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Case Report

Malignant Transformation of a Neurenteric Cyst in the Posterior Fossa Presenting with Intracranial Metastasis: A Case Report and Literature Review

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Intracranial neurenteric cysts are relatively rare and almost exclusively benign. Here we present a case of an intracranial neurenteric cyst that was histologically benign in the first surgery and later demonstrated significant growth and intracranial metastasis with malignant transformation. A 47-year-old woman presented with a headache, which had gradually worsened over 1 year. Initial magnetic resonance (MR) images revealed a solitary cystic lesion in the left cerebellopontine angle with significant mass effect. Subtotal resection leaving a small mass strongly adhered to the brainstem was achieved. Histopathological diagnosis was neurenteric cyst with no malignant features. This lesion recurred 4 years after the first surgery in the form of a cystic mass adjacent to the brainstem. In addition, histopathological examination of a specimen from the second surgery revealed malignant transformation. The patient declined to undergo radiation therapy and was conservatively managed. Three years after the second surgery, MR imaging showed recurrence of the solid mass. Although the patient had been treated with subtotal resection and radiation therapy, she died with metastatic masses in the right frontal lobe and cervical cord. A specimen from the third surgery revealed diffuse malignant features similar to mucinous adenocarcinoma. Our case and literature review indicate that, although rare, malignant transformation can occur particularly among intracranial neurentreric cysts. This finding suggests the importance of long-term follow-up for subtotally or partially resected intracranial neurenteric cysts.

Keywords: intracranial tumor, malignant transformation, neurenteric cyst, posterior fossa

Introduction

A neurenteric cyst, also known as enterogenous cyst, endodermal cyst, respiratory cyst, and bronchogenic cyst, is a rare benign cystic lesion,[1)] generally arising in the intradural extramedullary space in the lower cervical and upper thoracic spine.[2,3)] While the incidence of spinal neurenteric cyst has been reported to be 0.3%–0.5% of all spinal tumors,[4,5)] neurenteric cysts in the posterior fossa are relatively rare.[2,3)] Because one-third of patients treated by subtotal or partial resection experience symptomatic recurrence,[6)] total resection is considered to result in favorable outcomes based on the benign nature of these cysts.[1)] Other than the cases of originally malignant neurenteric cysts,[7–11)] the malignant transformation of benign neurenteric cysts is extremely rare.[12–14)] In this report, we describe a case of a neurenteric cyst in the posterior fossa that eventually showed malignant transformation and intracranial metastasis and review of the relevant literature.

Case Report

A 47-year-old woman with no past medical history presented with a headache, which had gradually worsened over the past 1 year. Her neurological examination revealed no deficit on the initial visit. Magnetic resonance (MR) images were obtained for prolonged headache and demonstrated a solitary cystic lesion in the left cerebellopontine angle with a significant mass effect on the left cerebellar hemisphere (Fig. 1A). To relieve her headache and confirm the pathology, she was treated via left suboccipital approach for subtotal resection, which left a small membranous residual lesion strongly adhered to the brainstem. The residual portion was not significantly visible on the postoperative MR images, and the mass effect was completely resolved (Fig. 1B). The histopathological examination revealed that the cyst wall was composed of a single-layered columnar epithelium similar to the respiratory and intestinal tract (Fig. 1C). Immunohistochemistry for glial fibrillary acidic protein (GFAP; clone 6F2, DAKO, Carpinteria, California, USA), vimentin (clone V9, DAKO, Carpinteria, California, USA), neuron specific enolase (clone BBS/NC/VI-H14, DAKO, Carpinteria, California, USA), and S-100 was negative. The epithelium showed weak staining for carcinoembryonic antigen (clone A0115, DAKO, Carpinteria, California, USA, Fig. 1D) and diffuse staining for epithelium membrane antigen (EMA; clone E29, DAKO, Carpinteria, California, USA, Fig. 1E) and with anti-cytokeratin antibodies AE1/AE3 (clone AE1+AE3, Novocastra, Newcastlle, UK, Fig. 1F). Periodic acid-Schiff (PAS) staining demonstrated mucins along the epithelium (Fig. 1G). Staining for the p53 mutation was negative (Fig. 1H). These results were consistent with a diagnosis of a neurenteric cyst. The MIB-1 labeling index was almost 0% (antibody; clone MIB-1, DAKO, Carpinteria, California, USA, Fig. 1I). The patient developed postoperative pharyngeal and vocal cord paralysis on the left side. After over 1 month, when she showed a considerable recovery from these

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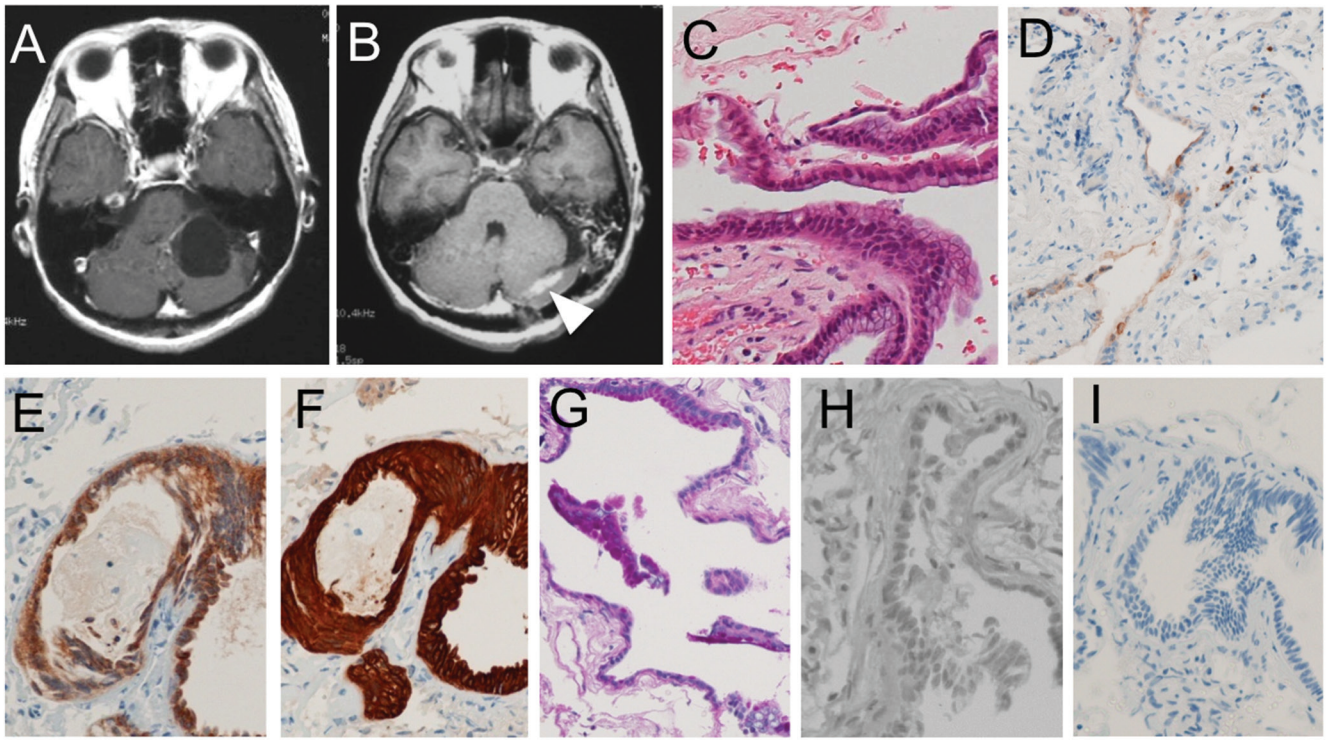

Fig. 1 A: An axial T_1-weighted magnetic resonance (MR) image with gadolinium enhancement demonstrated a cystic lesion at the left cerebellopontine angle. The wall of a cystic lesion along with the brainstem was slightly enhanced with gadolinium. B: Postoperative T_1-weighted MR image showed remarkable shrinkage of the cyst. The hyperintense region indicated a small accumulation of blood inside the cyst cavity (arrowhead). C: The wall of the cyst was lined by a single layer of columnar epithelium (hematoxylin and eosin, 400×). Immunohistochemical analysis showed that the epithelium stained positive for carcinoembryonic antigen (CEA) (D, 200×), epithelium membrane antigen (E, 400×), and cytokeratin (AE1/AE3; F, 400×). Staining for the p53 mutation was negative (H). Periodic acid-Schiff staining demonstrated mucins along the epithelium (G, 200×). The MIB-1 labeling index was almost 0% (I, 400×).

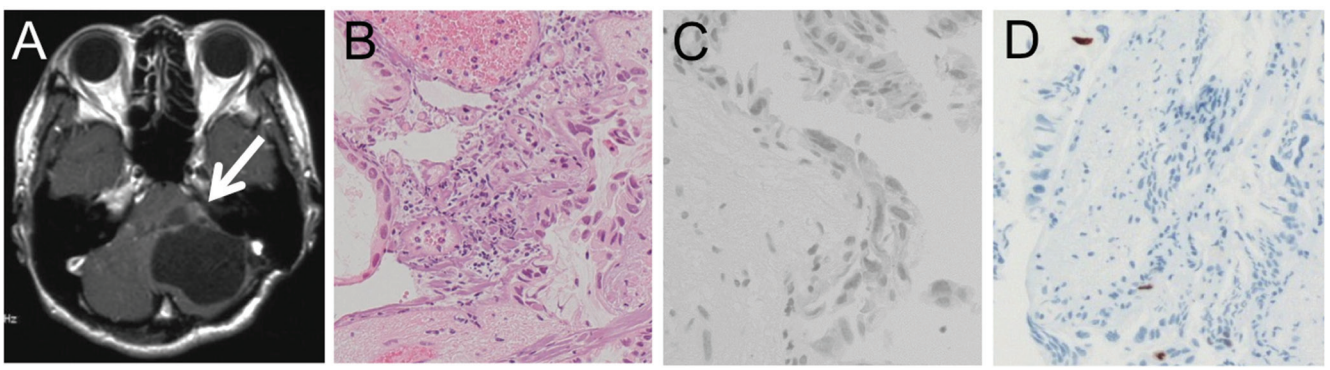

Fig. 2 A: Axial magnetic resonance (MR) images demonstrating recurrence of a cystic lesion with a small and slightly enhanced solid portion adjacent to the brainstem (arrow). B: Atypical nuclei and loss of cell polarity were noted (hematoxylin and eosin, 400×). C: Staining for the p53 mutation was weakly positive. D: Immunohistochemical staining with MIB-1 antibody showed approximately 3% nuclear staining in the tumor cells.

symptoms, she was discharged with a plan for follow-up.

However, the patient abandoned follow-up visits at 6 months after surgery because she believed that her condition was stable. Four years after her final follow-up visit, she returned to our department complaining of headache, taste disorder, and gait disturbance. MR images demonstrated recurrence of a cystic mass with a small and slightly enhanced solid portion adjacent to the brainstem that was considered to be a regrowth from the residual lesion of the initial resection (Fig. 2A). She underwent subtotal resection and placement of a cyst-cisternal shunt. We again had to leave a small solid portion of the tumor because of the severe adhesion to the brainstem. Histopathological examination of the specimen obtained during the second resection revealed that the basic structures had not changed, but some atypical nuclei and loss of cell polarity were evident (Fig. 2B). Results

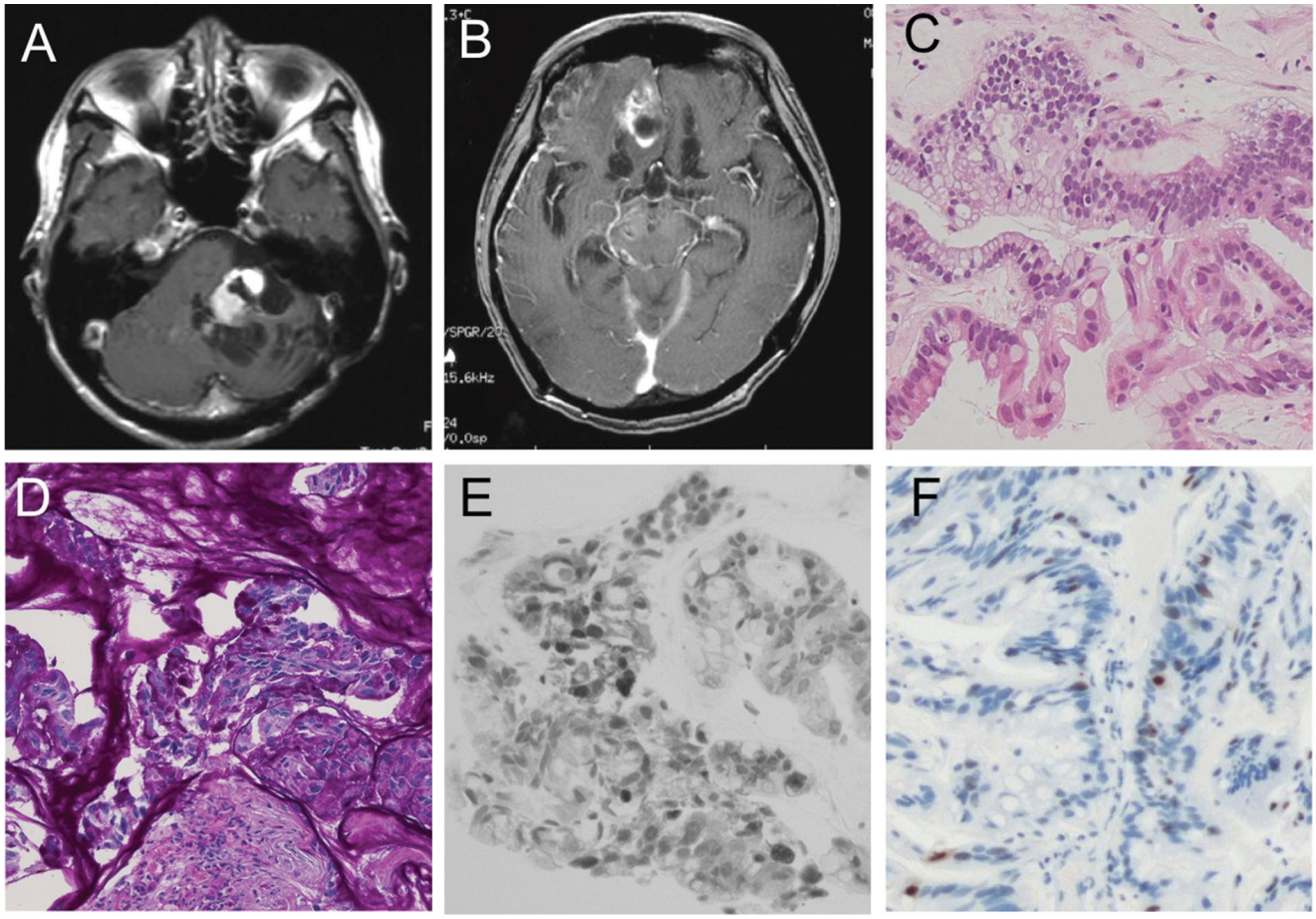

Fig. 3 Axial magnetic resonance (MR) images revealing significant recurrence of the solid mass with compression of the brain stem (A) and a new gadolinium-enhanced lesion in the right frontal lobe (B). C: Atypical and mitotic nuclei with more prominent than normal nuclei. Pseudostratified nuclei and loss of cell polarity were widely observed (hematoxylin and eosin, 400×). D: Periodic acid-Schiff staining showed strong positivity for mucins. E: Immunohistochemistry for the p53 mutation was positive. F: The MIB-1 labeling index was elevated to 9%.

of immunohistochemistry for EMA, carcinoembryonic antigen, GFAP, vimentin, neuron specific enolase, S-100, and AE1/AE3 were the same as those of the specimen obtained from the first surgery. No p53 mutation was detected (Fig. 2C). The MIB-1 labeling index was 3% (Fig. 2D), suggesting an increased proliferative potential as well. One month after surgery, she was discharged with good relief from symptoms. After a thorough discussion regarding the treatment options including radiation therapy, she declined treatment with radiation and was followed up in our outpatient clinic every 3 months with regular imaging every 6 months.

Although her condition remained stable since the second surgery, she presented with hyperacusis 3 years later. MR imaging showed a rapid recurrence of the solid mass with significant compression of the brainstem (Fig. 3A). Although she underwent partial resection of the tumor followed by fractioned stereotactic radiation therapy (isocenter dose total 50 Gy/25fr), local tumor control failed. A metastatic lesion was noted in the right frontal lobe on MR images (Fig. 3B). Metastasis also occurred in the cervical cord. Histopathological examination of the specimen from the third surgery revealed cells with mitotic nuclei and more prominent cellular atypia (Fig. 3C). Pseudostratified nuclei and loss of cell polarity were widely observed. PAS staining confirmed an enhanced mucin production (Fig. 3D). These findings were similar to a mucinous adenocarcinoma. Immunohistochemistry for the p53 mutation was this time strongly positive (Fig. 3E). The MIB-1 labeling index was 9% (Fig. 3F). She did not respond to the radiation therapy and died of aspiration pneumonia followed by aggressive deterioration of systemic conditions.

Discussion

Neurenteric cysts represent a rare pathological condition and account for approximately 0.01% of all central nervous system tumors and 0.3%–0.5% of spinal tumors.[1)] Although the most common location of neurenteric cysts is ventral to the lower cervical and upper thoracic spine,[1,2,15)] they can also arise in the intracranial regions.[1)] Bejjani et al. reported that 90% of intracranial neurenteric cysts were located in the posterior fossa.[2)] Neurenteric cysts originate from imperfect separation of neuro-ectodermal elements and endodermal elements during the third week of gestation.[16)] The cyst wall

consists of a single layer cuboidal or columnar epithelium similar to gastrointestinal or respiratory epithelium.[1,17] Therefore, their epithelium is positive for cytokeratin, carcinoembryonic antigen, and EMA, but negative for GFAP and S-100 protein on immunohistochemical analysis.[1,18] Although most neurenteric cysts are histologically benign,[1,18,19] Perrini et al. reported that one-third of cases treated by partial or subtotal resection later experience symptomatic recurrence.[6] On the other hand, pathological proof of malignant transformation in the surgical specimen is extremely rare. Our literature search identified three cases of neurenteric cysts that underwent malignant transformation.[12–14] Combined with cases of intracranial neurenteric cysts with malignant features, eight cases of malignant neurenteric cysts have been reported in the literature (Table 1). Notably, all of these eight cases were observed in intracranial neurenteric cysts, and malignant transformation of a spinal neurenteric cyst has never been reported, although they occur much more frequently in the spinal cord. The reason for this discrepancy is not clear, but approximately 50% of neurenteric cysts in the spine and the cervicomedullary junction occur with other bony anomalies such as scoliosis, spina bifida, and Klippel-Feil syndrome,[20] whereas intracranial neurenteric cysts are very rarely associated with bony changes.[21] This might suggest that some genetic or embryological backgrounds differ from intracranial lesions to spinal ones. Staining for the p53 mutation was negative in the specimens obtained from the first and second surgeries, but was strongly positive on the third specimen. Along with the similar case report,[13] p53 mutation might be indicative of malignant transformation of neurenteric cysts. Although we had left only a small membranous tumor tissue on the brainstem in the first surgery, the patient experienced devastating recurrence and metastasis. The cyst-cisternal shunt placed on the second surgery might have induced the intracranial metastasis, but it might have eventually happened irrespective of the shunt considering the highly malignant features of the third specimen. Based on our case and previous reports of malignant transformation after gross total resection, recurrence with malignant transformation of a histologically benign neurenteric cyst can occur several years after the initial treatment, indicating the importance of long-term follow-up even when surgeons believe that gross total resection has been achieved.

Malignant neurentreric cysts are difficult to treat. Because of the paucity of cases in the literature, information regarding the prognosis and optimal treatment for malignant neurenteric cysts is lacking. Conventional radiotherapy and chemotherapy have shown little effect on histologically benign neurenteric cysts.[1,18] As shown in Table 1, among previously reported cases, two patients underwent radiation therapy and one died 1 year later and the other was not followed-up over the long term.[13,14] Sahara et al. reported a case of a neurenteric cyst in the foramen magnum with malignant transformation.[13] They administered chemotherapy (carboplatin and etoposide) in conjunction with radiation therapy after the

Table 1 Summary of previously reported cases of malignant transformation of neurenteric cyst

	Authors, year	Age, sex	Symptoms	Location	Initial resection	Initial pathology	Postoperative adjuvant therapy	Recurrence, follow-up period
Malignant transformation of benign neurenteric cyst	Sahara et al. (2001)[13]	54, M	neck pain	lt. anterior cervicomedullary junction (extra-axial)	GTR	NC	radiation chemotherapy	yes, 3.5 years
	Surash et al. (2009)[14]	46, M	headache and dizziness	rt. CP angle, (extra-axial)	GTR	NC	radiation	yes, 14 years
	Okabe et al. (2014)[12]	50, F	headache	rt. periventricular (intra-axial)	PR and Biopsy	NC	no	yes, 2 years
	Present case	38, F	headache	lt. CP angle	GTR	NC	radiation	yes, 8 years
Malignant neurentreric cyst	Ho et al. (1998)[9]	45, F	seizures and abnormal sensation	rt. parietal lobe (extra-axial)	GTR	NC with a well differentiated papillary neoplasm	no	yes, 15 months
	Monaco et al. (2003)[10]	36, M	headache, vomiting, drowsiness	cisterna magna	GTR	NC with focal malignant features	no	no, 2 years
	Gessi et al. (2008)[8]	25, M	hypoacusia, facial hemiparesis, visual disturbances, gait instability	rt. CP angle	GTR	NC with focal malignant features	no	yes, 5 months
	Wang et al. (2009)[11]	26, F	pain at the left occipital region	lt. CP angle, (extra-axial)	GTR	NC with focal malignant features	no	yes, 6 months (dissemination)
	Dunham et al. (2009)[7]	58, F	headache	rt. parietal lobe, (intra-axial)	GTR	NC with focal malignant features	no	no, 3 years

GTR: gross total resection, NC: neurenteric cyst, PR: partial resection.

second resection, and the patient achieved stable disease for 6 months. Although we did not treat our patient with chemotherapy, the effect of radiation appears to have been limited in our case.

In conclusion, malignant transformation of a histologically benign neurenteric cyst can occur although its incidence remains unknown. Our literature search revealed that malignant transformation of benign neurenteric cysts occurs almost exclusively in intracranial cases. This appears to indicate the importance of long-term follow-up for subtotally or partially resected neurenteric cysts, particularly for intracranial cysts.

Conflicts of Interest Disclosure

None of authors have any disclosure to report.

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