56. SMARCA1 (BRG1) was also positive. However, SMARCB1(INI-1) was negative (Fig. 2D and E). Over 40% of tumor cells demonstrated positivity for Ki-67. These observations corroborated the diagnostic criteria for AT/RT.

Following the surgical intervention, the patient received chemotherapy (MTX iT (intrathecal) + VDC/ICE; methotrexate, vincristine, doxorubicin, cyclophosphamide, ifosfamide, cisplatin, and etoposide) and proton therapy (54 Gy/30 fractions). Although asymptomatic, neoplastic lesions recurred within the intradural extramedullary space near Th10 eight months post-surgery. Since the tumor invaded the dorsal root of the spinal cord, a subtotal resec-

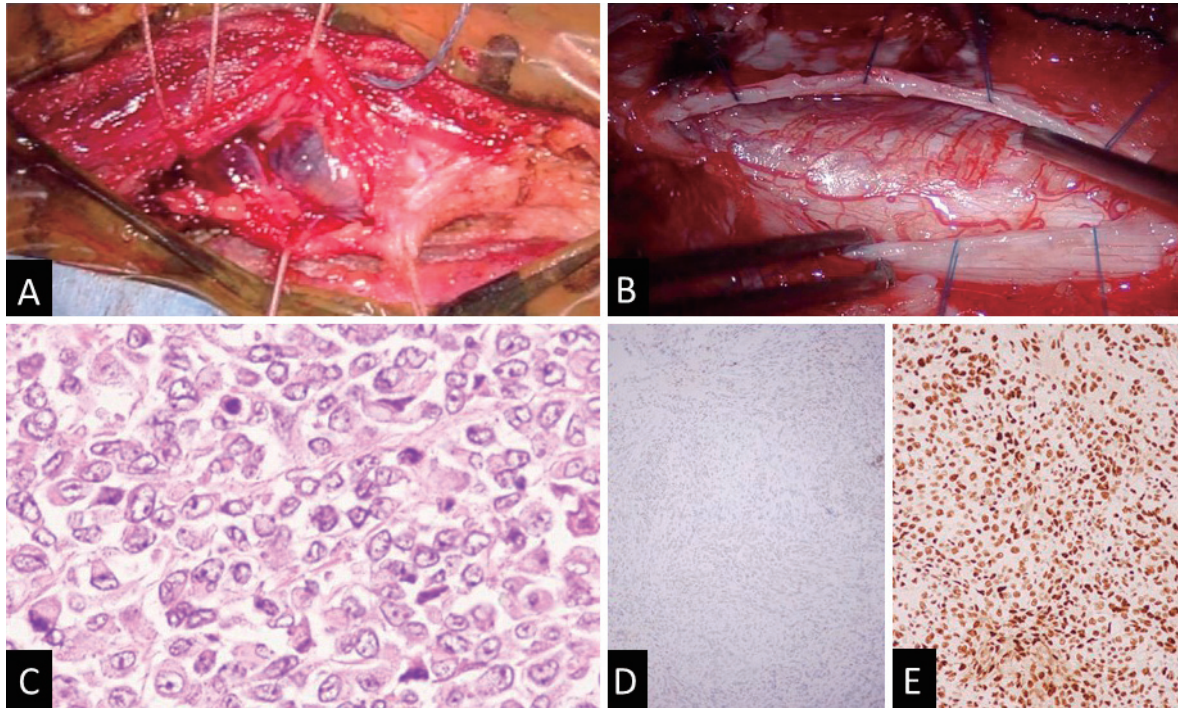


Fig. 2 Surgical findings and pathological findings. (A) Surgical findings showing a grayish cyst-like tumor tissue in the muscle layer. (B) An incision in the dura revealing a thinned spinal cord and tumor mass. (C) Hematoxylin and eosin staining showing a malignant neoplasm composed of rhabdoid cells. (D) Although the INI1 protein is negative. (E) the BRG1 protein is positive on immunohistochemistry.

tion was performed. Notwithstanding the chemotherapy cycle (MTX iT), the tumor recurred in the corpus callosum and the cerebellopontine angle 10 months following the initial surgery.

The tumor was refractory to treatment and had multiple disseminated lesions in the spinal cord. The patient is presently receiving palliative care.

Case 2

A 49-year-old man presented with right-sided chest pain. The patient had an unremarkable medical history, and no neurological deficits were identified. MRI revealed an Eden type III dumbbell tumor with heterogeneous enhancement at the T9-10 vertebral body level. The tumor exhibited contact with the pleura from the right side of the T9-10 spinal canal through the intervertebral foramen (Fig. 3).

The surgical procedure was conducted with the patient in the prone position. A 7-cm skin incision was performed, and a laminectomy of T8-10 was conducted. A distinct, grayish, elastic, and soft neoplastic lesion was observed in the extradural and intradural space adjacent to the T9-10 intervertebral foramen. The intradural lesion adhered to the T9 dorsal root, slightly swollen with abnormal color, while the T9 anterior root appeared unaltered. Consequently, the T9 root was amputated, and the tumor was entirely excised (Fig. 4A and B).

Histological examination revealed a malignant neoplasm

partially comprising rhabdoid cells with necrotic areas (Fig. 4C). Immunohistochemical examination demonstrated positive pan-CKAE1/AE3 expression, with over 80% of the tumor cells exhibiting Ki-67 positivity. Due to the rhabdoid or epithelioid features of tumoral cells, cancer metastasis was initially suspected, including lung cancer. However, the cytokeratin immunostaining pattern, CK20 (+)/CK7 (-), did not align with the pulmonary origin. Given the spinal cord localization, epithelioid malignant peripheral nerve sheath tumor (MPNST) was also considered. Nevertheless, the S-100 protein expression was not distinctive, even though focal and faint immune reactions were seen for vimentin, synaptophysin, and CD56. Subsequently, SMARCB1 (INI1) and SMARCA4 (BRG1) expressions were examined. While SMARCB1 expression was retained, SMARCA4 was undetectable (Fig. 4D and E). These findings substantiated the diagnostic criteria for AT/RT. Despite the patient being asymptomatic, conventional radiation therapy (66 Gy/30 fractions) was initiated 37 days after the surgery.

Unfortunately, disseminated lesions were identified in the cerebellopontine angle, hypothalamus, lateral ventricle, and cisterna magna 7 months post-surgery. Although chemotherapy (modified ICE: ifosfamide/carboplatin/etoposide therapy) was initiated, it was discontinued due to adverse effects. The patient expired approximately 11 months post-surgery.

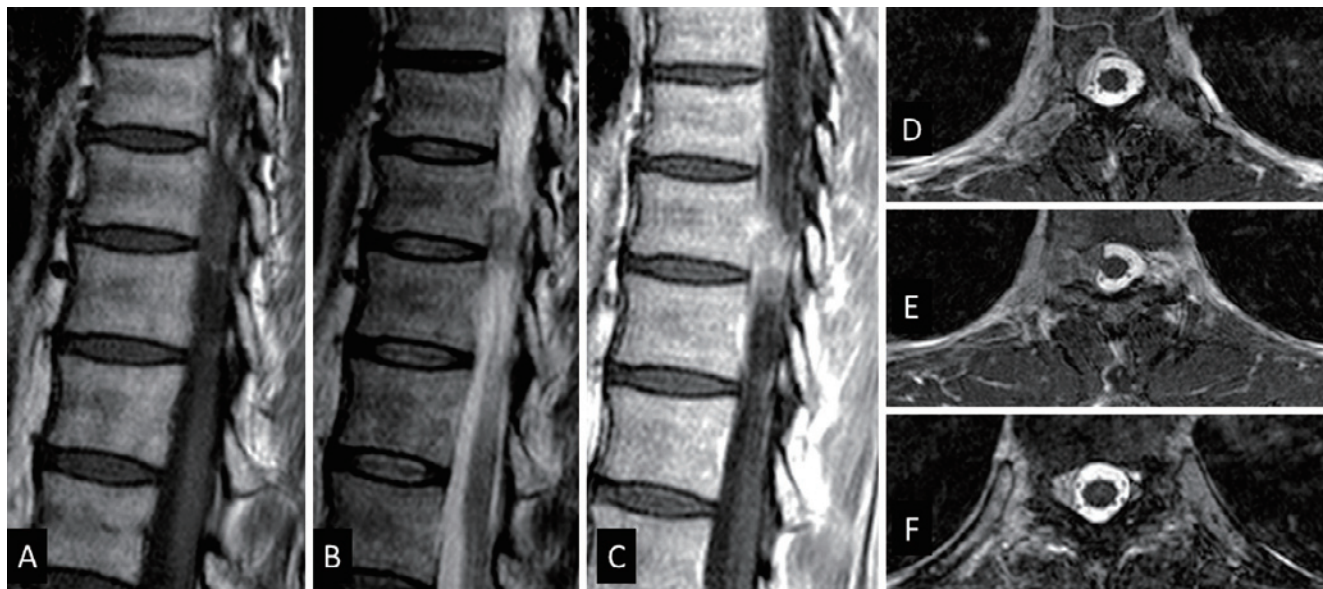


Fig. 3 Magnetic resonance imaging of the spine showing a dumbbell tumor of Eden type III, with heterogeneous enhancement at T9 and T10 vertebral body levels. The tumor was in contact with the pleura from the right side of the T9/10 spinal canal through the intervertebral foramen. (A) T1-weighted sagittal image, (B) T2-weighted sagittal image, (C) gadolinium-enhanced T1-weighted sagittal image, (D) gadolinium-enhanced T1-weighted T9 axial image, (E) gadolinium-enhanced T1-weighted T9/10 axial image, (F) gadolinium-enhanced T1-weighted T10 axial image.

Discussion

Incidence of AT/RT in the adult spinal cord

AT/RT represents a rare and highly malignant neoplasm, with most cases occurring in children below 5 years old.² Consequently, its prevalence in adults is exceptionally low.³ AT/RT accounts for 1.6% of all pediatric CNS tumors, and 4.4% of those occur in children aged 0-5 years. While AT/RT has been typically reported in various CNS regions, encompassing the supratentorial region, its occurrence in the cerebellopontine angle cistern, meninges, cranial nerves,⁴ and spinal canal is rare.⁵ To date, merely seven adult cases and 53 pediatric cases have been documented.¹⁰

Histologically, AT/RT comprises rhabdoid tumor cells, with additional but variable components of neuroectodermal, epithelial, and mesenchymal origin. Some tumors may consist only of rhabdoid cells, whereas others show a combination of rhabdoid cells with other cell types.^{2,11} In our first case, the proliferation of rhabdoid cells was notably observed, presenting a relatively typical pathological image. In contrast, in the second case, even though the tumoral cells exhibited rhabdoid or epithelioid features, the unusual tumoral localization and the patient's age rendered the differential diagnosis of AT/RT challenging.

Different molecular pathological characteristics of AT/RT

Immunohistochemical investigation is crucial for AT/RT diagnosis. AT/RT shows variable expression of GFAP, S-100, and cytokeratin to exclude candidates in the differential

diagnosis, such as epithelioid MPNST and rhabdoid meningioma.¹² Recently developed INI1 antibody has been introduced as a useful marker to show the lack of expression of INI1 protein in tumor cells of AT/RT.^{12,13} INI1, the gene product of *SMARCB1*, is typically expressed in all normal tissues and most neoplasms. However, deletion or mutation of the *SMARCB1* locus on 22q11.2 leads to the loss of this protein in AT/RTs.¹⁴ Nearly all AT/RT cases exhibit loss of INI1 protein, and approximately 70% of all cases detect *SMARCB1* loss, whereas loss of *SMARCA4* expression is seen in a small number of cases.¹⁵ Therefore, *SMARCB1* positivity alone cannot rule out the diagnosis of AT/RT. In cases in which the diagnosis of AT/RT is strongly suspected clinically, additional testing is warranted, including *SMARCA4* analysis.

SMARCA4 expression for an ATPase subunit of the SWI/SNF chromatin-remodeling complex associated with inherited germline mutations is responsible for rhabdoid tumors.¹⁶ As previous reports of AT/RT with *SMARCA4* mutations suggest that *SMARCA4*-mutated tumors are biologically aggressive,^{15,16} as case 2 showed, where the tumor rapidly disseminated. Even if age or tumor site are atypical, additional testing, including *SMARCA4* or SMARCA4 (BRG1) protein analysis, is warranted in cases where the tumoral cells show rhabdoid or epithelioid features.

Therapeutic strategy for primary spinal AT/RT

Given the lack of standardized treatment for spinal AT/RT, especially in adults, treatment protocols are often extrapolated intracranial pediatric AT/RT management. Sur-

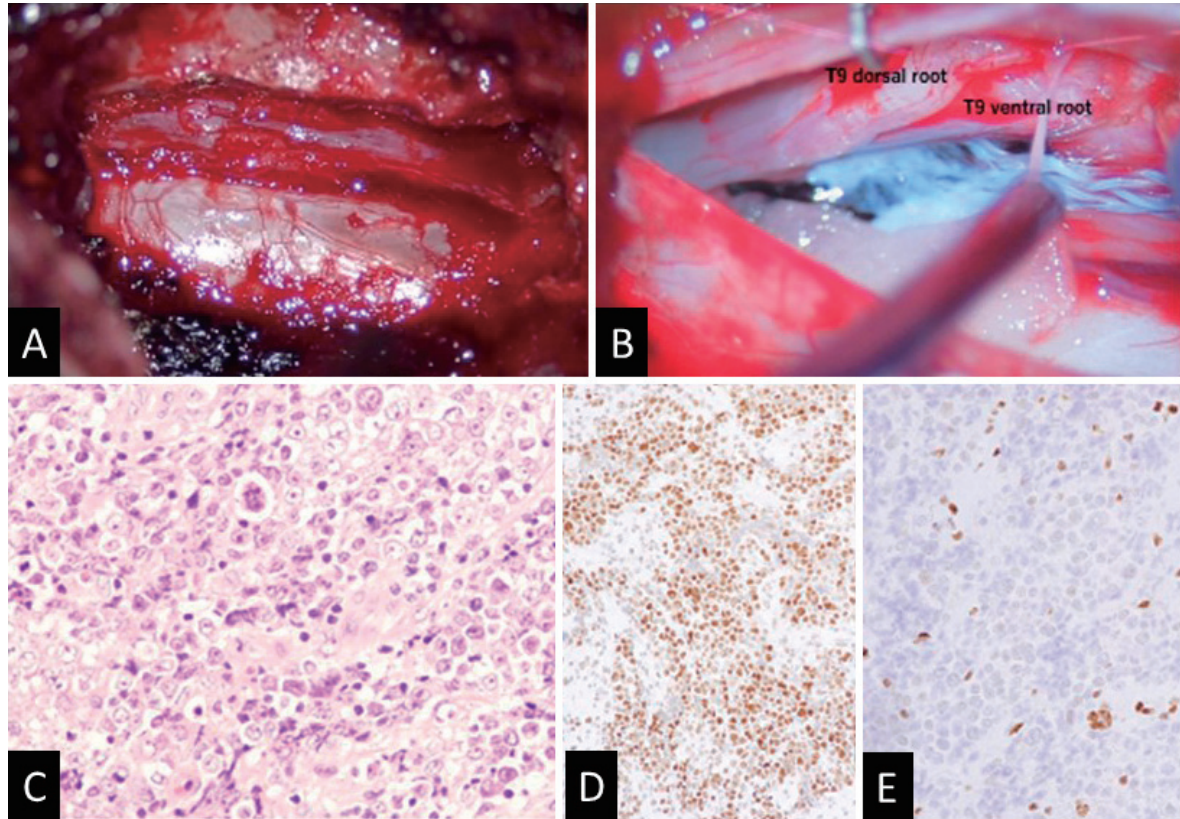


Fig. 4 Surgical findings and pathological findings. (A) A grayish, elastic, soft, well-defined neoplastic lesion was confirmed epidurally in the T9-10 intervertebral foramen. (B) The dura is incised, a yellow tumor piece adheres to the dorsal root of T9, and the ventral root is slightly swollen with abnormal color. (C) Hematoxylin and eosin staining showing a malignant neoplasm partly composed of rhabdoid cells with necrosis. (D) Although the INI1 protein is positive, (E) the BRG1 protein is negative on immunohistochemistry.

gical resection constitutes the primary therapeutic approach, complemented by chemotherapy and radiotherapy.⁵⁾ Despite aggressive treatment, the prognosis of spinal AT/RT is considerably worse than that of intracranial AT/RT, with a median survival time of under six months.^{5,17)} Although these approaches have yielded a modest improvement in overall survival, therapy-induced toxicity remains a critical problem, as case 2 illustrated. Recently, clinical trials of the enhancer of Zeste 2 (EZH2) inhibitor, Tazemetostat, are being promoted. While the role of EZH2 is being evaluated, previous studies have suggested that EZH2 disruption alters cell-cycle progression and may be an important new therapeutic target, particularly in combination with radiation in AT/RT with INI-1 loss.¹⁸⁾

The primary causes of death resulting from AT/RTs include recurrence and dissemination.⁵⁾ The rate of leptomeningeal dissemination in spinal AT/RT ranges from 20% to 40%.³⁾ Interestingly, in our cases involved tumors originating from nerve roots recurred in a similar cranial region, specifically the cerebellopontine angle. Although some case reports have detailed AT/RT originating from the cranial nerves,^{4,19,20)} the dissemination pattern from the spinal cord to the cerebellopontine angle had not been

previously reported.

Conclusions

We presented rare pediatric and adult spinal tumor cases, which meet the AT/RT diagnostic criteria. Primary spinal AT/RT was atypical. Particularly, our adult primary spinal AT/RT with loss of SMARCA4 expression is a rare case. There is no standard treatment for spinal AT/RT, especially in adults. Further clinicopathological and genetic studies are warranted to unravel AT/RT.

Consent for Publication

All the patients have consented to submitting the case report for consideration by the journal.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest to declare.

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