Child's Nervous System
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CASE REPORT

A rare case of intraparenchymal subependymoma in a child

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Abstract
Subependymoma is a slow-growing, exophytic, intraventricular glial neoplasm that commonly arises in the ventricular system. However, a report found that the frequency of intracerebral subependymoma was 0.4% in 1000 routine autopsies. To the best of our knowledge, only seven cases of intracerebral subependymoma have been reported. We report a rare case of intracerebral subependymoma in a child. An 11-year-old girl with generalized tonic-clonic seizures visited the emergency room and had an intraparenchymal tumor on the left frontal lobe on magnetic resonance imaging (MRI). Craniotomy with gross total removal was performed without any perioperative morbidities. The tumor was finally histopathologically diagnosed as a subependymoma.

Keywords Subependymal glioma · Neuropathology · Pediatrics · Sequence analysis

Introduction

Subependymoma is a slow-growing, exophytic, intraventricular glial neoplasm characterized by a cluster of normal to mildly pleomorphic, mitotically inactive cells embedded in an abundant fibrillary matrix with frequent microcystic changes, and it accounts for 0.2–0.7% of all intracranial tumors [19]. According to Dho et al. [3], the incidence rates of "ependymoma/anaplastic ependymoma and ependymoma variants" in South Korea were 0.7% and 0.2% in 2013, respectively.

Subependymoma is most commonly located on the fourth ventricle (50–60%), followed by the lateral ventricle (30–40%), and less frequently on the septum pellucidum [13, 18]. The frequency of intracerebral subependymoma was reported to be 0.4% in 1000 routine serial autopsies [10].

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Intraparenchymal subependymoma is extremely rare. To date, only seven cases of intraparenchymal subependymoma have been reported [8]. They rarely occur in children and are mostly found in middle-aged and older men [7]. Here, we describe a rare case of intracerebral subependymoma in a child.

Case report

An 11-year-old girl experienced generalized tonic-clonic type seizures and underwent brain magnetic resonance imaging (MRI), which showed a tumor on the left frontal lobe. She complained of a headache for several years. She also had precocious puberty, which led her to receive growth hormone injections for 6 months recently.

The brain computed tomography (CT) showed iso- and hypodense lesions, which were significantly apart from the lateral ventricle showing adjacent bone erosion on left frontal convexity. On MRI, a heterogeneous, strong contrast-enhanced, 4.5-cm-sized mass was revealed in the strong heterogeneous contrast enhancement T1-weighted image (CE T1WI), and the frontal skull of the adjacent site showed a thinned and bulging contour, suggesting that the lesion had grown slowly (Fig. 1). It was also well demarcated with a nodular growth pattern consisting of multiple lobules. There was little vascularity in the central portion of the tumor, which indicated a mild or moderate degree of hypervascularity (Fig. 2). No signs of steno-occlusive lesions or aneurysms were

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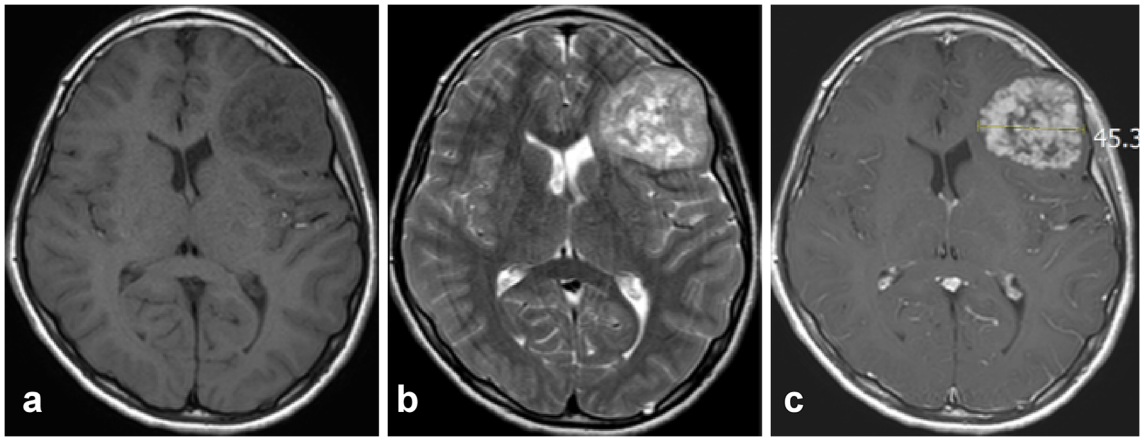

Fig. 1 In the T1WI protocol of MRI, a 4.5-cm-sized intra-axial mass that caused frontal bone erosion with low signal intensity was observed (**a**). Also, T2WI showed multilobulated with high signal intensity accompanied by minor edema (**b**). This tumor showed heterogeneous contrast enhancement in contrast enhancement T1WI (**c**)

detected with MR angiography. The total dose-length product value of ^{18}F-fluoro-2-deoxyglucose (F-18 FDG) brain positron emission tomography (PET) was 46.06 mGy-cm. F-18 FDG PET showed that the tumor was hypometabolic, which indicated that it was characterized by low cellular density and slow growth.

Based on these radiological evaluations, a tumor, such as a ganglioglioma, a dysembryogenic neuroepithelial tumor, or ependymoma, was preoperatively suspected.

The tumor was gross totally resected without significant changes in intraoperative neurophysiologic monitoring. The adjacent skull bulged, and the dura on the tumor surface, was protruded. The tumor was partially exposed to the cortex and relatively well defined, and the frontal cortex showed grayish-pink discoloration.

The histopathological features of this intraparenchymal tumor showed a mild increase in cellularity and nuclear pleomorphism (Fig. 3a). No malignant pathological findings, such as mitotic activity, vascular endothelial hyperplasia, and necrosis, were present. There were clusters of isomorphic nuclei embedded in a dense, fine, glial fibrillary background, and microcystic formations were observed. Tumor cell nuclei resembled those of subependymal glia. In immunohistochemical staining (Fig. 3b), glial fibrillary acid protein staining was diffusely positive, and CD99, CD56 (NCAM), and synaptophysin staining were focally positive. The proliferative index based on nuclear staining with Ki-67 was positive in 1 to 5% of tumor cells. Isocitrate dehydrogenase-1, epithelial membrane antigen, and p53 staining were all negative in tumor cells. Fluorescence in situ hybridization analysis confirmed that there was not a 1p19q codeletion, so oligodendroglioma was ruled out from the differential diagnosis.

For molecular diagnostic confirmation, the next-generation sequencing (NGS) analysis (SNUBH Pan Cancer Ver1.0) was performed at a mean depth of 771×, and 99.4% of sequences had 100× coverage. No single-nucleotide variants, small insertions or deletions (allele frequency ≥ 2%, depth ≥ 100×), translocations, or copy number alterations were detected. Finally, the tumor was confirmed as a subependymoma, and the patient discharged without specific neurological deficits.

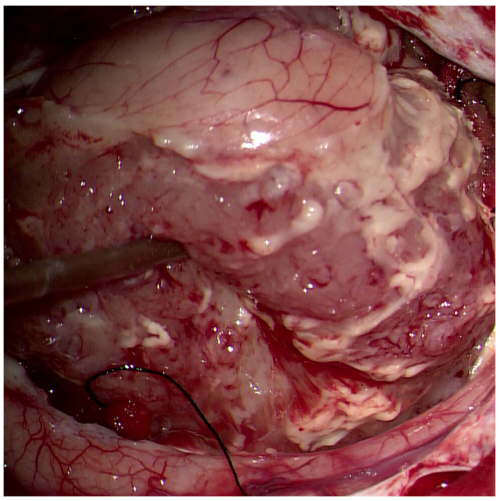

Fig. 2 Intraoperative findings of the tumor. Although the boundary is unclear, the tumor has a distinguishable consistency from surrounding normal brain parenchyma showed relatively mild to moderate vascularity

Discussion

To the best of our knowledge, previous reports describe only 8 cases of this disease, and this is the ninth case report on intraparenchymal subependymoma (Table 1). This condition is even rarer in the child, and this is the second pediatric intraparenchymal subependymoma ever reported.

Symptomatic subependymoma of the lateral ventricle in a single institute has been reported as 0.57% of 1400 brain tumors [9]. However, because these tumors are indolent and

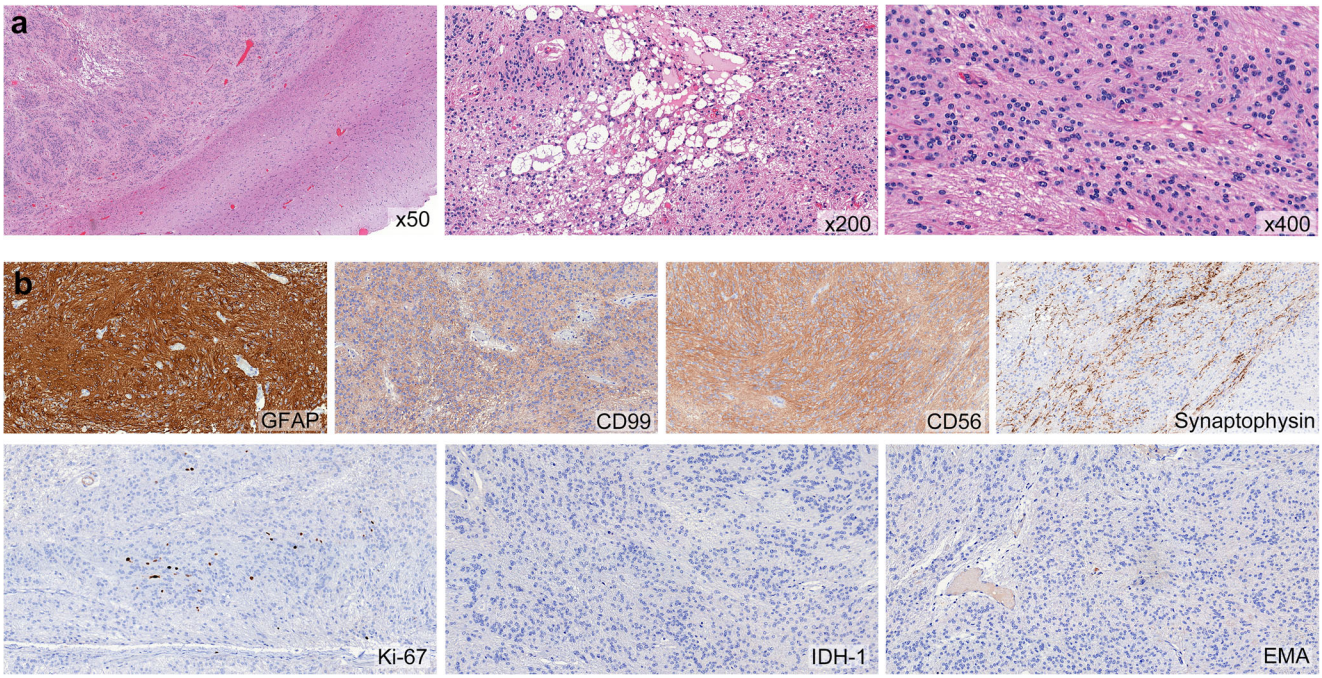

Fig. 3 Histologic findings of the intraparenchymal subependymoma. Hematoxylin and eosin (**a**) and immunochemistry (**b**). **a** x50: tumor composed of a cluster of small uniform cells next to the normal brain parenchyma. × 200: frequent occurrence of multiple small cysts. × 400: tumor nuclei appear isomorphic and resemble those of subependymal glia. **b** Glial fibrillary protein (GFAP), CD99, CD56, Synaptophysin, Ki-67, isocitrate dehydrogenase-1 (IDH-1) and epithelial membrane antigen (EMA)

often clinically silent and asymptomatic subependymoma is incidentally discovered or are discovered at autopsy, the actual incidence remains unknown [2]. According to the SEER database, the overall incidence of intracranial subependymoma is 0.055 per 100,000 person-years (95 % confidence interval (CI) = 0.05–0.06), from 2003 to 2018, only seven cases (0.1%) of subependymoma were treated out of 5803 brain tumors [12]. Matsumura et al. reported that symptomatic subependymoma showed a slightly higher frequency (0.7%) than of asymptomatic subependymomas (0.4%) [10].

Subependymoma likely grows slowly, and the natural course of intracranial subependymoma remains controversial. However, approximately 40% of these tumors become symptomatic, and the tumor location and size are major factors [9]. Unlike typical subependymoma, in our case, the patient complained of a nonspecific headache for several years without any cognitive dysfunction or gait disturbance, but generalized tonic-clonic seizures occurred, which brought the patient to the hospital.

A parenchymal lesion may cause neurological symptoms associated with the location of the tumor and previous reports on other patients with parenchymal subependymoma described neurological deficits, such as hemiparesis and seizures, according to the tumor location. In eight intraparenchymal subependymomas, including the current case, the most common location of the tumor was the parietal lobe (n = 4, 50%, including a parietooccipital lesion), and the most common clinical manifestation was a seizure (n = 4, 50%) (Table 1).

Typical subependymoma showed a well-demarcated and lobulated intraventricular mass, and the majority of these tumors appeared as well-defined iso- or hypodense lesions with numerous cystic components and little to no contrast enhancement on CT scans [18, 19]. On MRI scans, these tumors show signal hypointensity on isointense T1-weighted imaging (T1WI), signal hyperintensity on T2-weighted imaging (T2WI), and little or no contrast enhancement [18]. In our case, the tumor showed moderate contrast enhancement, which is rather prominent than usual subependymoma cases was observed in CE T1WI. MRI contrast agents for central nervous system tumor workup generally use gadolinium (Gd) chelates [4]. In normal brain tissue, Gd does not pass through the blood-brain barrier (BBB), but in brain tumors, BBB collapses and accumulates in extracellular space [4]. Moreover, as is well known, the vascular endothelial growth factor is a potent promoter of vascular permeability [17]. However, in our case, intraoperative and pathological findings, no blood vessel hyperplasia was observed. Contrast enhancement in the CE T1WI of previously reported intraparenchymal subependymoma was mostly mild or absent (Table 1).

Most subependymomas are less than 2 cm, and the majority of patients with subependymomas are asymptomatic; however, they may become symptomatic if they have large tumors [18, 19]. In symptomatic series, hydrocephalus was present in

Table 1 Previous case reports of intraparenchymal subependymoma

No.	Author (year)	Age	Sex	Clinical symptoms	Tumor location (ventricle as the standard)	Diameter (cm)	CT	MRI			PET	NGS	Remarks
								T1WI	T2WI	Contrast			
1	Hankey et al. [5] (1989)	21	F	Hemiparesis and partial seizures	Rt. parietal lobe	N/A	Hemorrhagic cyst	N/A	N/A	N/A	N/A	N/A	
2	Shuangshoti et al. [20] (2005)	N/A	N/A	Not available	Parietal lobe	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Lack of data; no clinical significance
3	Shuangshoti et al. [20] (2005)	N/A (no clinical information is available due to following up loss)											
4	Ragel et al. [18] (2006)	34	M	Partial complex seizures	Rt. temporal (adjacent to the temporal horn)	3	N/A	Mixed	↑	Moderate	N/A	N/A	Peritumoral edema
5	Ragel et al. [18] (2006)	57	M	Headache, left lateral hemianopsia, and left hemiparesis	Rt. Parietooccipital (posterolateral to rt. lateral ventricle)	2.5	N/A	↓	↑	None	N/A	N/A	
6	Natrella et al. [11] (2011)	45	M	Generalized seizures	Lt. frontal lobe (far from the ventricle)	N/A	N/A	N/A	N/A	Minimal	N/A	N/A	Cystic extra-axial mass with a mural nodule
7	Hou et al. [7] (2013)	5	M	Drowsiness, headache, and right hemiparesis	Lt. parietal lobe (adjacent to the lateral ventricle)	N/A	Hypodense	N/A	N/A	N/A	N/A	N/A	Peritumoral edema
8	Kim et al. [8] (2014)	28	M	Intermittent headache	Lt. cerebellum (adjacent to the fourth ventricle)	4.3	Well-defined cystic and solid mass with internal calcifications	Iso	↑	None	N/A	N/A	
9	Current case	11	F	Headache and generalized tonic-clonic seizure	Lt. frontal lobe (far from the ventricle)	4.5	Heterogeneous, hypodense to isodense without calcifications or hemorrhage	↓	↑	Moderate	↓	Analyzed	Bone thinning, slow-growing, long-standing benign tumor

CT, computed tomography; *MRI*, magnetic resonance image; *PET*, positron emission tomography; *N/A*, not available; *NGS*, next-generation sequencing

94% of patients [1]. Symptomatic subependymomas usually have a maximal diameter of over 4 cm [19]. In the four available cases, all parenchymal subependymomas were larger than 2 cm in diameter (3.6 cm on average).

Intratumoral cyst formation may occur in typical subependymomas, and peritumoral edema is occasionally present but is usually absent [19]. Two cases among the previously reported cases presented peritumoral edema, which arose in the temporal and parietal lobes [7, 18].

Subependymomas are solid, well-delineated, white to gray-tan masses, which commonly present calcification, cysts, and hemorrhage in larger lesions [14]. Intratumoral calcification has been frequently reported in cases of infratentorial subependymomas. However, it is an unusual finding in lateral ventricle subependymomas [1].

In previous reports on intraparenchymal subependymomas, there was only one infratentorial cerebellar subependymoma, which presented intratumoral calcification.

Subependymomas have a dense fibrillary matrix of glial cell processes, and small cysts frequently occur, particularly in lesions originating in the lateral ventricles [6]. These typical pathologic findings were similar to those in previously reported intraparenchymal subependymoma cases.

In addition, molecular diagnosis using NGS can provide useful information for research and diagnosis. . However, according to a "PubMed" search with the keywords "subependymoma" and "next-generation sequencing," this might be the first-ever report of subependymoma analyzed with NGS. Many recent oncology studies have focused on genomic alteration. Subependymoma is a subgroup of ependymoma. Moreover, ependymoma is divided into three anatomical regions (supratentorial compartment, posterior fossa, and spinal compartment). These consist of nine molecular groups [15]. More than two-thirds of the supratentorial ependymal tumors contain oncogenic fusions between RelA, the canonical NF-kB signaling member, and an uncharacterized gene, C11orf95 [16]. These data improved that human cancer with a genetic variation of RelA is highly recurrent, and the RelA-C11orf95 fusion protein may be a potential therapeutic target for supratentorial ependymoma [16]. Structural mutations in gene 11 (11q12.1 and 11q13.3) were also detected by NGS [16]. Molecular analysis of rare tumors, such as subependymoma, provides clues not only for accurate diagnosis but also for discovering new treatment targets and discovering factors that can predict prognosis. Since subependymoma is a rare tumor, more NGS analysis might be needed to obtain reliable results in further studies.

Complete surgical excision is the treatment of choice for symptomatic subependymomas. However, the extent of resection does not appear to influence survival rates [8]. Surgical resection of subependymoma plays a role not only in curing the disease but also in relieving mass effects on nervous system structures, associated obstructive hydrocephalus, and histological confirmation [12].

Conclusion

We report a rare case of intraparenchymal subependymoma in a pediatric patient. Even though the atypical tumor location and radiological features made diagnosis difficult, radical surgical resection might be considered a treatment of choice for the treatment of subependymoma in a typical location. For more accurate diagnosis and further study, NGS might be mandatory.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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