Turk Neurosurg, 2024

Original Investigation

DOI: 10.5137/1019-5149.JTN.45592-23.4

Received: 02.10.2023
Accepted: 14.03.2024

Published Online: 25.07.2024

Choroid Plexus Tumors of the Central Nervous System: A Review with a Case of Disseminated Choroid Plexus Papilloma

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ABSTRACT

AIM: To highlight the critical role of molecular profiling of choroid plexus epithelium tumors (CPTs) in guiding individualized treatment strategies.

MATERIAL and METHODS: Histopathological diagnoses were obtained from surgically resected tumors at Centro Medico Nacional 20 de Noviembre, Mexico City (Department of Neurosurgery). The cohort comprised four children (two females and two males) and three adults (one male and two females).

RESULTS: This study retrospectively analyzed data from seven patients diagnosed with CPT over a 5-year period. The pathological distribution consisted of three carcinomas, three papillomas, and one disseminated choroid plexus papilloma. Patient ages ranged from 1 to 62 years. All patients received chemotherapy, with four patients additionally undergoing radiotherapy. The median survival rate was six months, with one patient (carcinoma diagnosis) succumbing to the disease.

CONCLUSION: CPT, characterized by low incidence, present a significant clinical challenge. Histological grade remains the primary prognostic factor. Disseminated choroid plexus papilloma, an infrequent entity with limited reported cases, exhibits no response to radiotherapy. Moving forward, this field urgently requires the exploration of targeted molecular therapies and minimally invasive surgical approaches to address these rare and intricate tumors.

KEYWORDS: Choroid plexus, Papilloma, Carcinoma, Disseminated papilloma

ABBREVIATIONS: WHO: World Health Organization, **MRI:** Magnetic resonance image, **CPP:** Choroid plexus papilloma, **EVD:** External ventricular drainage, **CSF:** Cerebral spinal fluid, **CPC:** Choroid plexus carcinoma

INTRODUCTION

Arising infrequently within the central nervous system's ventricles, choroid plexus tumors represent a distinct challenge for clinicians due to their rarity. These neoplasms constitute approximately 0.5% of all brain tumors in both children and adults (7). However, despite their uncommon occurrence, a comprehensive understanding of CPT is crucial due to the variability in their clinical presentation and unique morphological features. Within this group, choroid plexus papilloma (CPP) stands out as a particularly uncommon entity. Further complicating the clinical scenario, CPP has the potential to disseminate, posing unique challenges in treatment and management.

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This study comprehensively explores choroid plexus tumors (CPTs), investigating their epidemiological features, clinical manifestations, and histopathological characteristics. We further investigate the management complexities of disseminated CPP by recognizing the unique challenges of this rare subset of neoplasms. By emphasizing the value of early diagnosis through symptom recognition and the critical role of histopathology in determining prognosis, we explore the intricate clinical landscape of these tumors (18).

Differentiating CPP from aggressive choroid plexus carcinoma (CPC) presents a significant challenge in the clinical management of these tumors. This study explores the complexities associated with differentiating these tumors. By elucidating the unique histological markers and underlying genetic factors that define CPP and CPC, we aim to pave the way to develop targeted therapeutic therapies and improved clinical management strategies.

In this study, we also present a compelling case of an 11-year-old patient diagnosed with disseminated CPP. This case exemplifies diagnostic complexities, treatment challenges, and subsequent clinical courses associated with this rare entity. Highlighting the limited literature on disseminated CPP, this case underscores the need for further comprehensive research (13).

MATERIAL and METHODS

This study retrospectively analyzes a series of choroid plexus epithelial tumors (Committee of Ethics in Research, Project Number 2023-10-271, Date: October 26, 2023). Patient data were retrieved from our in-house electronic medical record system (SIAH), and neuroimaging studies were obtained through Synapse, the web-based Picture Archiving and Communication System software utilized at our medical center. Surgical procedures were performed by a single neurosurgeon, and a dedicated neuropathologist meticulously evaluated all histopathological specimens. The study cohort included four children (two females and two males) and three adults (one male and two females). Details on patient demographics are provided in Table II. The observed patient cohort consisted of three men and four women, ranging in age from 1 to 62 years.

RESULTS

Initial imaging utilized unenhanced computed tomography. All patients underwent magnetic resonance imaging, but magnetic resonance spectroscopy was not performed due to lack of the resource. Presenting symptoms began 1–6 months before diagnosis, with headaches being the most frequent complaint. Hydrocephalus was observed in 5 patients, requiring the placement of external ventricular drains (EVD).

To further illustrate the diagnostic challenges, we present the case of an 11-year-old female patient who initially presented with headache and hydrocephalus. Initial magnetic resonance imaging suggested a presumptive diagnosis of CPP. The patient underwent surgical resection, and histopathological examination confirmed the diagnosis (CPP). Unfortunately, the patient experienced disease recurrence with a disseminated pattern. The tumor, initially confined to the lateral ventricles, disseminated throughout the ventricular system, reaching the foramen magnum in the posterior fossa. Additionally, an isolated sellar lesion was identified. Given the greater clinical significance of the posterior fossa lesion, a second surgical procedure was undertaken to achieve macroscopic resection. However, followup magnetic resonance imaging revealed progressive growth of both the previously identified lesions and the sellar mass. Consequently, the patient was referred to pediatric oncology for further management. Following a comprehensive review of the case, the pediatric oncology team opted for a two-phase radiotherapy regimen. The first phase consisted of 39 Gray (Gy) delivered in 22 fractions, followed by a second phase of 14.4 Gy in eight fractions, for a total cumulative dose of 54 Gy.

Within our pediatric cohort, a bulging fontanel emerged as a crucial clinical sign for identifying elevated intracranial pressure. This finding prompted further investigation, ultimately leading to the diagnosis of CPP in pediatric patients. Histopathological examination identified papillary structures with true fibrovascular cores lined by a neoplastic cell population in four patients (consistent with CPP). In the remaining three patients (consistent with CPC), findings included a single epithelium layer with focal areas of pseudostratification, bland nuclear atypia, and an absence of mitotic figures.

The established treatment strategy prioritizes gross-total surgical resection whenever feasible. Moreover, the use of adjuvant chemotherapy and radiotherapy for CPC and disseminated CPP remains under debate. Chemotherapy was administered to all patients. Radiotherapy was reserved for patients with CPC and those diagnosed with disseminated CPP. The overall median survival for the entire cohort surpassed six months. Interestingly, the pediatric patient with disseminated papilloma who received radiotherapy in addition to chemotherapy achieved a survival exceeding 12 months.

DISCUSSION

Choroid plexus epithelial tumors are uncommon intraventricular neoplasms, constituting only 0.5% of all brain tumors across both pediatric and adult populations. The age-standardized incidence rate is approximately 1.0 per million, with a distinct peak during infancy, reaching 6.1 per million, particularly within the first year of life (7,19). These tumors are notably well-vascularized and arise from the choroid plexus, a highly vascular structure lining the ventricular cavities. The choroid plexus is characterized by its lobulated architecture, resembling a cauliflower-like appearance, often reflected in the morphology of these neoplasms (18). In children, these tumors primarily manifest in the supratentorial compartment, typically presenting within the first year of life. Conversely, adult patients with CPT exclusively exhibit infratentorial involvement. Several factors contribute to the surgical complexity of these tumors. Young patient age, intraventricular location, and a high incidence of requiring temporary cerebrospinal fluid drainage and permanent postoperative shunting collectively elevate perioperative morbidity, potentially independent of tumor characteristics (7).

Diagnosing CPP can be challenging due to the nonspecific nature of its clinical presentation. These symptoms often overlap with other conditions, making a high index of suspicion crucial, particularly in children presenting with nonspecific complaints like vomiting and lethargy. Evaluation of elevated intracranial pressure should guide the diagnostic workup. This can be achieved through various imaging modalities, including unenhanced cranial tomography or magnetic resonance imaging. Additionally, noninvasive approaches such as presurgical ultrasound measurement of the optic nerve sheath diameter can be employed (10).

Consistent with previous literature, our study observed a high prevalence of hydrocephalus. Ellenbogen et al. reported hydrocephalus in 78% of cases, and Humphreys et al. noted an even higher incidence (95%) (3,8). This can be attributed to two main mechanisms: either overproduction of cerebrospinal fluid (CSF) by the tumor itself or obstruction of CSF outflow pathways, particularly in tumors involving the fourth ventricle. The frequent presentation of symptoms of hydrocephalus-related intracranial hypertension (18) underscores the criticality of early suspicion of CPP in children experiencing such signs. Prompt diagnosis facilitates timely intervention, often including the initial decision regarding the necessity of CSF drainage.

Histopathological examination typically reveals multiple papillary structures with fibrovascular cores (Figure 1). Immunohistochemical analysis often demonstrates positive staining for cytokeratin, vimentin, and S-100 proteins in CPP. Conversely, the absence of Epithelial Membrane Antigen and Glial Fibrillary Acidic Protein (GFAP) further strengthens the diagnostic suspicion for CPP. Previous studies suggest potential variations in immunohistochemical marker expression based on tumor location and patient age. Tumors located in the fourth ventricle may exhibit higher S-100 levels than those in the lateral ventricles. Additionally, patients exceeding 20 years tend to express more GFAP and transthyretin (TTR) compared to their younger counterparts (17).

Papillomas are characterized by infrequent mitotic activity and rare foci of necrosis (Figure 2). In contrast, atypical papillomas share similar histological features but demonstrate mitotic activity, generally exceeding 2 per 10 high-power fields. Additionally, atypical papillomas may exhibit increased cellular crowding, hypercellularity, and moderate degrees of nuclear pleomorphism (18). Histological diagnosis of CPC often relies on the identification of several key features: increased cell density, a high mitotic rate (typically exceeding 5 mitoses per 10 high-power fields), pronounced nuclear pleomorphism, and the presence of necrosis (Figure 3).

CPC is a rare central nervous system neoplasm, with few reported cases in adolescence (15). These tumors are most frequently located in the lateral ventricles (50% of cases), followed by the fourth ventricle (40%), with a minority in the third ventricle (5%), and involving multiple ventricles (5%). CPC has a poor prognosis, particularly with incomplete resection. Neuroimaging typically demonstrates a large, hyperdense, contrast-enhancing intraventricular mass, frequently associated with hydrocephalus and possible hemorrhage (Figure 4)

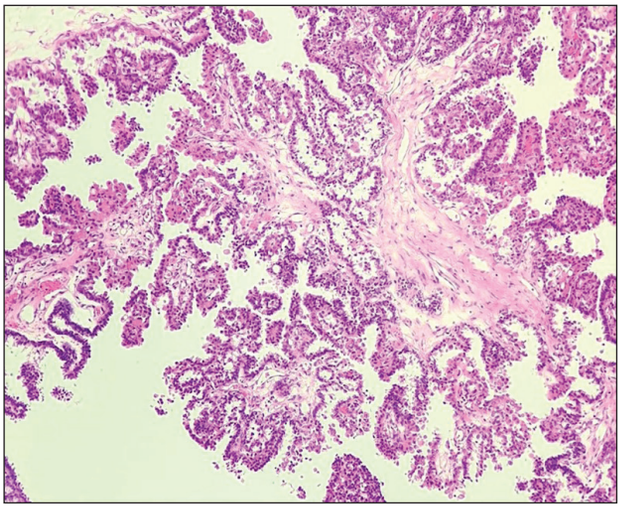

Figure 1: Hematoxilin and eosin 10x. This image reveals multiple papillary structures with fibrovascular cores, typically found on CPP.

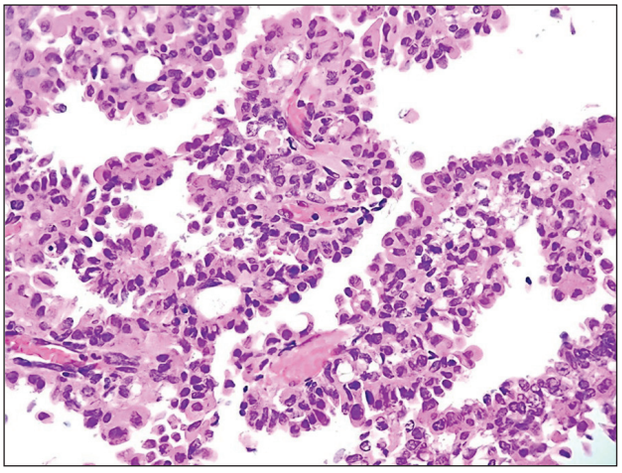

Figure 2: Hematoxilin and eosin 40x. CPP with few mitotic activity and rare foci of necrosis.

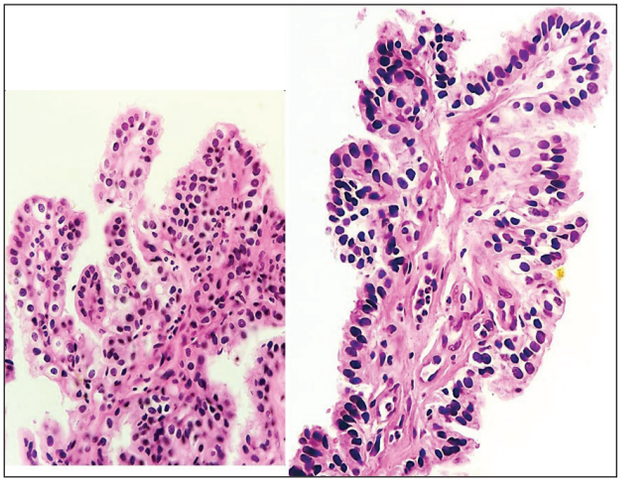

Figure 3: Hematoxilin and eosin staining 20x and 40x. We can observe here increased cell density, a high mitotic rate, pronounceed nuclear pleomorphism, and necrosis, key features of CPC.

(4). Differential diagnosis of CPC from other intraventricular papillary neoplasms, particularly ependymoma, can be challenging. However, histological examination typically reveals characteristic cytological and morphological features that facilitate distinction (4). While advancements like genome-wide DNA methylation and gene expression profiling hold promise for improved tumor risk stratification, the optimal treatment strategy for CPC remains under investigation. Nevertheless, gross-total surgical resection is associated with improved overall survival, and adjuvant therapies, including chemotherapy, may be beneficial, particularly in patients harboring TP53 mutations (21).

CPC demonstrates aggressive behavior characterized by rapid growth. The 5-year survival rate remains approximately 40%. Unfortunately, a standardized treatment regimen for CPC is lacking. The primary goal is gross-total surgical resection; however, complete tumor removal is only achievable in 40%–50% of pediatric patients. Moreover, central nervous system infections associated with the tumor and its treatment modalities further compromise patient outcomes.

Adult-onset CPC is a rare entity, as evidenced by the scarcity of reported cases in the literature (11). This article contributes to the existing body of knowledge by presenting two distinct cases of adult CPC with unique clinical presentations and courses. One patient underwent surgical resection and radiation therapy but unfortunately succumbed to the disease before long-term followup could be established. This study underscores the critical role of timely diagnosis and intervention in CPC management. Additionally, our findings highlight the potential survival benefit associated with adjuvant therapies such as chemotherapy and radiation therapy. However, the efficacy of these modalities remains variable, warranting further investigation to optimize treatment regimens for individual patients (16).

As previously reported (6), late recurrence of CPC is an exceptionally rare event. This underscores the necessity for long-term followup and dedicated research efforts to elucidate the natural history, patterns of recurrence, and potential prognostic factors influencing long-term relapse in patients with this condition. Future research endeavors should prioritize the identification of patient-specific risk factors for late CPC recurrence. Additionally, investigating the potential influence of adjuvant therapies on mitigating this risk is warranted. Given the scarcity of reported CPC cases and the evolving treatment landscape, this study underscores the significance of comprehensive case reporting to inform optimal management strategies (6).

Unlike CPC, CPP (Figure 5) typically involves benign intraventricular neoplasms. However, they can exceptionally metastasize within the craniospinal axis. In rare cases, patients may exhibit multifocal cystic lesions disseminated throughout the neuroaxis. The authors present three unique cases of fourth ventricle CPP (WHO grade 1) confirmed by pathology. Additionally, a review of the literature identified five prior reports of cystic dissemination. In light of the presented cases and literature review, the authors recommend incorporating preoperative and routine postoperative imaging of the entire neuroaxis for patients diagnosed with CPT, regardless of WHO grade. This comprehensive imaging strategy would facilitate the detection of potential cystic dissemination and help to determine optimal treatment planning (9).

Figure 6 illustrates a case of disseminated CPP involving the ventricular system, extending to the foramen magnum in the posterior fossa. Additionally, an isolated sellar lesion was identified. The patient underwent radiotherapy in two phases: the first delivered 39 Gy in 22 fractions, followed by a boost of 14.4 Gy in eight fractions for a total dose of 54 Gy.

We report a rare case of disseminated CPP in a pediatric patient, a tumor type characterized by aggressive potential and dissemination throughout the neuraxis. Our patient presented with acute hydrocephalus and seizures, and neuroimaging revealed a large left intraventricular mass with numerous intraparenchymal and extra-axial cysts throughout the neuraxis, mirroring the clinical and imaging features reported in the lit-

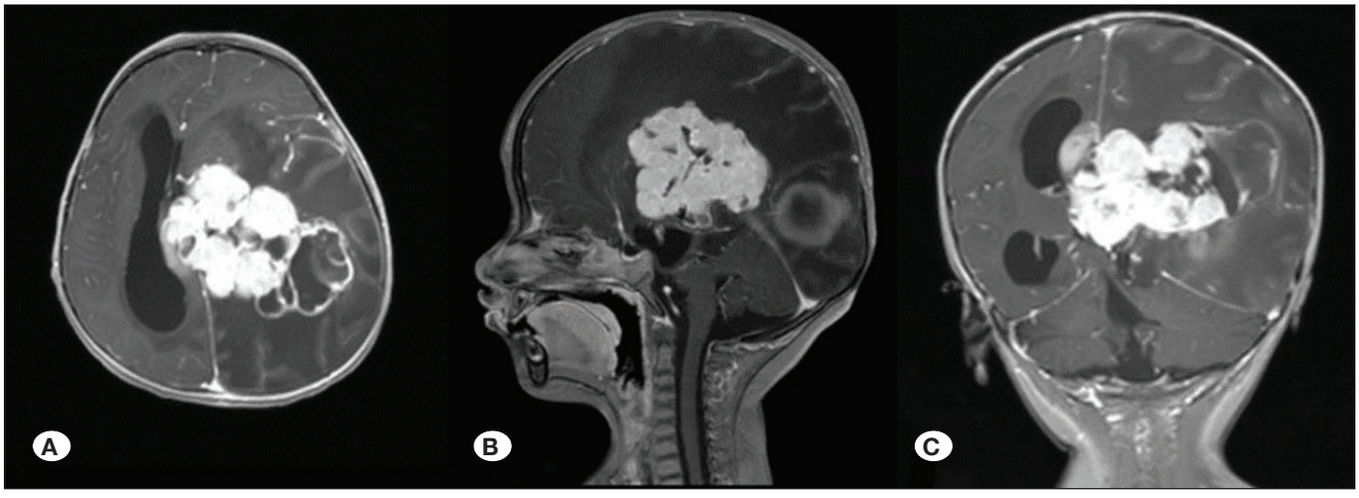

Figure 4: Contrast-enhanced T1 MRI, with an intraventricular lesion, with a polycystic component, heterogeneous gadolinium enhancement and a “cauliflower” appearance, hydrocephalus and perilesional edema, in axial **(A)**, sagittal **(B)** and coronal **(C)** sections.

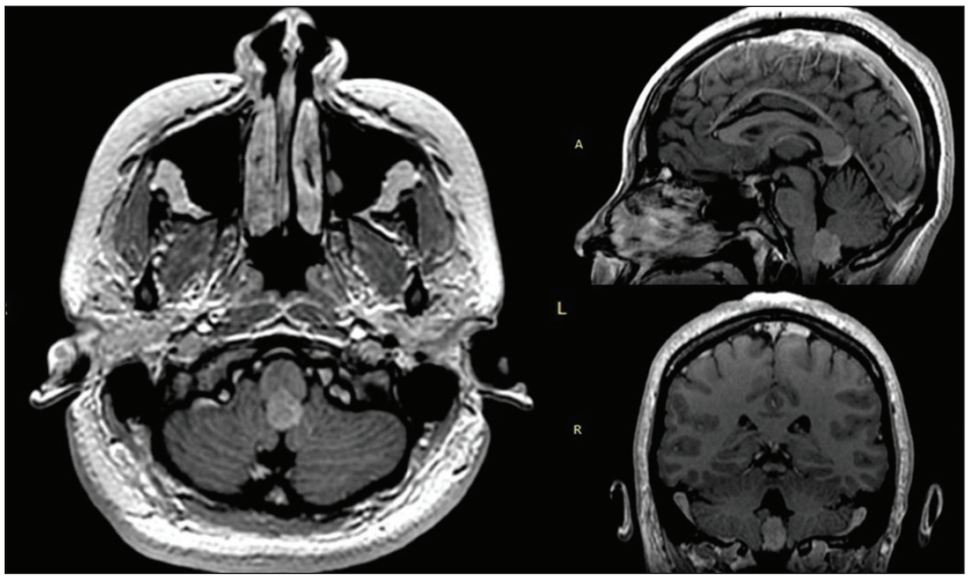

Figure 5: A brain MRI of a 21-year-old woman with a fourth-floor ventricle tumor with homogeneously enhanced contrast injection, with a "cauliflower" appearance.

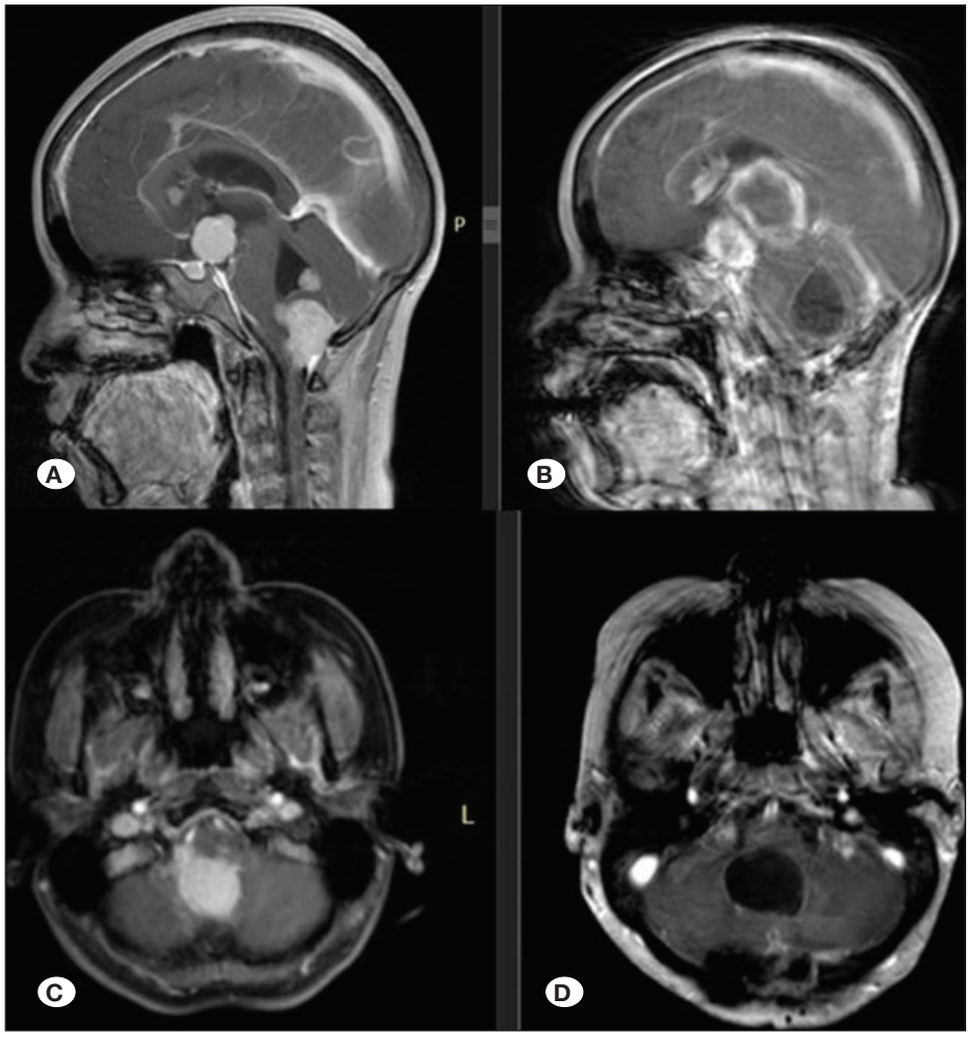

Figure 6: MRI contrasted T1 images. On the left **(A,C)** showing multiple extra-axial lesions, homogeneous, with contrast enhancement, in the sellar region, fourth ventricle, and foramen magnum. Images on the right **(B,D)**, same patient, after receiving radiotherapy for a sellar lesion and resection of posterior fossa lesions.

erature (13,14). This study advocates for a novel radiographic classification system for CPPs, aiming to improve the characterization of their diverse radiographic presentations. The proposed system restricts the term "metastatic disease" to WHO grade II and III CPPs, atypical CPP, and CPC (Table I). Our classification (Table I) subdivides WHO grade I CPPs into four distinct radiographic patterns: disseminated disease, multifocal disease, zuckerguss sign (referring to the spread of gout to other places in the central nervous system through the cerebrospinal fluid as if it were a dripping frosting coating), and ependymal involvement. Another bibliographic report described three patients exhibiting a similar dissemination pattern (1). The authors propose a large-scale collaborative study to investigate the intricate molecular pathways underlying choroid plexus tumorigenesis. Such an endeavor is crucial to foster meaningful advancements in treatment strategies for this disease (1).

Disseminated CPP is a rare phenomenon, documented in fewer than 10 cases within the current literature. The reported prognosis for patients with this condition exhibits significant heterogeneity, ranging from stable disease and persistent symptoms to mortality within months.

Elucidating the genetic underpinning of this variable clinical course in CPP is critical; however, such mechanisms remain elusive. A study employed number variation analysis, gene expression profiling, and DNA methylation profiling to differentiate CPC from CPP and atypical CPP (13). Notably, none of the analyzed tumor samples harbored evidence of secondary dissemination.

Atypical CPP occupies a histological intermediate position between CPP and CPC. While some studies have outlined diagnostic criteria for atypical CPP, including increased cellularity, nuclear atypia, and mitotic activity (2), the long-term prognosis remains unclear. This uncommon type of CPP exhibits a behavior intermediate between CPP and CPC, potentially necessitating more aggressive treatment strategies compared to CPP (2).

Surgical intervention remains the cornerstone therapy across all treatment eras, with gross-total resection demonstrably impacting patient survival irrespective of adjuvant therapies (5,9,12,13,20). The role of radiotherapy in CPC management is less clear due to the high propensity for cerebrospinal fluid dissemination. When employed, radiotherapy typically encompasses the entire neuraxis (5). The authors of this study (13) reviewed the outcomes of four patients who received radiotherapy following incomplete resection (Table II). None of these patients achieved long-term survival, casting doubt on the efficacy of radiotherapy in this setting. The analysis of chemotherapy regimens revealed encouraging results with vinblastine, cisplatin (with or without etoposide), and thiotepa. Notably, a single case of disseminated PPC demonstrated a positive response to bevacizumab (13).

Table I: This Proposed Classification States a Subclassification of the Choroid Plexus Papilloma, WHO Grade I, with 4 Different Patterns: Disseminated Disease, Multifocal Disease, Zuckerguss, and Ependymal

Name, Grade	Lesion	Disease Pattern
Choroid plexus	Solitary lesion Multiple lesions	1. Disseminated disease 2. Multifocal disease 3. Zuckerguss 4. Ependymal
Atypical choroid plexus papilloma, WHO grade II	Solitary lesion Multiple lesions	Metastatic disease
Choroid plexus carcinoma, WHO grade III	Solitary Lesion Multiples lesions	Metastatic disease

Table II: Show Results Based on the Age and Sex of the Patients, Histopathology Results, Location, and Given Adjuvant Therapy

Case No.	Age (yrs)/Sex	Histopathology	Tumor location	Radiotherapy
1	11 / F	Plexus choroid papilloma	Multiple (Fourth ventricle, parasellar, foramen magnum).	Yes
2	58 / M	Plexus choroid papilloma	Fourth ventricle.	No
3	2 / M	Plexus choroid carcinoma	Left lateral ventricle.	Yes
4	49 / F	Plexus choroid papilloma	Fourth ventricle	No
5	4 / M	Plexus choroid carcinoma	Left lateral ventricle.	Yes
6	21 / F	Plexus choroid papilloma	Floor fourth ventricle	No
7	1 / F	Plexus choroid carcinoma	Lateral ventricles and parenchyma extension.	Yes

Limitations

Our study is limited by its relatively small sample size, encompassing only seven (9) patients identified over a 5-year period. Nonetheless, consistent neuropathological evaluation by a single pathologist ensured result accuracy. Our findings, in agreement with previous reports found in the literature, further highlight the rarity of this disease entity. Unfortunately, one patient succumbed to a central nervous system infection and ventriculitis.

This study is limited by its retrospective design and analysis from a single center. Additionally, the relatively small sample size (n=7) and incomplete gross resections in some of the studied cases limit the generalizability of our findings.

CONCLUSION

CPT are uncommon intracranial neoplasms. Presenting symptoms typically include headache and signs of elevated intracranial pressure secondary to mass effect and hydrocephalus, which may have multiple contributing factors. Recent classifications based on molecular and neuroimaging data can effectively guide effective treatment strategies. Surgical intervention remains the cornerstone of management, prioritizing gross-total resection when feasible. However, anatomical location, tumor size, and pre-existing hydrocephalus can pose significant challenges to achieving complete resection. Histological grade serves as the primary prognostic indicator. Additionally, emerging molecular characterization holds promise for personalized therapeutic strategies, potentially improving survival outcomes for patients with aggressive tumors. Disseminated CPPs are exceptionally rare and have been documented in a limited number of cases. Further comprehensive reporting of disseminated CPP presentations and management strategies is crucial to enhance our understanding of this complex disease entity. Future advancements in targeted molecular therapies and minimally invasive surgical approaches hold promise for improved treatment outcomes in patients with disseminated CPP.

ACKNOWLEDGEMENTS

Funding: This research has not received specific aid from public sector agencies, the commercial sector, or non-profit entities.

AUTHORSHIP CONTRIBUTION

Study conception and design: OP
Data collection: KG
Analysis and interpretation of results: KG
Draft manuscript preparation: OP
Critical revision of the article: OP
Other (study supervision, fundings, materials, etc...): FC, AP, RV
All authors (OP, KPG, FC, AP, RV) reviewed the results and approved the final version of the manuscript.

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