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Atypical teratoid/rhabdoid tumours: clinicopathological characteristics, prognostic factors and outcomes of 22 children from 2010 to 2015 in China

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Summary

Atypical teratoid/rhabdoid tumours (AT/RTs) are rare, highly malignant tumours of the central nervous system (CNS) with poor prognosis that usually affect young children. The aim of this study was to assess the clinicopathological features and prognostic factors of AT/RTs. Here, we describe the clinicopathological and immunohistochemical characteristics, along with the treatments and outcomes, of 22 patients with AT/RTs treated in our hospital from 2010 to 2015. Morphologically, cytoplasmic vacuoles, the most common characteristic in our cases, were observed in 68% of the cases. Similarly, vesicular nuclei were detected in 68% of the cases. However, rhabdoid cells were found in only 59.1% of the cases and were not observed in 40.9% of the cases. Immunohistochemical analysis revealed loss of nuclear INI1 expression in all 22 cases. Age, surgical resection and adjuvant therapy, but not tumour location, were associated with AT/RTs patient prognosis. Our results showed that cells with cytoplasmic vacuoles or with vesicular nuclei are more common than rhabdoid cells in patients with AT/RTs and that a lack of INI1 protein expression is the most useful marker for the differential diagnosis of AT/RTs. Young age is a negative prognostic factor, whereas gross total surgical resection and adjuvant therapy are positive prognostic factors for AT/RT patients.

Key words: Atypical teratoid/rhabdoid tumour; immunohistochemistry; INI1; diagnosis.

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INTRODUCTION

Atypical teratoid/rhabdoid tumours (AT/RTs) are rare and aggressive brain tumours that primarily occur in childhood, predominantly presenting in children under the age of 3 years (mean age of approximately 2 years) and rarely manifesting in children over the age of 6 years.[1] AT/RTs account for approximately 1–2% of paediatric brain tumours and approximately 10% of central nervous system (CNS) tumours in infants.[2] There is a male predominance, with approximately 1.6–2.0 males diagnosed with an AT/RT for every female.[3,4] These forms of tumours have been found throughout the CNS, and the ratio of supratentorially to infratentorially located tumours is 1.3:1. Occasionally, AT/RTs are located in the spinal cord or the pineal region.[5]

AT/RTs are often misdiagnosed, usually as primitive neuroectodermal tumours (PNETs) if manifesting in the supratentorial region or as medulloblastomas (MBs) if located in the cerebellum or the fourth ventricle, due to shared clinical, imaging, and morphological features. However, distinguishing AT/RTs from PNETs and MBs is of great clinical significance, as the reported 2-year survival rate of patients with AT/RTs is approximately 15% compared with the far longer 5-year survival rate of approximately 85% among patients with standard-risk PNETs or MBs.[6] The most useful immunohistochemical diagnostic marker of AT/RTs is a lack of INI1 (also referred to as SMARCB1, hSNF5, or BAF47) protein expression. Initial genetic studies suggested that approximately 75% of AT/RTs are characterised by biallelic *INI-1* inactivation.[7] However, these tumours were often atypical with respect to both morphology and immunohistochemistry. The aim of this study was to assess the clinicopathological features of AT/RTs in our hospital to better define prognostic factors and identify new patterns in the determinants of AT/RT patient outcome.

MATERIALS AND METHODS

Patients

A total of 414 patients of paediatric CNS tumours, including 22 patients with AT/RTs, were diagnosed at Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, from 2010 to 2015.

Immunohistochemistry

Immunohistochemistry was performed on 10% neutral formalin fixed, paraffin embedded tissue sections (4 μm thick) using the EnVision method with a panel of antibodies including those specific for INI1 (BAF47/INI-1; Santa Cruz, USA), glial fibrillary acidic protein (GFAP; Dako, Denmark), synaptophysin (Syn; Novocastra, UK), vimentin (Dako), epithelial membrane antigen (EMA; Novocastra), cytokeratin (AE1/AE3; Dako), S100 protein (S100; Dako), neuronal nuclei (NeuN; Dako), oligodendrocyte transcription factor 2 (Olig2; Dako), smooth muscle actin (SMA; Dako), and Ki-67 (Dako). We replaced the primary antibody with phosphate-buffered saline (PBS) as a negative control and used known antigen-positive sections as positive controls.

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Statistical analysis

Of the 22 patients, five were lost to follow-up. Therefore, 17 patients were included in our statistical analysis. The statistical analysis was performed using SPSS 20.0 (IBM, USA). Estimations of overall survival (OS) and event-free survival (EFS) were performed using Kaplan–Meier analysis, and significance testing ($\alpha = 0.05$) was based on the log-rank test. The level of significance was $p = 0.05$.

RESULTS

Clinical features

The characteristics of all 22 patients are listed in Table 1. The age at diagnosis ranged from 5 months to 9 years (median, 24 months); 68% (15/22) of the patients were under 3 years old; and 16 of the 22 patients were males (male:female ratio, 2.7:1). The most common signs and symptoms were progressive limb limpness (10/22) and vomiting (7/22).

Neuroimaging

The primary tumour site was supratentorial in nine patients, infratentorial in 11 patients, and the spinal canal in two patients. Initial magnetic resonance imaging (MRI) data, which were recorded in our hospital, were available for 20 cases but were unavailable in the other two cases in which MRI was performed at a local hospital. In 20 cases, the tumours were isointense or slightly hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging, and the tumours exhibited inhomogeneous contrast enhancement and hyperintensity on diffusion-weighted imaging (DWI). Some tumours showed a partially cystic appearance ($n = 9$) or oedema surrounding the tumour ($n = 5$) (Fig. 1).

Histopathological features

Tumour sizes ranged from 2 to 8 cm, with a mean size of 4.6 cm. Morphologically, the cellular sheets of tumour cells were interrupted by fibrovascular septa. Most tumours contained heterogeneous components with primitive neuroectodermal, mesenchymal and epithelial features. In spite of the designation, the AT/RT lesions were typically not composed solely or even predominantly of cells with obvious rhabdoid features. Instead, the tumour cells exhibited cytoplasmic vacuolation or vesicular nuclei. Typical cytoplasmic vacuolation, which was the most common characteristic in our AT/RT cases, was detected focally or diffusely in 68% of the cases (15/22) (Fig. 2A). Similarly, cells with vesicular nuclei, which were different from rhabdoid cells with eccentrically placed nuclei and eosinophilic cytoplasm, were also observed in 68% of the cases (15/22) (Fig. 2A, inset). Although cells with classic rhabdoid features (eccentrically placed nuclei containing vesicular chromatin, prominent eosinophilic nucleoli, abundant cytoplasm with evident eosinophilic globular cytoplasmic inclusions and well defined cell borders) were found in 59.1% of the cases (13/22) (Fig. 2B), these cells were not found in the other 40.9% (9/22). Small, round, blue cells were frequent in most cases (15/22, 68.2%) and usually showed a diffuse pattern similar to that observed in PNETs (Fig. 2C). Mesenchymal differentiation was common and manifested as slightly spindled tumour cells in more than half of the cases and as a basophilic or mucopolysaccharide-rich background in four cases (Fig. 2D,E). A few cases (5/22, 22.7%) also showed epithelial differentiation with a glandular component (Fig. 2F) or epitheloid nests (Fig. 2G). Focal or partial papillary structures were detected in a few cases (Fig. 2H), and rare perivascular pseudorosettes were observed in two cases (Fig. 2I). Nearly all cases showed necrosis, and broad areas of geographic necrosis were common in most cases. Dystrophic calcification was common. The majority of cases (19/22, 86.4%) showed more than 10 mitoses/10 high-power fields (HPFs), ranging from 10 to 36 mitoses/10 HPFs.

Immunohistochemical features

All 22 cases showed a loss of nuclear INI1 expression (Fig. 3A). Tumour cells demonstrated partial or diffuse expression of AE1/AE3 (19/22, 86.4%) (Fig. 3B) and EMA (19/22, 86.4%). Reactivity for SMA was common (16/22, 72.7%) (Fig. 3C), but detection of desmin was infrequent (2/22, 9.1%). Tumour cells were focally or regionally positive for GFAP (17/22, 77.3%) (Fig. 3D), Olig2 (9/22, 40.9%), and Syn (7/22, 31.8%). In all cases, tumour cells were positive for vimentin (22/22, 100%) but negative for NeuN (22/22, 100%). The Ki-67 proliferative labelling index was high in almost all cases analysed (ranging from 10% to 80%, data not shown). Although cells with vesicular nuclei or vacuolated cytoplasm were present in most of our cases, the immunohistochemical features of these specific areas was not distinct from those of other areas in the same tumour.

Electron microscopy

Ultrastructurally, tumour cells with vesicular nuclei and cells with vacuolated cytoplasm contained whorled bundles of intermediate filaments in their cytoplasm (shown in Fig. 4).

Therapy and outcome

All 22 patients received surgery, with 16 undergoing subtotal resection and six gross total resection. Five of the 22 patients were lost to follow up; thus, therapy and follow-up data were available for 17 patients (Table 1). Among these 17 patients, only five were survivors; the other 12 patients, all of whom were under 3 years of age, died of tumour progression. Treatment was abandoned by their parents for 10 of the patients who died, and the patients died within a short time (less than 6 months) after surgery without adjuvant treatment. Among the 17 patients who received therapy, only seven received adjuvant treatment (see Table 1 for details). Among the five survivors who were treated with radiation and/or systemic chemotherapy, two patients experienced long-term disease-free survival of greater than 24 months. The median durations of OS and EFS were 5 months and 3 months, respectively. The analyses of OS and EFS indicated that patients who were at least 3 years old showed a higher survival rate than younger patients (Fig. 5A for OS, Fig. 6A for EFS, $p = 0.001$ for both). The patients who underwent gross total surgical resection exhibited a higher survival rate than those who underwent subtotal surgical resection (Fig. 5B, $p = 0.004$ for OS; Fig. 6B, $p = 0.003$ for EFS), and children who received radiation treatment and/or chemotherapy exhibited a higher survival rate than those who did not receive post-surgery therapy (Fig. 5C, $p = 0.000$ for OS; Fig. 6C, $p = 0.001$ for EFS). However, the tumour location was not significantly associated with OS or EFS (Fig. 5D, $p = 0.329$ for OS; Fig. 6D, $p = 0.390$ for EFS). Additionally, the results for the positive