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An extremely rare case of choroid plexus carcinoma in the third ventricle of an infant – Case report and review of the literature

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ABSTRACT

Background: Choroid plexus tumors are rare intraventricular tumors. Most of these tumors are benign choroid plexus papillomas. Choroid plexus carcinoma is the most malignant choroid plexus tumor and constitutes a small percentage of these tumors. The most common location of these tumors is the lateral ventricle and fourth ventricle in pediatric and adult patients respectively. Rare locations such as the third ventricle are reported in the literature with 55 reports of choroid plexus papilloma and just 3 cases of carcinoma located in the third ventricle.

Case description: We present an extremely rare case of choroid plexus carcinoma of the third ventricle in a 9 months old boy which was resected successfully through transcortical-transforaminal approach along with a review of literature available around different aspects of these tumors.

Conclusion: Choroid plexus carcinomas even in rare locations such as the third ventricle can be effectively resected through the transcortical-transforaminal approach, although post-operative subdural effusion can be a potential complication.

1. Background

Third ventricular tumors are uncommon and account for about 0.6–0.9% of all brain tumors [1]. Choroid plexus tumors (CPTs) are rare CNS tumors and comprise 0.5%-0.6% of intracranial neoplasms in all ages [2,3]. These tumors are classified as WHO grade I choroid plexus papilloma (CPP), WHO grade II atypical choroid plexus papilloma (aCPP), and WHO grade III choroid plexus carcinoma (CPC) [4]. Ten percent of CPTs are seen in children younger than 5 years [5]. Its common location is in the lateral ventricle and fourth ventricle in children and adults respectively [6–8]. The third ventricle is an uncommon location for CPTs beside other rare locations such as the cerebellopontine angle, the Luschka foramen, or brain parenchyma [9–12]. aCPP and CPC together comprise about 25 percent of all CPTs [13]. To our knowledge, there are 55 cases of CPP and just 3 cases of CPC [14–16] reported in the third ventricle in the literature to date and this is the 4th report of an extremely rare third ventricle choroid plexus carcinoma till now. So, we present a case of CPC in anterior third ventricle which was successfully excised through a transcortical-transforaminal approach.

2. Case report

2.1. History and physical examination

A 9 months old male infant was referred to our institute with symptoms of a rise in intracranial pressure (ICP) such as macrocephaly (head circumference: 47 cm − 90th percentile) and sunset eyes since a couple of weeks before admission. Upon detailed examination, the patient was conscious but lethargic and without crying response to the stimulus. Bulging and tension of anterior fontanelle were evident. The infant's muscle tones were significantly diminished without noticeable paresis. Upon funduscopic examination, bilateral papilledema was encountered.

Abbreviations: CPT, Choroid Plexus Tumor; CPP, Choroid Plexus Papilloma; aCPP, Atypical Choroid Plexus Papilloma; CPC, Choroid Plexus Carcinoma; CNS, Central Nervous System; WHO, World Health Organization; ICP, Intracranial Pressure; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; VPS, Ventriculoperitoneal Shunt; ICU, Intensive Care Unit; CSF, Cerebrospinal Fluid; HPF, High Power Field; EVD, External Ventricular Drainage; ETV, Endoscopic Third Ventriculostomy

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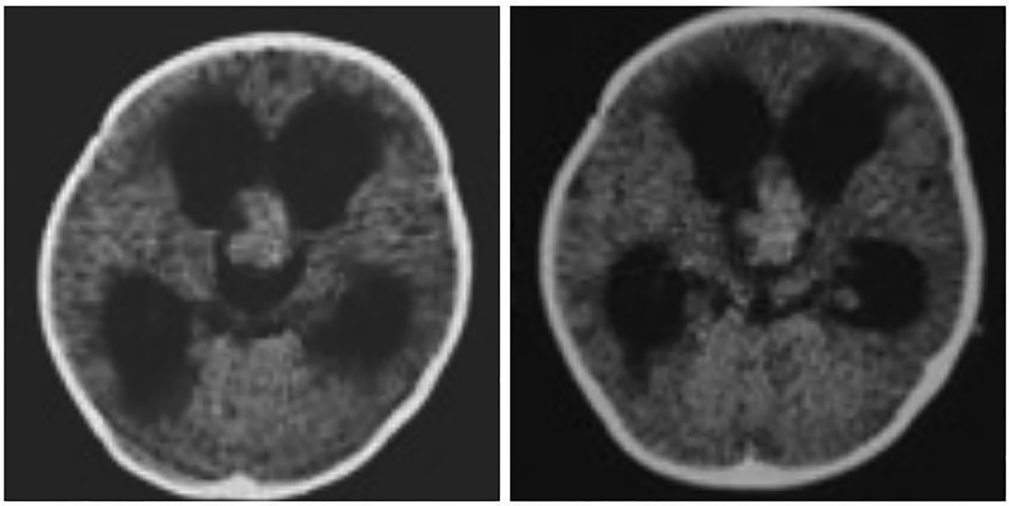

Fig. 1. Pre-operative non-contrast brain CT scan of the infant showing a lobulated hyperdense lesion within the third ventricle along with significant hydrocephalus.

2.2. Imaging findings

In non-contrast computed tomographic (CT) scanning, a large lobulated relatively hyperdense mass lesion was evident in anterior third ventricle causing significant hydrocephalus (Fig. 1). Following MRI evaluation, the lesion appeared as isointense lobulated mass relative to white matter on both non-contrast T1 and T2 with significant homogenous bright enhancement on contrast-enhanced T1 images. The lesion diameters measured approximately 26.5*33.2*28.4 mm and it was located within the anterior two-thirds of the third ventricle causing significant ventriculomegaly and periventricular edema (Fig. 2).

2.3. Management and surgical technique

Due to progressive drowsiness and unresponsiveness of the patient during the course of admission and suboptimal situation for emergent tumor resection, he was initially treated with an emergent ventriculoperitoneal shunting (VPS) procedure which led to significant improvement in patient symptoms. As a result of the higher infection rate of external ventricular drains, we preferred a shunt over ventriculostomy. Two days later, the patient has undergone an elective total resection of the tumor through a right frontal transcortical-transforaminal approach to the third ventricle. After general anesthesia, the patient was positioned in a supine position on a horseshoe head holder and with 20 degrees of head elevation (Fig. 3A). After the administration of local anesthetic, a horseshoe incision was made on the right side centered 2 cm lateral to the midline and anterior to the coronal suture (Fig. 3B). After performing a minor craniotomy mostly located anterior to the coronal suture (Fig. 3C), the dura was opened and reflected. Approach to the frontal horn of right lateral ventricle was made through superior frontal sulcus and after placement of retractors, a dilated Monroe foramen occupied by a cauliflower friable grayish-red colored tumor was evident. Due to significant bleeding of these tumors, microscopic circumferential dissection, coagulation, and disconnection of tumor vascular supply from the third ventricle roof were performed initially, and then the tumor was removed divided into a few large segments without significant bleeding (Fig. 3F). Exact intraoperative bleeding volume was measured as 180 cc by neuroanesthesia team which did not exceed calculated maximal allowable blood loss (MABL) of 200 cc and blood transfusion was not required during operation.

2.4. Post-operative course

The patient was totally alert and without any neurological deficit in the immediate post-op period and also passed an uneventful post-operative period. The infant was transferred from ICU and discharged from hospital on postoperative days 1 and 3 respectively. Postoperative MR imaging revealed total tumor removal with no residual enhancement, no evidence of injury to the fornix, a significant decrease in ventricular size, and a small right convexity hygroma (Fig. 4). The infant was brought for a follow-up visit 2 weeks after discharge along with a follow-up CT scan. Despite the lack of any signs and symptoms of intracranial hypertension or neurological deficit, significant shunt overdrainage and resultant hygroma were evident in the CT scan (Fig. 5). So, the patient was admitted and shunt closure was done at the level of the clavicle and after two days of monitoring the patient for hydrocephalus, it was completely removed. We discussed the available options for adjuvant therapy in a tumor board session in our institute with the participation of two neurosurgeons, a pediatric oncologist, a radiotherapist, a radiologist, and a pathologist and eventually, it led to the unanimous choice of chemotherapy as optimal adjuvant therapy for the patient. The patient was discharged free of any complaints or symptoms and referred to an oncologist for adjuvant chemotherapy. The patient received chemotherapy with Cisplatin, Etoposide, Vincristine regimen, and it was well tolerated by the patient. Up to now, the patient is followed for 11 months and there are no neurological or imaging findings of recurrence or complications.

2.5. Pathological findings

Histological examination showed a papillary neoplasm with fibrovascular connective tissue covered by multiple layers of cubic to columnar cells with significant hypercellularity. Multiple foci of necrosis and pleomorphism were evident. Conspicuous mitoses were seen and the measured Ki67/MIB-1 labeling index was 20%. So, the diagnosis of choroid plexus carcinoma (WHO grade 3) was reported (Fig. 6).

3. Discussion

3.1. Epidemiology

CPTs are rare CNS tumors and account for 0.5%-0.6% of all intracranial neoplasms in all ages [2,3]. About 5% of all CPTs are located in the third ventricle [17]. According to multiple reports, third ventricle CPP comprises a very rare entity [11,18,19]. 14% of choroid plexus tumors occur during infancy although there are reports of third ventricle choroid plexus papilloma during the 5th decade of life [20,21]. In the majority of reports, there is no reported sex predilection in CPTs

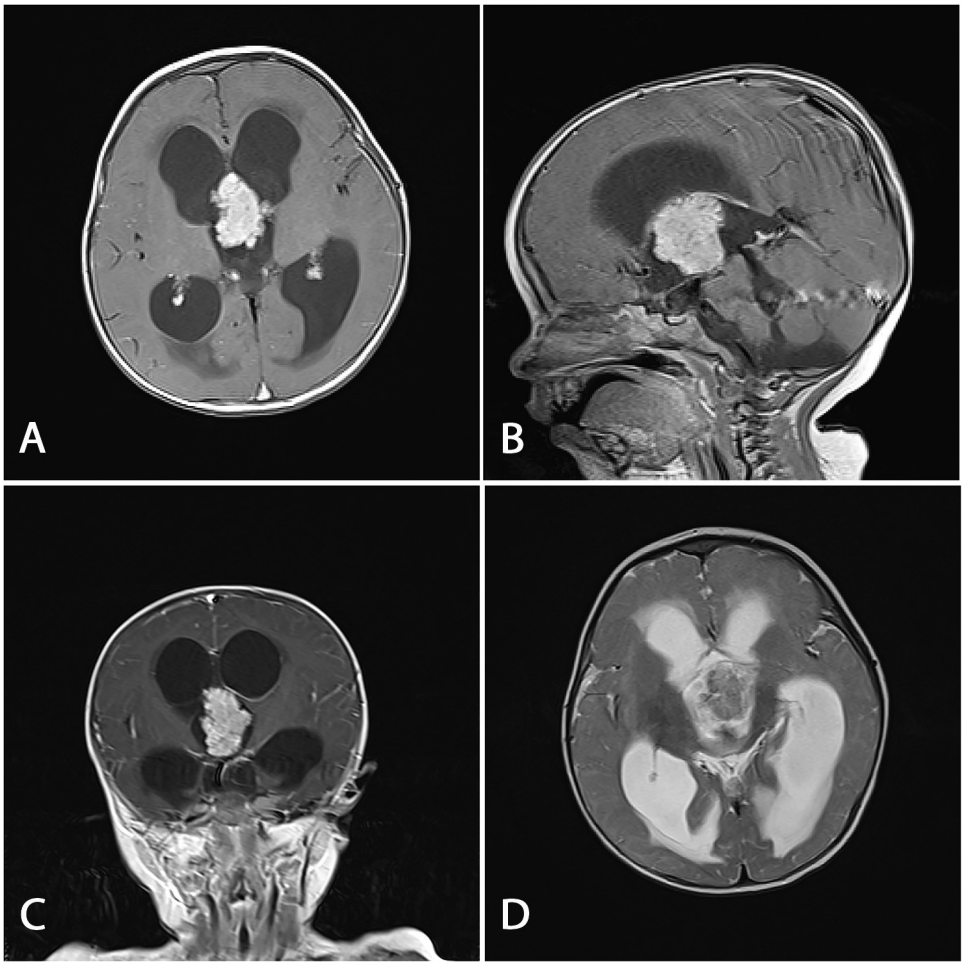

Fig. 2. Pre-operative contrast-enhanced axial (A), sagittal (B), and coronal (C) brain MR imaging of infant showing lobulated homogenous brightly enhanced lesion within the third ventricle. Axial T2 imaging (D) shows a lobulated mass with an isointense signal relative to white matter and significant periventricular edema.

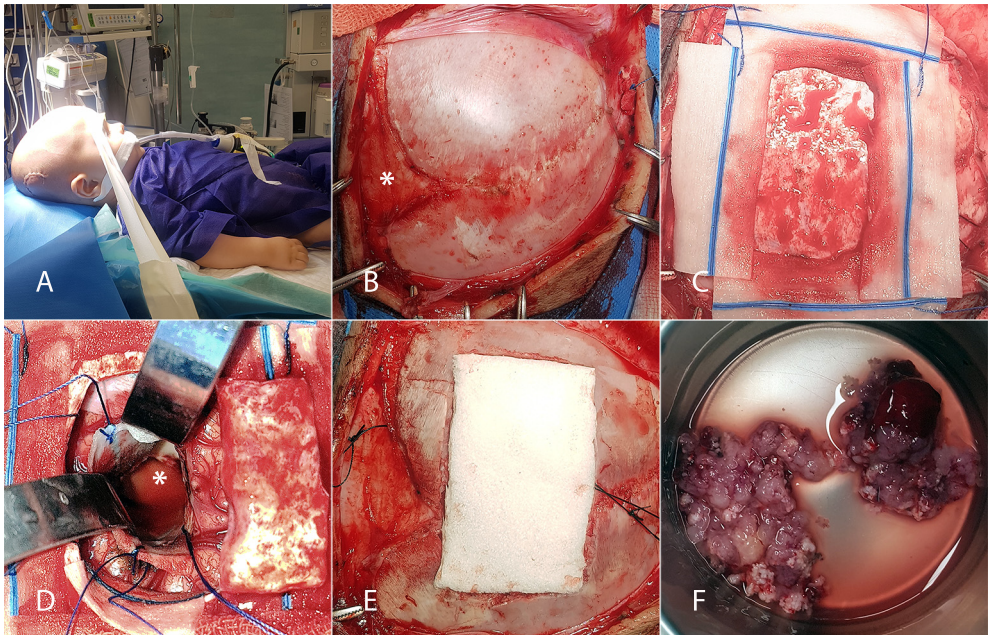

Fig. 3. Intra-operative images. The patient was positioned supine with slight neck flexion and head elevation (A). After skin flap reflection and shaving of the pericranium, the anterior fontanelle (*) and the coronal suture was a useful guide to demarcate the extents of craniotomy (B). A 3*2cm craniotomy was performed (C). After complete tumor removal the tumor-free dilated third ventricle (*) can be seen through the Monroe foramen (D). After dural closure, a layer of Gelfoam was placed over the craniotomy site to prevent adhesion of bone flap to the underlying dura and facilitate future approaches in case of tumor recurrence (E). Excised tumor segments had cauliflower appearance indicating choroid plexus origin of the tumor (F).

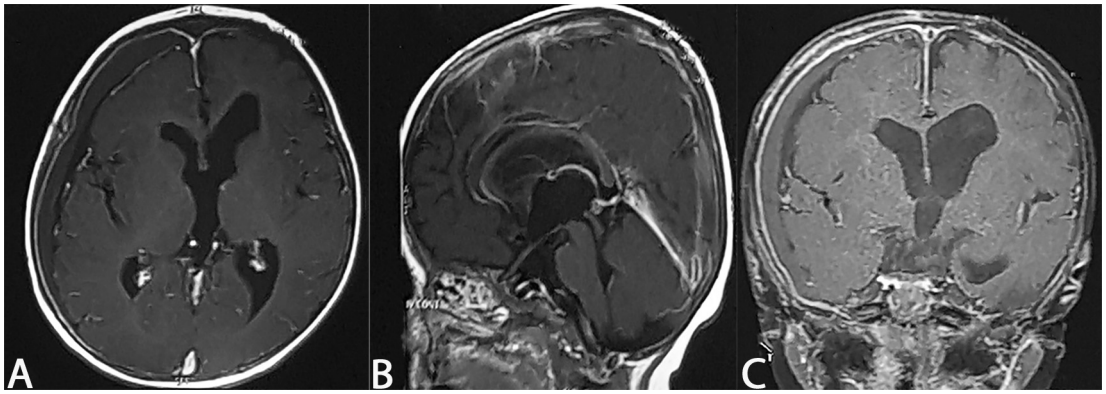

Fig. 4. Post-operative contrast-enhanced axial (A), sagittal (B), and coronal (C) brain MR imaging of patient showing total tumor removal without any residual enhancement and a small right convexity hygroma.

[22,23]. CPCs are almost 4 fold more common in children than adults [13]. In the literature, there are 55 cases of reported CPPs and just three cases of CPC located in the third ventricle which elicits extreme rarity of third ventricle CPC.

3.2. Clinical features

According to anatomic specifications of the third ventricle, CPTs in this location tend to be symptomatic earlier in life than tumors located in other common locations [24]. Common presentation in the pediatric population is hydrocephalus manifested as macrocephaly, splaying of cranial sutures, fontanel widening/bulging, and forced downward gaze, also known as sunset eyes. Older patients suffer from headaches, nausea, vomiting, and visual disturbances [25]. These tumors can infrequently manifest as bobbing head doll syndrome or endocrine abnormalities [25,26]. In our case, ICP rising manifestations such as sunset eyes and sutural splaying were dominant regarding the patient's age.

3.3. Imaging characteristics

In CT and MR imaging, CPTs present as well-defined large lobulated masses. They appear as hyperdense structures in CT images as a result of micro-hemorrhages and micro-calcifications [27]. On MR imaging, tumor signal usually seems to be isointense on T1 and isointense to moderately hyperintense on T2 sequences. Due to the high vascularity of structures derived from choroid plexus, these tumors enhance brightly and homogenously after administration of contrast agent on both CT and MRI. Calcifications are rare in children but may be seen in 14–25% of cases in all ages [26,28]. There are no specific imaging criteria for CPCs, but parenchymal invasion or heterogeneous enhancement as a result of necrotic areas, calcifications, or micro-hemorrhages may be a clue [29]. As can be seen, there were no such imaging characteristics of carcinomas in our case which emphasize the fact that CPCs can't be diagnosed solely on radiological grounds. CPTs are often accompanied by significant hydrocephalus. Pathophysiology of hydrocephalus can be related to CSF overproduction, obstruction of CSF pathways, hemorrhage from tumor leading to arachnoid villi dysfunction, and high CSF protein content [7,11,26]. Despite all these imaging specifications, diagnosis may be challenging in uncommon locations.

3.4. Histopathology

Microscopically, CPPs are composed of well-structured fibrovascular papillary formations lined by a single layer of columnar or cuboidal epithelium without malignant features. In contrast, CPCs are recognized with the presence of at least four of five malignant features such as increased cellularity, high mitotic activity (more than 5 in 10 HPF), multiple areas of necrosis, highly pleomorphic nuclei and blurring of papillary architecture [4]. Occasionally, CPTs show one or a few of the aforementioned malignant parameters but not enough to classify

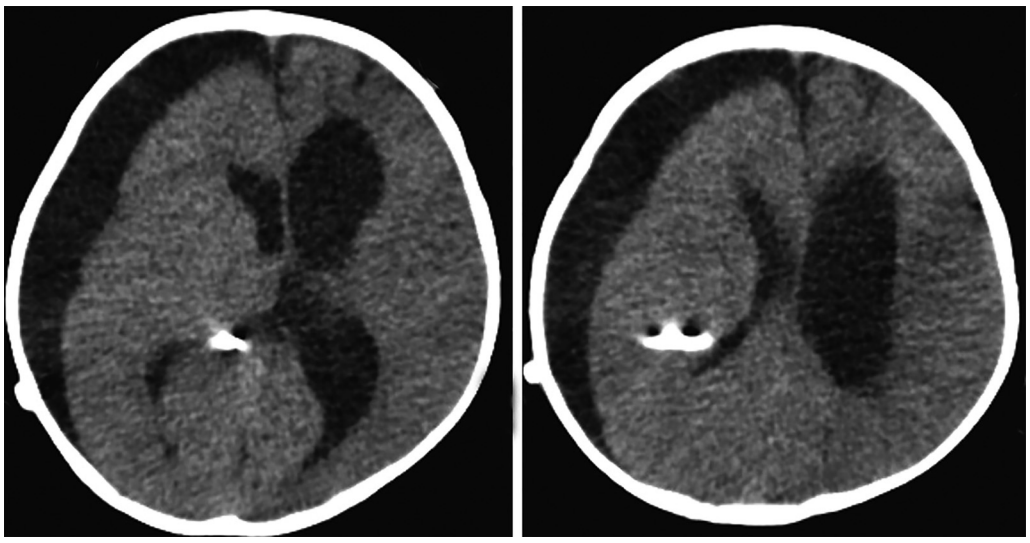

Fig. 5. Follow-up brain CT scan of patient 2 weeks after discharge showing significant shunt overdrainage and marked right convexity hygroma.

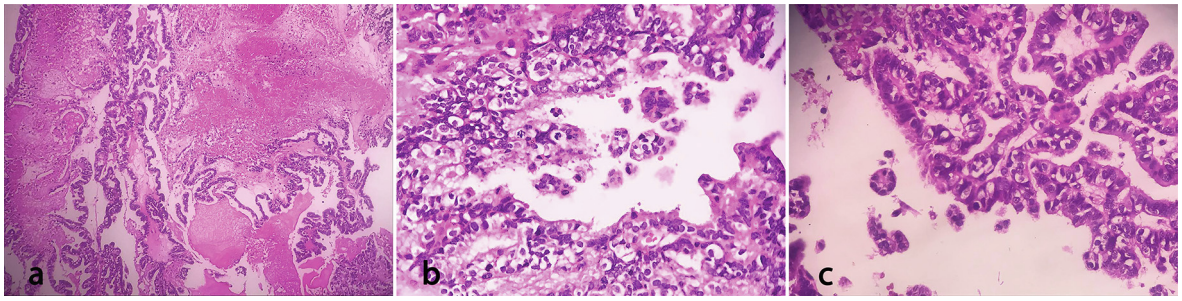

Fig. 6. Histological examination of the resected tumor showing focal necrosis (A), hypercellularity and pleomorphism (B), and increased mitosis (C) leading to the diagnosis of choroid plexus carcinoma (Hematoxylin-Eosin staining).

them as CPC. So, aCPP is recognized as an intermediate entity regarding mitotic activity since the 2007 WHO classification. Clear diagnostic criteria have not been established but high mitotic figures (more than 2 in 10 HPF) without other malignant features can lead to the diagnosis of aCPP[13]. There is a direct relationship between Ki-67/MIB-1 staining and tumor grade. Mean values of MIB-1 index in CPP, aCPP, and CPC are reported as 1.3–4.5, 5.8–9.1, and 13.4–20.3 percent respectively [30–32]. In the histological examination of tumor specimens in our case, diffuse blurring of papillary structures, increased cellularity, multiple areas of necrosis, and significant pleomorphism was leading to the diagnosis of CPC. Measured MIB-1 index was 20% which is also in favor of CPC.

3.5. Management

Surgical resection is the first-line treatment in all CPTs. Because of small diameters and complex neuroanatomy of the third ventricle, resection of tumors in this area are challenging and highly demands expertise [33]. Due to the high vascularity of these tumors, significant blood loss during resection should be anticipated and effectively managed especially in the pediatric population [7,11,22,26]. Blood loss can be limited by initial finding and securing of arterial feeders which are branches of adjacent choroidal arteries and subsequent coagulation and en-bloc or piecemeal removal of tumor bulk [7,10,25]. There are some reports of preoperative embolization of the feeder artery, however, this approach is challenging and has potential risks of vessel injury or stroke [26,33,34]. Neoadjuvant chemotherapy can be considered as an alternative approach that reduces tumor size and vascularity and facilitates total resection [35].

Optimal management of hydrocephalus in these patients is a matter of debate. The majority of reports suggest emergent ventriculoperitoneal shunting (VPS) procedure in cases of neurological deterioration and definite resection of tumor a few days later after patient stabilization, when facilities for emergent total tumor resection is not accessible. In patients with a stable neurological situation, semi-urgent external ventricular drainage (EVD) placement and tumor resection in one session will be feasible. In these circumstances, EVD tapering and removal or change to VPS should be considered as soon as possible given the high risk of meningitis with EVD in place [11,36]. Pre-operative endoscopic third ventriculostomy (ETV) is another option in patients with non-communicating hydrocephalus with different reported success rates [7]. In three previously reported CPCs of the third ventricle, only one report mentioned preoperative VPS placement and two others did not discuss hydrocephalus management or did not provide individual patient data about this subject (Table 1). In our case, the patient showed significant neurological deterioration as drowsiness and lack of response to stimuli upon admission and severe hydrocephalus on imaging. So, because facilities for emergent resection of the tumor were not available, we decided to emergently place a VPS which resulted in a dramatic clinical response. But, our patient experienced shunt related over-drainage in the follow-up period which is a drawback of this approach, and placement of programmable shunt systems instead of fixed pressure valves can be possibly useful to avoid this complication. As an uncommon complication, intraabdominal seeding of CPC tumor cells through ventriculoperitoneal CSF diversion is reported in the literature and it should be kept in mind in the management of these patients [37]. But, it is a rare complication and can not be considered as a contraindication for VPS placement in patients with CPC.

Although we resected the tumor through the transcortical-transforaminal approach, there are different surgical approaches for different locations of CPTs. Specifically for third ventricle CPTs, transcallosal, transcortical-transforaminal, and endoscopic approaches can be used for resection of tumors located in the anterior third ventricle and infratentorial-supracerebellar, occipital-transtentorial and transcallosal approaches are among the described approaches to posterior third ventricle tumors [10,11,38]. As can be seen in Table 1, among the three previously reported CPCs of the third ventricle transcortical transforaminal approach was used for tumor resection in one case similar to our case, and in another report, the tumor was resected through the transcallosal approach. The choice of surgical approach varies based on location, anatomy, size, and blood supply of the tumor. The transcortical-transforaminal approach is ideal for patients with larger tumors and larger ventricles as in our case. Of the most frequent complications of this approach are seizure and subdural collection, the latter occurred in our case [39]. Although the aim of surgery is gross total resection, it may be not possible as a result of significant bleeding (especially in children) or invasion of critical structures. In the former situation, reoperation at a later time is suggested but adjuvant therapy can be used in the latter [11,36]. Neuroendoscopic biopsy followed by chemoradiotherapy is the best treatment option in cases where the tumor is not resectable [40]. Only in three out of four previously reported cases, gross total resection was achieved (Table 1).

The role of adjuvant therapies in the management of CPTs is controversial. As a consensus, completely removed CPP can be followed without any adjuvant therapy. There are some reports of radiotherapy or radiosurgery in CPTs but they all suggest that these modalities be reserved for patients with the unresectable residual tumor or aggressive subtypes [36,41,42]. Chemotherapy is suggested in cases of higher grade tumors or recurrences, although it showed mixed results. The most debate in this regard is about the role of adjuvant therapy in aCPPs which is a relatively newer entity with few cases reported in the literature [43,44]. The role of adjuvant therapy in CPC is more obvious with some reports of a significant increase in overall survival following adjuvant chemoradiotherapy or chemotherapy alone [29,44–46].

3.6. Outcome

The main prognostic factors in CPTs are the extent of resection and tumor grade. The best outcome is expected for totally resected CPPs with10 year survival of about 100% in different reports [6,25,47]. Whereas, the 5-year survival rate of CPC patients are approximately 58% and 20% after complete or partial resection respectively [29]. In

Table 1
A summary of reported cases of third ventricle choroid plexus carcinoma in the literature and their available preoperative, intraoperative, and postoperative data to be compared to our presented case. GTR: Gross total resection; STR: Subtotal resection; VPS: Ventriculoperitoneal shunt; *Our presented case; ©Some individual patient data were not reported about this exact case in this case series of choroid plexus tumors.

Author, Year	Age at diagnosis	Gender	Tumor location	Surgical approach	Extent of resection	CSF diversion	Adjuvant therapy	Outcome	Follow-up duration	Complications
Broad, 1984	1 day	Male	Anterior 3rd ventricle	Transcallosal	GTR	Preoperative VPS	No adjuvant	Complete remission	12 months	None
Sato, 1989	14 months	Female	Anterior 3rd ventricle	Transcortical Transforaminal	GTR	Not mentioned	Radiotherapy	Not mentioned	Not mentioned	Not mentioned
Zhou, 2018©	25 months	Male	Anterior 3rd ventricle	Not mentioned	STR	Not mentioned	Chemotherapy	Partial remission	Not mentioned	Not mentioned
Tavallaii, 2020*	9 months	Male	Anterior 3rd ventricle	Transcortical Transforaminal	GTR	Preoperative VPS	Chemotherapy	Complete remission	11 months	Shunt related overdrainage

three available reports of CPCs located within the third ventricle, complete remission was achieved in one case after 12 months follow-up but in another case, that gross total resection was not possible the partial remission was the eventual result (Table 1). Natural history and outcome of aCPPs fall somewhere in between, but is not well recognized and needs to be elucidated.

4. Conclusion

As we presented, a highly malignant tumor such as CPC in a surgically challenging location such as the third ventricle can be managed effectively and safely through the transcortical-transforaminal approach. A well-known drawback of this approach is post-operative subdural effusion that can be managed on an individualized basis.

The practical take-home messages of this report can be summarized as below:

1. As previously reported, CPC cannot be differentiated from CPP based on radiological characteristics and this pathology should be in mind in approaching any lesion with suspected choroid plexus origin even in rare locations such as the third ventricle.
2. The transcortical transforaminal approach can be safely and effectively implemented for resection of third ventricle CPC if the tumor blood supply can be found and terminated early in the circumferential dissection of the tumor.
3. Pre-operative ventriculoperitoneal shunting, although reported as an option for management of hydrocephalus in patients with deteriorating conditions, can lead to post-operative overdrainage-related complications. Therefore, if a pre-operative shunting procedure was planned, these complications can be effectively avoided by the implementation of a shunt system with a programmable valve design.

Statement of ethics

This case report is conducted in accordance with the world medical association declaration of Helsinki. Parents of the presented patient (as their legal guardians) have given their written informed consent for publication of data and images of this patient, although all information revealing subject's identity is avoided in this manuscript.

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Author contributions

Amin Tavallaii: Conception and design, Drafting, Critical revising, Final approval. Ehsan Keykhosravi: Data acquisition, Drafting, Final approval. Hamid Rezaee: Data acquisition, Drafting, Final approval. Mohsen Khamoushi: Data acquisition, Drafting, Final approval.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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