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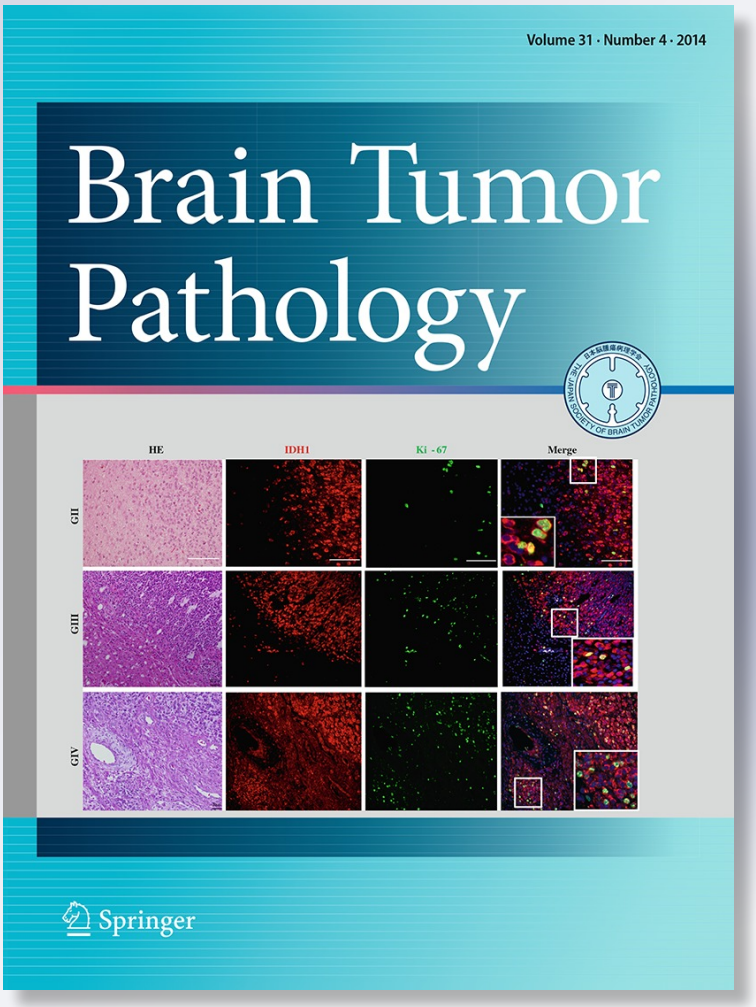

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CASE REPORT

Anaplastic ependymoma of the third ventricle

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Abstract Supratentorial ependymomas are rare, especially in the third ventricle. We report the case of an ependymoma of the posterior third ventricle that was endoscopically removed just by aspiration through a flexible scope. Histologically, beside the typical pattern of growth with perivascular pseudorosettes, the tumor featured hypercellular areas with more than 10 mitoses per 10 high-power fields, consistent with grade III-anaplastic tumor. A few months later, a second neuroendoscopy offered the unique chance to appreciate the total absence of tumor tissue and the restored anatomy. However, consistently with the high grade, the tumor recurred in two different locations including the endoscopic trajectory, and spread through the cerebrospinal fluid. The patient underwent a second resective surgery and radiosurgery. Despite a cycle of chemotherapy, multiple lesions both in the ventricular system and at the level of cauda equina appeared 12 months later. A comprehensive review of intraventricular anaplastic ependymomas is also provided.

Keywords Anaplastic · Ependymoma · Intraventricular · Third ventricle

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Introduction

Ependymomas are glial tumors usually arising from the ependymal cells of the cerebral ventricles, and the central canal of the spinal cord, or from ependymal remnants of the cerebral hemispheres [1, 2]. They are very uncommon in the third ventricle where, when they abut from its posterior part, they cause obstruction of the cerebrospinal fluid (CSF) pathways, and hydrocephalus [1, 3]. In particular, the anaplastic variant of ependymomas of the III ventricle is exceptional, and worth to be reported in the literature.

Opinions regarding the treatment of ependymomas of the third ventricle are diverging. Furthermore, outcome of ependymomas is not always predictable, and often seems to be unrelated to the commonly used prognostic factors [4–9]. Recent studies claim that reliable prognostic factors could be linked to different genetic profiles. For posterior fossa ependymomas, these genetic patterns could overcome the significance of the traditional gliomas grading [10]. Besides the grading, radicality of tumor removal and absence of CSF seeding are considered significant prognostic factors [4, 11]. Gross total removal is not easily accomplished in the third ventricle, where tumors can reach considerable size before diagnosis. Especially, the posterior third ventricle represents a challenge for the neurosurgeon. Neuroendoscopy is a valid treatment option in those cases, offering the opportunity not only for a biopsy or a total or partial resection, but also for hydrocephalus treatment with an endoscopic third ventriculostomy (ETV) [12–15]. We report the case of a posterior third ventricle soft anaplastic ependymoma, which, despite the complete endoscopic removal documented by a subsequent endoscopy, recurred 16 months later. Differential diagnosis and therapeutic strategies are discussed.

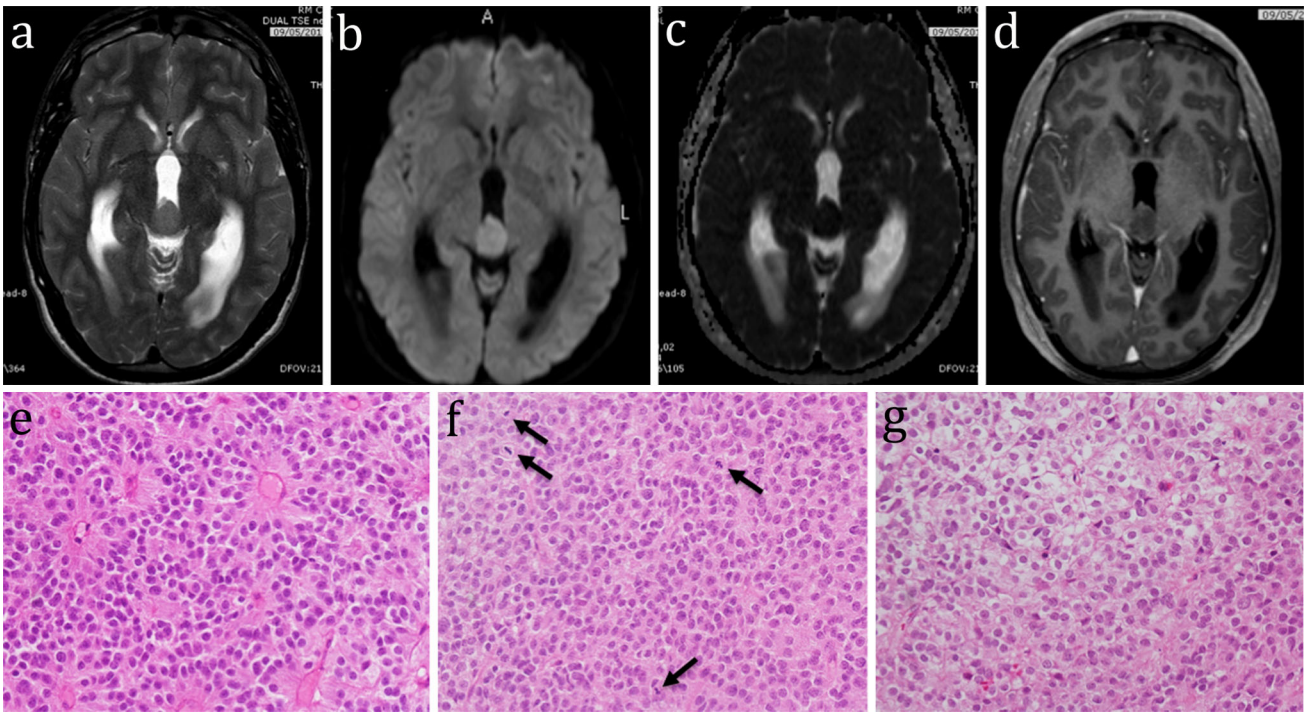

Fig. 1 **a** T2-weighted axial MRI showing an egg-shaped lesion, obstructing the aqueduct and producing hydrocephalus. The homogeneous hypointensity is consistent with high cellularity of the tumor. **b** Diffusion-weighted (DW) axial MRI and **c** DW ADC axial MRI appears slightly restricted, according to hypercellularity. **d** MPR T1-weighted axial MRI with gadolinium showing no enhancement of the lesion. **e** HE staining showing typical perivascular pseudorosettes, strips of epithelial cells partially lining the tumor fragments, and focal papillary structures. **f** HE staining revealing regions with high mitotic index (*arrows*), and **g** increased cellularity with focal clear cell morphology

Clinical summary

A 22-year-old male patient presented with a 40-day history of worsening headache, associated with nausea in the last week. Admission MR images showed a 2.1 × 1.6 × 1.4 cm (2.35 cm^3) mass located between the abenular and the posterior commissures, obstructing the aditus of the aqueduct and causing an occlusive hydrocephalus. The tumor presented as a predominantly solid, homogeneous mass, hypointense in T1 and T2. It showed a reduced diffusion, presumably due to high cellularity, and a slightly high intensity on FLAIR, due to the soft tissue components. It demonstrated no significant enhancement, remaining diffusely hypointense on postgadolinium T1-weighted images (Fig. 1a–d). Neurological examination at admission was normal.

Surgery

The patient underwent a neuroendoscopic procedure through a right frontal approach. A flexible scope (Karl Storz GmbH and Co., Tuttlingen, Germany) with a 3.7 mm diameter was introduced through a right precoronal burr hole placed 2 cm from the midline, with the help of a peel-away. The scope was then managed using a free-hand technique. Navigation of the third ventricle allowed a full visual control of the tumor. Close endoscopic examination showed a vascularized, soft mass. The tumor was removed using the work channel of the scope as a surgical aspirator directly placed on the tumor surface in the way experienced by the senior author to aspirate blood cloths in ventricular hemorrhages [16]. An ETV was performed to provide a higher chance to prevent hydrocephalus. The postoperative course was uneventful with symptoms resolution. An immediate postoperative cerebral MRI confirmed the gross total resection of the lesion. A spinal MRI did not show any pathological enhancement after gadolinium.

Pathological findings

The smear performed during surgery showed small cells with monomorphous nuclei suggesting a diagnosis of ependymoma. Consistently, histopathological examination revealed the presence of moderately cellular areas with perivascular pseudorosettes and focal papillary structures (Fig. 1e). Beside these typical areas, the tumor featured regions with increased cellularity, a more diffuse growth pattern, and focal clear cell morphology (Fig. 1f, g).

In these areas, proliferation activity was quite high, with a mitotic index of >10 per 10 HPF, and Ki67 expression in 30 % of neoplastic cells. Transition between these different areas was gradual, and a clear nodularity was not evident. Nuclei were relatively monomorphic with inconspicuous nucleoli throughout the tumor. Palisading necrosis and microvascular proliferation were absent. Immunophenotype analysis showed that the majority of neoplastic cells expressed GFAP, but not EMA. Neurofilaments were scattered, consistently with the solid growth pattern of the tumor. Neuroendocrine/neural markers (Synaptophisyn, Chromogranin and Neu-N), as well as epithelial markers (CAM5.2, CKAE1/AE3, CK18) were negative. Despite the absence of EMA staining, the morphological and immunophenotypical features argued for the ependymal differentiation of the tumor. We interpreted the tumor as an ependymoma, assigning a grade III designation based on both tumor cellular density and mitotic index, despite the absence of microvascular proliferation and necrosis. Consistently, at molecular level the tumor showed neither 1p/19q co-deletion, nor *IDH1*/*IDH2* mutation. Nonetheless, it demonstrated loss of 22q, 6q, 10q, which are frequently seen in intracranial ependymomas [17]. Although the tumor did not show gain at 1q25, which is considered an unfavorable prognostic marker, it showed heterozygous deletion of one copy of 9p, which includes the locus of the tumor suppressor gene CDKN2A [18, 19].

Adjuvant therapy and follow-up

The patient underwent conformational radiotherapy (60 Gy in 30 fractions), which was completed 3 months after surgery. Chemotherapy with Cisplatin and Lomustine was discontinued at cycle 2 because of bladder toxicity.

Four months after surgery, the patient complained of headache and nausea. A cerebral MRI showed the presence of triventricular hydrocephalus. Cine-flow sequences revealed a weak flow through both the third ventriculostomy and the aqueduct. For this reason, the patient was admitted to our department and underwent a second neuroendoscopic procedure to redo ETV. The posterior aspect of the third ventricle was also accurately inspected, showing no signs of neoplastic tissue. The postoperative course was uneventful with complete resolution of symptoms.

The patient was asymptomatic with negative scheduled MRIs until 16 months from the initial diagnosis, when he underwent a generalized epileptic seizure and was hospitalized. A new MRI showed a 3.5-cm frontal cystic lesion with an enhancing mural nodule. The mass was localized along the trajectory of the former neuroendoscopic procedure. A 30 × 18 mm non-enhancing tumor was also observed at the left Luschka foramen (Fig. 2a–j). The frontal mass was removed through a frontal craniotomy, and proved to be a tumor recurrence. Notably, the neoplasm was confined to the sub-arachnoidal space with no clear cortex invasion (Fig. 2k). Compared to the primary tumor, despite the nuclear monomorphic morphology and the clear-cut ependymal differentiation with pseudorosettes and canals, the cellular density and the proliferation activity were remarkably and homogeneously higher throughout the tumor, with a mitotic index of 26 mitoses per 10 HPF, and a Ki-67 of 40 %. Moreover, the tumor featured microvascular proliferation (Fig. 2k) and multiple foci of necrosis, lacking a genuine peripheral palisading (Fig. 2l).

The recurrence at the Luschka foramen was treated with stereotactic radiotherapy (2500 cGy in 5 fractions). A cerebral and spinal MRI performed 4 months after stereotactic radiotherapy showed no sign of disease with the disappearance of the fourth ventricular lesion. Cells of uncertain origin were detected in CSF after lumbar puncture. Chemotherapy was scheduled with temozolomide. Unfortunately, 8 months later an MRI showed the presence of multiple nodules at the level of the frontal surgical field, in the left ventricle, and at the level of cauda equina.

Discussion

Ependymomas are tumors of neuroepithelial tissue that occur in both brain and spinal cord. Intracranial ependymomas represent about 2 % of all intracranial tumors in adult patients, and 6–10 % of brain tumors in children [20, 21]. Aside from the subependymoma and the very rare myxopapillary ependymoma (WHO grade I), intracranial ependymomas are divided between classic (WHO grade II) and anaplastic (WHO grade III) tumors. In accordance to the last WHO classification, anaplastic ependymomas are characterized by "increased cellularity and brisk mitotic activity, often associated with microvascular proliferation and pseudopalisading necrosis" [17]. After a PubMed research using the words "anaplastic", "intraventricular", and "ependymoma", we found only 53 cases of intraventricular anaplastic ependymoma (Table 1). The male:female ratio is 3:1, and affected patients are usually children or young adults (average age is 10 years). The third ventricle is the least common location for an intraventricular anaplastic ependymoma (6 cases). Symptoms are often related to intracranial hypertension due to hydrocephalus. Surgery is the treatment of choice, and is usually followed by radiotherapy. Chemotherapy is commonly reserved for children to defer radiotherapy, or for those patients with recurrent tumor [11, 35]. There is a wide consensus on the prognostic value not only of the extent of tumor resection, but also of age and tumor site.

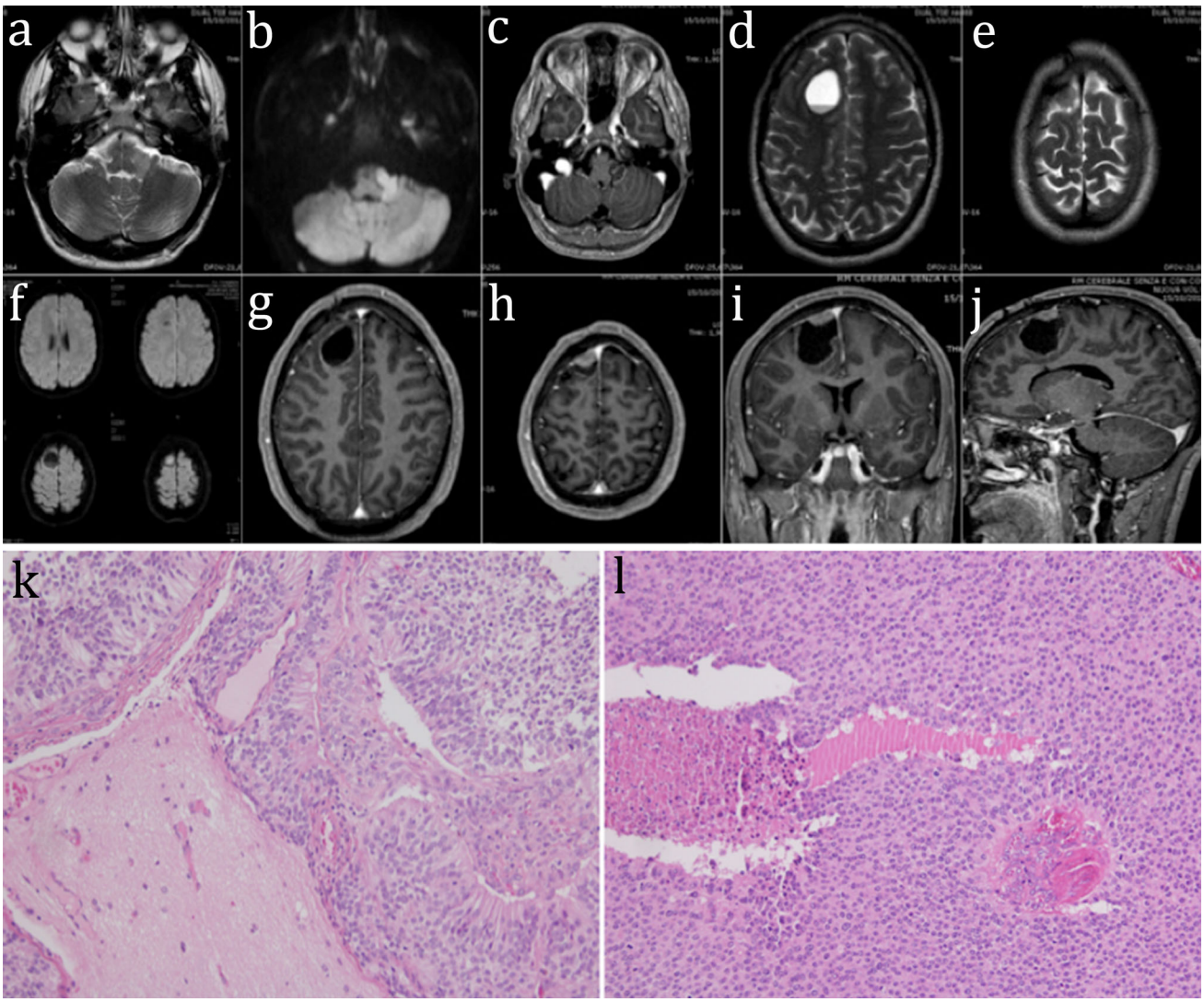

Fig. 2 **a** T2-weighted axial MRI showing a hypointense relapse at the level of the *left* Luschka foramen, with **b** restricted diffusion and **c** no enhancement on T1-weighted MPR after gadolinium. **d**–**e** T2-weighted axial MRI showing a *right* frontal cystic lesion with fluid level in the posterior part and a solid component at the *top*. The *solid tissue* shows restricted diffusion (**f**), and pathological enhancement after gadolinium on axial (**g**, **h**), coronal (**i**), and sagittal (**j**) MRI. **k** 20× HE staining showing no clear cortex invasion of the neoplastic cells. **l** 40× HE staining displaying multiple areas of necrosis and microvascular proliferation

Elder age and spinal location are actually associated with longer survival [11, 36]. Conversely, the importance of the histological grade is still debated [11]. While the WHO criteria for anaplasia led to a successful correlation between grade and outcome in some series [4, 9], they failed in others [37, 38]. In our case, despite the absence of necrosis and microvascular proliferation, the degree of cellular density and more importantly the mitotic index were far beyond those generally accepted for grade II ependymomas. For this reason, particularly in the context of an intracranial location, we decided to assign a grade III WHO. Actually, the histological grade unfortunately proved to be predictive of the outcome. For posterior fossa ependymomas, gain of 1q and more recently expression of LAMA2 have been associated either with anaplastic histology or more aggressive behavior [10, 18, 39]. Interestingly, our case showed loss of 9p, in accordance with previous CGH studies. A homozygous or a heterozygous deletion at 9p21.3 spanning *CDKN2A* locus has been observed almost exclusively in supratentorial tumors [38, 40, 41]. Moreover, most of the cases bearing this chromosomal alteration featured an anaplastic morphology or behaved aggressively [38, 40, 41].

When a lesion of the third ventricle occurs in a young adult the differential is broad and includes germinoma, papillary tumor of the pineal region, pineal parenchymal tumor and astrocytoma. In these cases, histology is crucial to make the correct diagnosis. In our patient, MRI was not

Table 1 Intraventricular anaplastic ependymomas: literature review

References	No. of patients	Sex	Age	Ventricle	Symptoms	Treatment	Recurrence	Recurrence treatment	Metastasis	Follow-up (months)	Outcome
Nijssen et al. [22]	3	M	5 years	IV	Headache, vomiting, somnolence, right hemiataxia	Surgery + RT + CT				120	Alive
		M	21 months	Lateral	Vomiting, lethargy, macrocephaly delayed development of motor skills	Biopsy				4	Dead
		M	8 months	IV	Vomiting, delayed motor skills	Surgery + CT	22 months	Surgery		30	Alive
Spagnoli et al. [23]	6		Average 18 years	IV	Intracranial hypertension	Surgery + RT + CT				Average 75	Dead
Guyotat et al. [24]	7		Average 46 years	Lateral (2), III (3), IV (2)	Intracranial hypertension	Surgery + RT				Average 108	
Endo et al. [25]	2	F	14 years	R lateral	Headache, nausea and vomiting	Surgery + RT	53 months	Surgery + GK + CT	Brain	120	Alive
		M	14 years	IV	Headache, nausea	Surgery + CT + RT	19 months	GK + Surgery + CT	Spine	53	Alive
Iddrissu et al. [26]	1	M	4 years	IV	Neck pain, unsteady gait, vomiting	Surgery + RT				13	Alive
Rutten et al. [27]	1	M	5 years	IV	Headache, vomiting, dysmetria, nystagmus	Surgery + RT	12 months	Surgery + RT	Spine	108	Alive
Rodriguez et al. [28]	1	F	5 years	IV	Headache, nystagmus	Surgery + RT					
Kumar et al. [29]	1	M	10 years	R lateral	Progressive loss of vision, headache, vomiting	Surgery + RT + CT	72 months	Surgery + CT	Scalp	120	Alive
Lopez-Gines et al. [30]	1	M	34 years	III	Right hemiparesis, headache, dizziness	Surgery + RT	12 months	Surgery		15	Dead
Sharma et al. [31]	23		Average 13 years	Lateral (22), III (1)							
Ghosal et al. [32]	1	M	16 years	IV	Cerebellar ataxia, right hemiparesis	Surgery	12 months	Surgery		17	Alive
Saito et al. [33]	5	F	<1 year	IV		Surgery + CT	3 months			4	Dead
		F	9 years	IV		Surgery	10 months	Surgery + CT + GK		Lost	
		M	14 years	IV		Surgery + CT	26 months	GK + surgery + CT		65	Dead
		M	2 years	IV		Surgery + CT				71	Alive
		M	1 year	IV		Surgery + CT				5	Alive

Table 1 continued

References	No. of patients	Sex	Age	Ventricle	Symptoms	Treatment	Recurrence	Recurrence treatment	Metastasis	Follow-up (months)	Outcome
Sung et al. [34]	1	M	16 months	III		Surgery + CT + RT				37	Alive
Present case	1	M	22 years	III	Headache, nausea	Surgery + CT + RT	16 months	Surgery + SR	R frontal, L ventricle, cauda equina	28	Alive

M male, *F* female, *R* right, *L* left, *CT* chemotherapy, *RT* radiotherapy, *GK* Gamma-knife, *SR* stereotactic radiotherapy

suggestive of ependymoma since the lack of enhancement is quite unusual for this entity. However, based on the histology, the diagnosis was straightforward. The possibility of a papillary tumor of the pineal region, consistent with the focal presence of papillary structures, was ruled out because of the lack of expression of epithelial markers, particularly CK18. Similarly, pineal parenchymal tumor of intermediate differentiation with a diffuse pattern of growth was taken into consideration based on the relatively small size of the cells and nuclear monomorphism. However, the absence of synaptophysin expression as well as the diffuse GFAP expression argued against this hypothesis. Moreover, the possibility of an oligodendroglioma, which was evoked by the presence of clear cells, was ultimately excluded by the absence of IDH1/2 mutation and 1p/19q co-deletion.

Conversely, the tumor showed loss of 22q and 6q, as it is frequently seen in intracranial ependymomas [39]. According to the anaplastic morphology, the tumor showed loss of 9p.

The therapeutic strategy should always include the surgical removal of the tumor. We usually plan an endoscopic biopsy for intraventricular tumors. When the tumor is small, pedunculated, and it shows soft consistency at direct intraoperative examination, it is possible to remove it during the same procedure [13]. However, it is worth noting that in this case the tumor recurred 1 year later in two different locations, including along the endoscopic trajectory. Although to our knowledge this pattern of relapse has not been previously described for ependymomas, spread through surgical approach can occur with other histotypes including craniopharyngioma [42], pineoblastoma [43], and medulloblastoma [44]. This phenomenon seems to be independent on the surgical strategy, as it has been reported after both open surgery and stereotactic biopsy. In our case, the anaplastic features of the tumor make this unlucky event not surprising. Follow-up information about anaplastic ependymomas of the third ventricle is mostly lacking. Of the 2 patients with a complete clinical history, one died 15 months after recurrence.

Anaplastic ependymomas of the third ventricle are very rare. When they are small, soft, and pedunculated, they are potentially amenable of radical removal through a neuroendoscopic procedure. However, spread through CSF is possible, and recurrences are extremely frequent. Adjuvant therapy should be considered also after gross total surgical removal of the tumor.

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

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