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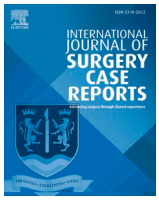

Case report

Atypical teratoid/rhabdoid tumor of the central nervous system: Clinicopathological features of two challenging cases

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ABSTRACT

Introduction: Atypical Teratoid/Rhabdoid Tumor (AT/RT) is a rare aggressive neoplasm that mainly affects the pediatric population with a peak incidence in the first two years of life and a slight male predominance, whereas presentation of this neoplasm in older ages is extremely rare.

Case presentation: Herein, we present two cases of AT/RT. In the first case, a 9-year-old female presented with diplopia, dizziness, headache, and morning vomiting. CT Scan of the head demonstrated a heterogeneous mass in the left frontal-parietal region with vasogenic edema and midline deviation. In the second case, a 57-year-old female presented with severe generalized headache, numbness, and tingling in the right hand. MRI revealed a lobulated cystic mass in the right occipitotemporal region, with surrounding edema compressing the left lateral ventricle and causing a midline shift to the left, and enlargement of the right lateral ventricle. In both case, histopathological and immunohistochemical examinations revealed the diagnosis of Atypical teratoid/Rhabdoid tumors.

Clinical discussion: Microscopic examination demonstrated the proliferation of medium-sized to large cells with abundant eosinophilic cytoplasm, large vesicular eccentric nuclei, and conspicuous nucleoli with areas of necrosis and hemorrhage, thus confirming the diagnosis with adequate immunohistochemical staining. The first patient developed signs of recurrence and passed away six months later, whereas in the second case, the 57-year-old female received radiotherapy for 6 weeks before being put on chemotherapy.

Conclusion: Despite the challenges facing the diagnosis of this aggressive neoplasm, we managed to present our cases with detailed histopathological and immunohistochemical examinations.

1. Introduction

Atypical Teratoid/Rhabdoid Tumor (AT/RT) is defined as a rare highly aggressive neoplasm that mainly affects the pediatric population aging less than three years old. On the other hand, adulthood AT/RT is extremely rare and affects patients aged between 18 and 61 years old with a median age of 32 years old and a male predominance. (AT/RT) is characterized by a heterogeneous proliferation of rhabdoid cells combined with epithelial cells, mesenchymal elements, and primitive neuroectodermal components [1]. Rhabdoid tumors were first described in 1978 as an aggressive variant of Wilms tumor by Beckwith and Palmer [2]. Later, Rorke et al. defined atypical teratoid/rhabdoid tumor (AT/RT) in 1996 as a distinct entity of RT that mainly affects the central nervous system [3]. Since the 2000 World Health Organization classification of central nervous system tumors, AT/RT has been classified as an embryonal tumor of the central nervous system grade II [1,4].

In the United States, AT/RT constitutes approximately 1.6 % of pediatric central nervous system CNS tumors with a peak incidence in the first two years of life and a slight male predominance. This rare tumor with an annual incidence of 0.7 per 1,000,000 cases constitutes the most prevalent tumor of the CNS in children younger than 6 months [5,6]. The difficulties in differential diagnosis, the high aggressiveness of the neoplasm, and the lack of specific radiological and clinical features contribute to the challenges in the diagnosis of this aggressive neoplasm.

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Therefore, morphologic, immunohistochemical, and molecular examinations are essential to establish the diagnosis [1]. Herein, we present two case reports of AT/RT that were diagnosed in two females aged 9-year old and 57-year old respectively. The work has been reported in line with the SCARE criteria [7]. Also work has been reported in line with the PROCESS criteria [8].

2. Presentation

2.1. Case 1

We report a case of a 9-year-old female who was referred to our hospital with a 17-day history of diplopia, dizziness, headache, and morning vomiting. Medical, surgical, and family history were unremarkable. The patient was conscious, responsive, and oriented during physical examination with no signs of imbalance or walking deficit. Examination results of movement, sense, and visual ability were normal. However, there was a slight esotropia in the right eye with vertical diplopia that increased with looking to the right, and ophthalmoscopy demonstrated papilledema in the right eye.

Laboratory examination revealed a high white blood cell count (28,1 × 103 u/l) including an increase in the granulocyte count (20,5 × 103/ul), whereas the lymphocyte count was low (2,5 × 103/ul). A computed tomography Scan of the head demonstrated a heterogeneous mass measuring (4 × 3) cm in the left frontal-parietal region with vasogenic edema and midline deviation (Fig. 1). Subsequently, the patient was transferred to the neurosurgery department for subtotal surgical resection and the lesion was sent to our pathology department for examination. Macroscopic examination revealed a light brownish mass that was soft in consistency with ill-defined borders.

Microscopic examination demonstrated the proliferation of medium-sized to large cells with abundant eosinophilic cytoplasm, large vesicular eccentric nuclei, and conspicuous nucleoli with extensive necrosis and hemorrhage (Fig. 2). Immunohistochemistry revealed positive expression of Vimentin, CK, EMA, and NSE, and negative expression of S100, CD45, and Melan-A (Fig. 3). INI1 testing wasn't available at our institution. Nevertheless, based on the detailed morphological examination and the classical immunohistochemical results, the diagnosis was confirmed by three histopathologists as an Atypical teratoid/Rhabdoid tumor.

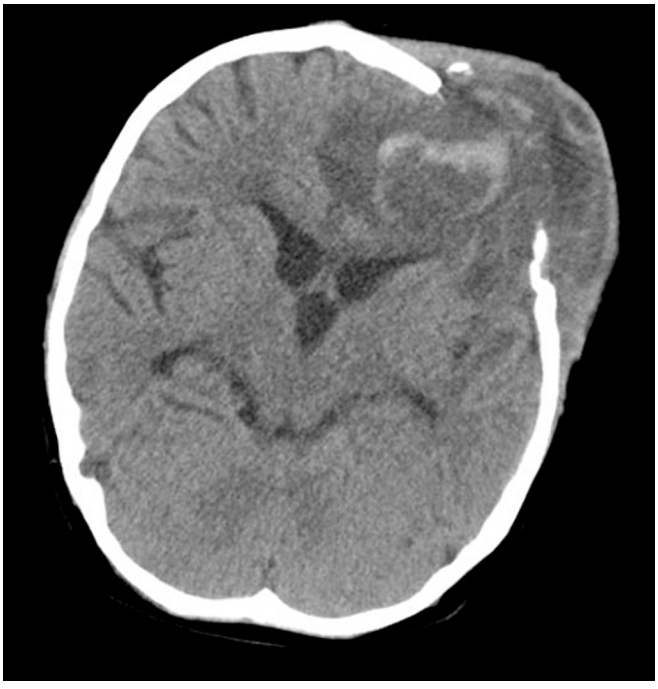

Fig. 1. Computed Tomography Scan of the head demonstrating a heterogeneous mass measuring (4 × 3)cm in the left frontal-parietal region with vasogenic edema and midline deviation.

Following surgery, the patient was put on adjuvant radiation therapy. However, two months later, the patient presented with projectile vomiting associated with photophobia, diplopia, and headache. CT scan demonstrated signs of recurrence in the site of the resected mass with vasogenic edema, and midline deviation in addition to signs of bony destruction after the aggressive surgical resection. Subsequently, the patient was put on a chemotherapy regimen consisting of vincristine, ifosfamide, doxorubicin, and etoposide. Unfortunately, the patient couldn't tolerate the treatment and she passed away six months later. The work has been reported in line with SCARE criteria [7].

2.2. Case 2

A 57-year-old female with a medical history of treated hypertension and hypertriglyceridemia presented with a one-month history of severe generalized headache unresponsive to analgesics, with numbness and tingling of the right hand. On examination, the patient was alert, responsive, and oriented. Laboratory and neurological examinations were normal with unremarkable surgical and family histories.

Magnetic Resonance Imaging MRI of the head revealed a lobulated cystic mass measuring (49 × 32 × 35) mm in the right occipitotemporal region, with surrounding edema compressing the left lateral ventricle and causing a midline shift to the left, and enlargement of the right lateral ventricle (Fig. 4). The lesion contained mixed cystic-solid content, with rim enhancement and homogenous gadolinium enhancement. Thoraciabdominopelvic CT scan was normal. Subsequently, the patient underwent subtotal surgical excision of the mass. The surgical biopsy measured (25 × 23) mm with a white-greyish color of viscous and hard pieces of tissue. Microscopic examination demonstrated large cells with abundant eosinophilic cytoplasm, and large eccentric nuclei with areas of hemorrhage (Fig. 5: A, B, C). Primary differential diagnoses included anaplastic meningioma (Grade 3) and Atypical Teratoid/ Rhabdoid Tumor. Immunohistochemical examination revealed focal positive expression of Vimentin, EMA, SMA, and CK (Fig. 5 E, F, G), whereas TTF1, Napsin A, ER, and PR were negative, favoring the diagnosis of Atypical Teratoid/Rhabdoid Tumor. INI1 testing wasn't available at our institution. Nevertheless, based on the detailed morphological examination and the classical immunohistochemical results, the diagnosis was confirmed by three histopathologists. After surgery, the patient received radiation therapy at a dose of 60 Gy in 30 fractions over 6 weeks, followed by chemotherapy using CCG-9921 regimen (vincristine, cyclophosphamide, cisplatin, and etoposide) with routine MRI monitoring. The work has been reported in line with SCARE criteria [7].

3. Discussion

Atypical Teratoid/ Rhabdoid Tumors are extremely rare aggressive neoplasms that mainly affect the pediatric population with ages younger than 3 years old and a slight male predominance [5]. However, in our cases, it was diagnosed in two female patients aged 9 and 57 years respectively. This tumor mainly originates in the posterior fossa, with a cerebellopontine angle predilection in pediatric populations. In adults, the frontal lobe represents one of the most commonly affected regions [9,10]. In our report, the cases were detected in the left frontal lobe and the occipital temporal lobe respectively.

Clinical manifestations vary according to the site of the neoplasm. The most common symptoms include vomiting, headache, lethargy, and other signs of increased intracranial pressure, similar to the symptoms of the first case. Other symptoms include ataxia, seizures, and cranial nerve palsies. Numbness of the right hand represents another symptom that was detected in our second case [9,11].

Gadolinium-enhanced MRI is considered the gold-standard method

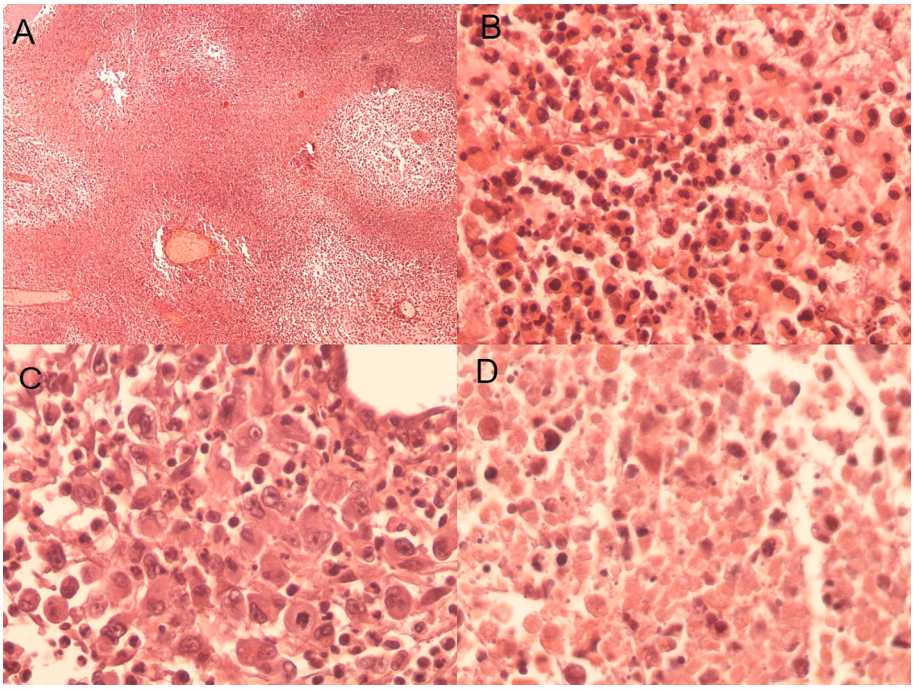

Fig. 2. A: The mass demonstrates the proliferation of medium-sized to large tumor cells (Hematoxylin and Eosin x40).
B: Histopathological examination demonstrates the proliferation of medium-sized to large cells with abundant eosinophilic cytoplasm, large vesicular eccentric nuclei (Hematoxylin and Eosin x100).
C: Histopathological examination demonstrates tumor cells with abundant eosinophilic cytoplasm, large vesicular eccentric nuclei and conspicuous nucleoli ((Hematoxylin and Eosin x400).
D: Microscopic examination demonstrating Necrosis and Hemorrhage).

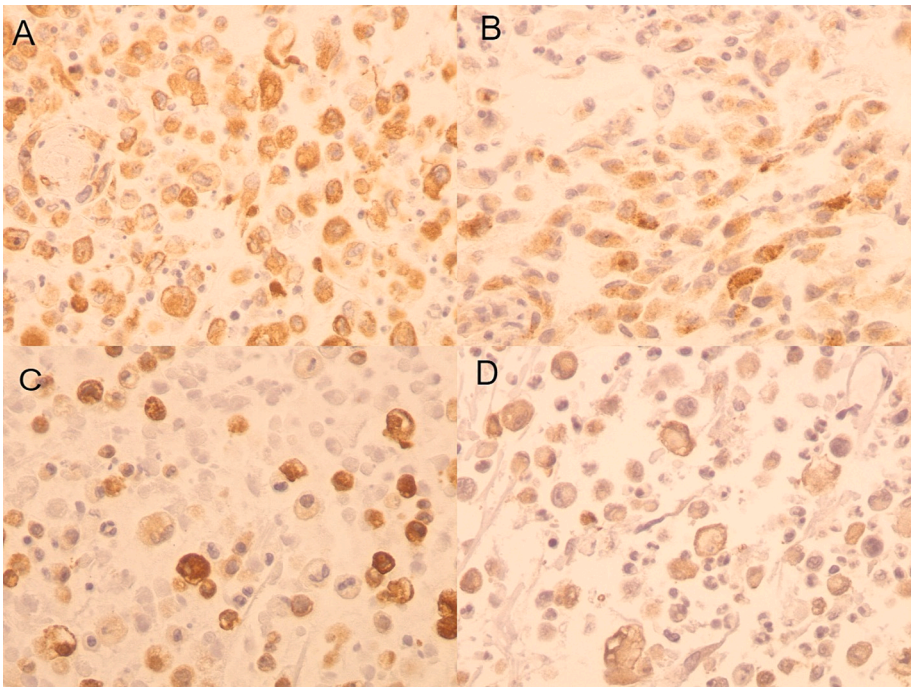

Fig. 3. Immunohistochemical results: (A: Positive expression of Vimentin, B: Positive expression of EMA, C: Positive expression of CK, D: Focal Positive expression of NSE.)

of radiologic diagnosis [12,13]. In the first case, the patient didn't undergo an MRI scan, but in the second case, the MRI revealed a lobulated cystic mass located in the right occipitotemporal region, with surrounding edema compressing the left lateral ventricle and causing a midline shift to the left, and enlargement of the right lateral ventricle. In our cases, the mass measured (4 × 3)cm in the first case and (2 × 3)cm in the second one. In the second case, MRI showed that the lesion contained mixed cystic-solid content, with rim enhancement and

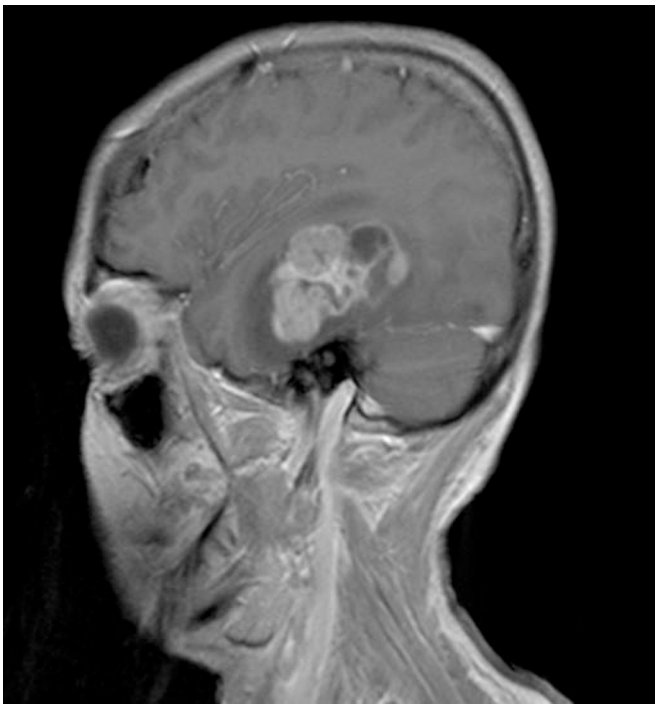

Fig. 4. Magnetic Resonance Imaging of the head revealing a lobulated cystic mass in the right occipitotemporal region, with surrounding edema and mixed cystic-solid content, with rim enhancement and homogenous gadolinium enhancement.

homogenous gadolinium enhancement.

The non-specific clinical and radiological features contribute to the challenges in reaching an accurate diagnosis. Therefore, diagnosis mainly depends on histological, immunohistochemical, and molecular features. The main differential diagnosis of AT/RT is medulloblastoma. Nevertheless, choroid plexus carcinoma, gemistocytic astrocytoma, pilocytic astrocytoma, anaplastic ependymoma, and other embryonal tumors should also be considered in the differential diagnosis [1,9].

Distinguishing AT/RT from medulloblastoma is crucial since medulloblastoma is more radiosensitive and has a better prognosis than the former. AT/RT usually presents at younger ages than medulloblastoma and mainly arises in children younger than 3 years old, whereas medulloblastoma has a higher incidence between 5 and 9 years of age, and both tumors are rarely present in adults [9,14,15]. However, our two cases of AT/RT demonstrated significant presentation in two female patients aged 9 and 57-year-old respectively.

While both tumors usually arise in the posterior fossa, medulloblastoma mostly arises from the cerebellar vermis as a midline tumor with a tendency to grow into the fourth ventricle, whereas AT/RT usually presents off-midline from the cerebellar hemispheres causing a compression of the fourth ventricle. Radiological features including heterogeneity of the lesion, calcification, intratumoral hemorrhage, cyst formation, and cerebellopontine angle (CPA) involvement favor the diagnosis of AT/RT over medulloblastoma [9,14,15]. However, histological and immunohistochemical examinations are essential to confirm the diagnosis. Histologically, the presence of the rhabdoid cells with their large size, abundant eosinophilic cytoplasm, and eccentric nuclei with hemorrhage and necrosis are the clues for the diagnosis similar to our case. And immunohistochemistry usually demonstrates positive expression of SMA, EMA, and Vimentin, GFAP. Whereas loss of expression of SMARCB1 (INI1) is considered the most sensitive immunohistochemical feature of AT/RT and plays a major role in differentiating it from medulloblastoma and other tumors. Furthermore, molecular examinations demonstrate mutation in the SMARCB1 gene or a partial deletion of chromosome 22 [14–17]. It's worth mentioning that the classical staining for Vimentin, SMA, and EMA alongside the

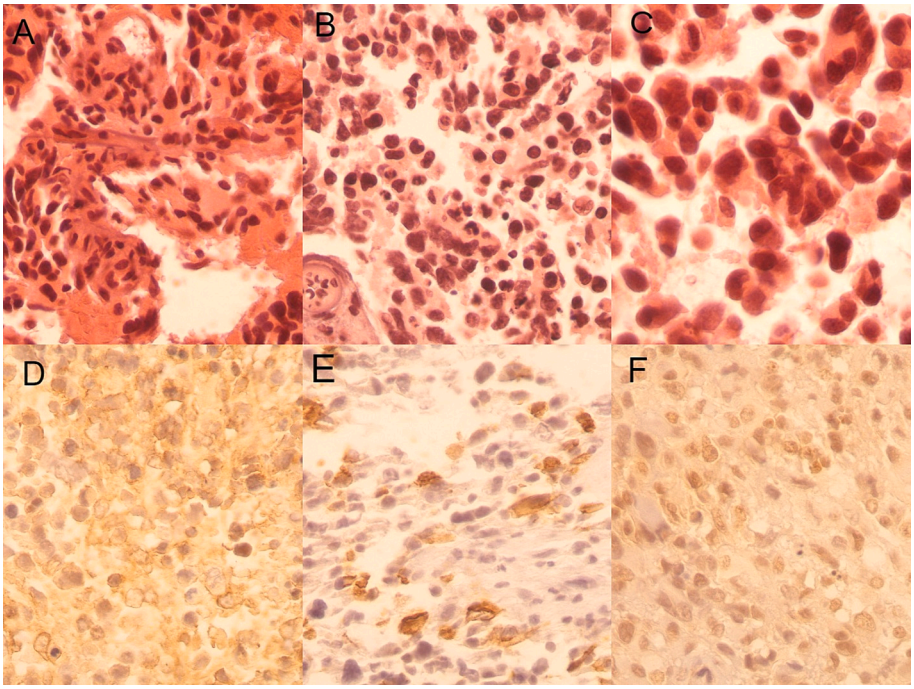

Fig. 5. A & B: Microscopic examination of the second case demonstrating the proliferation of medium-sized to large cells with abundant eosinophilic cytoplasm, and large vesicular eccentric nuclei (Hematoxylin and Eosin x200).
C: Microscopic examination demonstrating Necrosis and Hemorhage.
D: Positive IHC expression of Vimentin.
E: Positive IHC expression of EMA.
F: Positive IHC expression of SMA.

morphological features of the rhabdoid cells played a critical role in confirming the diagnosis before the advent of INI1 testing [14]. In our case, INI1 staining and molecular tests were not available due to economic restrictions, and the challenging diagnosis was built based on the classical method and confirmed by three histopathologists.

According to recent retrospective studies, most treatment regimens include surgical excision, radiation therapy, and neoadjuvant chemotherapy. Despite the rapid aggressive growth of the neoplasm, surgical resection is considered the first-line treatment due to its role in alleviating the symptoms of increased intracranial pressure and improving overall survival. Adjuvant radiotherapy is usually recommended following the surgery due to the high recurrence rate of the neoplasm. Focal radiation methods could decrease the negative effects of radiotherapy on the surrounding tissue. And in cases including children younger than 3 years old, radiotherapy could be replaced by chemotherapy [17–19].

Despite the absence of a standardized chemotherapy regimen, several studies recommended two protocols including the Intergroup Rhabdomyosarcoma III (IRS III) protocol which includes: vincristine, cisplatin, doxorubicin, cyclophosphamide, dacarbazine, etoposide, actinomycin-D, and triple intrathecal chemotherapy with methotrexate, hydrocortisone, and cytarabine. The Children's Cancer Group (CCG)-9921 protocol which was used in the second case includes (vincristine, cisplatin/carboplatin, cyclophosphamide/ifosfamide, and etoposide) [17–20].

Despite the advent of novel targeted therapy and the use of intensive multimodal regimens, AT/RT usually demonstrates poor prognosis and decreased survival rates. In our cases, both patients underwent subtotal resection of the tumor with adjuvant radiation therapy following the surgery. However, in the first case, the 9-year-old girl who was treated with the VIDE protocol experienced severe complications and died shortly after relapse. Whereas in the second case of the adult patient who was treated with the CCG-9921 protocol, the patient demonstrated a better prognosis [1,19,20]. Nevertheless, further studies are needed to investigate the potential causes of the aggressive behavior and poor prognosis of AT/RT to assess better treatment strategies.

4. Conclusion

Diagnosis of Atypical Teratoid/Rhabdoid Tumor is challenging due to the rarity of this neoplasm and the non-specific clinical and radiological features. Nevertheless, with detailed histopathological and immunohistochemical examinations, we managed to present two cases of AT/RT in two Syrian female patients, highlighting its presentation in rare age groups and the aggressive behavior of this neoplasm.

Ethical approval

Our institution does not require ethical approval for reporting case reports or case series.

Informed consent

Written informed consents was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Written informed consents was obtained from the patient's parents for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of conflicting interest

The authors declare no conflicts of interest with respect to the research, authorship, and publication of this article.

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