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Original Article

Primary atypical teratoid/rhabdoid tumor of central nervous system in children: a clinicopathological analysis and review of literature in China

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Abstract: Atypical teratoid/rhabdoid tumor (AT/RT) is a very rare and highly malignant embryonal tumor in the central nervous system (CNS). Five patients (4 girls and 1 boy) with AT/RT were treated in our hospital. The clinical histories, symptoms, neuroimaging aspects, therapies, histological and immunohistochemical findings and follow-up information were reviewed. The patients ranged from 8 to 40 months with a mean age of 20.6 months. One tumor was located in the spinal cord, two in cerebellum and two in the pineal region. The imagings of the tumors resemble medulloblastomas. Pathological examinations showed that one patient had medulloblastoma differentiation, one had choroid plexus carcinoma differentiation, and one had mesenchymal components. Immunohistochemical staining showed that all of the tumors lost the nuclear expression of integrase interactor 1 (INI1), and were positive for Vimentin, S-100 protein and epithelial membrane antigen. One case with no recurrence after 24 months may have benefited from radical excision and postoperative radiotherapy. The other 4 patients died 8, 4, 1 and 1-month respectively after operation without radiotherapy. The diagnosis of AT/RT depends on full sampling, careful observation the morphological characteristics and INI1 examination, even when the tumor are presented in uncommon sites, such as the spinal cord and the pineal region.

Keywords: Atypical teratoid/rhabdoid tumor, integrase interactor 1, spinal cord, pineal gland, cerebellum

Introduction

Atypical teratoid/rhabdoid tumor (AT/RT) is a very rare and highly malignant embryonal tumor in the central nervous system (CNS). It was defined in 1996 by Roker [1] and was introduced to the WHO brain tumor classification in 2000 [2]. Histopathologically, AT/RT is characterized by rhabdoid tumor cells, which have vesicular nuclei, large nucleoli, and cytoplasmic filamentous inclusions. There were or no various areas such as primitive neuroectodermal, epithelial, and mesenchymal differentiation [3]. It is difficult yet important to differentiate AT/RT from other malignant CNS tumors since it has a complex morphology. Also, many CNS tumors have rhabdoid cells, and the prognosis of AT/RT is extremely dismal compared with other CNS tumors. The number of diagnosed AT/RT patients is increasing because of the improved understanding towards the pathological and immunohistological characteristics of the tumor, especially after the identification of SMARCB1/INI1 (Integrase interactor 1) as the biological marker. In this study, we presented the clinical, MRI, pathological and immunohistochemical features of 5 patients with AT/RTs that located in the spinal cord, pineal region and cerebellum.

Materials and methods

Here we reported five patients with CNS AT/RTs who were treated surgically in our hospital between January 2008 and December 2012. The clinical features, neuroimaging findings, pathology, therapy and follow-up were reviewed.

Pathology and immunohistochemistry

The excised tumor tissues were fixed with 10% buffered neutral formalin and processed for

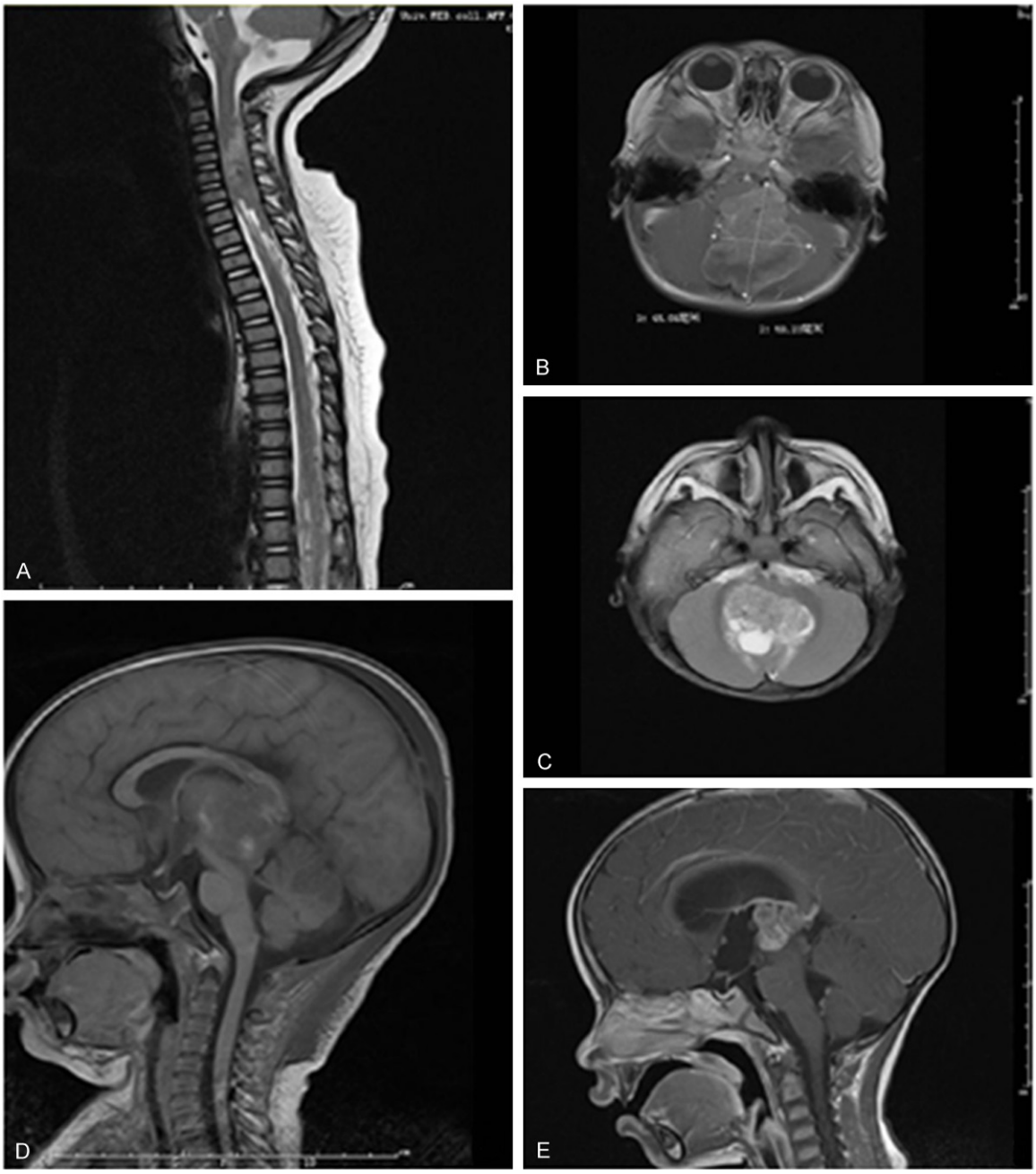

Figure 1. Magnetic resonance images of atypical teratoid/rhabdoid tumor. A: T1-weighted midline sagittal image from case #1 shows an intramedullary tumor of C2-T2. B: T2-weighted image from case #2 demonstrates abnormal signal in the cerebellum and relative intermediate signal intensity of the lesion. C: T1-weighted image from case #3 shows Cerebellar mass and enhance with contrast. D and E: Images of brain from case #4, #5 show an intermediate signal intensity tumor respectively on the pineal and protruding into the ventricular lumen.

paraffin embedding and sectioning. Sections were stained with hematoxylin and eosin for routine histological evaluation. Immunohistochemistry was performed on sections by using the streptavidin-peroxidase system (Ultrasensitive; MaiXin Inc., Fuzhou, China) according to the manufacturer's manual. Antibodies used include INI1 (BD Biosciences, San Jose, CA, USA), vimentin (Vim, V-9, Merck), epithelial membrane antigen (EMA, E29, Merck), desmin (Des, DE-B-5, Merck), smooth muscle actin (SMA, DE-B-5, Merck), actin (Act, HHF35, Merck), cytokeratin (CK, AE1/AE3, Merck), glial fibrillary acidic protein (GFAP, Merck), S-100

Table 1. Clinical features, imaging findings and therapy in five cases of AT/RTs

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (months)	8	23	15	17	40
Gender	Female	Female	Male	Female	Female
Clinical symptom	Progressive Limbs limply	Weak spirit, Reluctant to move, vomiting	Vomiting, twitching	Drowsiness, vomiting, coma	Headache, vomiting
Tumor site	C2-T2 spinal cord	Cerebellar vermis	Cerebellum	Pineal gland	Pineal gland
Size (cm)	2.0 × 2.0 × 1.0	5.9 × 4.6 × 4.8	4.4 × 3.2 × 2.9	3.1 × 4.2 × 3.9	2.2 × 2.0 × 2.5
Tumor margin	Ill-defined	Well-defined	Ill-defined	Ill-defined	Ill-defined
CT/MRI homogeneity	Heterogeneous	Heterogeneous, partly cystic degeneration	Heterogeneous	Heterogeneous	Heterogeneous
CT/MRI constrast enhancement	Heterogeneous	Heterogeneous	Heterogeneous	Heterogeneous	Heterogeneous
Imaging diagnosis	Occupying lesions in spinal cord	Medulloblastoma	Medulloblastoma	Germ cell tumor	Germ cell tumor
Metastases	None	None	None	None	None
Surgical resection	Subtotal, a few residue	Complete	Partly excision	Complete	Partly excision
Radiotherapy	None	CSI 25 times	None	None	None
Follow-up	One month died after operation	24 months Survived after operation	One month died after operation	Eight months died after operation	Four months died after operation

CSI: craniospinal axis irradiation.

(1B2, Merck), CD99 (12E7, Dako), neuron-specific enolase (NSE, NC/VI-H14, Merck), synaptophysin (Syn, 27G12, Merck), placental alkaline phosphatase (PALP, RAB-0108, Maixin) and Ki-67 (MIB1, Dako).

Results

Clinical features and imaging findings

A total of 90 patients of pediatric CNS tumors were confirmed by pathological examinations in our hospital from January 2008 to December 2012. AT/RT accounted for 5.56% (5/90) of them. Of the 5 patients, 4 were girls and 1 was a boy, age ranged from 8-40 months, with mean of 20.6 months. One tumor was located in the cervical spine, two were located in pineal region, and two were located in cerebellum. The diameter of tumors ranged from 2.0-5.9 cm, with average 3.8 cm. The most common symptoms included vomiting and lethargy according to patients' age and the location of tumors. The imaging of the tumors resembled medulloblastomas, and CT scan revealed that the tumors were heterogeneous. MRI (**Figure 1A-E**) showed the hyperintense on T1-weighted images and equal or hyperintense on T2-weighted images, and pronouced enhancement after using MR contrast agent (Omniscan).

One tumor was resected completely and subjected to postoperative radiotherapy, and survived after 24 months. In other patients without radiotherapy, two were dead 8, 4 months after operation respectively, and two patients died one month after surgery because of poor physical status.

The clinical features, imaging findings, therapy and follow-up of the five patients of AT/RTs are presented in **Table 1**.

Pathological examination

Grossly, the tumors have tender fish flesh-like appearance, similar to medulloblastoma, hemorrhage, and necrosis in all of them and partially cystic in one tumor.

Microscopically, the most tumor cells were medium sized, round or ovoid, had a large and eccentric vesicular nucleus and abundant cytoplasm, mitotic cells are common. There were prominent nucleoli in 4 of the tumors, and infiltrative growth and necrosis could be found in all cases. In Case 1, the atypical cells with dark nucleus diffusely distributed in myxoid stroma in some regions of the tumor. The tumor cells were very large and atypical oval nuclei with vesicular chromatin and prominent nucleoli. A few cells were strongly eosinophilic cytoplasm with eccentric nuclei (**Figure 2A**), focal necrosis, a small amount mature ganglion cells in the tumor margin. Case 2 displayed tumor cells with a sheet-like pattern of growth, vesicular chromatin, and prominent nucleoli. A few cells were eosinophilic and abundant cytoplasm with

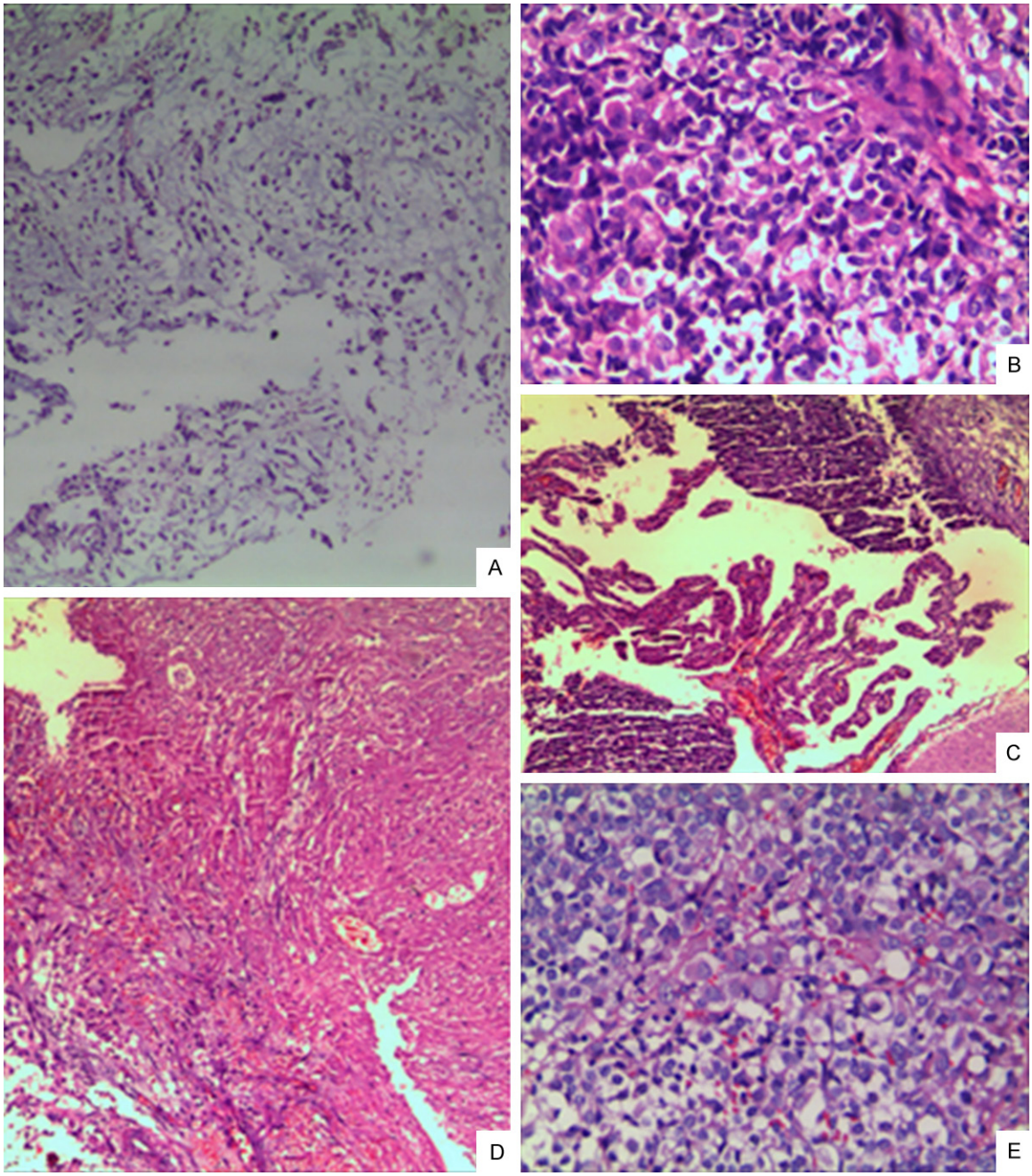

Figure 2. Sections from case #1-5 stained with hematoxylin and eosin (A-E). (A) Case 1. The atypical cells with dark nucleus diffuse distributed in myxoid stroma in some regions of the tumor. (B) Case 2. Tumor cells with a sheet-like pattern of growth, vesicular chromatin, prominent nucleoli. A few cells were eosinophilic plenty cytoplasm with eccentric nuclei. (C) Case 3. There were some papillary structures in some regions of the tumor. (D) Case 4. The mesenchymal component with short spindle tumor cells, focal myxoid stroma in some regions of the tumor. (E) Case 5. The tumor cells were very large and atypical oval nuclei with vesicular chromatin and prominent nucleoli. A few cells were eosinophilic plenty cytoplasm with eccentric nuclei. A few cells were of clear cytoplasm. Original magnification: × 100 (A), × 200 (B), × 100 (C), × 100 (D), × 200 (E).

eccentric nuclei (**Figure 2B**). Case 3 showed that tumor cells are diffusely distributed or in a dense perivascular arrangement, part of them with papillary pattern, which was similar to choroid plexus carcinoma differentiation (**Figure 2C**). Case 4 had mesenchymal component, it showed short spindle tumor cells (**Figure 2D**), some structure like neural tube was seldomly

Table 2. Pathological findings in five cases of AT/RTs

	Case 1	Case 2	Case 3	Case 4	Case 5
Pathological finding					
Grossly	Fish-flesh	Fish-flesh	Fish-flesh	Fish-flesh	Fish-flesh
Necrosis, hemorrhage	Yes	Yes	Yes	Yes	Yes
Mitoses	Yes	Yes	Yes	Yes	Yes
Rhabdoid cells	Yes	A few and atypical	Yes	Yes but atypical	Yes
Primitive neuroectodermal tumor/medulloblastoma	None	yes	None	None	None
Papillary/epithelial component	Epithelial cells	None	Papillary component	None	None
Sarcomatoid/Mesenchymal component	None	None	None	None	Yes

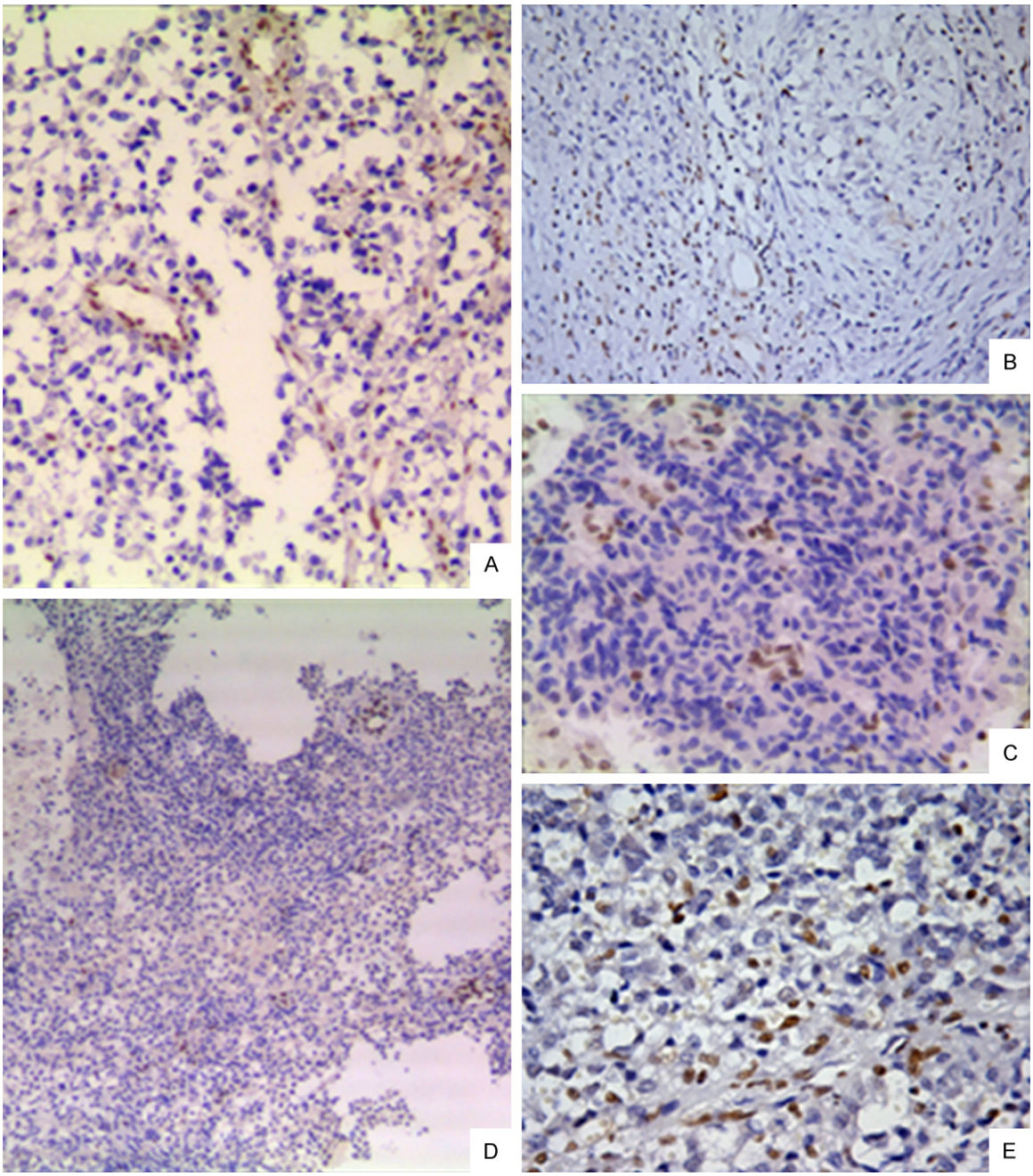

Figure 3. IHC from cases 1-5 (A-E) stained for SMARCB1/INI1. SMARCB1/INI1 reactivity is absent in tumor cells but retained in endothelial cells and infiltrating inflammatory cells. Original magnifications, ×100 (A), × 200 (B), × 200 (C), × 40 (D), × 200 (E).

Table 3. Immunohistochemical staining in five cases of AT/RTs

Case	INI1	Vim	EMA	GFAP	SMA	S-100	CK	Syn	NSE	CD99	Des	Act	PALP
1	-	+	+	-	+	+	+	-	-	-	-	-	-
2	-	+	+	+	+	+	+	-	-	-	-	-	-
3	-	+	+	+	-	+	-	-	-	-	-	-	-
4	-	+	+	+	+	+	-	+	-	-	-	-	-
5	-	+	+	+	-	+	+	-	-	-	-	-	-

INI1: integrase interactor 1; Vim: Vimentin, EMA: epithelial membrane antigen, GFAP: glial fibrillary acidic protein; SMA: smooth muscle actin; CK: Cytokeratin; Syn: Synaptophysin; NSE: Neuron-specific enolase; Des: Desmin; Act: Actin; PALP: Placental Alkaline Phosphatase.

Table 4. Summary of the clinicopathological features of AT/RTs in Chinese literature

	Clinicopathological data	
Age	24/60 (38.7%) ≤ 5-year-old; 19/60 (30.4%) ≥ 18-year-old	
Location	Supratentorial	48/60 (77.4%)
	Infratentorial	8/60 (12.9%)
	Spinal cord	2/60 (3.2%)
	Pineal region	2/60 (3.2%)
Pathological findings	Rhabdoid cells	100%, 11.1% only composed of rhabdoid cells
	PNET/MB	50%
	Epithelial component	47%, but has no typical adenoid structure or squamous epithelial nests
	Mesenchymal component	25%
Follow-up		Ranged from 1 to 59 months, 77.8% (21/27) patients' survival were less than 1 year; 90.5% (21/23) below 5 years old were dead in one year

noted. In case 5, a few cells were eosinophilic plenty cytoplasm with eccentric nuclei. A few tumor cells were clear cytoplasm like some germ cell tumors. The cells were very large and atypical oval nuclei with vesicular chromatin and prominent nucleoli (**Figure 2E**). The histological features are summarized in **Table 2**.

Immunohistochemical staining showed that the tumor cells lost nuclear expression of INI1 in all patients (**Figure 3A**), the Vim (**Figure 3B**), EMA (**Figure 3C**), S-100 (**Figure 3D**) positive expression in all patients, GEAP (**Figure 3E**) positive expression in 4 patients, CK, SMA positive expression in 3 patients, CD99, Desmin negative expression in all patients. The results of immunohistochemical staining are listed in **Table 3**.

Discussion

AT/RT (WHO grade IV) are rare and highly malignant CNS tumor that mostly afflicts children younger than 3 years. According to recent epidemiological data collected during 1996-2006 in Austria, for the pediatric population below the age of 14, AT/RT was the sixth most common pediatric CNS tumor (6.1%, 19/311) [4]. In China, the first patient of AT/RT was reported in 1997, and the number of the diagnosed patients has increased after 2006. The incidence of AT/RT is rising because of improvement in diagnostic imaging, histopathology and immunohistology, specifically introduction of the marker INI1 [5]. From 2008 to 2012 in our hospital, there were 5 patients of AT/RT among 90 patients with CNS tumor (5.56%) who were less than age of 15.

According to reports, AT/RT may locate anywhere in the CNS, about 52% of them were found in supratentorial brain, 40% in infratentorial brain, other less sites include the pineal gland (5%) and the spinal cord (2%) [6]. In our series, one was located in the cervical spine, 2 were located in the pineal gland, 2 were located in the cerebellum. The former 2 sites (pineal gland and spinal cord) were very rare. In Chinese literature, only one tumor was located the spinal cord [7], but no AT/RT in the pineal gland has ever been previously reported. We reviewed the published cases in the literature since 1997 in China, including 4 papers in English [8-12] and 34 papers in Chinese [13], and compared the data with English literature of other countries. There were 60 patients in

China after eliminating repetitive cases. We found there were a few differences about the age and locations of tumors between Chinese and English literature, as well as a few morphological differences (the summary of Chinese literature was presented in **Table 4**). To summarize the correlation with the patient's age and the tumor location, we found the AT/RT of 0-4 years old children more commonly occured in the infratentorial region, while those in ≥ 5-year-old children were more commonly found in the supratentorial region, especially in ≥ 15-year-old patients, from the review of both Chinese literature and German literature [14]. The patients were usually ≥ 5 years old in Chinese literature, according to these reported cases. But whether the differences of ages, locations and morphology are affected by geography, environment and dietary factors, genetic polymorphism, ethnic differences in the domestic and foreign population, and whether the differences of morphology related to location and age. These questions remain to be further investigated.

AT/RT is the particular malignant rhabdomyoid tumor in CNS, with complicated histopathologic morphology and immunophenotype. There are rhabdoid cells in almost all patients of AT/RT; however, some were lack typical rhabdoid cells [15]. The tumor typically contains rhabdoid cells, with or without various components like primitive neuroectodermal, epithelial and mesenchymal components etc. Some patients may be misdiagnosed as choroid plexus tumors (CPC) [16], or accompanied by ependymoblastic differentiation [17]. Rhabdoid cells can be found in a variety of CNS tumors, such as PNET [18], medulloblastoma [19], meningeoma, glioma etc. It is difficult to differentiate AT/RTs histological from other CNS tumors. The morphological appearance of our patients very varied. All of them contained rhabdoid cells, 2 patients had myxoid mesenchymal components, 1 patient had primitive neuroectodermal component resembling medulloblastoma, one patient had papillary component resembling CPC.

Immunohistochemical staining showed that AT/RTs are consistently negative for INI1, consistently positive for vimentin (100%), EMA (91-100%), GEAP (73-100%), SMA (50-97%), CK (64-66%), S-100 (50-82%), NF (27-38%), and Desmin (9-27%) [1, 15, 20]. All AT/RTs are consistently negative for germ cell markers such as PLAP and HCG [1]. In our patients, all of them were Vim, EMA, S-100 positive expression, and without nuclear expression of INI1. CD99, Desmin, PLAP were negative expression, GFAP was positive expression in 4 patients, CK and SMA were positive expression in 3 patients.

Besides presence of rhabdoid cells, the lack of nuclear INI1 expression is the most important prerequisite to secure the diagnosis [3, 20]. Immunohistochemical INI1 protein analysis should be routinely performed in all CNS tumors. Alterations of INI1 have been documented in the majority of CNS AT/RTs [21], usually as an important marker to distinguish from other CNS tumors. But in rhadoid tumor predisposition syndrome (RTPS), due to SMARCB1 (hSNF5/INI1) mutations, individuals may also develop CPC, medulloblastoma, and CNS PNETs [21]. And more and more literature suggested that INI1 appears to function as an important tumor suppressor gene [22-29].

In addition, Hasselblatt [30] reported a case of AT/RT without deletion of SMARCB1/INI1 by immunohistochemical and genetic testing, but another SMARCA4 gene in the SWI/SNF chromatin remodeling complex was mutated with loss of protein expression. Miller [31] proposed that there is a subtype of PNET which has INI1 deletion, without typical rhabdoid cells, and immunohistochemical phenotype (Vim+/EMA-), but treatment and prognosis judgment of the tumor should be based on the AT/RT. Therefore, the AT/RT diagnosis needs to be combined with the morphology, immunohistochemical staining and genetic test of INI1, even other hSWI/SNF components.

The tumor of spinal cord in our patients must be distinguished from poorly differentiated chordomas. There was a background of myxoid matrix in both tumors, and overlap of immunohistochemical findings, such as negative expression of INI1, but several rhabdoid cells can be found in AT/RT by careful observation. AT/RT patients are usually less than 3 years of age, and the patient of our series is a 10-month-old baby, but the poorly differentiated chordomas are more commonly found in children older than three years old. The tumor with papillary component in our patients needs to be differentiated from CPC. The rhabdoid cells can be found in this patient and the age of patient was 15 months. The tumors (cases 3, 4) had a few

rhabdoid cells or atypical ones, and all of this series of tumors could be diagnosed as AT/RT based on immunohistochemical stain (positive Vim, EMA and GFAP but typically negative INI1).

The multiple therapeutic strategies for AT/RT include radical resection of tumor, radiotherapy and systemic chemotherapy. But the prognosis for patients with AT/RT is still dismal, and the median survival time ranges from 1 month to 46 months [32, 33]. Some research presented the younger patients may derive even more survival benefit from intensive chemotherapy and initial radiotherapy [34, 35]. In our study, one patient's tumor was resected completely and subjected to postoperative radiotherapy and survived 24-mon after operation. Other patients did not receive radiotherapy. Two patients died after 8 and 4 months after operation respectively, and two died 1 month after operation because of bad physical status. Therefore complete removal of the tumor and early postoperative radiotherapy may improve the survival of patients, and close follow-up is necessary to ensure that there is no sign of recurrence and metastasis.

In summary, the AT/RT is confirmed by full sampling, careful observation the morphological characteristics. Whether or not there are rhabdoid cells within the tumor, INI1 should be examined by immunohistochemical stain or cytogenetic mutations exam, even the other SWI/SNF component in order to make the diagnosis. The deletion INI1 of CNS malignant tumor can be as a marker of molecular subtype, and the treatment and judgment of prognosis according to the AT/RT. Along with better understanding on INI1 gene and SWI/SNF complex variation, the relationship between the INI1 or SWI/SNF complex and tumors will be better understood, which may lead to discovery targeted therapeutic strategies.

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Disclosure of conflict of interest

None.

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