Cystic dissemination of choroid plexus papilloma: illustrative cases

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BACKGROUND Choroid plexus papillomas are benign tumors of the choroid plexus. Although typically focal, they can metastasize. Rarely, patients may present with numerous cystic lesions throughout the craniospinal axis.

OBSERVATIONS The authors present three cases of pathologically confirmed fourth ventricular World Health Organization (WHO) grade 1 choroid plexus papillomas presenting with numerous cystic lesions throughout the craniospinal axis. Two cases were treated with only resection of the fourth ventricular mass; one was treated with a partial cyst fenestration. During follow-up, there was only mild interval growth of the cystic lesions over time, and all patients remained asymptomatic from their cystic lesions. The authors summarize five additional cases of cystic dissemination in the published literature and discuss hypotheses for the pathophysiology of this rare presentation.

LESSONS Choroid plexus papillomas may present with numerous, widely disseminated cystic lesions within the craniospinal axis. Thus, the authors recommend preoperative and routine imaging of the entire neuroaxis in patients with choroid plexus tumors, regardless of WHO grade. Although the role of adjuvant therapy and cyst fenestration in the treatment of these lesions remains unclear, watchful waiting may be indicated, especially in asymptomatic patients, because the lesions often demonstrate slow, if any, growth over time.

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KEYWORDS choroid plexus papilloma; dissemination; cystic dissemination; choroid plexus tumor

Illustrative Cases

Case 1

A 40-year-old female presented with headaches for the past 4–5 years that she described as “microbursts,” along with periodic headaches when coughing or sneezing that would last for approximately 15 seconds. In the 2 weeks before presentation, she began experiencing severe headaches, unlike her “microburst” headaches, that would wake her from sleep and that were unremitting and unresponsive to pain medication.

On examination, she had no focal neurological deficits. Head computed tomography (CT) demonstrated multiple hypodensities in the bilateral temporal lobes, right occipital lobe, and bilateral cerebellum, as well as a hyperdense lesion in the foramen of Magendie.

ABBREVIATIONS CPP = choroid plexus papilloma; CSF = cerebrospinal fluid; CT = computed tomography; GFAP = glial fibrillary acidic protein; MRI = magnetic resonance imaging; POD = postoperative day; WHO = World Health Organization.

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The patient was placed on dexamethasone and levetiracetam and underwent magnetic resonance imaging (MRI), which showed a calcified lesion in the foramen of Magendie with mild enhancement and T2 hyperintense signal (Fig. 1A). The MRI also showed multiple nonenhancing cystic lesions of the subarachnoid spaces of the bilateral posterior fossa, interpeduncular cistern, along the tentorium, and adjacent to the left fusiform gyrus and sylvian fissure (Fig. 1B). These lesions did not restrict diffusion and followed cerebrospinal fluid (CSF) signal intensity on all sequences. Spinal MRI showed multiple nonenhancing extramedullary cystic lesions along the thoracic and lumbar spine (Fig. 1C-F).

The patient underwent resection of her fourth ventricular tumor and fenestration of a large cyst in the left cerebellopontine angle causing compression of the fourth ventricle. Her postoperative course was uncomplicated. She was discharged home on postoperative day (POD) 5 but returned to the hospital for a CSF leak that was managed nonoperatively. Pathological analysis of her ventricular lesion demonstrated CPP, WHO grade 1. Microscopic examination revealed epithelial cells diffusely positive for pan-cytokeratin with focal but strong positivity for glial fibrillary acidic protein (GFAP) and faint staining for transthyretin. Pathology of the fenestrated cyst wall demonstrated simple epithelium with clusters of cap cells and underlying fibrotic stroma. The arachnoid cap cells were positive for epithelium membrane antigen and progesterone receptor but were negative for GFAP and transthyretin.

The patient fared well clinically after her resection and remained asymptomatic 4.5 years after surgery. Follow-up imaging at 1 year showed mild interval increase in the size of her previously seen left cerebellopontine angle cyst. Postoperative imaging at 4.5 years revealed mild interval enlargement of her left sylvian fissure lesion; her other cystic lesions remained stable in size.

**Case 2**

An 11-year-old female presented to the emergency department with approximately 1 year of headaches and right arm weakness. She also reported 1 month of occasional morning nausea and vomiting and 4 months of blurred vision, and her parents noted that she was slow to grow and seemed “skinny” and “stunted” for her age. On examination, she was found to be small for her age, with slightly lower muscle volume and trace weakness in the right upper extremity compared with the left. She also demonstrated dysmetria in her right upper extremity and 3+ reflexes throughout her upper extremities, with clonus bilaterally.

Brain MRI demonstrated a homogeneously enhancing mass in the posterior fossa, centered in the fourth ventricle and extending inferiorly just below the foramen magnum (Fig. 2A and B). The lesion demonstrated elevated T2 signal and isodense T1 signal and did not restrict diffusion. The lesion contained multiple low-signal foci at the periphery of the lesion on T1-weighted sequences, which were thought to demonstrate calcifications. MRI also revealed multiple small nonenhancing cystic foci that followed CSF on all sequences that were scattered throughout the brain in the preoptic cistern, bilateral cerebellar hemispheres, and bilateral sylvian fissures (Fig. 2C).

The patient underwent craniotomy for resection of her tumor, which she tolerated well. She presented again to the hospital 1 month later for a CSF leak that required operative repair on POD 35. Pathology revealed CPP, WHO grade 1. The cystic lesions were not resected and thus were not examined microscopically. On follow-up imaging 3 years postoperatively, a new cyst in the right temporal lobe was noted, with several cysts also having increased in size (Fig. 2D and E). The following month, spine imaging was performed, which demonstrated multiple discrete nonenhancing intradural extramedullary T2 hyperintense cystic lesions scattered throughout the cervical, thoracic, and lumbar spine to the level of the conus, which remained stable on imaging 8 years postoperatively (Fig. 2F). Although imaging showed mass effect on the spinal cord, the patient remained asymptomatic, so the family declined further surgery of these lesions. At 8 years postoperatively, the patient was still doing well with stable cystic disease for the last 5 years.

**Case 3**

A 24-year-old male underwent imaging after 4 years of nasal and sinus symptoms. The MRI demonstrated multiple cerebral cysts and a large enhancing fourth ventricular lesion. The patient reported occasional mild headaches at the time of presentation, but nothing of note or severe in nature. On examination, he had no focal neurological deficits.

MRI revealed an enhancing mass in the fourth ventricle that extended through the foramen of Magendie (Fig. 3A and B). The lesion did not restrict diffusion and exhibited multiple foci of calcification. MRI also revealed multiple cystic lesions (Fig. 3C), with many

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**FIG. 1.** Case 1. A 40-year-old female with headaches was found to have a fourth ventricular lesion and multiple cystic lesions. A: Sagittal postcontrast T1-weighted MRI shows mildly enhancing fourth ventricular CPP. B: Axial postcontrast T1-weighted MRI shows nonenhancing cystic lesions (arrows). C: Sagittal T2-weighted MRI of the thoracic spine shows a cystic lesion at T8 (circle). D: Axial T2-weighted MRI at T8 shows a cystic lesion (arrow). E: Sagittal T2-weighted MRI of the lumbar spine shows a cystic lesion at L2 (circle). F: Axial T2-weighted MRI at L2 shows a cystic lesion (arrow).
located in the posterior fossa and the largest located along the an-
terior cranial fossa and measuring 2.6 cm in size (Fig. 3D). On cor-
relation with head CT, many of the cystic lesions demonstrated
associated punctate calci-
fications.

The patient underwent craniotomy for resection of his fourth ven-
tricular tumor and did well postoperatively. Pathology revealed CPP,
WHO grade 1, with immunohistochemical staining showing wide-
spread positivity for CAM 5.2 and patchy positivity for GFAP, pan-
cytokeratin, and cytokeratin 7. Microscopic examination of one
of the cysts revealed fragments of a single-layer columnar epithelium
overlying thin pieces of fibrous tissue. Immunohistochemical stain-
ing of the cyst lining showed strong widespread positivity for CAM
5.2 and patchy positivity for GFAP. Ki-67 staining also showed a
small subset of epithelial nuclei at variable densities, reaching up to
3.2%. Genomic testing was performed, and no genomic alterations
were identified. However, variants of unknown significance were
identified in various genes, including GATA6, INPP4B, MYST3,
NOTCH1, NTRK1, SMAD2, SMAD4, and RANBP2.

Postoperatively, the patient had some difficulties with range of
motion, balance, and a mild right facial weakness. Approximately
1 year after resection, the patient began experiencing intermittent
pressure behind his eyes. On follow-up imaging at 2 years, the cyst
located in the anterior cranial fossa showed interval increased size
(Fig. 3E and F), and the decision to aspirate was made due to the
considerable increase in the size of the cyst over time. The patient
was subsequently admitted for elective stereotactic aspiration of his
largest intracranial cyst 3 years after initial resection. During the
procedure, upon passing the catheter for fenestration, there was re-
turn of slightly cloudy fluid that was aspirated continuously and
freely. At this point, it was suspected that the cyst communicated
with the cisternal system, and draining was halted. Intraoperative
MRI suggested drainage of a portion of the cyst (50% decompress-
ion), but significant cyst remained.

On retrospective review, his cysts were noted to be present in a
cranial imaging examination 9 years prior (Fig. 3G and H), though
they were fewer in number and smaller in size. Postoperatively, the
patient did well. In follow-up over the subsequent 3 years, there
was minimal increase in the size and number of the cystic lesions.
The patient remained asymptomatic with the exception of the occa-
sional pressure behind his eyes.

Discussion

Observations

CPPs are characteristically benign tumors of the choroid plexus
that exhibit slow growth and are typically cured after complete re-
section.1–3 Despite their benign pathology, however, they have been
shown to metastasize within the craniospinal axis. Typically, these
metastatic lesions present as enhancing mass lesions or “drop

FIG. 2. Case 2. An 11-year-old female with fourth ventricular CPP and multiple cystic lesions. A: Sagittal post-
contrast T1-weighted MRI shows a large enhancing fourth ventricular lesion. B: Axial postcontrast T1-
weighted MRI shows a fourth ventricular lesion. C: Axial T2-weighted MRI shows multiple cystic lesions
(arrows). Axial T1-weighted (D) and T2-weighted (E) MRI shows multiple hypodense cystic lesions (arrows)
3 years after resection of the fourth ventricular tumor. F: Sagittal T2-weighted MRI of the cervical spine shows
multiple hyperintense cystic lesions (arrows) 8 years after resection of the fourth ventricular tumor.
metastases” similar to the primary lesion or as leptomeningeal enhancement and seeding.4–10 In 2006, McCall et al.12 explored two differing phenotypes of CPP dissemination; one case was a solid mass lesion, and the other presented as multiple cystic lesions with a concurrent enhancing lesion in the fourth ventricle. These widely disseminated cystic lesions, first described by Leblanc et al.11 in 1998, are far more rare, with only four imaging-confirmed cases of cystic dissemination in WHO grade 1 CPP in the literature.11–15 This microcystic metastatic behavior has also been seen in WHO grade 2 atypical CPP.15 Recently, a new naming schema, the Pettersson-Mazur-Hart classification system, was proposed by Mazur-Hart et al.13 to more accurately describe choroid plexus tumors in the setting of this unique disseminated presentation. Under their proposed classification, CPPs presenting with multiple lesions would be classified as disseminated disease, multifocal disease, zuckerguss-like seeding of the leptomeninges, and ependymal disease.13

Here, we describe three more cases of patients presenting with CPP and widespread cystic dissemination. We summarize the pertinent details of the previously published cases, as well as our cases, in Table 1. Seven of these cases were WHO grade 1 lesions, whereas one was classified as atypical CPP (WHO grade 2). Of the eight cases, six exhibited solitary lesions, five of which were located in the fourth ventricle. (The other was located in the lateral ventricle.) All of these solitary lesions were contrast enhancing, and five of them exhibited calcifications. All cystic lesions were nonenhancing on imaging and widely distributed throughout the subarachnoid spaces. In two cases, multiple solid lesions were reported.

Due to the rarity of this pathology, there remains no standard-of-care treatment for these cystic lesions. Although gross total resection is the standard treatment for CPP with low rates of recurrence,11–13 often in patients with these disseminated cystic lesions, the number of lesions is far too numerous for resection. In the case of the McCall et al.12 patient, the patient was treated with temozolomide with a good clinical response. The Rivière et al.15 case (WHO grade 2) was treated with etoposide, carboplatin, vincristine, and craniospinal radiation with stabilization of the disease. However, in the cases of the other six patients, no adjuvant therapy was pursued. Although in four patients there was mild interval enlargement of the cystic lesions at some point over the course of their care, many of these patients remained asymptomatic despite enlargement.

The pathophysiology of these cystic lesions remains uncertain, and we have hypothesized various causes for these lesions. One hypothesis is that microscopic deposits released from the tumor within the arachnoid space cause inflammation and subsequent adhesions of the arachnoid mater. However, in the cases of our three patients, there were no signs of hemorrhage or inflammation on susceptibility-weighted imaging, and the cystic lesions did not demonstrate membranes, as one would expect with arachnoid adhesions.16 Another possibility is multiple arteriovenous shunts, though in two of our three cases, MRI angiography was used to assess vascularity. Another mechanism is that the primary tumor sheds cells that are unable to develop their own vascularity and become self-sustaining metastases but that retain the ability to secrete CSF for variable periods of time; alternatively, these microdeposits may represent “burned out” metastases, or metastatic deposits that were unable to survive on their own, but for a period of time were able to secrete CSF and subsequently formed these cystic lesions. Finally, we propose that the primary tumor may be releasing “unhinged” arachnoid cap cells, which were found in case 1’s pathology. Arachnoid cap cells are highly secretory,17–19 and we posit that these microdeposits may have the ability for aberrant secretion of fluid to form these cystic lesions. We do, however, acknowledge that longer-term follow-up is necessary to truly define the natural history of these seemingly benign lesions.

Lessons

Though rare, CPP can present with multiple leptomeningeal cystic lesions. Recently, a reclassification of choroid plexus tumors has been proposed (the Pettersson-Mazur-Hart classification) to reclassify choroid plexus tumors in the setting of this rare presentation.13 These cysts can be numerous and widely disseminated within the cranial and spinal spaces. The pathophysiology underlying this rare presentation remains unclear, and there are various possible mechanisms by which these lesions may develop. However, the natural history of such lesions appears to be benign, with cysts exhibiting slow, if any, growth over time, and often with radiological imaging looking far worse than the clinical presentation of the patient.
| Case No. | Authors & Year | Age (yrs), Sex | WHO Grade | Tumor Location, Features | Cyst Location & Features | Treatment & Outcomes of Cysts |
|----------|----------------|---------------|-----------|-------------------------|--------------------------|-------------------------------|
| 1        | McCall et al., 2006\(^{12}\) | 38, F | 1 | 4th ventricle, enhancing | Nonenhancing; scattered at cerebellum, brainstem, cervical cord, middle cranial fossa, & frontal lobe | Empirical trial of temozolomide; no change in size or distribution on serial MRI after initiation of treatment |
| 2        | Leblanc et al., 1998\(^{11}\) | 19, F | 1 | 4th ventricle, enhancing, calcified | Nonenhancing; scattered diffusely w/in infratentorial & supratentorial subarachnoid spaces; w/ spinal lesions | Enlargement of many residual cysts at 2 & 3 yrs after resection; patient remained asymptomatic |
| 3        | Doglietto et al., 2005\(^{14}\) | 16, M | 1 | Multiple solid lesions: cisterna magna, bilat CPA, lumbosacral space | Frontal lobes, cerebellum | Stable at 1 yr after resection of cisterna magna tumor |
| 4        | Rivière et al., 2018\(^{15}\) | 15, M | 2 | Numerous cystic & solid nodules in the craniofacial junction & along the internal auditory canal | Leptomeningeal disease of posterior fossa, supratentorial space & spine; numerous cystic & solid nodules in craniofacial junction & along the internal auditory canal | Etoposide, carboplatin, vincristine; craniospinal radiation (41.4 Gy); stable disease at 17 mos |
| 5        | Mazur-Hart et al., 2022\(^{23}\) | 2, M | 1 | Lat ventricle, enhancing, calcified | Nonenhancing; scattered along medial cerebral peduncles & anterior temporal lobes along the bilat sylvian fissures; w/ spinal lesions causing mass effect on the cord at T3–5; w/ leptomeningeal enhancement of brainstem & spinal cord | Laminoplasties for largest spinal lesions; CSF positive for atypical cells favored to be choroid plexus cells; intracranial cysts stable in size; resolution of leptomeningeal enhancement at 1 yr |
| 6        | Present report | 40, F | 1 | 4th ventricle, enhancing, calcified | Nonenhancing; scattered throughout posterior fossa, interpeduncular cistern, along the tentorium, adjacent to left fusiform gyrus & sylvian fissure; w/ spinal lesions | Mild interval enlargement, patient remained asymptomatic |
| 7        | Present report | 11, F | 1 | 4th ventricle, enhancing, calcified | Nonenhancing; scattered throughout prepontine cisterns, bilat cerebellar hemispheres, & bilat sylvian fissure; w/ spinal lesions | Interval enlargement of cystic lesions w/ appearance of new lesions; stable cystic disease for last 5 yrs before stopping surveillance imaging; patient remained asymptomatic |

CONTINUED ON PAGE 8 »
Although the role of adjuvant chemotherapy and cyst fenestration remains unclear, watchful waiting and observation in cases of these disseminated cystic lesions may be indicated, especially in the case of an asymptomatic patient, as well as preoperative and routine imaging of the entire neuroaxis in patients with choroid plexus tumors, regardless of WHO grade.

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Author Contributions

Conception and design: Johnson, Mian, Dahiya, Chicoine, Limbrick. Acquisition of data: Johnson, Mian, Dahiya, Limbrick. Analysis and interpretation of data: all authors. Drafting the article: Johnson, Chicoine, Limbrick. Critically revising the article: Mian, Chicoine, Limbrick. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Johnson. Statistical analysis: Rich. Administrative/technical/material support: Limbrick. Study supervision: Limbrick.

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