

The association of ectopic craniopharyngioma in the fourth ventricle with familial adenomatous polyposis: illustrative case

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BACKGROUND Craniopharyngioma (CP) often arises in the sellar and suprasellar areas; ectopic CP in the posterior fossa is rare. Familial adenomatous polyposis (FAP) is a genetic disorder involving the formation of numerous adenomatous polyps in the gastrointestinal tract, and it is associated with other extraintestinal manifestations.

OBSERVATIONS The authors reported the case of a 63-year-old woman with FAP who presented with headache and harbored a growing mass in the fourth ventricle. Magnetic resonance imaging (MRI) findings revealed a well-circumscribed mass with high intensity on T1-weighted images and low intensity on T2-weighted images and exhibited no contrast enhancement. Gross total resection was performed and histopathology revealed an adamantinomatous CP (aCP). The authors also reviewed the previous reports of ectopic CP in the posterior fossa and found a high percentage of FAP cases among the ectopic CP group, thus suggesting a possible association between the two diseases.

LESSONS An ectopic CP may be reasonably included in the differential diagnosis in patients with FAP who present with well-circumscribed tumors in the posterior fossa.

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KEYWORDS craniopharyngioma; familial adenomatous polyposis; fourth ventricle; β -catenin

Craniopharyngioma (CP) is a benign tumor derived from the embryonic tissue of the sellar region and its surrounding structures.¹ There are two types of CP: adamantinomatous CP (aCP) and papillary CP (pCP). The aCP type arises from the cells of the embryonic structure, known as the craniopharyngeal duct whereas pCP arises from the cells of the anterior part of the pituitary gland.¹ CPs usually grow in the sellar-suprasellar area. An ectopic CP arising from other sites is rare; CP of the posterior fossa is even rarer and has only been reported in 19 cases so far.^{2,3} Moreover, there have only been five reports of CP arising from the fourth ventricle.^{4,5}

Familial adenomatous polyposis (FAP) is an autosomal dominant genetic disorder in which adenomatous polyps form in the epithelium of the gastrointestinal tract. The disorder is caused by germline mutations in the adenomatous polyposis coli (*APC*) gene, which is a tumor suppressor.⁶ FAP is also associated with other extraintestinal manifestations, such as gastric fundic gland polyps, duodenal polyps, pancreatobiliary tumors, congenital hypertrophy of retinal pigment epithelium, fibromas, fibromatosis, nasal angiofibromas, thyroid carcinomas, hepatoblastomas, and brain tumors.⁶

Herein, we report a case of CP located purely in the fourth ventricle in a patient with FAP. We also review the previous literature

ABBREVIATIONS aCP = adamantinomatous CP; CP = craniopharyngioma; FAP = familial adenomatous polyposis; MRI = magnetic resonance imaging; pCP = papillary CP.

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on ectopic CP and discuss the possible relationship between these rare diseases.

Illustrative Case

A 63-year-old woman with FAP was referred to our department because of a mass in the fourth ventricle that was detected using magnetic resonance imaging (MRI), which was performed because of chronic headaches. She had a known history of FAP and underwent prophylactic colectomy at the age of 32 years. Later, the patient developed rectal cancer, which was resected when she was 57 years old. Apart from the gastrointestinal manifestations, she had frontal bone osteoma and received surgery for its removal at the age of 22 years. Her mother died from colon cancer at the age of 60 years, and her brother had colon cancer in his 30s. Also, her sister had received surgery for sigmoid colon cancer in her 40s. The target sequence by NCC oncopanel FC v2.0 revealed a truncating frameshift variant in the 15th exon of the germline APC gene (NM_000038.5: c.3180_3184del: p.I1060fs), thus confirming the diagnosis of FAP.

The patient exhibited no neurological deficits, except for chronic headaches. MRI demonstrated a well-circumscribed mass with a maximum diameter of 32 mm in the fourth ventricle, with heterogeneously high intensity on T1-weighted images and low intensity on T2-weighted images (Fig. 1A and B). No contrast enhancement of the mass was observed (Fig. 1C), and no evidence of obstructive hydrocephalus was found. MR angiography showed that the mass was located near the left posterior inferior cerebellar artery; however, digital subtraction angiography showed no evidence of thrombosed aneurysm. Computed tomography showed a small component of calcification inside the mass (Fig. 1D), whereas fluorodeoxyglucose positron emission tomography showed no accumulation in the mass. Based on imaging findings, a preoperative diagnosis of epidermoid, or neurenteric cyst, was made. The patient was followed-up with serial MRI. Eleven months after the first visit, the mass showed a tendency to grow, and the patient agreed to proceed with surgical removal of the mass.

The patient was placed prone, and a midline suboccipital craniotomy was performed under general anesthesia. The mass in the fourth ventricle was cystic (Fig. 2A) and was found to have no connection with the posterior inferior cerebellar artery. Puncture of the cyst revealed a fluid component resembling motor oil. The capsule had no adhesion to the floor of the fourth ventricle, and the cyst was easily dissected and removed en bloc (Fig. 2B).

Hematoxylin and eosin staining revealed that the cyst wall was proliferated with basal cell-like p40-positive squamous epithelial

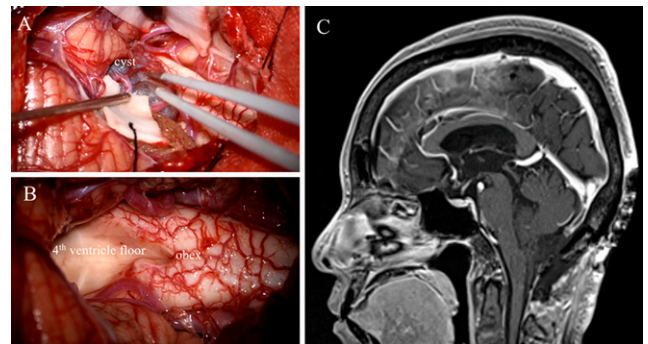


FIG. 2. Intraoperative findings and postoperative MRI. **A:** The cyst wall was observed to be occupying the fourth ventricle. **B:** The tumor was removed en bloc without adhesion to the floor of the fourth ventricle. **C:** Postoperative sagittal T1-CE images showing gross total resection of the tumor.

cells with high nuclear-to-cytoplasmic ratio and was accompanied by wet-keratin (Fig. 3A). The contents were keratinized and characterized by a well-differentiated squamous epithelium with palisading columnar epithelium (Fig. 3B). Immunohistochemistry revealed positive staining for β -catenin in the membrane and focally in the nucleus (Fig. 3C). The BRAF (V600E) staining results were negative. Overall, the pathological diagnosis was concluded to be aCP.

The patient had an uneventful postoperative recovery, and postoperative MRI revealed complete resection of the tumor (Fig. 2C). At the 2-month follow-up visit, MRI showed no evidence of any recurrence.

Discussion

Observations

CP is a benign tumor arising from the remnant tissue of the craniopharyngeal canal and is known to be predominantly located in and around the sella turcica, accounting for 3% of all intracranial tumors.¹ Clinical symptoms include headaches and vomiting due to increased intracranial pressure and visual field disturbances due to optic nerve compression. Pathologically, there are two types of CP: aCP and pCP.¹ Although the common site of CP is around the sella turcica of the pituitary stalk, primary ectopic CP occurring in other locations in the cranium has also been reported, including in the nasopharynx, sphenoid bone, and third ventricle.⁷⁻⁹ A total of 19 patients with ectopic CP in the posterior fossa have been reported

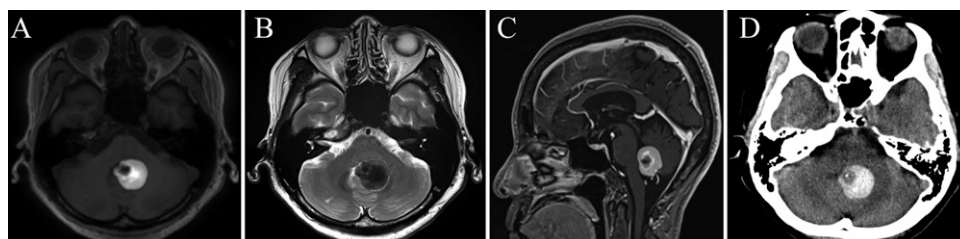


FIG. 1. Preoperative images. **A:** Axial T1-weighted images showing a hyperdense cystic mass. **B:** Axial T2-weighted images showing a hypodense mass in the fourth ventricle. **C:** Sagittal T1-contrast enhanced images showing a cystic mass without enhancement. **D:** Axial computed tomography (CT) images demonstrate small calcifications within the mass.

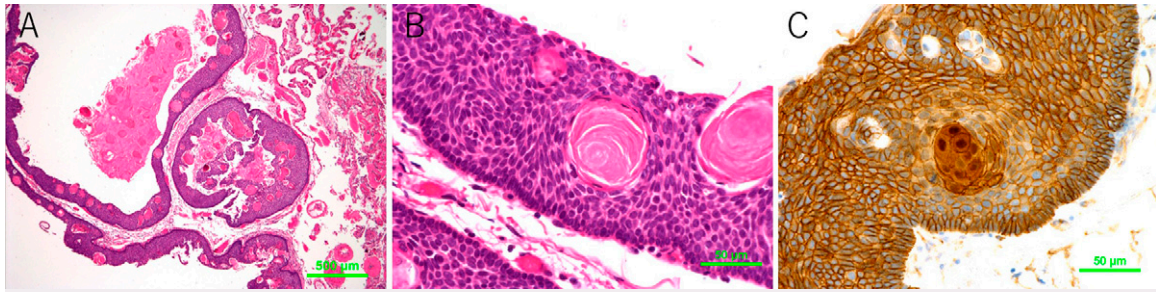


FIG. 3. Histopathology. **A:** The cystic lesion contained “wet” keratin (hematoxylin and eosin stain). Bar = 500 μm . **B:** The well-differentiated squamous epithelium was surrounded by palisading columnar epithelium (hematoxylin and eosin stain). Bar = 50 μm . **C:** Immunohistochemistry for β -catenin showed that some foci of epithelial cells were positive for β -catenin in their nuclei. Bar = 50 μm .

to date, of whom 6 patients, including ours, were diagnosed with CP in the fourth ventricle (Table 1).^{2,4,5,10–23} The high incidence of FAP among patients with ectopic CP in the posterior fossa suggests an association between these two rare diseases. Of the 20 cases involving the posterior fossa, 14 were men and 18 were younger than 40 years. The average age of patients with CP who have FAP (mean [SD] age: 33.9 [13.6] years) was approximately 10 years more than patients without FAP (mean [SD] age: 23.8 [12.0] years). There were no patients younger than 20 years among the patients with FAP, whereas 5 of 13 patients without FAP were younger than 20 years. Our case is unique because it is the first reported case of this condition in a woman; moreover, she had the greatest age at surgery among the patients with FAP. Headache was the most common clinical symptom observed in patients with ectopic CP of the

posterior fossa (71%). Diplopia and hearing impairment were also observed in 7 patients (33%). All pathological findings were aligned with aCP in patients with FAP, except for 1 case in which it was not mentioned; however, 2 cases of pCP were reported in patients without FAP. As for the extent of tumor removal, total resection was performed in 14 cases, whereas near-total and subtotal resection were performed in 3 cases each. Excluding our case, CP with FAP has been reported in 7 patients to date,^{2–5} of whom most (6 of 7 cases) occurred in the posterior fossa. Of the 6 cases of CP, 2 cases that were complicated by FAP occurred in the fourth ventricle.

FAP is an autosomal dominant genetic disorder characterized by multiple adenomatous polyps in the gastrointestinal mucosa. It is also associated with extragastrintestinal lesions and brain tumors, including medulloblastoma, ependymoma, and pituitary adenoma.⁶

TABLE 1. Literature review of ectopic craniopharyngiomas in the posterior fossa

Author & Year	Age (yrs)/Sex	FAP	Clinical Symptoms	Location	Histopathology
Altinörs et al., 1984 ¹⁰	14/M	–	Rt hearing loss, diplopia, neck pain	CPA	pCP
Gökalp & Mertol, 1990 ¹¹	17/M	–	Headache, vomiting, hearing loss, ataxia	CPA	N/A
Bashir et al., 1996 ¹²	23/M	–	Headache, neck pain, dizziness, truncal ataxia	Fourth ventricle	pCP
Xu et al., 2006 ¹³	22/F	–	Tinnitus, dizziness, hearing loss	CPA	aCP
Shah et al., 2007 ¹⁴	12/F	–	Headache, diplopia, walking disorder	Fourth ventricle	aCP
Powers et al., 2007 ¹⁵	12/F	–	Headache, vomiting	CPA	aCP
Yan et al., 2009 ¹⁶	54/F	–	Headache, tinnitus, ataxia, hemiparesis, deficit of V-X	CPA	aCP
Yilmaz et al., 2010 ¹⁷	14/M	–	Rt hearing loss, diplopia, neck pain	CPA	N/A
Sharma et al., 2012 ¹⁸	26/F	–	Headache	CPA	aCP
Khalatbari et al., 2012 ¹⁹	40/M	–	Headache, diplopia, tinnitus, lt hearing loss, palsy of V, VI	CPA	aCP
Khalatbari et al., 2012 ¹⁹	22/M	–	Headache, vomiting, diplopia, tinnitus, ataxia	CPA	aCP
Khalatbari et al., 2012 ¹⁹	28/M	–	Headache, vomiting, diplopia	CPA	aCP
Algahtani et al., 2018 ²	25/M	–	Headache, dizziness	Fourth ventricle	aCP
Link et al., 2002 ²⁰	29/M	+	Headache, tinnitus, deficit of V-X	CPA	aCP
Aquilina et al., 2006 ²¹	31/M	+	Headache, vomiting, ataxia, blurred vision	CPA	N/A
Bozbuga et al., 2011 ²²	34/M	+	Hemiparesis, tinnitus, lt hearing loss	CPA	aCP
Kim et al., 2014 ²³	31/M	+	Headache, dizziness	CPA	aCP
Álvarez Salgado et al., 2017 ⁴	29/M	+	Rt facial paresis, diplopia	Fourth ventricle	aCP
Pena et al., 2016 ⁵	20/M	+	None	Fourth ventricle	aCP
Present case	63/F	+	Headache	Fourth ventricle	aCP

Recent studies have correlated the severity of gastrointestinal disease and the prominence of extraintestinal findings to specific mutations within the *APC* gene.²⁴ Patients with FAP who have *APC* gene mutations between codons 697 and 1224 have a three-fold increased risk of developing brain tumors in general and a 13-fold increased risk of developing medulloblastoma when compared with patients with FAP who have other *APC* gene mutations.²⁵ Among the 7 cases of CP with FAP reported to occur in the posterior fossa, there was only 1 case in which a similar genetic diagnosis was made.²⁰ In that case, a truncating frameshift mutation in the *APC* gene was detected in the 16th exon (NM_000038: c.4541_4547del:p.P1514fs), leading to a stop at the position of the 18th codon.

There are two possible hypotheses that explain the high incidence of FAP among ectopic CP cases in the posterior fossa. First, a report explains the mechanism of primary ectopic CP as possibly being the migration of squamous epithelial cell remnants to the obliterated craniopharyngeal canal.²⁶ The craniopharyngeal canal usually disappears during the fetal period. If it is left behind, it is called the Rathke's pouch, and it can be the site of CP, which occurs in close proximity to the pharynx as described above.⁷⁻⁹ However, in our case, it was located purely in the fourth ventricle, with no apparent continuity with the pharynx. This suggests that in patients with FAP, squamous cells in the craniopharyngeal canal may migrate to the posterior fossa in the early stages of development by an unknown mechanism or the maldifferentiation of cells in the posterior fossa by germline mutations in the *APC* gene. Second, it has been reported that mutant *APC* proteins are unable to induce the degradation of β -catenin, resulting in the accumulation of β -catenin in the cells.²⁷ β -catenin mutation is also found in aCP heterozygotes.²⁴ The pathological accumulation of β -catenin in aCP is known to be associated with FAP, suggesting the possible molecular level association between these diseases. However, compared to medulloblastoma, CPs are less common in patients with FAP, which could be because of the relationship between CP and FAP that has not yet been fully established or because of regulatory elements in the developing epithelium where aCP occurs and nullifies the pathogenicity of *APC* deficiency.³ The precise molecular or cellular mechanism remains unelucidated, and the association between these two diseases is notable, necessitating the need for further studies.

Lessons

Ectopic CPs in the posterior cranial fossa are rare. However, ectopic CP may be reasonably included in the list of differential diagnoses in patients with FAP who present with well-circumscribed tumors in the posterior fossa, especially in the fourth ventricle.

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Disclosures

Dr. Kawasaki reported "The genomic medicine course I belong to is an industry-academia joint research course with Konica Minolta. However,

it has nothing to do with the content of this research.” No other disclosures were reported.

Author Contributions

Conception and design: Tanji, Uemura, Kosugi, Yoshida. Acquisition of data: Tanji, Uemura, Natsuhara, Takeuchi, Sugimoto. Analysis and interpretation of data: Tanji, Uemura, Sugimoto. Drafting the article: Tanji, Uemura, Sugimoto, Kawasaki. Critically revising the article: Tanji, Uemura, Sugimoto, Torishima, Kosugi, Mineharu, Arakawa, Yoshida, Miyamoto.

Reviewed submitted version of manuscript: Uemura, Sugimoto, Minamiguchi, Arakawa. Approved the final version of the manuscript on behalf of all authors: Tanji. Statistical analysis: Uemura. Administrative/technical/material support: Tanji, Minamiguchi. Study supervision: Tanji, Kawasaki, Yoshida, Miyamoto. Pathology diagnosis: Hoki.

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