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Ventriculoperitoneal shunt as a risk factor for extraneural dissemination of atypical teratoid/rhabdoid tumor in children

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Atypical teratoid/rhabdoid tumor (ATRT) is a rare but aggressive malignancy of the pediatric central nervous system (CNS), predominantly affecting children under the age of three. Despite its low frequency, ATRT constitutes a notable proportion of embryonal CNS tumors, particularly within the first year of life. The prognosis for ATRT patients is generally poor, with a significant decline in survival rates when metastasis is detected at diagnosis. Treatment typically involves a multimodal approach including surgery, radiation therapy, and chemotherapy, although outcomes remain suboptimal, especially in cases with younger age at diagnosis and metastases. ATRT exhibits distinct radiological and histopathological characteristics, presenting challenges in diagnosis and treatment planning. Additionally, extraneural metastatic spread of ATRT, although rare, can occur, with ventriculoperitoneal (VP) shunts identified as potential routes for dissemination. We present an extremely rare case of extraneural dissemination into the abdominal cavity along ventriculoperitoneal shunt in a 4-year-old boy. This is a type of extraneural dissemination in children that has only been published once and we are the first to present in Croatia.This case report highlights the diagnostic and therapeutic complexities associated with ATRT, emphasizing the importance of comprehensive staging, genetic evaluation, and vigilant surveillance for potential metastatic spreading via VP shunt. Furthermore, it emphasizes the need for further research to improve treatment outcomes and identify prognostic factors for risk stratification in pediatric patients with ATRT.

Key words: RHABDOID TUMOR; CENTRAL NERVOUS SYTEM NEOPLASMS; ABDOMINAL CAVITY; VENTRICULO-PERITONEAL SHUNT; MAGNETIC RESONANCE IMAGE

INTRODUCTION

Despite representing only 1–2% of all pediatric central nervous system (CNS) tumors, atypical teratoid/rhabdoid tumor (ATRT) emerges as a notably common malignancy during early childhood, with approximately three-quarters of afflicted individuals being under the age of three. Within this age cohort, ATRT comprises around 20% of embryonal CNS tumors and an even more substantial proportion, ranging from 40% to 50%, of all CNS malignancies within the first year of life. While early studies indicated an average survival of around 12 months, there have been reports of long-term survivors, especially among individuals who underwent intensive multimodal therapy (1, 2).

ATRT presents as a histologically diverse neoplasm, characterized by the presence of dispersed rhabdoid cells alongside large epithelioid cells, primitive neuroectodermal cells, and mesenchymal and/or glial cells. It is categorized within the broader spectrum of rhabdoid tumors. Throughout this

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case report, the term ATRT specifically pertains to CNS tumors, while the term rhabdoid tumor encompasses both CNS and non-CNS variants. This case report exclusively focuses on CNS ATRT. Notably, in pediatric cases, approximately half of all ATRTs originate in the posterior cranial fossa. The World Health Organization (WHO) formally recognized ATRT as a distinct diagnostic category in 2000, and in the 2021 WHO classification, there is an emphasis on the necessity of genetic examination alongside neuropathologic assessment for definitive diagnosis. Furthermore, according to the 2021 WHO classification, ATRT is classified as a grade IV tumor (2–4).

The prognosis notably deteriorates in cases where metastasis is detected at the time of diagnosis, a scenario encountered in around 20% of instances. Typically, patients undergo multimodal treatment regimens incorporating a blend of surgical intervention, radiation therapy, conventional chemotherapy, intrathecal chemotherapy, and/or high-dose, marrow-ablative chemotherapy with autologous hematopoietic cell rescue (5).

ATRT possess a distinctively aggressive biological behavior, marked by local invasiveness and a propensity for dissemination through cerebrospinal fluid pathways. Consequently, timely detection of ATRTs is imperative as these tumors necessitate prompt, targeted, and aggressive therapeutic interventions compared to other high-grade malignancies (6).

Magnetic resonance imaging (MRI) of the brain, along with lumbar puncture for cerebrospinal fluid (CSF) analysis, is imperative for comprehensive staging of the disease extent and guides the intensity of therapeutic interventions. Approximately 25% to 40% of patients exhibit manifestations of posterior fossa syndrome, typified by the triad of mutism, emotional instability, and ataxia, which may result in enduring neuropsychiatric complications (7).

The majority of ATRT cases are characterized by bi-allelic loss of function mutations in the SMARCB1 gene, while the remaining cases exhibit mutations in the SMARCA4 gene. Despite significant morphologic variability, rapid histologic diagnosis of ATRT is facilitated by the loss of INI1 (SMARCB1) or BRG1 (SMARCA4) through immunohistochemical staining. Approximately one-third of ATRT patients harbor an underlying germline SMARCB1 alteration, predisposing them to rhabdoid tumor predisposition syndrome and the risk of multiple CNS and non-CNS rhabdoid tumors. The recognition of ATRT as a distinct entity has led to disease-specific approaches employing intensive multimodal therapies, resulting in improved survival outcomes. However, current treatment options are associated with high toxicity, and there is ongoing exploration of how molecular subgroups and other prognostic factors can inform treatment stratification in future clinical trials. While survival rates have seen improvement with the implementation of multi-modality therapies, outcomes remain suboptimal, particularly in cases with younger age at diagnosis and metastases. Somatic inactivating alterations of SMARCB1, occurring in over 95% of ATRT patients, and mutations in SMARCA4 are hallmark features of this tumor (4, 8).

ATRT can be categorized into three main molecular subgroups based on distinct genetic and epigenetic signatures, each with unique histopathological and clinical features. These subgroups include ATRT-SHH, ATRT-MYC, and ATRT-TYR. In this case report, we have no intentions going into immunohistochemical details of ATRT, but we will highlight key features of each subgroup to emphasize the importance of combining immunohistochemical findings with MRI images of the tumor, all in order to achieve a timely diagnosis.

ATRT-SHH subgroup is associated with activation of the sonic hedgehog pathway and Notch signaling. Histopathologically, it is presented with small-round-blue-cell morphology. The ATRT-MYC subgroup is defined by dysregulation of the MYC pathway. Immunohistologically, it may present with mesenchymal or rhabdoid features and epigenetically is similar to extracranial malignant rhabdoid tumors. The third subgroup, ATRT-TYR, is characterized by overexpression of tyrosinase, one of the key enzymes in neural tube development, and often display epithelial features. Epigenetically, this subgroup is linked to cribriform neuroepithelial tumors, suggesting shared developmental pathways (1).

CASE REPORT

We present a retrospective case report from 2017, when a 4-year-old boy was admitted with symptoms that began with a headache accompanied by occasional vomiting. After 10 days, the headaches recurred, primarily located in the occipital region, and during a period of 3 days, vomiting occurred twice daily, mostly in the afternoon or early morning. Throughout this time, the patient remained afebrile. Physical examination showed an uncoordinated walk. Brain MRI revealed a 4.9x3.9x4.6 cm mass filling the suprasellar region, third ventricle, and left lateral ventricle, consequently resulting in hydrocephalus. The mass showed an isointense signal to the cortex in T1, slightly hyperintense in T2 and BLADE, high signal in DWI with restriction in ADC, without postcontrast enhancement (Figure 1). Also, there was evidence of CSF and leptomeningeal dissemination presented as small nodular masses with the same MRI characteristic in the pineal region, olfactory sulcus, interpeduncular fossa, fourth ventricle, insular region, and left parietal lobe. Spinal MRI was normal. According to the heterogeneous MRI characteristics

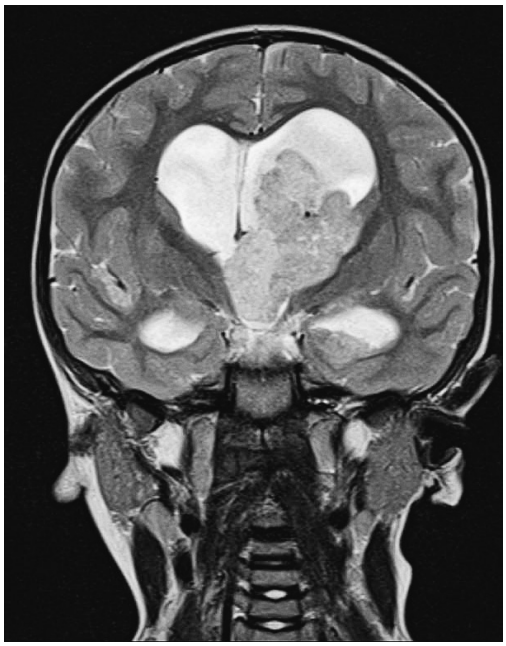

FIGURE 1. T2 coronal: extensive mass in third and left lateral ventricle

of the mass and its location, the neuroradiologist concluded that it was most likely an ATRT. The next day after the initial MRI, parietal craniotomy was performed, and the gross tumoral mass was resected. Due to hydrocephalus, a ventriculoperitoneal (VP) shunt catheter was inserted. The histopathologic diagnosis was an atypical teratoid rhabdoid tumor (ATRT) due to the tissue consisting of densely packed small mitotically active primitive neuroectodermal cells, positive for vimentin, while negative for GFAP, neurofilament, NeuN, chromogranin A, IDH, and INI1. INI1 was negative due to the SMARCB1 gene expression being lost. Ki67 was 80%. DNA methylation was not performed at that period as it was not available. The postoperative staging based on histopathology and intraoperative phenotype of the mass resulted in a diagnosis of ATRT stage M2. Chemotherapy was performed in the post-operative period following the European Rhabdoid Registry (EuRhab) protocol with a combination of IT for a total of four months. At another hospital, the patient received whole-brain (35 Gy, proton radiotherapy with pencil-beam scanning (PBS)) and spine radiation (19.8 Gy PBS) for two months. After 8 months of follow-up, MR revealed frontal lobe necrosis with radiation-induced leukoencephalopathy and tumor recurrence in the IV. ventricle with postcontrast enhancement (Figure 2). Also, MR showed bilateral pleural effusion with ascites in the abdominal cavity (Figure 3) and a tumor mass in the posterior wall of the bladder (Figure 4). Urgent ultrasound-guided drainage of ascites was performed. Immunohistochemical analyses of abdominal fluid revealed identical phenotypic patterns as for the primary CNS tumor, including small-round-blue-cell morphol-

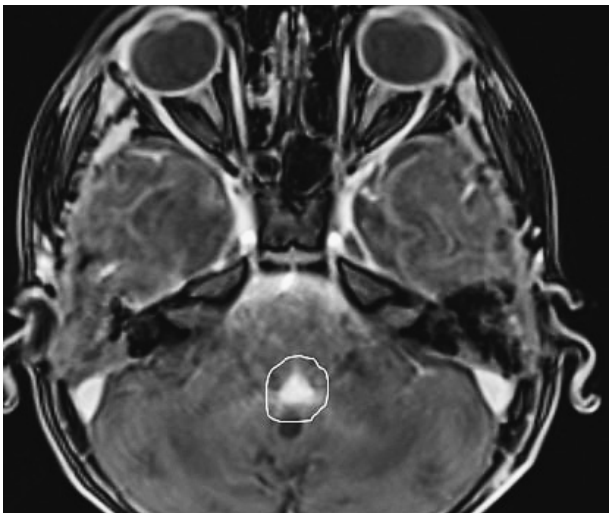

FIGURE 2. Postcontrast T1 fat sat axial: tumor recurrence in the IV. ventricle with postcontrast enhancement

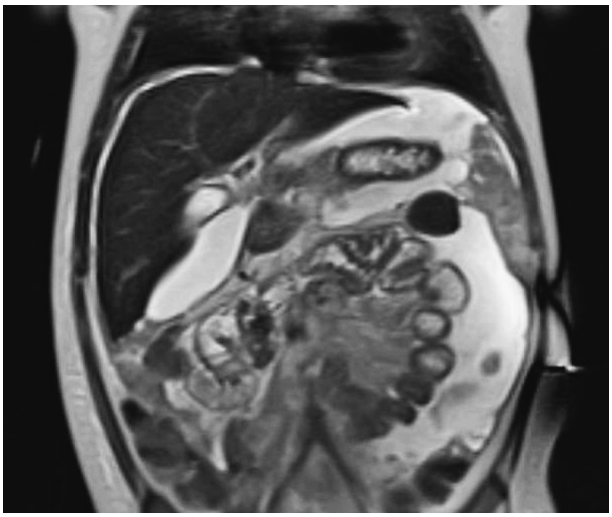

FIGURE 3. T2 coronal abdomen: extensive intraperitoneal fluid (ascites)

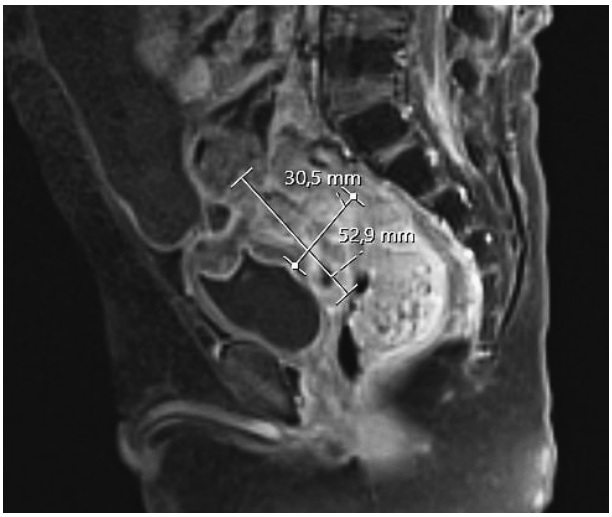

FIGURE 4. Postcontrast T1 fat sat sagittal: thick urinary bladder posterior wall with heterogeneous postcontrast enhancement tumor mass

ogy, indicative of a metastatic spread of the AT/RT to the abdominal cavity. During chemotherapy and radiotherapy, the patient experienced various complications, including Klebsiella pneumonia, myoclonic seizures, and an infection caused by methicillin-resistant Staphylococcus aureus (MRSA). The patient died due to the complications and was on palliative therapy 12 months after diagnosis.

DISCUSSION AND CONCLUSION

We present a patient who had a highly malignant CNS tumor, ATRT, and extraneural spread associated with a VP shunt. Firstly, there are many potential pitfalls in diagnosing ATRT. The radiological appearance of ATRT is highly heterogeneous, lacking pathognomonic features, and may emerge throughout the CNS, warranting consideration during the assessment of any aggressive intracranial tumor in young children. Typically, they manifest as large, heterogeneous masses with varying signs of necrosis, hemorrhage, and peritumoral edema. While primarily found within brain tissue, ATRTs can also originate along cranial nerves or within the skull base. Due to their dense cell structure, ATRTs often show limited diffusion on MRI (9). The majority of ATRT cases occur in very young children, whose unfused skull sutures allow for progressive cranial pressure build-up during tumor growth. Consequently, symptom onset may be delayed. Furthermore, nonspecific symptoms such as irritability and vomiting can be challenging to articulate in these young patients, leading to diagnostic delays (10). Achieving complete surgical resection is often difficult, primarily due to both the tumor's location and the potential for ATRT dissemination upon initial examination. Additionally, germline mutations of SMARCB1/SMARCA4 have been linked to poorer survival outcomes. Factors such as the extent of resection, older age, and the presence of metastases at presentation are significantly correlated with overall survival (11). There are several reports where the VP shunt is evaluated as the key risk factor for seeding along the track (12). However, there is only one case report of ATRT metastatic spread to the abdominal cavity due to a VP shunt in children (13). Extraneural metastatic spreading of the CNS primary tumor is very rare, but radiologists during follow-up MRI reporting need to be aware of potential risk factors such as the spread via a VP shunt and consider including the abdomen in MRI follow-up, especially if the amount of intraabdominal fluid increases. While this occurrence is exceptionally rare, it's essential to highlight VP shunts as a potentially "dangerous pathway" for tumor spread to peripheral areas. This is particularly significant given that VP drainage is frequently necessary, as hydrocephalus is a common feature in the initial presentation of brain tumors in approximately 50% of pediatric cases (14).

Abbrevations:

ATRT – atypical teratoid/rhabdoid tumor
CNS – central nervous system
MRI – magnetic resonance imaging
CSF – cerebrospinal fluid
VP – ventriculoperitoneal
EurRhab – European Rhabdoid Registry
PBS – pencil-beam scanning
MRSA – methicillin-resistant Staphylococcus aureus

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SAŽETAK

Ventrikuloperitonealna drenaža kao rizični faktor ekstraneuralne diseminacije atipičnog teratoidnog/rabdoidnog tumora u djece

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Atipični teratoidni/rabdoidni tumor (ATRT) rijetki je, ali agresivni maligni tumor središnjeg živčanog sustava (SŽS), koji se uglavnom javlja kod djece mlađe od tri godine. Unatoč niskoj učestalosti, ATRT čini značajan udio embriogenih tumora SŽS-a, posebno u prvoj godini života. Prognoza za pacijente s ATRT-om općenito je loša, s značajnim padom stopa preživljavanja kada se otkrije metastaza pri dijagnozi. Liječenje uključuje multimodalni pristup koji obuhvaća kirurgiju, radioterapiju i kemoterapiju, iako su rezultati i dalje suboptimalni, posebno u slučajevima s mlađom dobi pri dijagnozi i metastazama. ATRT pokazuje specifične radiološke i histopatološke karakteristike, što predstavlja izazove u dijagnostici i planiranju liječenja. Dodatno, ekstraneuralno metastatsko širenje ATRT-a, iako rijetko, može se dogoditi, pri čemu su ventrikuloperitonealni (VP) šuntovi identificirani kao potencijalne rute širenja. Predstavljamo izuzetno rijedak slučaj ekstraneuralnog širenja u trbušnu šupljinu duž ventrikuloperitonealnog šanta kod dječaka u dobi od 4 godine. Ovo je vrsta ekstraneuralnog širenja kod djece koja je objavljena samo jednom, a mi smo prvi koji je predstavljamo u Hrvatskoj. Ovaj prikaz slučaja ističe dijagnostičke i terapijske kompleksnosti povezane s ATRT-om, naglašavajući važnost staginga, genetske evaluacije i redovnih kontrola zbog potencijalnog metastatskog širenja putem VP šanta. Nadalje, ističemo potrebu za daljnjim istraživanjem radi poboljšanja ishoda liječenja i identifikacije prognostičkih čimbenika za stratifikaciju rizika kod pedijatrijskih pacijenata s ATRT-om.

Ključne riječi: RABDOIDNI TUMOR; NEOPLAZME SREDIŠNJEG ŽIVČANOG SUSTAVA; ABDOMINALNA ŠUPLJINA; VENTRIKULO-PERITONEALNI ŠANT; MAGNETSKA REZONANCIJA