

Case Report

Intracranial atypical teratoma/rhabdoid tumor in adults: report of 2 cases and literature review

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Abstract: Background: Intracranial atypical teratoid/rhabdoid tumor (AT/RT) is a rare lesion in neurosurgery, and adult intracranial AT/RT is even more rare. Case presentation: The two cases described in this study were both adult females. They all presented the onset symptoms of increased intracranial hypertension, such as headaches, dizziness, nausea, and vomiting. The course of symptoms before treatment was short, with one month in one case and three months in the other case. Preoperative imaging examinations showed intracranial space-occupying lesions. Preoperative diagnosis was not clear. The lesions were surgically removed. The pathological examination and immunohistochemistry confirmed the diagnosis of AT/RT. The prognosis of the patients was poor. One patient received radiotherapy and chemotherapy and then was followed-up for 12 months. The other patient received radiochemotherapy and was lost follow-up at the 6th month after surgery. Conclusions: Histopathological changes are the main basis for diagnosis. The surgery-based individualized comprehensive treatment is the key for therapy.

Keywords: Adult, central nervous system, atypical teratoma/rhabdoid tumor

Introduction

Intracranial atypical teratoid/rhabdoid tumor (AT/RT) is a rare and highly invasive malignant tumor affecting the central nervous system [1-3]. So far, more than 200 cases have been reported internationally, and of them, only 10 cases are from China [4]. In 1987, Biggs et al [5] reported the first case of primary rhabdoid tumor of the central nervous system. Rorke et al [6] named this tumor as "AT/RT" in 1996. The AT/RT together with primitive neuroectodermal tumors and medulloblastoma were classified as a separate subtype of embryonic tumors (IV level) according to WHO in 2007 [4]. The AT/RT can occur at any age, rarely adults, most commonly in children, especially those less than 2 years of age [7, 8]. AT/RT is mostly solitary tumor that can occur on different parts of the brain. In adults, supratentorial lesions on the frontal lobe are commonly seen [9]. In children, infratentorial lesions often locate in the cerebellar hemisphere [1]. The clinical manifestations of AT/RT are usually more non-specific

with poor prognosis. Most patients died within one year [10]. In this study, two cases with intracranial AT/RT were reported. The diagnosis and treatment methods of intracranial AT/RT were discussed.

Case presentation

Case 1

A 22-year-old Han female was admitted because of headache, dizziness and nausea for 3 months and aggregating symptoms for 7 days. Routine blood tests, chest X-ray, ECG and neurology examinations were all unremarkable. CT showed hybrid density in the right temporal lobe, suggesting glioma (**Figure 1A**). MRI showed significant cystic mass on right temporal lobe, suggesting glioma or neuronal-glioma mixed tumor (**Figure 1B-D**). The patient was diagnosed as glioma preoperatively and underwent glioma resection. Biopsy of the resected tumor confirmed malignancy. The tumor was grayish yellow and soft. The size of tumor was 7 * 6 * 5

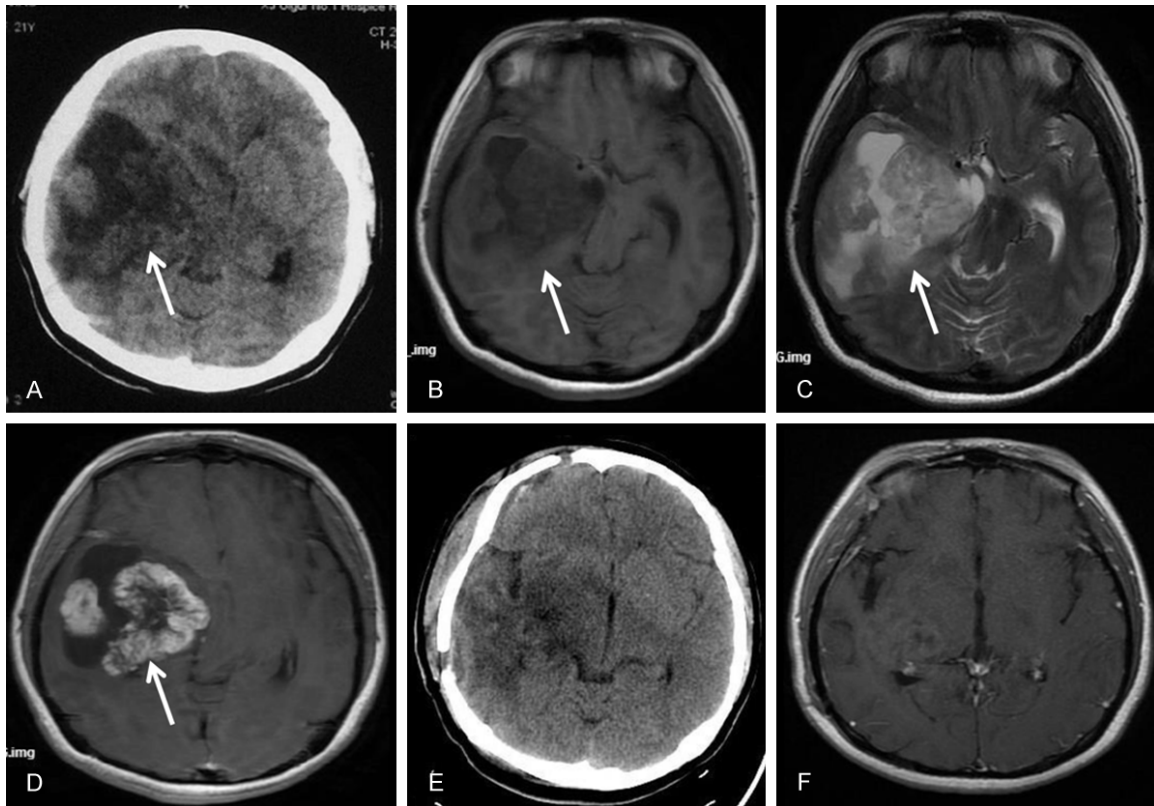


Figure 1. Case 1: CT and MRI images of patients with atypical teratoma/rhabdoid tumor before and after operation. A. Preoperative CT showed large patch of mixed density on the right temporal lobe (arrow). B. Preoperative MRI T1WI showed huge mass of mixed signal on the right temporal lobe with cystic long T1 signal (arrow). C. Preoperative MRI T2WI showed huge mass of mixed signal on right temporal lobe with cystic long T2 signal (arrow). D. Preoperative enhanced MRI showed significant lace-like enhancement, with no enhancement of the cyst (arrow). E. Postoperative CT showed slightly low density on the right temporal occipital lobe. F. Postoperative enhanced MRI (2-month) showed postoperative changes, with mild flocculent enhancement in the operation area.

cm with clear boundary and insufficient blood. The blood loss of operation was about 800 ml. Histopathological examination showed rhabdomyoid tumor cells of medium size, with oval and deviated nuclear, obvious nucleolus, and abundant cytoplasm. The interstitial spindle cells were loose arranged with some mucus changes. The embryonic small striated muscle cells with cone-shaped tail scattered among the spindle cells (**Figure 2A**). Immunohistochemistry showed GFAP (-), Ki-67 (70%), CD34 (-), AFP (-), PLAP (-), Des (-), EMA (+) (**Figure 2B**), Vim (+) (**Figure 2C**), CD99 (+) (**Figure 2D**), Syn (+) (**Figure 2E**), CK (+) (**Figure 2F**), CD117 (-), CD3 (-), CD20 (-), CD30 (-), scattered S-100 (+) (**Figure 2G**), CD38 (+/-) (**Figure 2H**), CEA (-), Myogenin (-), MPO (-), and CD43 (-). The final pathological diagnosis was AT/RT (WHO IV level). Postoperative CT showed postoperative changes in right temporal lobe with peripheral brain edema (**Figure 1E**). The patients recovered quickly and

was discharged, with alleviated symptoms (less headache and dizziness), great surgical incision healing (no infection, hemiplegia, epilepsy or recurrence of bleeding), and Glasgow Outcome Scale (GOS) score of 5. Two weeks after surgery, patients received radiotherapy and chemotherapy. The MRI at 2-month after surgery showed intracranial postoperative changes (**Figure 1F**). The patient has been followed up for 12 months via hospital visit and telephone interview, and no complications were reported.

Case 2

A 20-year-old Han female was admitted because of aggravating dizziness, nausea and vomiting for 1 month. She received surgery to resect the intracranial space-occupying lesions in a local hospital. **Figure 3A** and **3B** shows the preoperative CT and enhanced MRI images

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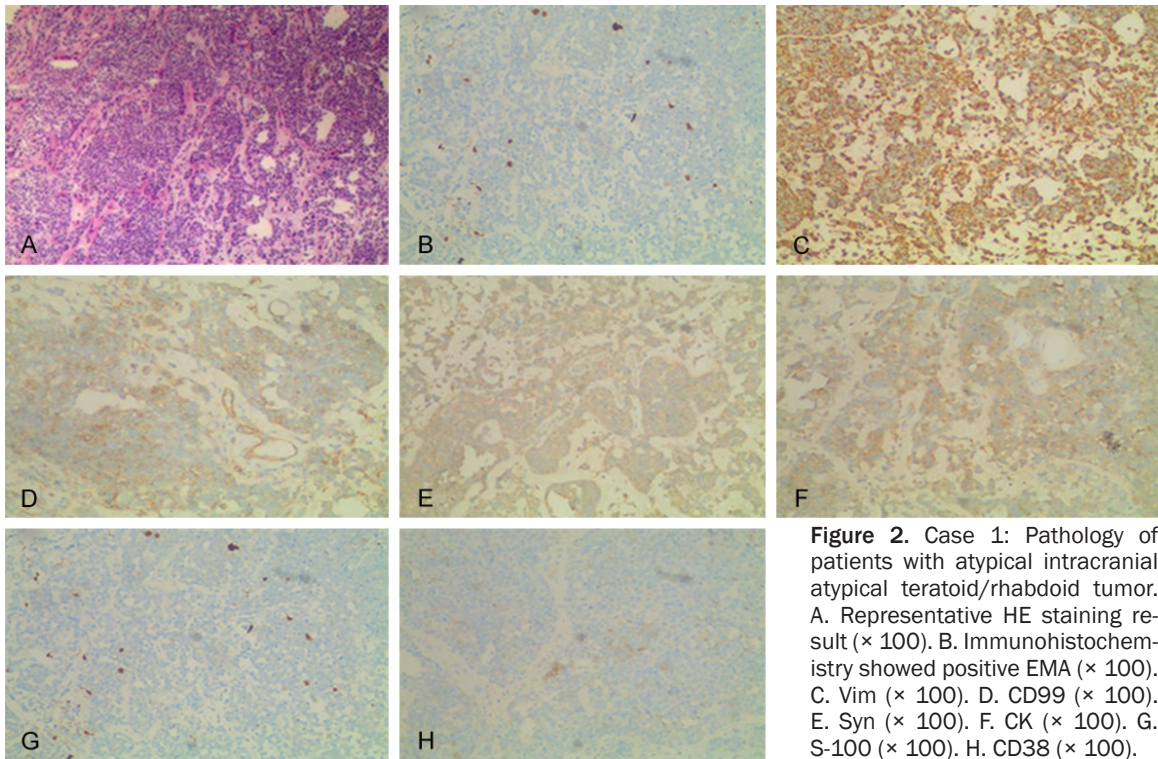


Figure 2. Case 1: Pathology of patients with atypical intracranial atypical teratoid/rhabdoid tumor. A. Representative HE staining result ($\times 100$). B. Immunohistochemistry showed positive EMA ($\times 100$). C. Vim ($\times 100$). D. CD99 ($\times 100$). E. Syn ($\times 100$). F. CK ($\times 100$). G. S-100 ($\times 100$). H. CD38 ($\times 100$).

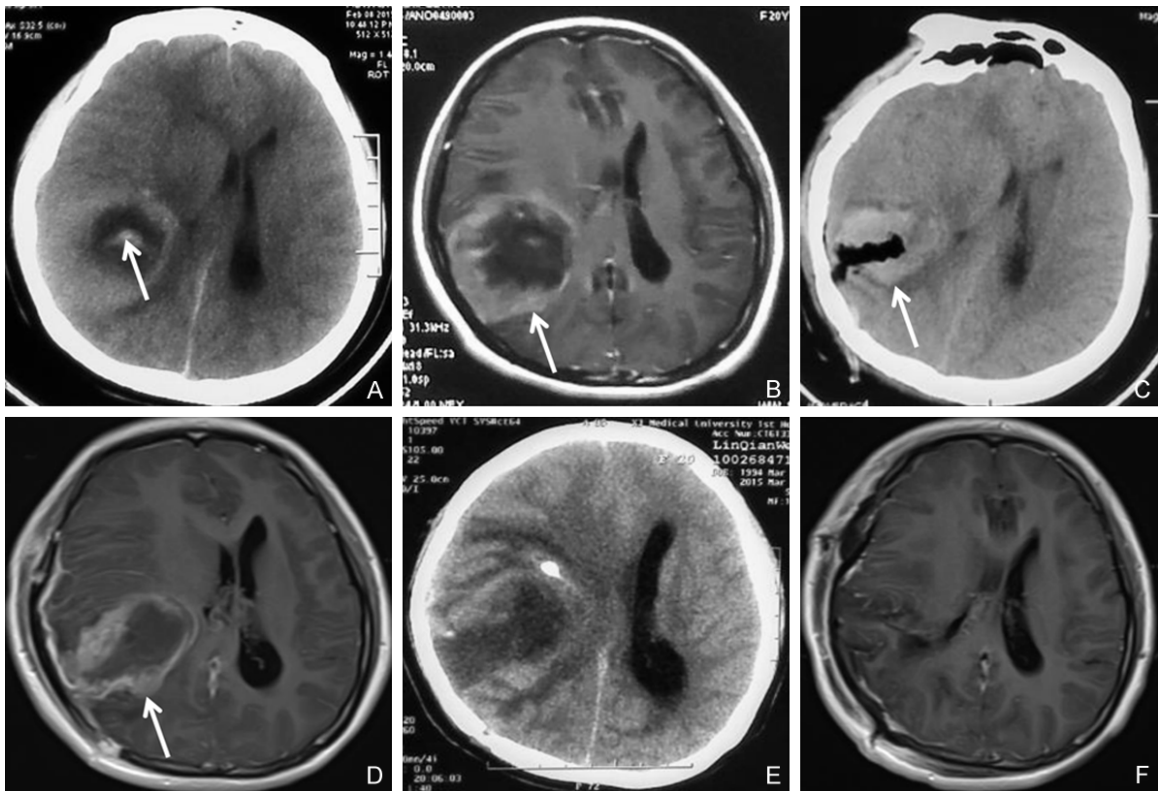


Figure 3. Case 2: CT and MRI in patients with atypical teratoma/rhabdoid tumor before and after operation. A. Preoperative CT showed large patch density on right temporal lobe (arrow). B. Preoperative enhanced MRI showed lace-like enhancement with no cystic enhancement (arrow). C. Postoperative CT showed patch density on the right temporal lobe (arrow). D. Postoperative enhanced MRI (20-day) showed significant lace-like enhancement in opera-

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tion area, without enhancement in the cyst (arrow). E. CT before the second surgery showed mixed patchy signal on the right temporal lobe. F. MRI of 48 h after the second surgery showed complete resection and no enhancement in the operation area.

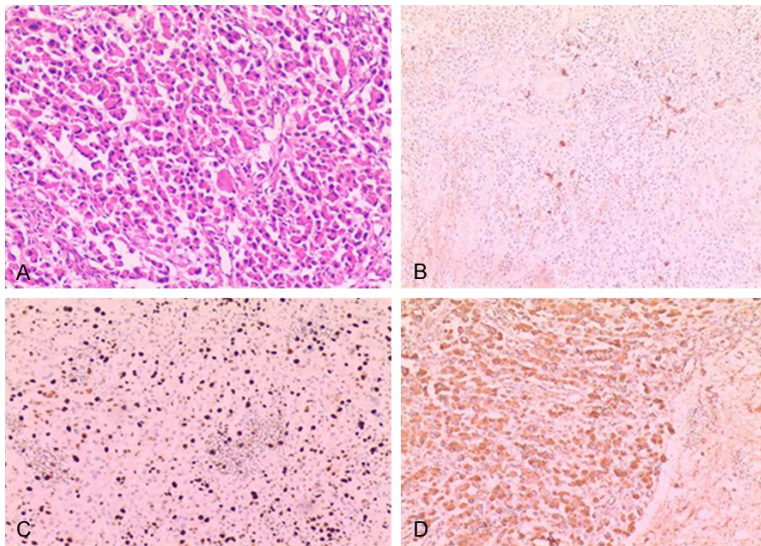


Figure 4. Case 2: Pathology of patients with atypical intracranial atypical teratoid/rhabdoid tumor. A. Representative HE staining result ($\times 100$). B. Immunohistochemistry showed positive EMA ($\times 100$). C. Ki-67 ($\times 100$). D. Vim ($\times 100$).

obtained from the local hospital, respectively. Postoperative pathological diagnosis was malignant melanoma. However, the dizziness and fatigue persisted after the surgery. Thus, she was admitted to our hospital for further treatment. The neurology examination showed level 4 muscle strength of left limb without positive signs. CT showed hybrid density with postoperative changes in the right temporal parietal lobe (**Figure 3C**). MRI showed huge cystic mass on the right temporal parietal lobe, suggesting neuron-glioma mixed tumor (**Figure 3D**). Therefore, patient was diagnosed as malignant melanoma in the right temporal parietal lobe. Then, this patient received the right temporal lobe tumor resection and skull bone decompression surgery. During surgery, it was observed that the tumor was gray and tough. The size was about $6 * 6 * 5$ cm with clear boundary and sufficient blood supply. The intraoperative bleeding was about 600 ml. Pathology showed oval rhabdomyoid tumor cells of medium size, with rich cytoplasm, mitotic feature, deviated nuclear, and obvious nucleolus. The interstitial spindle cells were loose arranged with partial mucus change (**Figure 4A**). Immunohistochemistry showed CK (-), HMB45 (-), A103 (-), GFAP (-), S100 (-),

EMA (+) (**Figure 4B**), Ki-67 (60%+) (**Figure 4C**), Des (-), Olig-2 (-), Vim (+) (**Figure 4D**), SMA (-), NF (-), MgoD1 (-), Myogenin (-). Thus, the tumor was diagnosed as AT/RT (WHO IV level). Postoperative CT showed postoperative changes on right temporal lobe with peripheral brain edema (**Figure 3E**). Postoperatively, the symptoms of dizziness and nausea significantly improved, and the patient had great surgical incision healing, left limb muscle strength of 4, secondary epilepsy, and GOS score of 4. The MRI at 48 h after surgery showed complete tumor resection with no significant enhancement (**Figure 3F**). The patient was followed up for 6 months

via hospital visit and telephone interview. Now, the patient was lost follow-up 6-month.

Discussion

AT/RT is a rare neurological malignancy and is rare in adults [1-3]. The histological morphology is difficult to distinguish from glioma and primitive neuroectodermal tumor (PNET) [11]. Final diagnosis relies on preoperative imaging, intraoperative microscopic findings, postoperative immunohistochemical staining and electron microscopy observation.

The information on the incidence of AT/RT is limited. The disease is rare in adults but common in children, especially infants and young children younger than 2 years [7, 8], accounting for 1.3% among all pediatric primary central nervous system tumors and 6.7% among central nervous system tumors of children under 2 years [7, 12-16] (**Table 1**). Common clinical manifestations are headache, vomiting, drowsiness, epilepsy, vision loss and mental disorders [1, 2]. In this study, the two patients both experienced headache, dizziness and nausea. The main cause of death is tumor recurrence

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Table 1. Characteristics of adult pure AT/RT cases, including demographics, immunochemistry staining, treatment and outcome

Author	Age/ y	Gender	Compartment	Location	Vim	EMA	INI/ BAF47	MS 22	RT	CT	Surgical options	Status/ months
Our case	22	F	Supratentorial	Right temporal iobe	P	P	NA	NA	Y	Y	GTR	Dead/12
Our case	20	F	Supratentorial	Right temporal iobe	P	P	NA	NA	Y	Y	GTR	Alive/ 6
Kuge A [12]	20	F	Supratentorial	Pineal gland	P	P	N	NA	Y	NO	Bx	Dead/27
Han [37]	25	M	Supratentorial	Left parieto-occipital lobes	P	P	NA	N	Y	Y	GTR	Dead/25
Han [37]	24	M	Supratentorial	Right temporo-occipital lobes	P	P	NA	N	Y	Y	GTR	Dead/10
Samaras [13]	18	M	Supratentorial	Right fronto-temporal area	P	P	N	P	Y	NO	GTR	Dead/4
Makuria [14]	23	M	Supratentorial	Left temporal lobe	P	P	N	NA	Y	Y	GTR	Alive/30
Makuria [14]	25	F	Supratentorial	Right frontal lobe	P	N	N	NA	Y	Y	GTR	Alive/17 y
Raisanen [15]	20	F	Supratentorial	Sellar region	P	P	N	Yes	Y	Y	Resection	Alive/28
Erickson [16]	20	F	Supratentorial	Right occipital lobe	P	P	NA	N	NA	NA	GTR	Alive

Note: M = male; F = female; y = year; Vim = vimentin; P = positive; N = negative; NA = not available; MS22 = monosomy 22; RT = radiotherapy. CT = chemotherapy; TMZ = temozolomide; SURG = surgery; GTR = gross total resection; STR = sub-total resection; PR = partial resection.

and metastasis, and bone is the most common target organ of external metastasis [10]. Adult patients have slightly better prognosis, occasionally long-term survival, and the longest survival period has been reported as 6 years [17].

There has been significant development in the etiology and pathogenesis of AT/RT, especially in the molecular genetics. It has been shown that most AT/RTs have deletions in chromosome 22, or inactivation of the hSNF/INI1 gene and loss of nucleus INI protein expression [18, 19]. The mouse knockout model showed that INI1 was a tumor suppressor gene of AT/RT [20]. Study also found that patients with germline mutations of remodeling gene INI1/hSNF5/BAF47/SMARCB1 on 22q11.2 chromatin were susceptible to malignant rhabdomyoid tumors in kidney and soft tissues and AT/RT in central nervous system [21]. The disease often progresses into malignant lesions within 1 year with familial inheritance [21]. INI1 protein has great value in differential diagnosis and the antibodies of INI1 protein have been clinically used to identify AT/RT and other types of brain tumors in children [22]. The origins of AT/RT have been proposed as the histological, histiocytic, neuroepithelial, meningogenic, and germ cell origins [21, 23, 24]. However, there is no definite conclusion and further studies are needed.

The imaging findings of AT/RT lack specificity [25]. Plain CT scans usually show high density and calcification of the tumor with heterogeneous enhancement and visible cystic changes of supratentorial lesions [26]. The incidence of tumor calcifications has been reported hetero-

geneously [26]. The change of signal intensity is high on plain and enhanced MRI, but is usually equal or low on T1WI, equal or high on T2WI. The tumor margin is clear and the edema and mass effect are different. Tumor edges are marginally enhanced with central capsule or necrosis, or partial band-like enhancement [27]. It is reported that the ring-like enhancement is the more characteristic manifestation [1]. The dispersion value of the tumor is limited on the DWI, low on the solid parts, and high on the necrosis and cystic parts. DWI can distinguish the solid components from the cystic or necrotic components of the tumor. When subarachnoid metastasis occurs, the border of cerebellar and cerebellar lobes is blurred, and the scans are streaky or nodular strengthened. MRI features mainly include equal or low signal on T1WI. One case had high signal bleeding with uneven high signal on T2WI and heterogeneity on enhancement [28]. In this study, the preoperative CT of 2 cases showed heterogeneous enhancement without calcifications on the right temporal lobe. MRI scan showed lumpy and cystic mixed long T1 long T2 signal, with high signal on TWI, high signal edema in the perifocal area, and slightly high signal on diffuse sequence. MRI enhancement scan showed lace-like enhancement, without enhancement on cystic part. The above presentations reported in this study are in accordance with literature.

The pathology of AT/RT was complicated. Gross pathology shows bleeding, necrosis and unclear boundary with surrounding brain tissue. The tumor components are complex and diverse on microscope with multi-directional differ-

entiation and multifocal characteristics [29]. Part or all of the tumor is composed of rhabdomyoid cells, typically medium-sized, polygonal or round, nested or peripheral vascular radial arranged, rich cytoplasm, deviated nuclear, obvious nucleolus, and rich nuclear division, and multinucleated variants of rhabdomyoid-like cells [23, 24]. It has been shown that 15% of the tumors contain only rhabdomyoid cells, 2/3 of the tumors mainly compose of embryonic small cells, and 1/4 of the tumors consist of tumor-like epithelial cells, presenting as adenoid, squamous cell-like or arranged in nest [22]. Rhabdomyoid-like cells are the main basis for the diagnosis of AT/RT, however, only small number of AT/RT show the typical rhabdomyoid presentations. Most of the AT/RT lesions cannot be differentiated from PNET under light microscopy [30]. AT/RT has a variety of immunohistochemical characteristics, including positive vimentin, EMA, CKpan, GFAP, SMA, NF, CK, and Syn expressions, and negative germ cell markers such as PLAP and CD117 [31]. The immunohistochemical characteristics of PNET can help the differentiation. In the present study, the immunohistochemical staining results of 2 patients are consistent with previous reports, suggesting the diagnosis of AT/RT.

The first-line intracranial AT/RT treatment is still surgery, along with adjuvant chemotherapy and radiotherapy to prolong the survival. There is no uniform standard for radiotherapy dose and chemotherapy regimen. It has been proposed that the tumor survival is not related with surgical methods or adjuvant therapy [32]; however, high-dose chemotherapy and local radiotherapy can prolong survival time of patients [33]. Wang et al [34] showed that the complete tumor resection may not affect patient's survival, however, postoperative radiotherapy and chemotherapy can prolong survival, compared with chemotherapy alone. There are also reports of intrathecal chemotherapy, bone marrow or peripheral blood stem cell therapy for AT/RT, with heterogeneous efficacy [35, 36]. The prognosis of patients with AT/RT depends on treatment methods, age, tumor location and tumor size. However, the exact relationship of prognosis with tumor location, size and age is unclear [34]. Despite aggressive treatment, the prognosis remained poor. Children typically die within 7 months after diagnosis and the average survival time is approximately 26 months

for adults [37]. Our study showed that 1 patient received postoperative adjuvant chemoradiotherapy and survived for 12 months. The other patient lost follow-up 6 months after surgery.

In conclusion, the diagnosis and treatment intracranial AT/RT is difficult due to its rarity, high malignancy, aggressiveness, rapid growth, poor prognosis, and non-specific imaging presentations. The preoperative diagnosis rate is low. Although pathological changes are the gold standard for diagnosis, comprehensive information on clinical, imaging, pathology and genetic examinations can improve the diagnosis rate. Surgery, adjuvant radiotherapy and chemotherapy should be individualized to improve the survival and understanding of this disease.

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Disclosure of conflict of interest

None.

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