

The clinical features and surgical outcomes of intracranial tanycytic ependymomas: a single-institutional experience

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Abstract Tanycytic ependymoma is a rare subtype of ependymoma with a predilection for the spinal cord and intracranial tanycytic ependymoma is thus extremely rare. Most studies on intracranial tanycytic ependymomas included only one or two cases. Here we report nine patients with pathologically confirmed intracranial tanycytic ependymomas. The clinical characteristics, including radiological and histological examination, operative records, and prognoses were reviewed. The case series included six male and three female patients with an average age of 19.3 years. Tumors were located in the lateral ventricle (3/9), the fourth ventricle (2/9), and the supratentorial extraventricular (4/9). Gross total resection (GTR) of the tumor was achieved in seven cases, and subtotal resection (STR) was achieved in the other two cases. One patient died 21 months after discharge. The left eight patients showed improved symptoms after surgery, and no tumor recurrence was found in these cases during the follow-up. It

seems that intracranial tanycytic ependymoma has the best long-term prognosis compared to the other two subtypes of ependymoma. According to our experience, we recommend surgery including GTR and STR followed by radiotherapy for patients with intracranial tanycytic ependymomas.

Keywords Tanycytic ependymoma · Intracranial · Clinical features · Surgical outcomes · Prognosis

Introduction

The 2016 World Organization Classification (WHO) of tumors of the central nervous system (CNS) grades ependymal tumor as subependymoma (grade I), myxopapillary ependymoma (grade I), ependymoma (grade II), ependymoma with *RELA* fusion-positive (grade II or III) and anaplastic ependymoma (grade III) [1]. WHO grade II ependymomas are further divided into three major subtypes: papillary, clear cell, and tanycytic ependymoma (TE) [1].

Ependymomas are slow-growing tumors, accounting for 3–7% of all brain tumors and 3–9% of all neuroepithelial tumors [2, 3]. TE is the rarest variant of ependymal tumor [4]. In 1978, Friede and Pollak described the pathologic features of TE for the first time [5]. TE exists predominantly in the spinal cord [4]. Therefore, intracranial TEs are extremely rare and merely 20 cases have been reported up to date in the English literature (Table 1) [2–20]. Unfortunately, these studies had too few cases to show general characteristics of intracranial TEs. Here, we report a series of nine patients with histologically confirmed intracranial TEs and their long-term outcomes in a single center. To the best of our knowledge, this study is the largest case series of intracranial TE. We believe the clinical, radiological and

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Table 1 Reported cases of intracranial tanyctic ependymoma

Author/year	Sex/age (y)	Location	Symptom (duration)	Pathologic findings	Immunopositivity	Extent of resection	Prognosis
Friede et al. (1978) [5]	M/6	Temporal	Vomiting, headache, seizure (2 y)	Alternating polarity of cells	ND	ND	ND
Langford et al. (1997) [6]	F/40	Cerebellopontine angle	Headache, decreased hearing	Numerous slender surface microvilli, and microvilli-lined lumina	GFAP, S-100	ND	No recurrence (3 y)
	M/13	Parietal	Headache	Numerous slender surface microvilli, and microvilli-lined lumina	GFAP, S-100	ND	Died (8 m)
Daneyemez et al. (1999) [7]	M/42	Lateral ventricle	Legs weakness, dysarthria and headache (6 m)	Round to oval nuclei, high degree fibrillarity	GFAP, S-100	STR	No recurrence (3 y)
Hayashi et al. (2000) [8]	M/51	Frontal	Seizures, dizziness (6 y)	Spindle glial cells	GFAP, S-100, EMA	GTR	No recurrence (14 m)
Richards et al. (2004) [9]	M/17	Frontal	Epileptic seizure	Minor pleomorphism and scattered mitoses	EMA, GFAP	GTR	No recurrence (13 m)
Ragel et al. (2005) [3]	F/55	Lateral and third ventricle	Disequilibrium (several months)	Well-differentiated cells with elongated nuclei	GFAP, S-100, vimentin, EMA	STR	No recurrence (3 m)
Ito et al. (2006) [10]	M/59	Temporo-occipital	None (incidental detection by MRI)	Elongated and spindle cells	GFAP, S-100, vimentin	PR	ND
Zhang et al. (2008) [11]	M/38	Lateral ventricle	Headache (1 y), vomiting, and impaired vision	Long spindle monopolar or bipolar cells	GFAP, NF, S-100, vimentin, Nestin	GTR	No recurrence (8 m)
Du et al. (2009) [12]	M/36	Lateral ventricle	Headache (2 y)	Bipolar long spindles and resembled tanyocytes	GFAP, EMA, and CD99	ND	No recurrence (24 m)
Reis et al. (2011) [13]	M/6	Parieto-occipital	Focal seizures and headache	Elongated cells arranged in bundles	GFAP, vimentin, Ki-67	ND	ND
Arvanitis et al. (2013) [14]	M/40	Lateral ventricle	Vertigo, headaches (1 y)	Elongated spindle cells	GFAP, S-100	PR	ND
Rigante et al. (2013) [15]	M/14	Temporoparietal	Seizures	Elongated spindly bipolar cells	EMA, GFAP, Ki-67	ND	No recurrence (12 m)
Kambe et al. (2014) [16]	M/2	Parietal	Seizures	Spindly bipolar cells	GFAP, S-100, vimentin	GTR	ND
Shukla et al. (2014) [17]	M/8	Lateral ventricle	Vomiting and seizures	Elongated spindle-shaped cells	GFAP	ND	ND
Agarwal et al. (2014) [4]	F/44	Third ventricle	Headache, diplopia, nausea and disequilibrium (6 m)	Monotonous and spindle shaped cells with vague fascicle formation	GFAP, EMA	STR	No recurrence (1 y)
Liu et al. (2014) [18]	M/24	Frontal	Seizures	Perivascular pseudorosettes	GFAP, EMA, CD99, weKi-67	STR	No recurrence (2 y)
Kuga et al. (2014) [19]	M/24	Frontal	Seizures	Eosinophilic, elongated fibrillary cells	GFAP, EMA	GTR	No recurrence (6 m)
Divito et al. (2014) [20]	M/57	Cerebellopontine angle	Left-sided hearing loss, tinnitus (12 m) headaches (several years)	Spindle cells, perivascular pseudorosettes	GFAP, S-100, EMA	ND	No recurrence (1 m)

Table 1 (continued)

Author/year	Sex/age (y)	Location	Symptom (duration)	Pathologic findings	Immunopositivity	Extent of resection	Prognosis
Lopez et al. (2015) [2]	M/58	Frontoparietal	Seizures	Well-differentiated piloid cells	GFAP, Ki-67	ND	No recurrence (18 m)

M male, *F* female, *GTR* gross total resection, *STR* subtotal resection, *PR* partial resection, *y* year, *m* months, *GFAP* glial fibrillary acid protein immunostain, *EMA* epithelial membrane antigen, *Ki-67* Mib-1 labeling index, *NF* neurofilament, *ND* not described

pathological features of intracranial TE we showed here aim for better differential diagnosis in future.

Materials and methods

The study included nine consecutive cases of intracranial TE that were pathologically diagnosed in Beijing Tian Tan Hospital between August 2011 and May 2016 (Table 2). The first intracranial TE patient just admitted to our hospital at August 08, 2011. All patients had their primary tumor surgically resected in our centre.

The relevant clinical data (including presentation, radiological imaging, treatment, and follow-up outcomes) were collected through a chart review and telephone interviews with an approval of the institutional review board. The diagnosis of TE was pathologically confirmed by the Department of Neuropathology at Beijing Neurosurgical Institute using the 2016 WHO classification of tumors of the central nervous system.

The estimation of the extent of tumor removal was acquired from the operation records and postoperative magnetic resonance imaging (MRI). Gross total resection (GTR) and subtotal resection (STR) were defined as total and subtotal macroscopic removal, respectively. The Karnofsky Performance Scale (KPS) was applied to assess the neurological function of the patients. These assessments were performed before surgery, at discharge, and at the last follow-up.

Results

The clinic characteristics and treatment of the nine patients (including five children) of intracranial TE were detailed in Table 2. The average age at the time of diagnosis was 19.3 years (range from 8 to 39 years). The sex ratio (male: female) was 2:1. The durations of symptoms ranged from 10 days to 3 years. The initial symptom was related to the tumor-occupying effect and location, with headache (4/9) and nausea (3/9) being the most common symptoms. The preoperative KPS scores were 90 for all the patients.

Radiological features

The tumors were located in the lateral ventricle (3/9), fourth ventricle (2/9), frontal lobe (3/9), and parieto-occipital (1/9). T1-weighted imaging of MRI revealed hypointense signal in six patients, iso- to hypo-intense signal in two patients and isointense signal in one patient. T2-weighted imaging showed hyperintense signal in six cases, iso- to hyper-intense in two cases and isointense signal in one case. On contrast-enhanced T1-weighted images,

Table 2 Characteristics of nine patients with intracranial tanyocytic ependymoma

Case no.	Sex/age (y)	Symptom (duration)	Site	MRI findings		Preoperative diagnosis	Surgical approach	Treatment	KPS		Prognosis	
				T1WI	T2WI				Preoperative	Postoperative		Last-FU
1	M/39	Intermittent seizure, unconsciousness (3 y)	Right parieto-occipital	Hypo	Hyper	Mildly; heterogeneously	Right parieto-occipital approach	GTR+Radiotherapy	90	100	100	No recurrence (10 m)
2	F/8	Headache (7 m)	Left frontal	Hypo	Hyper	Moderately; heterogeneously	Left frontal approach	GTR	90	100	100	No recurrence (19 m)
3	M/13	Headache (6 m)	Left frontal, basal ganglia	Hypo	Hyper	Markedly; heterogeneously	Left frontoparietal approach	GTR+Radiotherapy	90	100	100	No recurrence (56 m)
4	M/34	Diplopia, nausea, drowsiness (1 m)	Mesencephalon, fourth ventricle	Iso-hypo	Iso-hyper	Markedly; homogeneously	Sub-occipital medline approach	STR	90	90	0	Died (21 m)
5	M/8	Repeated fever (1 m)	Right lateral ventricle	Hypo	Hyper	Moderately; heterogeneously	Temporal occipitoparietal approach	GTR+Radiotherapy	90	100	100	No recurrence (65 m)
6	F/22	Left facial palsy (6 m)	Fourth ventricle	Hypo	Hyper	Markedly; heterogeneously	Sub-occipital medline approach	STR+Radiotherapy	90	100	100	No recurrence (65 m)
7	M/12	Headache (1 m), nausea, vomiting, ophthalmodynia (3 d)	Right lateral ventricle	Iso-hypo	Iso-hyper	Markedly; heterogeneously	Transfrontoventricle approach	GTR+Radiotherapy	90	100	100	No recurrence (26 m)
8	F/8	Headache, nausea, vomiting (10 d)	Right frontal	Hypo	Hyper	Moderately; heterogeneously	Right frontal approach	GTR+Proton Therapy	90	100	100	No recurrence (15 m)
9	M/30	Tinnitus (1 m)	Right lateral ventricle	Iso	Iso	Moderately; heterogeneously	Right frontal approach	GTR+Radiotherapy	90	100	100	No recurrence (8 m)

M male, F female, y year, m months, d day, MRI magnetic resonance imaging, WI weighted image, hyper hyperintensity, hypo hypointensity, iso isointensity, KPS Karnofsky performance status, GTR gross total resection, STR subtotal resection, MFI magnetic field intensity, FU follow-up

three cases showed markedly heterogeneous enhancement, four cases showed moderately heterogeneous enhancement, one case showed mild heterogeneous enhancement, and the last one had markedly homogeneous enhancement.

Unfortunately, only three cases (33.3%) were diagnosed as ependymoma based on the preoperative MRI. The other six patients were misdiagnosed with glioma (4/6), subependymoma (1/6) or hemangioblastoma (1/6) (Fig. 1).

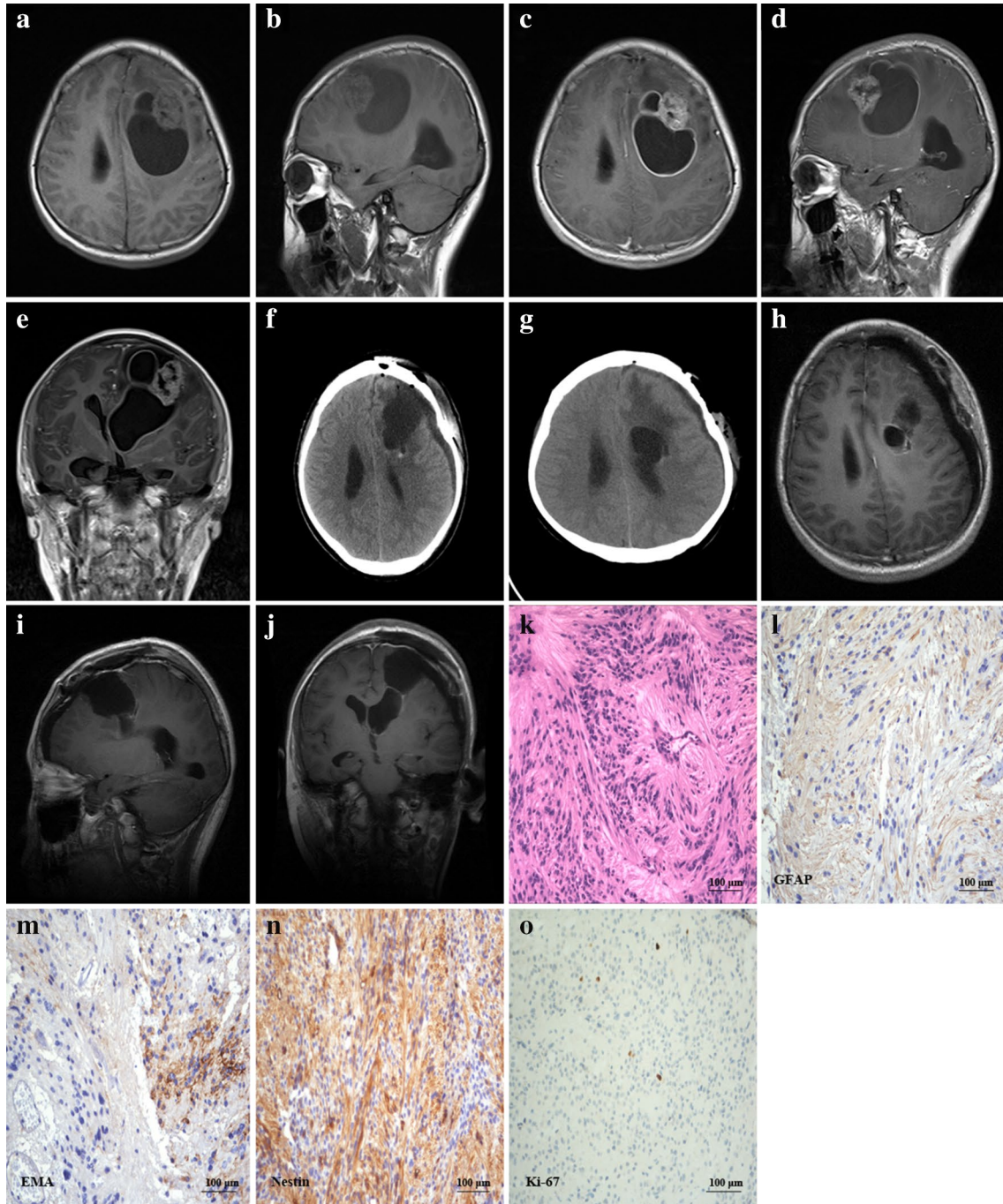


Fig. 1 Case 3: Preoperative MRI revealed a cystosolid lesion, which was misdiagnosed as astrocytoma. Plain T1WI (a, b) and enhanced T1WI signals (c–e) showing a lesion in the left frontal and basal ganglia. Postoperative CT and MRI (f–j) revealed gross total resection of the tumor. Pathological examination (k–o) revealed a spindle cell neoplasm of moderate cellularity arranged in interlacing fasci-

cles. The tumor cells had discreetly elongated bipolar nuclei (k). The immunohistochemical examinations showed that the tumor cells were strongly positive for GFAP (l), EMA (m) and Nestin (n), and 3% of cells are positive for Ki-67 (o). The pathological diagnosis was consistent with TE. Original magnification in (k–o) is $\times 200$

Intraoperative findings

All tumors were removed through craniotomy under operative microscope. Intraoperatively, the lesions typically appeared grayish red, smooth-surfaced, mildly vascular, and rubbery. Most of the masses were well circumscribed from the brain tissues, which made it facility for operators to expose and dissect. GTR and STR were achieved in seven and two patients, respectively. Failure of GTR occurred in two tumors located in the fourth ventricle.

Pathological examination

Microscopically, all tumors showed typical histological indications of TE according to the WHO classification. Tancytes (spindle cells with oval and elongated nuclei) were observed by hematoxylin and eosin staining in all nine cases. Immunohistochemistry showed expression of glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), and Nestin in tumor cells. The Ki-67 positive cells in all the lesions were less than 5%, suggesting a low proliferation capacity. Ultrastructural examination demonstrated sarciniform spindle cells with deficient extracellular matrix. Abundant slim surface microvilli, and microvilli-lined lumina were discovered at the intercellular junctions (Fig. 2).

Long-term outcomes

All patients were still alive except for one who died 21 months after the first surgery. The deceased underwent second surgery 16 months after the first one in our hospital. The follow-up time for the patients who were still alive was 8–65 months, with an average of 33.0 months. At present, all the eight patients have recovered, and their postoperative KPS scores were all reached 100. They live a normal life, including working or studying normally. Currently, there is no evidence of tumor recurrence according to the last MRI. None of the eight patients underwent second surgery and seven of them underwent further adjuvant therapy. External radiation therapy was administered to six of them. Also, one patient underwent the proton therapy in Germany. We have drawn a survival curve to compare our nine patients with previous reports (available data from Table 1) (Fig. 3). Our study includes complete patients follow-up data, with longer follow-up duration than previous reported. There was no significant difference in overall survival rate between the two groups, indicating favorable prognosis of intracranial TE.

Discussion

Epidemiology and clinical features

The Neurosurgery Department of Beijing Tian Tan Hospital performs brain tumor surgeries to about 7000 patients every year, among which, there are generally 300 cases of relapse. Hence, approximately 60,000 patients with primary brain tumors had their first surgery in Beijing Tian Tan Hospital from January 2008 to January 2017. We had reviewed the records of Beijing Tian Tan Hospital and identified nine patients with pathologically confirmed intracranial TE among a total of 1787 ependymoma patients. The proportion of intracranial TEs among ependymoma in our hospital was only 5%. Intracranial TE was so rare that only 29 cases (including the current study) were reported. The ages of these patients ranged from 2 to 59 years (median, 30.5 years) when diagnosed. Similar to ependymal tumors, which predominantly affect children and young adults, intracranial TE also happened to young people [21]. Actually, 15 of the 29 cases were diagnosed below 25 years old. The mean ages at the time of the diagnosis in male and female patients were 27.4 and 29.5 years, respectively. Obvious gender difference was found, with male patients seemed more likely to be affected (male:female=3.8:1). However, in our case series, the mean age at diagnosis was 19.3 years and the sex ratio (male:female) was 2:1. This may because the difference of race or due to relatively low number of cases included.

Locations varied among the cases, accompanied with corresponding symptoms in these patients. The most frequent affected location was supratentorial extraventricle (51.7%, 15/29), followed by intraventricle (41.1%, 12/29) and cerebellopontine angle (6.9%, 2/29). Similar to other intracranial tumors, the clinical symptoms of intracranial TE included headache, nausea, and vomiting, usually due to increased intracranial pressure. Particularly, headache and seizure were the most common initial symptoms. In addition, TE was occasionally found in supratentorial extraventricle locations and can present with seizures [15]. It was noteworthy that 10/15 (66.7%) patients with supratentorial extraventricle TEs suffered from seizures but only 1/12 (8.3%) patients with intraventricle TEs had seizures.

Pathogenesis

TE is a sort of WHO grade II tumor with a relatively better prognosis than other grade II ependymomas [4, 11, 16, 22]. The diagnosis and treatment of intracranial TE is critical to achieve a satisfying prognosis. The cell of origin for this neoplasm is still elusive. However, recent evidence shows that they may originate from radial glias such as the tancytes of ependyma and the initial cells of neurogliaocytes [4,

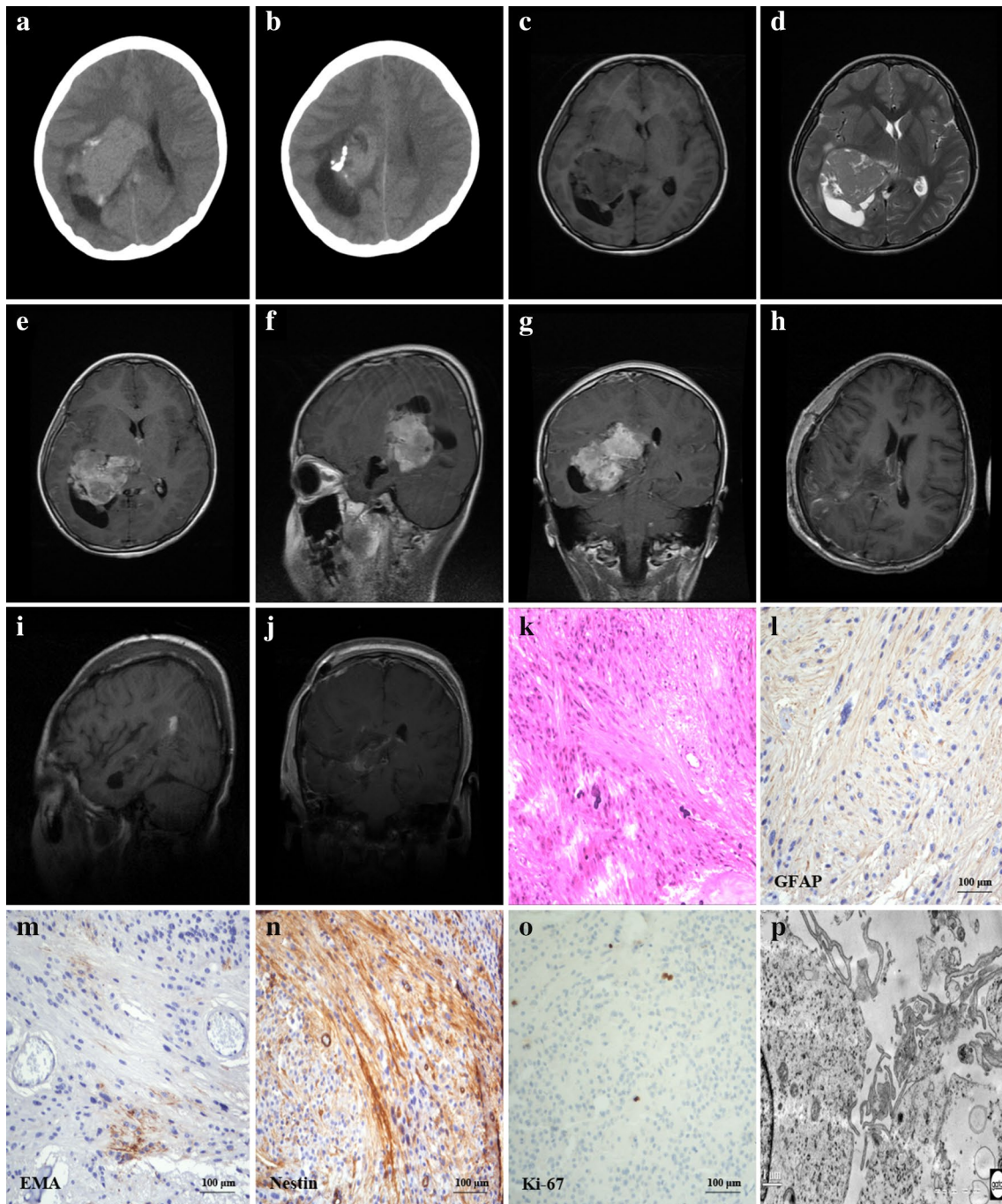


Fig. 2 Case 7: Preoperative CT (**a, b**) showing a partly calcified mass in the right lateral ventricle. MRI showing hypointense T1 (**c**) and isointense T2 (**d**) signals as well as heterogeneous enhancement (**e–g**). Postoperative MRI (**h–j**) revealing gross total resection of the tumor. Pathological examination revealed the diagnosis of TE (**k**)

with positivity for GFAP (**l**), EMA (**m**) and Nestin (**n**), and 2% of cells are positive for Ki-67 (**o**). Electron micrograph showing intercellular junctions and numerous slender surface microvilli (**p**). Original magnification in (**k–o**) is $\times 200$, **p** is $\times 6000$

20]. The tanyocyte is implicated in two CNS tumors, namely, tanyctic ependymoma and astroblastoma [3]. Tanyocytes are elongated spindly bipolar cells which generally present in the circumventricular organs especially in the third ventricle and central canal of spinal cord [18].

The electron microscopy shows ultrastructural features of TE including distinct intercellular junctions, abundant slender microvilli, and microvilli-lined lumina [4]. Ependymomas normally have strong GFAP reactivity and variable staining for S-100, vimentin and EMA [3]. Similarly,

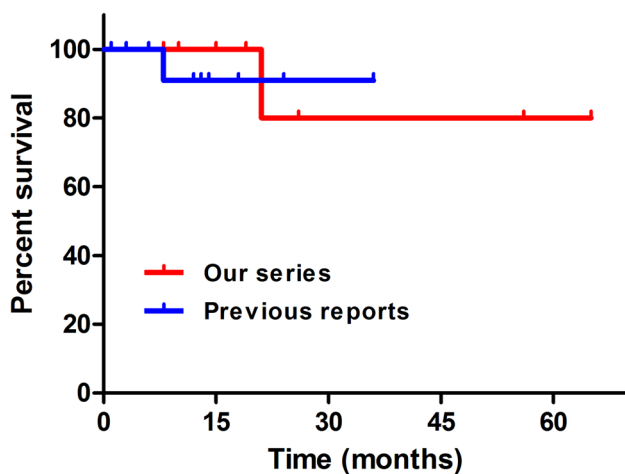


Fig. 3 The survival-curve for our series and previous reports

intracranial TEs are also positive for GFAP in most cases, including ours. However, the expression of Ki-67 in intracranial TE is usually lower than that of the other subtypes of WHO grade II ependymomas, and the Ki-67 index can be as low as 1% [16]. Our results of immunohistochemistry were consistent with the previous reports.

Radiological features and diagnosis

MRI plays important role in differential diagnosis and surgical plan of CNS tumors. In most of our cases showed hypointense to isointense on T1WI and isointense to hyperintense on T2WI, and contrast MRI sequences show moderately to markedly heterogeneous enhancement. Furthermore, boundaries of those lesions are relatively clear. There were a variant of diagnoses suggested by the imaging features, but these were not confirmed by the pathologic diagnosis. As intracranial TE is associated with no specific imaging features, the confirmative diagnosis depends on pathologic characteristics. The electron microscopy can contribute to diagnosis and differential diagnosis. Several cases were diagnosed as astrocytoma or subependymoma or hemangioblastoma by preoperative imaging examination, which, however, were pathologically confirmed as misdiagnosis. In pathological diagnosis, it is essential for pathologist to improve the understanding of the histological features of this tumor.

Treatments and outcomes

Currently, complete surgical resection remains the mainstay of therapy for patients with intracranial TE [23, 24]. GTR should always be attempted with microsurgical techniques if a diagnosis of ependymoma is suggested by intraoperative pathology. Most of the tumors did not adhere to the

brain tissue, and GTR was feasible with delicate microsurgical techniques. However, it can be difficult to remove the entire tumor if it is closely adherent to brain tissue or is rich in vascular supply. Since tancytic ependymoma is benign histologically and generally well demarcated, a good prognosis can be anticipated after complete removal. In reviewing the therapeutic strategy for intracranial TE, it was noted that most scholars are supportive of adjuvant radiotherapy following surgical resection, as this is expected to reduce the recurrent rate. Some other scholars argue that radiotherapy may not be mandatory following complete resection, especially for younger patients, and that adjuvant radiotherapy may be given in case of incomplete resection or recurrence [22–24]. What we recommend is to give postoperative radiotherapy regardless of whether it is a complete or incomplete resection, as this might be favorable for patient prognosis.

The prognosis of TE is related to the age of patient, the location of tumor and the extent of surgical resection. A high Ki-67 index is also associated with recurrence but is not closely related to outcomes [4]. Comparing to other subtypes of ependymomas, intracranial tumors have a low Ki-67 index [4], suggesting a better prognosis. Indeed, it has been reported that TEs have a higher 5- and 10-year survival rate than other subtypes of ependymoma [4, 11].

Conclusions

The current case series and literature review suggest that intracranial TE should be taken into consideration when intracranial lesions are detected in young patients, especially when the tumors show enhancement on MRI. TE is the rarest variant of ependymoma and its diagnosis largely depends on histopathological examination. Neurosurgeons should be aware of this lesion entity. Fortunately, intracranial TE usually has a favorable prognosis, and complete surgical resection is expected whenever possible. After surgery, follow-up imaging examination is helpful for monitor.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings described in this paper. No benefits in any form have been or will be received from any commercial party related directly or indirectly to the subject of this manuscript.

Ethical approval This retrospective study was approved by Institutional Review Board of Beijing Tian Tan Hospital, Capital Medical University.

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