Childs Nerv Syst (2015) 31:1305–1311
DOI 10.1007/s00381-015-2739-x

ORIGINAL PAPER

Investigation of the location of atypical teratoid/rhabdoid tumor

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Received: 15 February 2015 / Accepted: 27 April 2015 / Published online: 8 May 2015
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Abstract
Introduction The location of a brain tumor is a fundamental characteristic, because various brain tumors develop in relatively specific locations. An atypical teratoid/rhabdoid tumor (AT/RT) is a highly age-specific tumor that occurs in infants and young children. However, AT/RTs develop in a variety of locations in the brain. This study aimed at uncovering the tumor location pattern of AT/RTs to enhance diagnoses.
Material and methods Neuroimages from 27 patients with a pathologically proven AT/RT were reviewed, and the specific tumor locations were described and categorized. The association of imaging characteristics and tumor location was analyzed.
Results The posterior fossa was the most frequent locations accounting for 19 patients (70 %), followed by the diencephalon (four patients; 15 %), cerebrum (three patients; 11 %), and midbrain (one patient; 4 %). In the posterior fossa, the superior medullary velum (SMV) and cerebellopontine angle (CPA) areas were the most common sites (eight patients each) and three patients had a tumor in the inferior medullary velum (IMV) region. AT/RTs in the SMV area had a significantly higher chance of no/minimal enhancement compared with tumors in other locations (P=0.001) and a lower likelihood of leptomeningeal tumor seeding at presentation (P=0.053).
Conclusion The location spectrum of AT/RT follows a specific pattern, and some of the locations are linked with intriguing clinical characteristics. This information may not only help make correct preoperative diagnosis but also occasionally aid in postoperative pathological diagnosis.

Keywords Atypical teratoid/rhabdoid tumor · Location · Diagnosis · Seeding

Introduction

One intriguing finding for brain tumors is that each brain tumor develops in a relatively specific location in the nervous system. This location specificity is strong for some tumors such as central neurocytomas, and location information is nearly pathognomonic in many instances [1]. This fact is also true, at least partially, for other tumors with less potent location specificity. The tumor location upon preoperative neuroimaging is a primary clue for differential diagnoses. In this context, the World Health Organization (WHO) classification of brain tumors has indicated that the tumor location is a defining characteristic of disease entities together with patient age, histology, and the biological behavior of the tumor [2]. Among these four clinicopathological factors, tumor location information is a robust indicator for direct preoperative diagnoses, when combined with patient age.

Children exhibit different spectrums of brain tumors according to age group. Atypical teratoid/rhabdoid tumors (AT/RTs) are a typical example because the majority of these tumors develop at age <3 years. Although approximately half of AT/RT patients have tumors in the posterior fossa, it is

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known that AT/RTs develop nearly everywhere in the brain [3]. In the posterior fossa, clinicians should distinguish AT/RTs from other malignant neoplasms such as medulloblastomas and ependymomas in preoperative neuroimages. Therefore, the location specificity of AT/RTs has limited value compared with its robust age-specificity. If we could improve the knowledge of the detailed tumor locations of AT/RT, we could augment our ability to make preoperative diagnoses.

AT/RTs are highly malignant tumors with poor prognosis. Although the presence of rhabdoid cells is a histological characteristic of AT/RTs, the tumors are intrinsically heterogeneous and sometimes display a multi-lineage differentiation pattern. Fortunately, the loss of INI1 protein expression, as revealed by immunohistochemistry, is considered a hallmark of AT/RTs. Therefore, clinical information including age and tumor location can guide appropriate immunohistochemical studies of tumor specimens, augmenting the rapidity and accuracy of histological diagnoses.

In this study, we determined tumor locations in 27 patients with an AT/RT in the brain and revealed that AT/RTs display characteristic location patterns.

Materials and methods

Patients pathologically diagnosed with AT/RTs were retrieved from the operation database of the Seoul National University Children's Hospital from 2001 to 2014. We found 31 patients diagnosed with a AT/RT arising from the brain and spinal cord. We excluded four patients with spinal malignant rhabdoid tumors (MRTs) because they were located in extradural or intradural extramedullary locations, which should be considered extra-axial tumors. The pathological diagnoses were confirmed by the loss of INI expression as determined by immunohistochemistry in all patients. Twenty-six patients had preoperative brain magnetic resonance imaging (MRI). One patient presented with acute tumor bleeding and only brain computed tomography (CT) was available for this patient due to the patient's poor neurological condition.

The preoperative neuroimages were reviewed by a neuroradiologist to determine tumor locations. When tumors spanned two anatomical areas, the tumor-attached site and presumed tumor origin identified during surgery were considered. Postoperative neuroimages were also reviewed to identify exact tumor locations. Specific tumor locations were further categorized into the cerebrum (lobar and lateral ventricle), diencephalon (thalamus and structures around the third ventricle), midbrain, and posterior fossa (the superior medullary velum (SMV), cerebellopontine angle (CPA), and inferior medullary velum (IMV)). For this categorization, the relationship between the tumor and ventricles was considered, i.e., the lateral ventricle corresponded to the cerebrum and the third ventricle corresponded to the diencephalon and so on. The gadolinium-enhancement pattern and the presence of seeding in the brain and spinal cord at the time of presentation were also reviewed. Medical records were reviewed, and the attachment of tumors to critical structures such as the brainstem was searched for in operation records.

For statistical analyses, IBM SPSS Statistics 19.0 software (IBM SPSS, NY, USA) was used. To compare the distribution of categorical variables, a chi-square test was used. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital.

Results

Among the 27 patients diagnosed with AT/RT, 19 patients were male, and 8 patients were female. All patients received surgery for tumor removal and pathological diagnosis. The median age at the time of surgery was 1.4 years (range 1 month–9 years). One patient had previous surgery and received chemotherapy for a kidney MRT and later developed multifocal brain lesions in the SMV and foramen of Monro, suggesting the presence of a germline mutation in the INI1 gene.

The tumor locations are summarized in Table 1. With regards to categorical classification, the posterior fossa was the most common area in which tumors were found in 19 patients (70 %) followed by the diencephalon (four patients; 15 %), cerebrum (three patients; 11 %), and midbrain (one patient; 4 %).

In the posterior fossa group, the SMV and CPA areas were the most frequent sites, found in eight patients each. Three patients had a tumor located in the IMV area. Tumors in the SMV region tended to grow between the tectal plate and cerebellar vermis, displacing these structures. The tumor origin was thought to be the SMV for seven patients, based on the preserved tectal plate and cerebellar lingula upon postoperative imaging, and the inferior tectal plate plus the SMV in one patient. The tumors in the SMV area exhibited little or no gadolinium enhancement with the exception of two

Table 1 Locations of AT/RT in 27 patients

Location category	Specific location	Number of patients	Percent
Posterior fossa	Superior medullary velum	8	70
	Cerebellopontine angle	8	
	Inferior medullary velum	3	
Diencephalon	Thalamus	3	15
	Suprasellar area	1	
Cerebrum	Lobar	2	11
	Lateral ventricle	1	
Midbrain	Cerebral peduncle	1	4
Total		27	100

patients who had partially enhancing tumors (Fig. 1). All CPA tumors were large and had relatively strong gadolinium enhancement. These tumors invariably had an attachment to the brainstem (Fig. 2). All tumors in the IMV region had intense enhancement, but they had little attachment to the brainstem (Fig. 3).

In the diencephalon, three patients had a tumor originating from the thalamus. The tumors were large in size and extended into the lateral ventricles. One patient had a small suprasellar mass in the third ventricle. A patient had a tumor located in the cerebral peduncle adjacent to the posterior third ventricle. Three patients had a tumor in the cerebrum, including two patients who had tumors in lobar locations (fronto-temporal and occipito-temporal) and one patient with a tumor in the lateral ventricles. The lobar tumors were exposed to the lateral ventricles (the temporal horn and trigone, respectively). Six tumors from the SMV region had no or minimal enhancement on MRI, and two tumors from the SMV showed patchy enhancement in a portion of the tumors. In contrast, only two tumors in other locations (one thalamic and the other lateral ventricular tumor) had no/minimal enhancement. The difference in the proportion of non-enhancing tumors between SMV and other locations was significant (P=0.001; chi-square test).

Tumor seeding in the neuraxis at the time of presentation was identified in 11 patients (40 %). Diffuse leptomeningeal and/or nodular seeding along the spinal cord were found in 10 patients. Two of the patients also had leptomeningeal seeding in the brain. The patient with previous history of kidney MRT had a mass in the SMV and a separate lesion involving right foramen of Monro which was considered as ventricular seeding from the SMV lesion. Therefore, only one patient with AT/RT from SMV had tumor seeding at presentation (just ventricular seeding and not spinal seeding), whereas among the 19 patients with AT/RT in other locations, 10 patients had diffuse spinal (±brain) leptomeningeal seeding (P=0.053; chi-square test).

Illustrative case

A 15-month-old boy developed a gait disturbance for several weeks. At 18 months of age, the boy stumbled and began projectile vomiting. Upon admission, the patient was irritable. He had no cranial nerve palsy or motor weakness, but the coordination of both of his arms was hampered. A brain MRI revealed a large non-enhancing mass in the SMV region between the tectal plate and superior vermis and

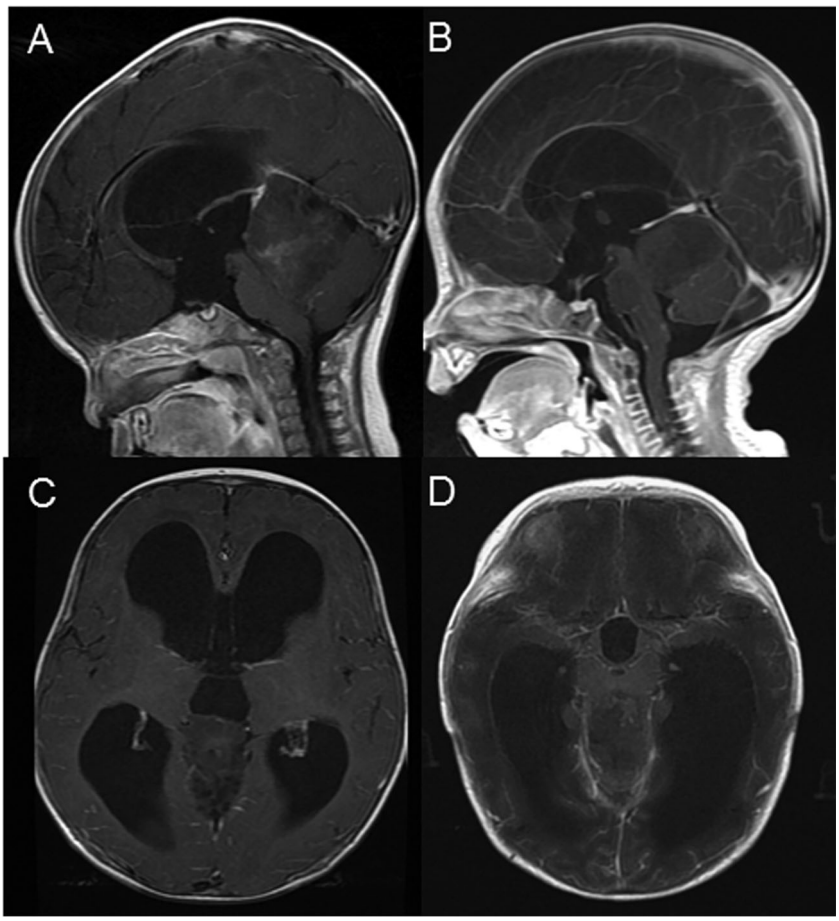

Fig. 1 AT/RTs in the SMV region. **a**, **c** Gadolinium-enhanced T1-weighted images of a 12-month-old girl, and **b**, **d** images of a 3-month-old girl. All tumors are lightly enhanced

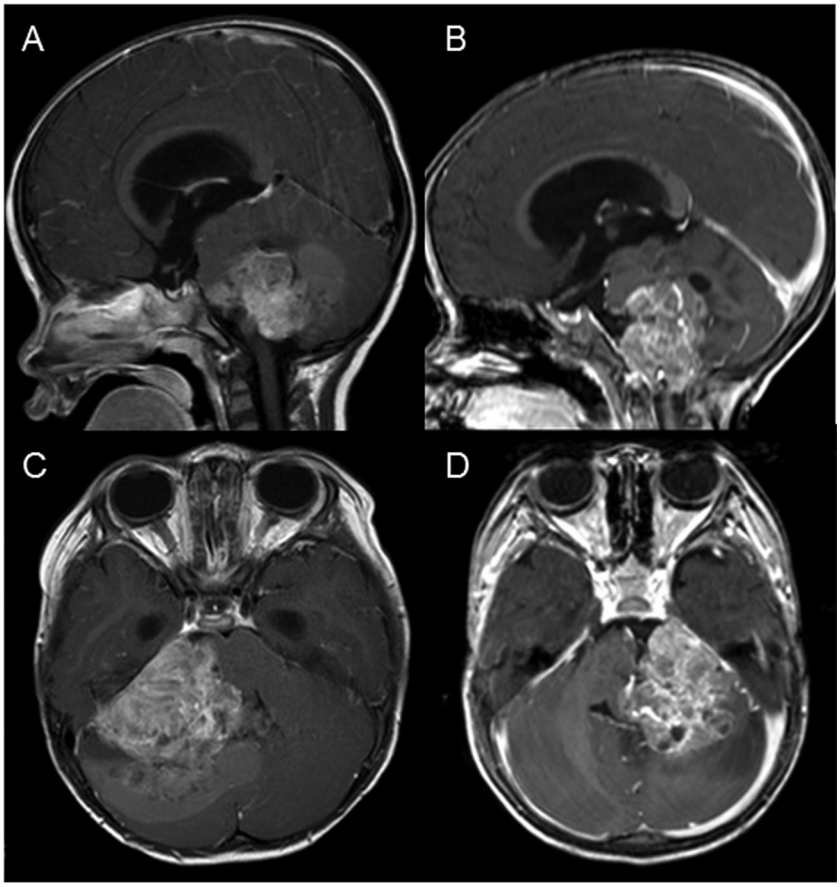

Fig. 2 AT/RTs located in the CPA. **a**, **b** Gadolinium-enhanced T1-weighted images of a 32-month-old girl. **c**, **d** Images of a 13-month-old boy. Tumors are heterogeneous and well enhanced

accompanying hydrocephalus. The thin tectal plate was compressed anteriorly. Upon axial images, the quadrigeminal cistern was effaced by the tumor. An emergent endoscopic third ventriculostomy was performed to relieve intracranial pressure. No tumor tissue was observed in the posterior third ventricle (Fig. 4). Spinal MRI revealed no tumor seeding. The preoperative imaging diagnosis was AT/RT and not medulloblastoma because of the tumor location. After 2 days, the tumor was approached via a midline suboccipital craniotomy and telovelar approach. The tumor protruded from the superior medullary velum into the fourth ventricle. Greater than 95 % of the tumor was resected, but a portion near the quadrigeminal cistern was left because the boy bled too much and developed coagulopathy.

The tumor was hypercellular with a high nuclear-cytoplasmic ratio and consisted of oval- and carrot-shaped cells. The initial pathological diagnosis was classic medulloblastoma based on typical microscopic findings. Because the radiological findings strongly suggested an AT/RT rather than medulloblastoma, INI1 immunohistochemistry was also performed, and loss of INI1 expression was identified (Fig. 4). The final diagnosis was AT/RT in the SMV. The boy received high-dose chemotherapy and awaits stem cell transplantation and radiation therapy.

Discussion

We found that approximately two thirds of pathologically proven AT/RTs develop in the posterior fossa. Previous studies have generally reported that AT/RTs develops more frequently in the infratentorial space than in the supratentorial area. An earlier review by Oka and Scheithauer [4] described that the posterior fossa comprises 61 % of AT/RT locations followed by the cerebral hemisphere (20 %), the suprasellar/third ventricular region (5 %), and the rare spinal cord (1 %). In a Canadian series, infratentorial AT/RTs accounted for 52 % and supratentorial tumors accounted for 44 % [5]. However, a German series reported a similar proportion of infratentorial and supratentorial AT/RTs [6]. The discrepancy may reflect the relatively small number of patients included in each study and warrants a comprehensive review of the data collected from multiple nations.

One peculiar finding in our study is that all of the AT/RTs were found adjacent to the ventricles. In particular, in the supratentorial area, all of the AT/RTs developed either within a ventricle or in a structure adjacent to the ventricle such as the thalamus. Even AT/RTs in lobar locations had contact with ventricular walls. It is highly intriguing that malignant brain tumors, including pilocytic astrocytomas and glioblastoma

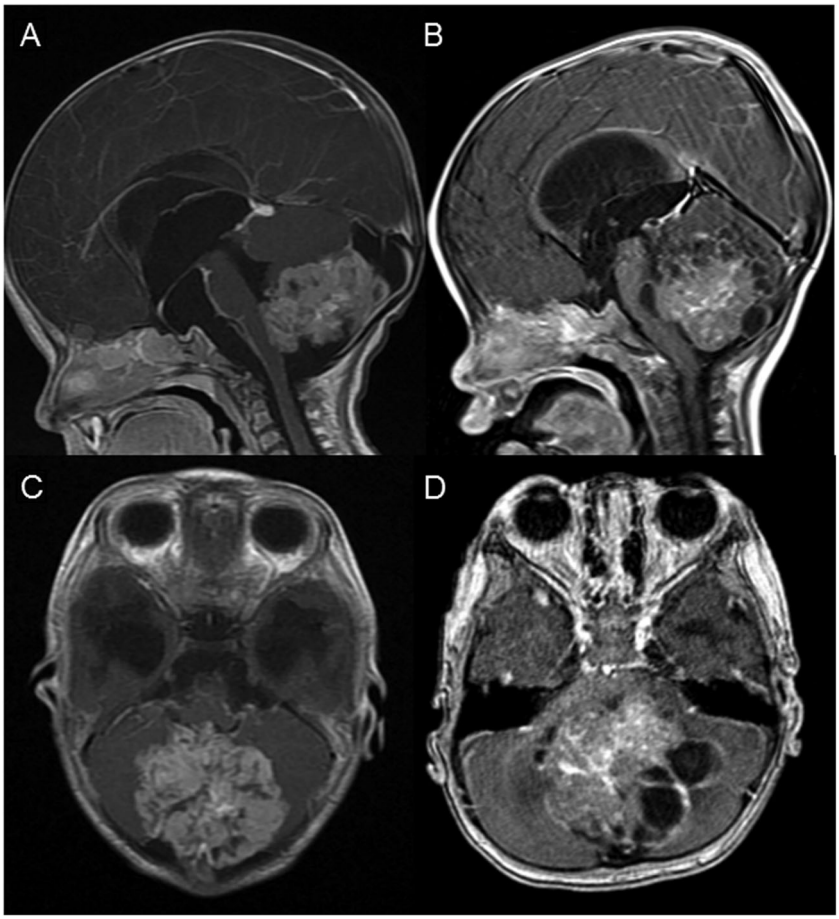

Fig. 3 AT/RTs located in the IMV. **a**, **c** Gadolinium-enhanced T1-weighted images of A 3-month-old girl. **b**, **d** Images of an 18-month-old boy. Tumors are heterogeneous and well enhanced

frequently, have a connection to the stem cell compartment near the ventricle [7, 8]. The cellular origin of AT/RTs is obscure, but the early age at diagnosis and specific locations along the ventricles indicate that their origin may be stem/progenitor cells residing in the ventricular walls.

Many authors have described posterior fossa AT/RTs as developing in the cerebellar hemisphere, CPA, and brainstem [3, 9]. Brainstem invasion has been recognized as a key characteristic of this disease. However, there are few studies that have attempted to further specify the location of AT/RTs. The analysis in our study revealed that the AT/RTs located in the posterior fossa could be divided into three groups: CPA, SMV, and IMV. These three regions correspond to the outline of the fourth ventricle in the lateral, superoposterior, and inferoposterior directions, which again are evidence of stem cell-rich areas promoting aggressive tumors.

The CPA is one of the main locations for AT/RTs in the posterior fossa [10]. Indeed, AT/RTs were the most common tumors found in the CPA of pediatric patients in our previous study [11]. AT/RTs in the CPA are large, heterogeneous, and well-enhancing masses that often intrude into the fourth ventricle. When encountering with a large mass in the CPA of infants and young children, AT/RTs should be considered. During operations, these CPA AT/RTs were found to be almost invariably attached to the brainstem, making total removal precarious.

AT/RTs in the SMV area have special concerns. Recently, Tomita and Frassanito [12] described the growth pattern and pathological spectrum of six tumors thought to originate from the SMV. The SMV is a thin layer of neural tissue constituting the anterior portion of the fourth ventricle roof. The tumors arising from the SMV displaced the tectal plate and quadrigeminal cistern anteriorly, and the cerebellum infero-posteriorly. The thinned tectal plate could be identified by preoperative imaging. These anatomical features led the authors to speculate that the tumors originated from the SMV and not the midbrain or pineal gland. The majority of tumors in the study was AT/RT (five patients) with one patient having a pilocytic astrocytoma. The imaging characteristics of AT/RTs in that report were almost identical to that in the SMV group in our study. Interestingly, these authors noticed that all of the AT/RTs in their series had no or minimal enhancement, which is consistent with our findings. AT/RTs usually display heterogeneous enhancement of varying degrees [13]. Most tumors show moderate to strong enhancement in solid portions [14, 15]. The characteristics of SMV AT/RT upon enhancement, i.e., minimal or no enhancement, were

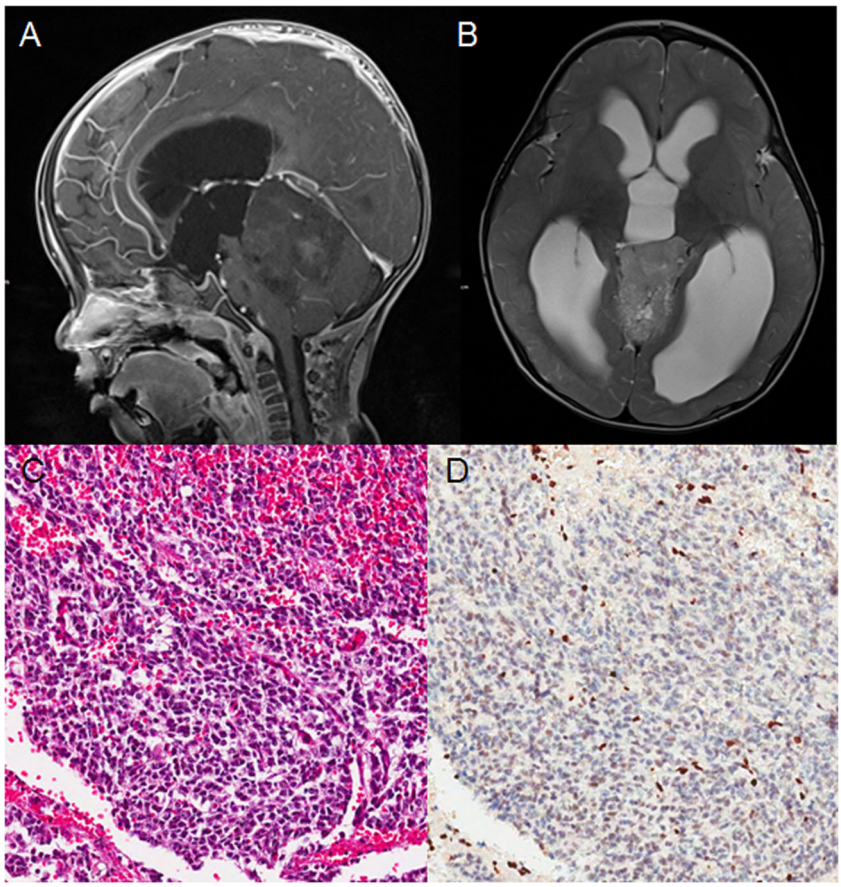

Fig. 4 Illustrative case: An 18-month-old boy. **a** Gadolinium-enhanced T1-weighted sagittal view. **b** T2-weighted axial image. **c** Pathological slide of the tumor (hematoxylin and eosin staining). **d** Loss of INI1 expression (INI1 immunostaining)

quite different from the usual pattern of AT/RTs. The reason for this enhancement pattern is unknown and requires further research.

We also found that AT/RT seeding from the SMV region is rarely observed. Tumor seeding along the neuraxis is a frequent finding for AT/RTs as 20–40 % of patients have evidence of tumor seeding at presentation [5, 15–17]. However, only one patient in the SMV location group had seeding in our study. Because this patient had a previous history of kidney MRT, it was highly likely that she had rhabdoid tumor predisposition syndrome (germline mutation of INI1 gene) [18]. Therefore, the lesion in the foramen of Monro may not be an actual metastasis from the SMV lesion, because it is not a common location for AT/RT seeding, and no other patients in our study had intracranial seeding without evidence of spinal seeding. The possibility of double primary lesions in the brain or metastases from the remitted kidney MRT exists. The fact that the patient had a partially enhanced tumor in the SMV area also raises the suspicion of a tumor with different characteristics. Admitting that the patient actually had seeding from the SMV lesion, the low likelihood of tumor seeding at presentation for this location group is still intriguing. However, Tomita and Frassanito [12] reported that all their patients with an SMV-originating AT/RT died within months of diagnosis mainly due to diffuse tumor seeding in the neuraxis, indicating that scarce seeding at presentation does not indicate a favorable biological behavior of tumor. The low rate of tumor seeding may be related to the lack of tumor enhancement which indicates an intact tumor-vessel permeability that prevents the easy spreading of tumor cells.

Our illustrative case demonstrates that information regarding tumor locations can greatly aid not only preoperative diagnoses but also pathological examinations. Patient age and tumor location combined with ancillary imaging characteristics such as enhancement patterns can lead to pertinent preoperative diagnosis and guide treatment planning accordingly. The clinical information also guides the pathological examinations to be fitted to the circumstance. For our patient, the suspicion of the AT/RT arising from the SMV, which was prompted by the characteristic location and lack of enhancement, urged the pathologist to proceed with further studies. In this regard, multidisciplinary cooperation between radiologists, neurosurgeons, and pathologists can enhance the accuracy and speed of diagnoses through sharing clinical and pathological information.

Conclusions

The location spectrum of AT/RTs follows a specific pattern, and some of the locations are linked with intriguing clinical

characteristics. This information may not only help make correct preoperative diagnoses but also sometimes aid in postoperative pathological diagnoses.

Acknowledgments This study was supported by a grant from the National Research Foundation of Korea (No. 2014R1A1A1005765) to Phi JH.

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