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A rare trifocal presentation of a choroid plexus papilloma: Case report and review of the literature

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ABSTRACT

Introduction: CPP's present as slow-growing intraventricular neoplasms arising from epithelium of choroid plexus. They account for approximately 0.5–4% of intracranial neoplasms in adults and children, respectively. A trifocal presentation is exceedingly rare.
Research question: We describe the case of a trifocal presentation of a CPP and explored the importance of genetic analyses.
Material and methods: We present the case of an 18-year old adolescent who was treated for a fourth ventricular and suprasellar neoplasm. Brain MRI revealed an intraventricular lesion in the fourth ventricle, as well as a suprasellar lesion and a lesion located in the left internal auditory meatus. An adult-subtype CPP (WHO grade 1) was confirmed by means of histological and genetic analyses in the first two regions.
Results: Optimal treatment strategy remains controversial, although it is accepted that surgical resection alone remains the gold standard, whereas chemoradiotherapy is reserved for specific cases. There are only a few articles reporting on a multifocal presentation or the coexistence of synchronous histologically different primary brain neoplasms. Reports on genetic examination are scarce.
Discussion and conclusion: CPP's should be included in the differential diagnosis of posterior fossa tumors, both in children and adults. Genetic analyses (TP53/TERT mutations) should be considered, since they entail important diagnostic, prognostic and therapeutic implications. When a TERT mutation is present, adjuvant radiotherapy should be used with caution, since it plays a role in tumorigenesis, even when GTR could not be achieved. There is an association between TERT methylation status and malignant transformation, indicating that these patients should be followed more closely.

1. Introduction

Choroid plexus papilloma's (CPP) present as slow-growing intraventricular neoplasms arising from the epithelium of the choroid plexus (Anh Tuan et al., 2021; Thomas et al., 2021; Bian et al., 2011; Turkoglu et al., 2014; Peyre et al., 2012; Hosmann et al., 2019). There are only a few studies reporting a multifocal presentation or the coexisting of synchronous histologically different primary brain neoplasms (Scholsem et al., 2012; Wolff et al., 2002; Safaee et al., 2013).

As a primary objective, we summarized the contemporary knowledge concerning the multifocal presentation of these neoplasms, as well as the diagnosis, treatment and basic genetics of CPP's. Moreover, we illustrate the importance of genetic screening and its implication on differential diagnosis, therapeutic stratification and prognostication in CPP. Reports on genetic examination of CPP's are scarce. Therefore, we believe that our case report provides novel insights in the understanding of the behavior and tumorigenesis of (multifocal) choroid plexus papilloma.

2. Case presentation

We present the case of an 18-year old adolescent male who came to our neurosurgical attention in October 2022 because of a fourth ventricular neoplasm. Brain magnetic resonance imaging (MRI), performed in the context of persistent headaches and intermittent paresthesia in his left hand, revealed a mass with homogenous contrast enhancement in the fourth ventricle reaching the craniocervical junction with a slight mass effect on the medulla oblongata (Fig. 1). This lesion did not

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protrude into the foramen of Magendie nor through the foraminae of Luschka. Moreover, two other lesions were noted. One located in the suprasellar region at the infundibular recess and pituitary stalk and another smaller lesion (6 × 5 mm) located in the left internal auditory meatus (Fig. 2). No compression of the pituitary gland was observed. These lesions did not show cystic components nor pathological diffusion restriction. Furthermore, a prominent supratentorial ventricular system was noted. A whole spine MRI did not show any abnormal signal intensities of the myelum nor any signs of drop metastases (Fig. 1). Based on clinical and radiological findings, the following differential diagnosis was postulated: multifocal germ cell tumor (due to midline localization), ependymoma, meningioma, schwannoma (for the lesion in the internal auditory meatus), hemangioblastoma and choroid plexus tumor. The preliminary diagnosis at that time, based on available clinical and imaging information, supported ependyoma.

Anamnesis revealed long-existing bifrontal headache, more pronounced in the morning and associated with nausea without vomitus, as well as intermittent paresthesia in all digits of his left hand. No other abnormalities or symptoms were described, in particular absence of paresthesia or motor deficits elsewhere, nor presence of B-symptoms. Examination of his medical records showed an uncomplicated birth at term, as well as absence of any antecedents or developmental delays. He did not take any prescription drugs. Familial anamnesis showed the following oncological status: mesothelioma (paternal grandfather),

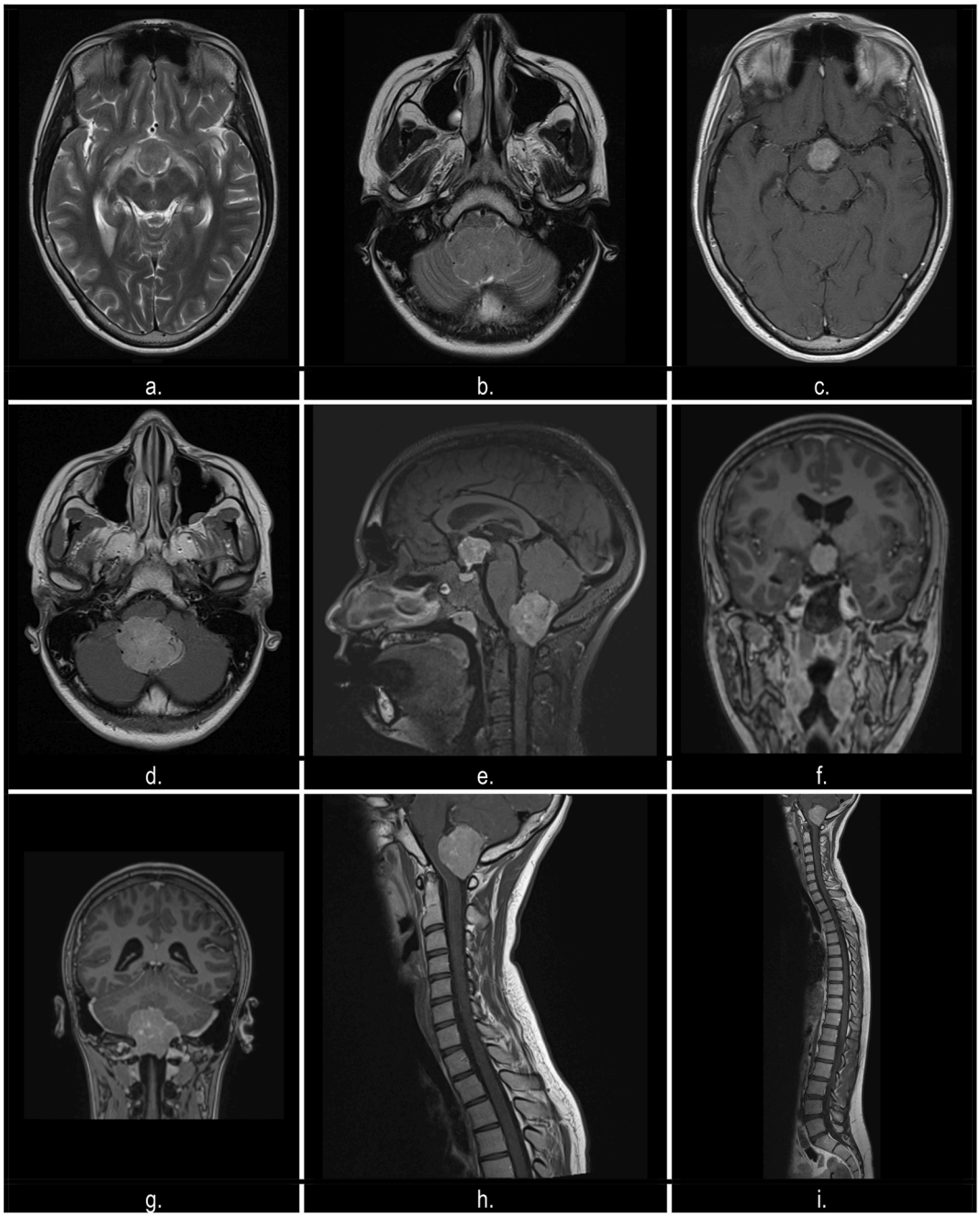

Fig. 1. Figure showing the preoperative MRI studies. The homogeneous contrast enhancing lesion in the fourth ventricle and the suprasellar lesion can be observed. a: T2-weighted imaging, axial plane |b: T2-weighted imaging, axial plane |c: T1-weighted imaging with contrast enhancement, axial plane |d: T1-weighted imaging with contrast enhancement, axial plane |e: T1-weighted imaging with contrast enhancement, sagittal plane |f: T1-weighted imaging with contrast enhancement, coronal plane |g: T1-weighted imaging with contrast enhancement, coronal plane |h: T1-weighted imaging with contrast enhancement of the cervicothoracic spine, sagittal plane |i: T1-weighted imaging with contrast enhancement of the full spine, sagittal plane.

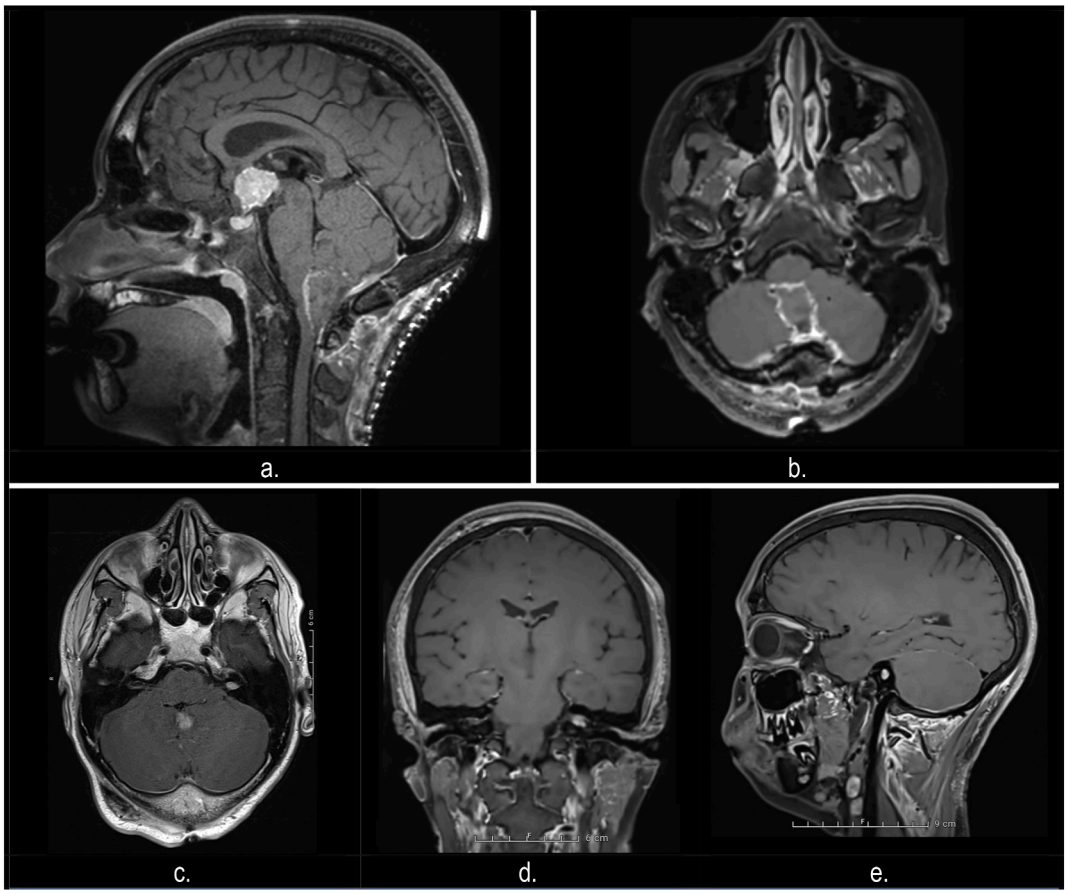

Fig. 2. Figure showing the postoperative MRI studies. The lesion in the left internal auditory meatus can be observed as well. a: T1-weighted imaging with contrast enhancement, sagittal plane |b: T1-weighted imaging with contrast enhancement, axial plane |c: lesion in the left internal auditory meatus, axial plane |d: lesion in the left auditory meatus, coronal plane |e: lesion in the left internal auditory meatus, sagittal plane.

BRCA-negative breast carcinoma (paternal grandmother) and urothelioma (paternal great-grandmother).

Clinical examination showed normal vital signs and a normal height and weight according to age was noted. No hepatosplenomegalia, dysmorphia's, syndactylia nor polydactylia was observed. Dermatological exploration showed a large naevus flammeus at the anterior aspect of his lower leg, as well as congenital café au lait spots at his right elbow and infra-umbilical region. Ophtalmological examination showed slight decreased vision at distance of his left eye (0.63 + 2 mec), as well as grade one papilledema of both eyes on fundoscopy. Fluoroscopy was negative, making the possible etiology of von Hippel-Lindau disease less presumable. Neurological examination was within normal limits, in particular normal cranial nerve function, normal vision, normal motor and sensory function in upper and lower limbs, as well as absence of limb ataxia and a normal gait.

Laboratory findings showed no abnormalities, with normal hormonal function (besides aspecific low IGF-1 values) and normal plasma concentrations of beta human chorion gonadotrophin (beta-hCG) and alpha fetoprotein (AFP).

First, we obtained cerebrospinal fluid (CSF) by means of placing a right frontal external ventricular drain (EVD). CSF results were negative for beta-hCG and AFP. Since germ cell tumor was not likely, we performed neuromonitoring-guided partial resection and obtained biopsies of the mass in the fourth ventricle during the same operation. With our patient in concord position, we performed a suboccipital craniotomy and partial resection of the posterior arch of C1. Because of the adhesion to the rhomboid fossa, partial resection was performed. Due to the association of CPP's and heritable cancer syndromes, a mutation analysis was formed.

Postoperative course was uneventful and without neurological deficits, although a normo-osmolar hyponatriemia did develop which resolved completely by means of fluid restriction. A postoperative MRI, performed the day after surgery, confirmed partial resection of the fourth ventricular mass with decrease of supratentorial ventriculomegalia. In the first day after surgery, the EVD had to be opened several times in the context of intracranial hypertension (short duration ICP's above 50 mmHg). Because the intracranial pressure normalized and he had no headaches, the EVD could be removed five days after primary surgery.

However, two days after removal of the EVD (eight days after primary surgery), our patient began to complain about increased headaches. A CT scan showed an increased volume of the supratentorial ventricular system. Therefore, we decided to place another EVD through the previously made burr hole. Since a second surgery was planned in order to remove as many tumor as possible in the fourth ventricle, we decided not to place a ventriculoperitoneal shunt (VPS) right away, in order to prevent shunt obstruction or possible peritoneal tumor seeding. Twelve days after first surgery, gross total resection through the same approach was performed under neuromonitoring (Fig. 2). Postoperatively, no neurological deficits were noted. However, due to persisting headaches two days after second surgery (fourteen days after first surgery), as well as increased caliber of the lateral ventricles and obstruction of the foramen of Magendie on MRI, removal of a blood cloth in the fourth ventricle was deemed necessary. The EVD was left in situ with controlled continuous evacuation of hemorrhagic CSF. Twentysix days after first surgery, our patient required permanent CSF diversion by means of a VPS.

No circulating tumor cells were found on CSF examinations.

Histological findings showed the presence of abundant calcifications, a papillary architecture with pseudostatified columnar epithelium, as well as absence of atypia or increased mitotic activity. Immunohistochemistry was negative for SSTR2a, EMA, H3K27M, NeuN, CK20, CK7, CD30, OCT3/4 and olig2, while positive for synaptophysin, S100 (low) and prealbumin. KI-67 showed a very low mitotic activity (2–3%). Next Generation Sequencing (QIAamp DNA Mini Kit) showed no mutations for ACRV1, ATRX, BRAF, CDK6, CDKN2A, CIC, DAXX, EGFR, FUBP1, H3F3A, H3F3B, HIST1H3B, HIST1H3C, IDH1, IDH2, MET, NF1, PIK3CA, PDGFRA, PTEN and TP53, although a TERTp (C228T, VAF 39%) amplification was found. No fusion mutations for EGFR, BRAF, FGFR1, FGFR2, FGFR3 or NTRK were mentioned. A DNA methylation assay (Infinium HD Methylation EPIC array and QIAamp DNA Mini Kit) showed no mutations for NF2, TP53, BRCA1, BRCA2, CHEK2, PALB2, ATM, BRIP1, RAD51C, RAD51D, MLH1, MSH2, MSH6 and BARD1. Final genetic analysis showed a CPP of the adult subtype with a negative MGMT promotor hypermethylation status. Therefore, based on these findings, adult-subtype CPP WHO grade 1 was eventually confirmed.

In the following months, regular clinical and MRI checkups were scheduled. An audiogram was performed, both in the context of the lesion in the internal auditory meatus, as well as in the follow-up after adjuvant chemotherapy. This showed a normal pure-tone audiometry and tympanometry (normal Jerger A curve) with presence of otoacoustic emissions in both ears.

In August 2023 (ten months after his first presentation) growth of the suprasellar lesion was noted. Our patient still did not notice any neurological deficits. Because of volume increase of the suprasellar lesion, a stereotactic biopsy was performed. We decided to obtain histological confirmation by means of a stereotactic biopsy rather than to pursue gross total resection, since there was still a possibility of a synchronous histological suprasellar germ cell tumor for which resection is not the preferred treatment modality. Postoperative course was uneventful and without neurological deficits. Anatomopathological examination was similar to our first results, in particular an adult-subtype CPP in the suprasellar region.

3. Discussion

3.1. Choroid plexus papilloma

Choroid plexus papilloma's (CPP) mostly present as slow-growing intraventricular neoplasms of neuroepithelial origin arising from the epithelium of the choroid plexus (Anh Tuan et al., 2021; Thomas et al., 2021; Bian et al., 2011; Turkoglu et al., 2014; Peyre et al., 2012; Hosmann et al., 2019). They account for approximately 1% of brain neoplasms in all age groups, of which 0.5% and 4% of intracranial neoplasms in adults and children, respectively (Anh Tuan et al., 2021; Turkoglu et al., 2014; Wolff et al., 2002; Browne-Farmer et al., 2021; Muñoz Montoya et al., 2019). Previously, it was thought that these tumors were most commonly seen in the pediatric population of which 70% of cases have been identified in patients under the age of two years old (Anh Tuan et al., 2021; Browne-Farmer et al., 2021). However, based on the National Cancer Database of the American Cancer Society (NCBD), 54% of choroid plexus tumors (CPT) were detected in patients older than eighteen years of age, of which CPP's were more commonly encountered in the adult population, while atypical CPP's (aCPP) and choroid plexus carcinoma's (CPC) were more commonly encountered in the pediatric population (Ruiz-Garcia et al., 2020). The average annual incidence for all CPT's is as low as 0.3 out of 1.000.000 per year (Ruiz-Garcia et al., 2020).

In children, CPP's are mostly located supratentorial in the atrium of the lateral ventricles, while in adults they mostly are found infratentorial of which 70% are found in the fourth ventricle (Anh Tuan et al., 2021; Bian et al., 2011; Turkoglu et al., 2014; Muñoz Montoya et al., 2019; Gong et al., 2017). Supratentorial lesions occur at a median age of one and a half years, whereas infratentorial tumors present at a median age of twentytwo years (Turkoglu et al., 2014). Therefore, unlike most other brain neoplasms, the typical adult-supratentorial and pediatric-infratentorial trend is been reverted in this type of tumour (Anh Tuan et al., 2021; Hosmann et al., 2019). Moreover, there seems to be a caudal progression of localization with age, since an infratentorial presentation is mostly seen in older children (Browne-Farmer et al., 2021). However, extraventricular locations have been described, such as pineal region, cerebellopontine angle (Bochdaleck's flower basket), brainstem, sellar and suprasellar region (Bian et al., 2011; Peyre et al., 2012; Muñoz Montoya et al., 2019; Gong et al., 2017; Kuo et al., 2018; Sameshima et al., 2010; Ma et al., 2008). Probably, these lesions develop from embryonic rests of choroid plexus, since both ependymal and choroid plexus cells have the same embryonic origin (Bian et al., 2011). Other reports suggest that these lesions exist through metaplastic transformation of ectopic choroid plexus cells (Bian et al., 2011; Gong et al., 2017).

According to the fifth edition of the WHO classification of central nervous system tumors, CPT's can be categorized as grade one (CPP), grade two (atypical CPP) or grade three (CPC) (Thomas et al., 2021; Turkoglu et al., 2014; Hosmann et al., 2019; Safaee et al., 2013). The later are most frequently encountered in the pediatric population (Turkoglu et al., 2014; Hosmann et al., 2019; Ruiz-Garcia et al., 2020). Based on the NCBD database, 69.2% are CPP's, 16.9% are aCPP's and 13.9% are CPC's (Ruiz-Garcia et al., 2020). There is an equal distribution between males and females, although there is a male predominance in aCPP and CPC (Ruiz-Garcia et al., 2020).

3.2. Symptoms and histology

It is reported that time to presentation of symptoms is shorter in CPP compared to aCPP and CPC, which seems counterintuitive since the former follows a rather benign and slowgrowing pattern (Browne--Farmer et al., 2021).

Microscopic examination typically shows papillary fronds, lined by cuboidal or columnar epithelium, giving it the so called "cauliflower-like" appearance, which can be appreciated macroscopically during surgery (Anh Tuan et al., 2021; Bian et al., 2011; Turkoglu et al., 2014; Peyre et al., 2012; Safaee et al., 2013; Gong et al., 2017).

3.3. Imaging

Imaging typically shows a hyperintense well-circumscribed lobulated lesion with homogeneous contrast enhancement, although presentation can be highly variable (Anh Tuan et al., 2021). In about 25% of cases, speckled ossification inside the tumor can be seen, as was the case in our patient (Anh Tuan et al., 2021). Initial misdiagnosis, as was the case in our patient, is common due to their varying clinical and radiographic presentation, a higher incidence of other brain neoplasms (such as ependymoma, medulloblastoma and pilocytic astrocytoma) and intralesional calcifications more commonly encountered in other brain neoplasms (only in 25% of CPP (Safaee et al., 2013; Muñoz Montoya et al., 2019)) (Anh Tuan et al., 2021; Muñoz Montoya et al., 2019). Perhaps the most challenging differential diagnosis is the one with ependymoma. Posterior fossa ependymoma typically spreads through the foramina of Luschka and Magendie, helping in the differentiation of both tumor types, although CPP can behave in the same way as well (Anh Tuan et al., 2021). Current imaging characteristics are not specific enough to differentiate these two tumor types effectively, necessitatying the need for biopsy (Anh Tuan et al., 2021; Bian et al., 2011).

3.4. Genetics

Until now, little is known about genetic alterations and tumorigenesis, as well as the prognostic value of epigenetic alterations in these neoplasms (Thomas et al., 2021; Ruland et al., 2014). Furthermore, chromosomal aberrations in CPP are complex (Ruland et al., 2014).

Histological appearances do not necessarily predict clinical behavior and histologically benign CPP's can possess genetic alterations that are associated with malignant features, such as dissemination and malignant transformation (Safaee et al., 2013). Therefore, genetic analyses implies important prognostic information.

Based on gene expression, these tumors can be clustered into three distinct DNA methylation subgroups: supratentorial pediatric low-risk CPT (pediatric A), supratentorial pediatric high-risk CPT (pediatric B) and infratentorial adult low-risk CPT (adult) (Thomas et al., 2016, 2021). This classification is based on DNA methylation profiling rather than patient's age (for example adult-type in a six year old and pediatric-type in a forthyfour year old) or localization (for example adult-type in both supratentorial or infratentorial localization) (Thomas et al., 2021).

These tumors can be associated with Li-Fraumeni syndrome, a cancer susceptibility syndrome caused by germline mutations of the TP53 tumor suprressor gene (Thomas et al., 2021). Presence of this mutation leads to a less favorable prognosis (Thomas et al., 2021). However, only a fraction of CPP's show these mutations, as was the case in our patient, suggesting that other tumor driving events have a strong influence on tumorigenesis in these neoplasms (Thomas et al., 2021; Browne-Farmer et al., 2021). In a large study, only seven out of forthyseven patients (15%) showed TP53 mutations, while another study showed only 5% TP53 mutations (Thomas et al., 2021)15]. Until now, recurrent driver DNA alterations are mostly absent, besides TP53 mutations in pediatric CPT's and TERT mutations in adult CPT's. The most frequently encountered genetic alterations in pediatric CPT's are TP53 mutations, while in the adult population TERT-promotor mutations or CCDC47-PRKCA fusion mutations (chromosome 17) show significantly higher expression (Thomas et al., 2021). However, future genetic studies remain necessary, since there still exist a large number of mutations with a so called "uncertain significance in tumorigenesis" of these lesions. Both TP53 mutations and TERT-promotor mutations might be associated with a higher recurrence rate, a significantly shorter PFS and lower OS (Thomas et al., 2021).

While it is already been described in previous literature that hypermethylation of the TERT-promotor is associated with tumor progression and a less favorable prognosis in the overall pediatric population, the exact role in CPT – and more specifically CPP – has not been illucidated yet (Castelo-Branco et al., 2013). In CPP, only limited data regarding the methylation status of TERT promotor is available and its prognostic value has not yet been evaluated (Ruland et al., 2014). As for other low-grade neoplasms, the TERT promotor methylation status in CPP is commonly low (Castelo-Branco et al., 2013). In one study, TERT-promotor methylation was found in 36% of CPP patients (13 out of 36 cases), more frequently encounterd in aCPP and CPC, and significantly associated with OS in CPT (Ruland et al., 2014). However, multivariate analysis showed that TERT-promotor methylation is not an independent predictor of OS in CPP, but rather related to the higher proportion of these mutations in CPC's (Ruland et al., 2014). In another study, it was observed that CPP's and aCPP's with a high TERT-promotor methylation status showed malignant transformation, while those tumors with a low methylation status did not (Castelo--Branco et al., 2013).

Only a few CPT's have been examined genetically so far, therefore we believe that our case adds information in current knowledge of the genetic landscape of these tumors (Thomas et al., 2021). Furthermore, DNA methylation profiling (such as TP53 and TERT mutation analyses) entails other benefits as well. It helps in the prognostication of these neoplasms and counseling of the affected patient, it provides added information in the therapeutic stratification of adjuvant treatment after surgery (in particular when GTR could not be achieved) and it helps in the differential diagnosis of other associated brain neoplasms, as was the case in our patient.

3.5. Multifocal presentation

Although the exact histological nature of the lesion in the internal auditory meatus was not confirmed in our patient, a trifocal presentation of a CPP is presumably. A multilesional presentation has been described in current literature by other authors (Thomas et al., 2021). Multifocal CPP's are believed to be caused by villous hypertrophy, dissemination of a primary CPP by CSF seeding due to surgical manipulation or exceptionally due to primary multifocality (Peyre et al., 2012; Scholsem et al., 2012). Some authors report that only five percent of these tumors show a multifocal presentation and are mostly seen in patients with Li-Fraumeni syndrome, Aicardi syndrome, hypomelanosis of Ito or a viral predisposition (such as polyomaviruses simian virus SV40, JC and BK) (Scholsem et al., 2012; Wolff et al., 2002; Safaee et al., 2013). Since this presentation is exceptionally rare, there exists no literature on the treatment strategy of these lesions. One article describes a 39-year old female with a CPP in the fourth ventricle, as well as a CPP in the prepontine cistern extending into Meckel's cave (Peyre et al., 2012). Another 46-year old female presented with CPP in the left internal auditory meatus, as well as a fourth ventricular CPP and a frontotemporal intraparenchymal CPP (Peyre et al., 2012). Screening for genetic predisposition was not mentioned in the article. Another 59-year old female presented with bilateral lateral ventricle CPP, in association with a fourth ventricular CPP (Scholsem et al., 2012). Immunohistochemistry did not show TP53 mutation and genetic analysis showed no anomalies (Scholsem et al., 2012). The presence of multiple lesions prior to surgery, the absence of tumoral atypia and the absence of leptomeningeal involvement pleads in favor of a multifocal origin rather than CSF-mediated spread in our patient. Another article described a 48-year old female with suprasellar tumor seeding eight years after resection of a CPP in the fourth ventricle (Irsutti et al., 2000). Due to loss of visual acuity, a resection of the suprasellar mass was performed, showing histopathological and immunohistochemical features identical to those of the previous lesion. The authors did not describe results of genetic analyses. The authors state that distant seeding is more frequently observed than multifocal presentation, which can occur several months or years after resection (Irsutti et al., 2000).

A few studies report on sellar and suprasellar region involvement, in which no extension into the third ventricle or attachment to normal choroid plexus could be observed (Bian et al., 2011; Gong et al., 2017; Kuo et al., 2018; Ma et al., 2008). The clinicoradiological differentiation with pituitary adenoma, papillary ependymoma, teratoma, melanoma and melanocytoma can be challenging (Gong et al., 2017). These cases also describe absence of hormonal excess or deficiencies, as was the case in our patient (Bian et al., 2011). All other cases described in current literature were female patients with a mean age of forthyfour years old (Bian et al., 2011). Unlike CPT's in other regions, those located in the sellar or suprasellar region do not show calcifications (Gong et al., 2017). There is no literature on the treatment of asymptomatic CPP in the sellar or suprasellar region. As in other locations, the role of chemotherapy or radiotherapy in the treatment of CPT's in the sellar or suprasellar region is also uncertain (Gong et al., 2017). One study reports on the need for radiotherapy after second debulking, caused by worsening of visual acuity due to tumor compression of the optic chiasm (Gong et al., 2017).

Since the lesion in the internal auditory meatus was not histologically confirmed, the coexistence of another primary brain neoplasm in our patient forms another possibility. The coexistence of other primary intracranial tumors have been described, such as a convexity meningioma, a frontal subependymal giant-cell astrocytoma, a vestibular schwannoma in the cerebellopontine angle, a germinoma in the fourth ventricle, a petro-tentorial meningioma, a cervical ependymoma, as well as two intraventricular CPT's in an infant. The diagnosis of synchronous histologically different primary brain tumors is rare and are mostly encountered in patients with neurofibromatosis, Carney complex, Li-Fraumeni syndrome, Aicardi syndrome, rhabdoid predisposition

syndrome or postirradiation (Peyre et al., 2012; Scholsem et al., 2012; Safaee et al., 2013; Lee et al., 2002). The majority of CPP's are sporadic, however (Safaee et al., 2013). In one case, a CPP is present simultaneously with a vestibular schwannoma, as could be the case in our patient (Lee et al., 2002). In this 43-year old female, without genetic predisposition, both a CPP in the right internal auditory meatus with exophytic growth into the cerebellopontine angle, as well as a vestibular schwannoma in the right internal auditory meatus was encountered (Lee et al., 2002).

3.6. Treatment

Although there still exists no consensus on the optimal approach in the management of CPT's, it is generally accepted that surgical resection alone followed by a watch-and-scan and close observation approach remains the cornerstone in the treatment of these tumors, usally with good long-term outcome if gross total resection (GTR) can be achieved (Thomas et al., 2021; Turkoglu et al., 2014; Peyre et al., 2012; Hosmann et al., 2019; Wolff et al., 2002; Safaee et al., 2013; Browne-Farmer et al., 2021; Muñoz Montoya et al., 2019). Extensive resection is associated with prolonged survival (Turkoglu et al., 2014). Due to their adjacency to the rhomboid fossa and brainstem nuclei and adherence to critical neurovascular structures, GTR can be challenging and the question for adjuvant treatment rises.

Furthermore, although it concerns histologically benign neoplasms, surgery is not without any risks. One study mentions a need for blood transfusion in 5.5% of patients (2/36 cases), as well as short-term complications (such as electrolyte imbalances, diplopia, facial nerve palsy, dysphagia and ataxia), as well as a mortality rate of 2.7% (1 out of 36 cases) (Hosmann et al., 2019). Some authors even suggest preoperative embolization of feeding arteries to reduce intraoperative blood loss in the pediatric population (Hosmann et al., 2019). Permanent neurological deficits are also described, such as diplopia (2/36 patients), unilateral hypacusis (1/36 patients) and dysphagia (1/36 patients) (Hosmann et al., 2019).

In a retrospective study of nine patients, GTR was achieved in 73% of patients, while another study of 36 patients mentioned a GTR rate of 92% (Turkoglu et al., 2014; Hosmann et al., 2019). The NCDB database describes a GTR rate of 52% (Ruiz-Garcia et al., 2020). Due to a young patient population and the risks of long-term neurological sequelae, it is of paramount importance to identify those patients that could benefit from adjuvant chemo- or radiotherapy (Browne-Farmer et al., 2021). Moreover, spontaneous resolution of metastases following surgical resection alone has been described in current literature (Browne-Farmer et al., 2021). Even in subtotal resections, aCPP's or concerning histological features (such as necrosis), surgery alone remains the treatment of choice (Browne-Farmer et al., 2021). In a large case series, all patients were managed successfully with surgical resection alone without the need for adjuvant therapies (Browne-Farmer et al., 2021). In particular, when TP53 or TERT mutations are present, adjuvant therapies should be avoided when possible in order to reduce the risk of chemotherapy- or radiotherapy-induced tumorigenesis. Adjuvant chemotherapy, radiotherapy or stereotactic radiosurgery is mostly reserved for the treatment of CPC's or metastatic CPP's, although it still remains controversial (Turkoglu et al., 2014; Hosmann et al., 2019; Wolff et al., 2002; Safaee et al., 2013). The role of conventional radiotherapy in CPP has not been examined thoroughly, although some successful cases have been described (Peyre et al., 2012; Wolff et al., 2002). There is no evidence suggesting that adjuvant therapies provide a significant increase in overall survival (OS) in patients with CPP (Safaee et al., 2013). Even in recurrent CPP, a recent literature review failed to clarify if radiosurgery is an efficient treatment modality, in which tumor control was unsuccessful in 64% of cases (Peyre et al., 2012; Safaee et al., 2013). Therefore, surgery alone remains the preferred treatment option in recurrent CPP (Hosmann et al., 2019). The NCDB database, analyzing 304 CPP cases, found no added value of chemotherapy or radiotherapy on OS (Ruiz-Garcia et al., 2020).

Similar to other cases, our patient needed permanent CSF diversion by means of ventriculoperitoneal shunting (Hosmann et al., 2019). The persistent hydrocephalus is probably caused by any or a combination of repeated hemorraghes, necrotic debris, arachnoiditis, prolonged external ventricular drainage, increased ependymal secretory surface and ependymitis (Turkoglu et al., 2014; Hosmann et al., 2019). In a retrospective study of fifteen patients, nearly all patients needed EVD prior to definitive surgery of which four patients (27%) required a VPS after definitive surgery (Turkoglu et al., 2014). Another study reports on 31% (11/36) and 19% (7/36) of patients who needed EVD or VPS, respectively (Hosmann et al., 2019). EVD placement is more frequently performed in the pediatric population (Hosmann et al., 2019). VPS was significantly more commonly performed in patients with aCPP or CPC, although equally distributed between the pediatric and adult population (Hosmann et al., 2019). EVD is most frequently performed prior to surgery in the pediatric population, whereas in the adult population most commonly placed after tumor resection (Hosmann et al., 2019). The need for CSF diversion should be planned on a case-by-case basis, since shunting may contribute to an increased tumor-independent morbidity in these patients (Hosmann et al., 2019).

3.7. Prognosis

Recurrences in CPP's are infrequent, metastases are rare and the general prognosis is good, with an event-free survival of 92% (Turkoglu et al., 2014; Hosmann et al., 2019). Adult patients show a higher tendency of recurrence compared to their pediatric counterparts (Thomas et al., 2021). Dissemination in CPP has been described in a few cases (Hosmann et al., 2019). A retrospective study analysed nine adult patients with CPP, with a mean follow-up time of 5.8 years. Progression-free survival (PFS) was noted in all patients until last follow-up. This retrospective study focused on patients with an age above eighteen years, with a mean age of thirtyfour years. In another retrospective study of thirtysix patients, five-year PFS and ten-year OS were 100% and 95%, respectively (Hosmann et al., 2019). These survival rates are also confirmed by other studies (Safaee et al., 2013; Ruiz-Garcia et al., 2020). The NCDB database, analyzing 304 CPP cases, showed a five-year and ten-year OS of 87% and 84%, respectively (Ruiz-Garcia et al., 2020).

Although extent of resection (EOR) and tumor progression were important predictors for OS, histological grading was not significantly associated with OS according to some studies (Hosmann et al., 2019). However, histological grading was significantly associated with PFS (Hosmann et al., 2019). This is in contrast to the NCDB database, in which a higher tumor histology was significantly associated with a lower OS (Ruiz-Garcia et al., 2020). Recurrence was observed in one out of thirtysix patients and was significantly associated with histological grading (Hosmann et al., 2019). PFS and OS are similar in the pediatric and adult population (Hosmann et al., 2019). The association between EOR and overall survival was not detected in all studies, such as those results based on the NCDB database (Ruiz-Garcia et al., 2020). Moreover, although there was a trent of better five-year OS according to EOR, these results were not significant (95% for GTR, 91% for STR and 84% for biopsy alone) (Ruiz-Garcia et al., 2020). Therefore, EOR may not be as relevant as claimed before. As mentioned previously, TERT promotor methylation is associated with malignant transformation in clinical follow-up, as was the case in our patient. Therefore, close observation is warranted.

We believe that this report adds in the comprehension of these rare tumors. Further studies and case reports are pivotal in the understanding of the behaviour and presentation of these uncommon brain neoplasms, which will improve future diagnostic and prognostic counseling of our patients. Furthermore, CPP should always be included in the differential diagnosis of adult tumors located in the posterior fossa. At last, a more profound understanding in the biological behaviour of these tumors is

required in order to delineate treatment strategies and reduce diagnostic delay.

4. Limitations

There are several limitations which need to be acknowledged. First, there is no histological confirmation of the lesion encountered in the internal auditory meatus. Therefore, we do not know if we have to deal with a trifocal presentation of a CPP rather than two histologically different neoplasms. Second, this review is largerly based on articles focusing on tumor aspects that are based on the obsolete classification according to patient's age and tumor localization, although nowadays a genetic classification offers a more precise insight in prognosis and treatment preferences of this tumor entity. Only the NCDB database included a large cohort of patients (304 CPP cases), although it did not provide any genetic information. Therefore, there is an urgent need for prospective studies focusing on the genetic background of CPP's. Third, most studies in current literature are based on the pediatric population. However, it is not possible to extrapolate these results directly to the adult population, as can be seen in the NCDB database. Therefore, we believe that CPT cases concerning adult patients have added value in current literature. Finally, there is no long term follow-up of our patient due to recent surgery, however this was not the main objective of our report.

5. Conclusion

Although rare, a CPP should be included in the differential diagnosis of posterior fossa tumors, both in the pediatric and adult population. Despite there still remain some controversies considering the appropriate treatment of CPP's, we believe that genetic analysis and screening for TP53 and TERT mutations should always be considered, since they entail important diagnostic, prognostic, therapeutic and follow-up implications, as well as a better understanding of the tumorigenesis of these neoplasms. When a TERT mutation is present, adjuvant radiotherapy should be used with extra caution, since it plays a role in tumorigenesis, even when gross total resection could not be achieved. Furthermore, there is an association between TERT methylation status and malignant transformation, indicating that these patients should be followed more closely. Articles that report on a multifocal presentation of CPP's or genetic analyses are scarce. Therefore, we believe that our case report provides novel insights in the understanding of the behavior and tumorigenesis of (multifocal) choroid plexus papilloma.

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Statement

During this case report, the CARE statement guidelines were followed.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

For this type of study formal consent is not required.

Informed consent

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

CRediT authorship contribution statement

Senne Broekx: Conceptualization, Methodology, Validation, Investigation, Writing – original draft, Writing – review & editing, critical revision, Visualization, Project administration. **Mania De Praeter:** Conceptualization, Validation, Resources, Supervision.

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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