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MUCINOUS LOW-GRADE ADENOCARCINOMA ARISING IN AN INTRACRANIAL ENTEROGENOUS CYST: CASE REPORT

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OBJECTIVE: Enterogenous cysts (ECs) of the central nervous system are developmental malformations that occur in the spinal canal, posterior fossa, or cerebral hemispheres. They are usually benign lesions, and malignant transformation is rare. To date, only three cases of malignant transformation have been reported in the literature. We present a case of a cerebellopontine EC showing foci of epithelial dysplasia and malignant transformation into a low-grade papillary mucinous adenocarcinoma.

CLINICAL PRESENTATION: A 25 year-old man with a 6-year history of hypoacusia presented to our department with facial nerve deficit, visual disturbances, and gait instability. A magnetic resonance imaging scan demonstrated a multiloculated cerebellopontine angle cyst with supratentorial hydrocephalus.

INTERVENTION: A retrosigmoidal approach was used to achieve cyst removal. This was followed several months later by ventriculoperitoneal shunt placement. The cyst was adherent to the brainstem, cranial nerves, and vessels, and it resembled a thin encapsulated structure filled with mucinous-like substance. No solid component was identified. Histopathological examination revealed an EC with foci of malignant transformation in a mucinous papillary adenocarcinoma. Magnetic resonance imaging was performed 5 months postoperatively due to progressive clinical worsening; this scan revealed lesion recurrence with severe brainstem compression. Emergency surgery was performed, and a large decompression was achieved. Subsequent follow-up computed tomographic scans showed progression of the residual tumor. The patient's neurological condition rapidly worsened, ultimately resulting in death.

CONCLUSION: The present report suggests that a careful histological examination of all ECs after surgery should be made to exclude dysplastic foci or carcinomatous transformation. Although the clinical behavior of ECs with malignant trasformation is unpredictable, surgery remains the treatment of choice. The use of possible adjuvant chemo- or radiotherapy has not been established.

KEY WORDS: Cerebellopontine angle, Enterogenous cyst, Low-grade papillary carcinoma

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Enterogenous cysts (ECs) of the central nervous system are considered developmental malformations. They usually occur within the spinal canal, pontomedullary region, cerebellopontine angle (11), or, rarely, cerebral hemispheres (2, 3). They are usually benign lesions formed by single columnar or ciliated epithelial cells. The cysts may contain goblet cells and maintain a fibrous capsule. Malignant transformation of an EC is very rare. To date, only three cases have been reported in the literature (8, 10, 13). We present a case of an intracranial EC showing foci of epithelial dysplasia and malignant transformation in a low-grade papillary mucinous adenocarcinoma.

Case Report

Clinical Presentation

Clinical Course and Radiological Findings. In October 2006, a 25-year old man was referred to our hospital after a recent occurrence of visual disturbances in the right eye, right facial hemiparesis, and gait instability. The patient also reported a 6-year

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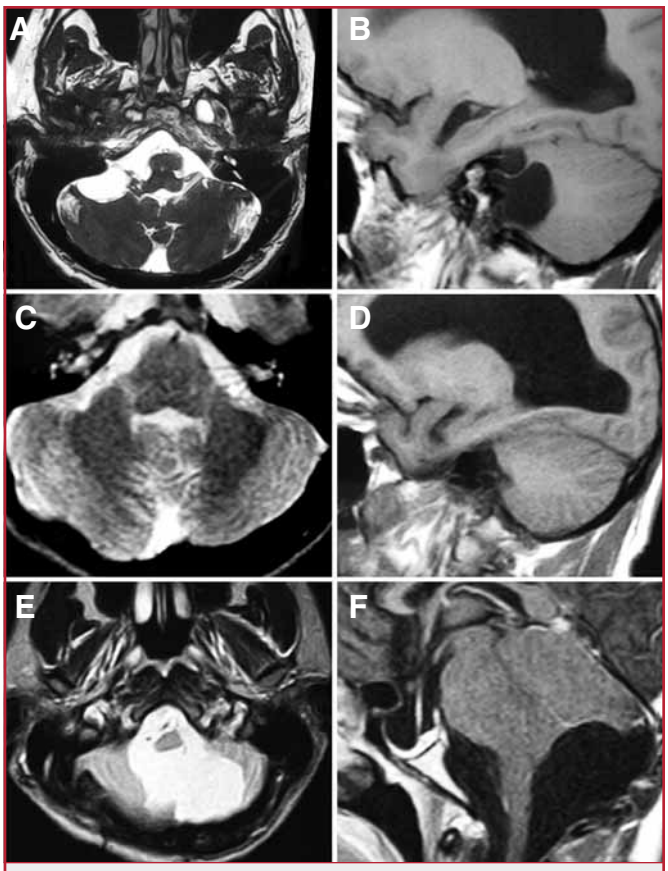

FIGURE 1. *Pre- and postoperative magnetic resonance imaging (MRI) scans of enterogenous cysts (ECs).* **A** *and* **B**, *T1- and T2-weighted MRI scans showing a multiloculated T1 hypointense and T2 hyperintense cystic lesion without contrast enhancement, within the right pontocerebellar angle extending contralaterally and toward the cerebellar vermis.* **C** *and* **D**, *T1- and T2-weighted postoperative MRI scans demonstrating the disappearance of the cystic lesion within the cerebellopontine angle.* **E** *and* **F**, *T1- and T2-weighted MRI scans obtained 4 months after surgery showing the EC recurrence within the posterior fossa causing severe brainstem compression.*

history of progressive hearing loss on the right side. Neurological examination demonstrated decreased visual acuity in the right eye, lateral gaze nystagmus, a right peripheral facial nerve deficit, gait difficulties, and an upper limb intention tremor.

Magnetic resonance imaging scans (*Fig. 1, A* and *B*) showed a multiloculated T1 hypointense and T2 hyperintense cystic lesion within the right cerebellopontine angle, which did not enhance with contrast and lacked a significant solid component. The cyst also extended contralaterally and toward the cerebellar vermis (5). A portion of the cyst invaded the petrous bone and the right internal auditory canal, which was significantly enlarged. Meckel's cave was also widened by the lesion. The scans also revealed an empty sella and triventricular hydrocephalus. Computed tomographic scans confirmed the enlargement of the right internal auditory canal with a well-defined erosion of the anterior part of the petrous bone, suggesting a long standing lesion.

Using a retrosigmoidal approach, the lesion was resected in entirety; the cyst was decompressed and its walls were dissected and removed. The cyst walls, which were composed of a thin capsule without major solid components, were adherent to the brainstem, cranial nerves, and vessels. The cystic fluid was mucinous. Postoperative magnetic resonance imaging scans demonstrated postoperative changes and gross total resection of the cystic lesion within the cerebellopontine angle (*Fig. 1, C* and *D*).

Three months later, the patient presented with walking difficulties, headache, and asthenia. A computed tomographic scan showed progression of the supratentorial hydrocephalus. Screening for possible primary tumor with positron emission tomography and serological tumor markers was negative. Therefore, a ventriculoperitoneal shunt was placed with subsequent improvement of neurological symptoms. A few weeks after ventriculoperitoneal shunt placement, the patient presented again with dysphagia, vomiting, and gait disturbances. Magnetic resonance imaging revealed reduction of supratentorial ventricular volumes with recurrence of a large, multiloculated cerebellar and cerebellopontine angle cyst causing severe brainstem compression. Emergency surgery was performed with partial resection of the lesion, which allowed for a large decompression of the brainstem. After a transient clinical improvement, however, the patient's neurological condition rapidly worsened. Follow-up computed tomographic scans showed persistence of brainstem compression, possibly due to progression of the residual tumor. The patient died and an autopsy was denied.

Histopathological Findings. Histological examination of the first surgical specimen revealed small cyst fragments, lined by simple columnar or cuboidal epithelium, with an underlying fibrous capsule and focal calcification, which is typical for ECs (*Fig. 2, A* and *B*). In some areas, the specimen showed a transition from flat, simple, columnar cells to dysplastic pseudostratified epithelium, organized in papillae, with hyperchromic nuclei and evident nucleoli, resembling a low-grade in situ mucinous papillary adenocarcinoma (*Fig. 2, C* and *D*). These areas showed high proliferative activity, as measured by Ki67/MIB-1 immunostaining (*Fig. 2F*), and numerous mitoses. No stromal or brain invasion was found. The cyst contained a dense mucoid substance.

The cyst epithelium stained intensively for cytokeratins, epithelial membrane antigen and carcinoembryonic antigen (*Fig. 2E*). Immunohistochemical staining for glial fibrillary acidic protein, vimentin, S100, synaptophysin, and p53 were negative, ruling out the diagnosis of endolymphatic low-grade carcinoma. The diagnosis of cystic teratoma with malignant changes was also excluded on the basis of the lack of histological evidence of ectodermal or mesodermal components. Histological examination of the recurrent lesion revealed a single layer of columnar epithelium similar to that found in the benign part of the first lesion but lacking dysplastic or malignant features.

DISCUSSION

ECs are benign lesions lined by mucin-secreting cuboidal or columnar epithelium of intestinal or respiratory type. Based on their cytological features, they have been referred to as enterogenous, neurenteric, respiratory, or bronchogenic cysts (2, 3). The cyst may contain clear, mucoid or xanthochromic liquid depending upon the cell type or the presence of previous hemorrhage (2, 3).

Although more frequently encountered within the spinal cord, ECs may develop intracranially within the posterior fossa, fourth ventricle, cerebellopontine angle (11) or, occasionally, cerebral hemispheres (1, 2, 3, 4, 6). Most ECs arise in the anterior part of the cervicothoracic region of the spinal cord and may be

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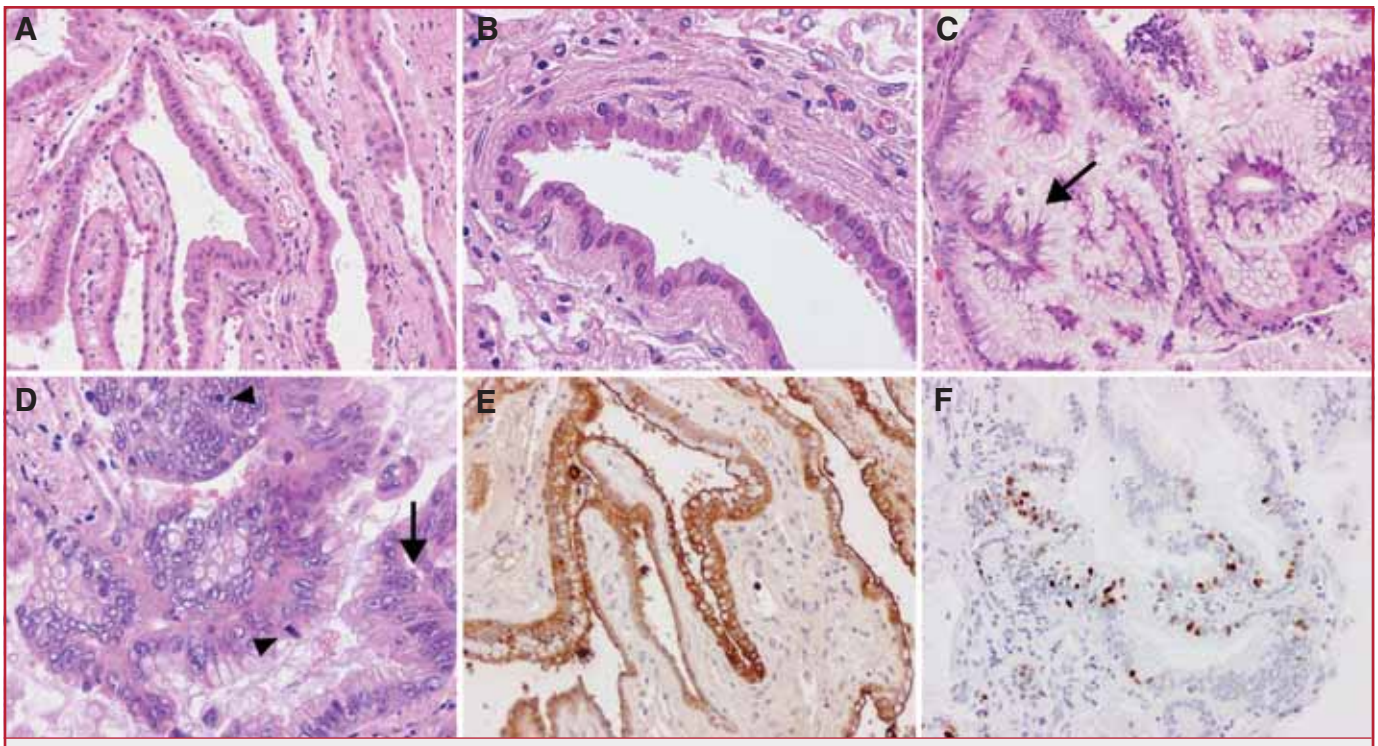

FIGURE 2. *Histopathological features of a mucinous low-grade adenocarcinoma arising in an EC.* **A** *and* **B**, *the cyst presented a cuboidal-columnar epithelial internal layer.* **C** *and* **D**, *in some areas the cyst presented dysplastic pseudostratified epithelium forming papillae* (arrows) *composed of atypical mucin producing cells, with large nucleus, prominent nucleoli, and scattered mitoses* (arrowheads). **E**, *the epithelium was intensely stained for carcinoembryonic antigen.* **F**, *in focal areas, the proliferation index (Ki67/MIB-1 immunostaining) was approximately 15 to 20%. Original magnification,* × *100 (*A, C, E, F*) and* × *200 (*B *and* D*).*

associated with bone anomalies (1). They are considered to be derived from an incomplete separation of the neuroectodermal and the endodermal folia during the embryogenesis (1).

Even though cases of ECs aggressive behavior, including widespread craniospinal dissemination, are well known (9, 12), "de novo" adenocarcinomas arising in ECs have previously been described in only three reports (*Table 1*) (8, 10, 13). Possible molecular events driving the progression from a brain endodermal cyst to an adenocarcinoma are unknown. Malignant transformations of benign brain cysts have mostly been reported as squamous carcinomas in epidermoid or dermoid tumors (7). The mechanism of this transformation is also unknown. It has been suggested that chronic inflammation due to repeated cyst ruptures or subtotal resection of the cyst wall may predispose to malignant transformation. Otherwise, malignant transformation could result from a long standing in situ carcinoma lesion (7).

Ho et al. (8) reported an EC affecting the right hemisphere, showing areas of papillary adenocarcinoma. The lesion recurred 2 years later and demonstrated the typical histopathological features of EC. The patient did not receive any adjuvant therapy. Sahara et al. (13) reported an EC at the cervicomedullary junction that recurred 3.5 years later. At the time of reoperation, the tumor was partially resected; the tumor specimen obtained revealed malignant transformation to an adenocarcinoma. The residual lesion was treated with radiotherapy

TABLE 1. Cases of enterogenous cyst with malignant transformation

Series (ref. no.)	Age (yr)/sex	Site	Recurrence	Therapy	Follow-up	Outcome
Ho et al., 1998 (8)	45/F	Right hemisphere	Yes	Surgery	2 yr	No evidence of disease
Sahara et al., 2001 (13)	53/M	Foramen magnum	Yes	Surgery + radiotherapy	4 yr	Dead from disease
Monaco et al., 2003 (10)	36/M	Posterior fossa	No	Surgery	2 yr	No evidence of disease
Current series	25/M	Posterior fossa	Yes	Surgery	6 mo	Dead from disease

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(50 Gy) and chemotherapy and remained stable for 6 months. The patient died 1 year after the second operation. Monaco et al. (10) reported a posterior fossa EC with areas of malignant transformation into a papillary adenocarcinoma. After surgical resection, the patient did not receive any adjuvant therapy and remained disease-free 2 years after surgery.

In the present case, the lesion showed very aggressive behavior, recurring only a few months after surgery and resulting in the patient's death. Notably, the cause of death was related to severe brainstem compression rather than infiltration or leptomeningeal dissemination. Despite proven histological malignant features, the lack of infiltrative behavior prompted us to consider surgery as the sole treatment. Therefore, we underestimated the adjuvant role of radiotherapy and chemotherapy that have been often administered in other cases of malignant transformation (i.e., squamous carcinoma arising from epidermoid cyst or dermoid). However, the effectiveness of adjuvant therapy in such cases, as well as timing and schedule, have not been established.

CONCLUSION

Intracranial ECs, especially those developing within the cerebellopontine angle, are rare and their malignant transformation is exceptional. The present report suggests that when evaluating an EC, a careful histological examination of the entire surgical specimen is recommended to exclude dysplastic epithelium or carcinomatous transformation. The clinical behavior of ECs with malignant transformation is unpredictable. Surgery remains the treatment of choice. The use of possible adjuvant chemo- and radiotherapy has not been fully established.

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COMMENTS

This is an unusual situation of malignant transformation in an otherwise typically benign lesion. Even the location, the cerebellopontine angle, is atypical for enterogenous cysts. The authors' recommendation is good advice and conforms to the best practice in neuropathology: Careful and complete histological examination of the tissue. You never know until you look!

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Gessi et al. have reported a new case of an enterogenous cyst located in the cerebellopontine angle. This cyst was treated surgically via a retrosigmoid approach with partial cyst removal. The main point made by the authors is that this cyst had foci of malignant transformation on histopathological examination. The lesion recurred 5 months later, leading to the patient's death. The histopathological finding of malignant characteristics on pathological examination should perhaps raise the index of suspicion of possible malignant transformation, suggesting that adjunctive radiotherapy should be considered. Although this single case report is not enough to necessarily justify adjunctive radiation therapy for these typically benign lesions, this article should heighten our awareness of the potential of enterogenous cysts to become malignant and might help us devise appropriate management schemes for individual patients in the future.

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Although malignant transformation of an enterogenous cyst is a very rare occurrence, the patient illustrated in this report is instructive and provides a moment of reflection. The magnetic resonance imaging scans (*Fig. 1*) show a rather benign-appearing lesion that does not enhance. The lesson from this patient is that benign-appearing lesions (such as this cyst) may still harbor or provide an area where foci of malignant transformation may occur. Although it is not known whether additional treatment would have made a difference in this patient, the discovery of such foci enables the neurosurgeon to provide the patient and family with appropriate additional treatment, follow-up, and expectations.

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The authors discuss a single patient presenting with a cerebellopontine angle enterogenous cyst that subsequently underwent transformation to a low-grade papillary mucinous adenocarcinoma. The report

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is interesting in that it reminds us of the small, but certainly present, risk of cyst transformation. The authors do an excellent job in describing the clinical, histological, and radiographic aspects of the case. In this case, it is interesting to note that there were elements of dysplasia and low-grade in situ adenocarcinoma present. In addition, there was a high proliferative index. Retrospectively knowing this, one must wonder if these two parcels of data would change surgical decision making with regard to the initial extent of resection.

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