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Surgical management of brain metastasis as a part of systematic metastases from adenoid cystic carcinoma of the external auditory canal: illustrative case

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BACKGROUND Adenoid cystic carcinoma (ACC) of the external auditory canal (EAC) is a rare tumor that accounts for approximately 5% of all EAC tumors. ACC is generally known as a slow-growing tumor, but patients often experience recurrence or distant metastasis in the long clinical course. While the major pattern of recurrence is pulmonary metastasis, brain metastasis of ACC of the EAC is rare.

OBSERVATIONS The authors describe the case of a 72-year-old male who was diagnosed with ACC of the EAC. Approximately 7 years later, brain magnetic resonance imaging revealed an intra-axial homogenously enhancing mass lesion that had no direct connection with the skull base in the left frontal lobe. The patient underwent tumor resection and histopathological examination revealed a mixture of cribriform and tubular patterns. The image and pathological characteristics of the tumor were similar to those of primary ACC or ACC from other sites of origin.

LESSONS While patients with ACC of the EAC often experience recurrence or distant metastasis in the long clinical course, they survive for a relatively long period of time, even though an optimal treatment has not been established. The authors therefore recommend surgical resection for brain metastasis of ACC of the EAC to improve neurological symptoms.

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KEYWORDS adenoid cystic carcinoma; external auditory canal; brain metastasis

Adenoid cystic carcinoma (ACC) is a malignant neoplasm that arises within the secretory glands, predominantly from the major and minor salivary glands of the head and neck. ACC infrequently originates in the external auditory canal (EAC), with an incidence of 0.004 per million.[1] The clinical features of ACC are unique among salivary gland tumors. It is characterized by slow-growing and extensive local invasion and perineural spread. It is not uncommon for distant metastasis, mainly to the lung, to occur over the course of several years. Because brain metastasis of ACC of the EAC is rare, most earlier reports lack detailed information on clinical and pathological findings and long-term follow-up outcomes. Here, we present a case of ACC originating from the EAC with an ipsilateral metastatic brain tumor that was treated with surgical resection.

Illustrative Case

A 72-year-old right-handed male was initially diagnosed with ACC of the left EAC (TNM staging; T1 N0 M0), following partial resection of the tumor at a nearby hospital (Fig. 1A–C). Two years later, multiple pulmonary nodules were identified using 2-deoxy-2-[fluorine-18] fluoro-D-glucose-positron emission tomography/computed tomography (CT). A CT-guided percutaneous lung biopsy was performed and revealed lung metastases of ACC (Fig. 1D and E). Almost a year later, a metastatic lesion was found in the left parotid lymph node, and a superficial parotidectomy was performed at the same hospital. Subsequently, the patient was treated with adjuvant chemotherapy including tegafur, gimeracil, oteracil, and docetaxel. He was followed up in the outpatient ward and did not receive any further

ABBREVIATIONS ACC = adenoid cystic carcinoma; CT = computed tomography; EAC = external auditory canal; MRI = magnetic resonance imaging.
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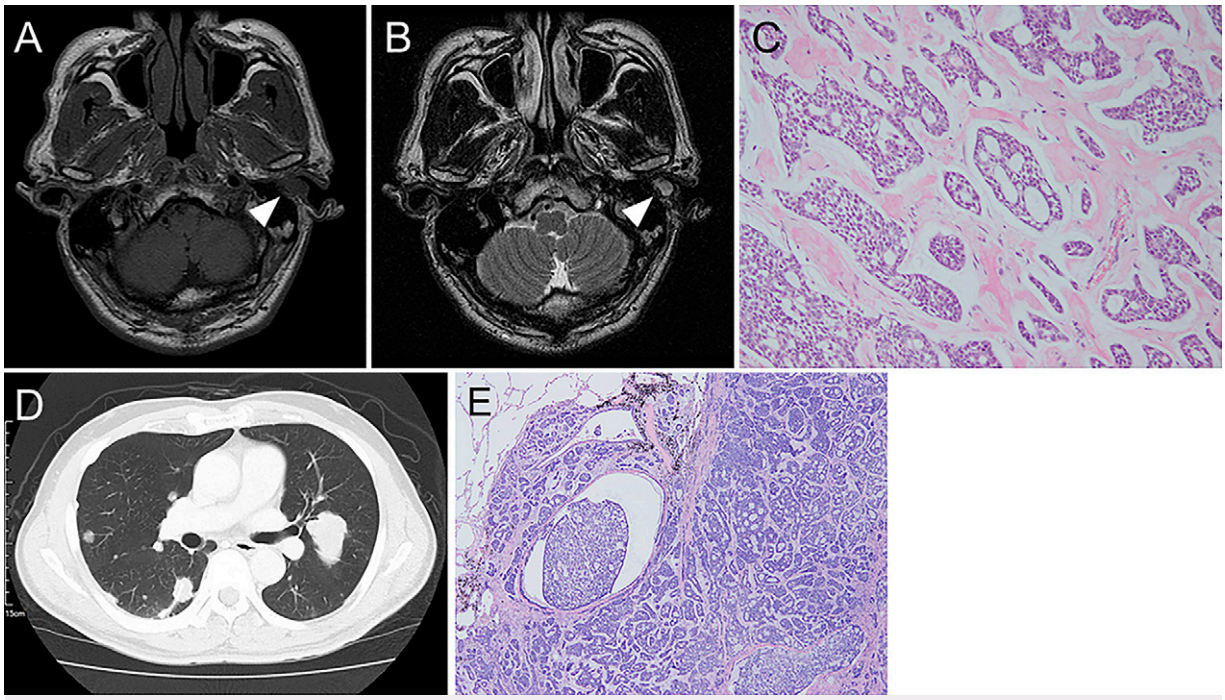

FIG. 1. Axial T1- (**A**) and T2-weighted (**B**) MRI showing a mass lesion in the left auditory canal (*arrowheads*). **C:** Histopathological findings showing the primary external auditory canal lesion (H&E staining ×200). **D:** Chest CT showing multiple nodular mass shadows in the bilateral lung field. **E:** Histopathological findings showing lung metastasis (H&E staining ×40). H&E = hematoxylin and eosin.

chemotherapy after January 2014. Approximately 1 year later, the patient presented with facial palsy and dysarthria, both of which he had experienced for several weeks already. Brain magnetic resonance imaging (MRI) revealed an intra-axial homogeneously enhancing mass lesion in the left frontal lobe (31 × 34 mm in size), which had no direct connection with the skull base (Fig. 2A–D). The patient was referred to

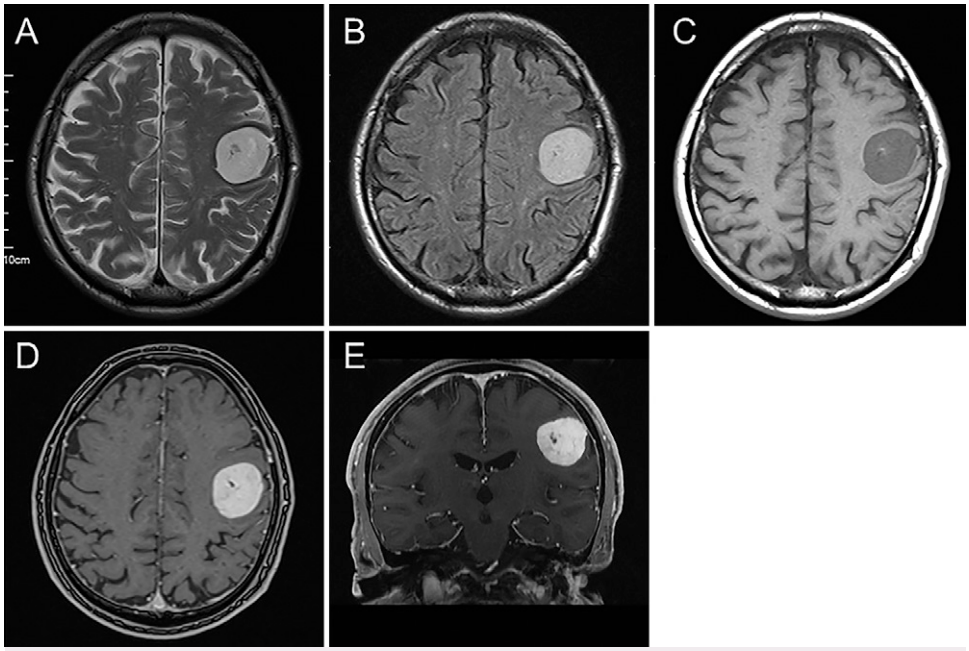

FIG. 2. Preoperative axial T2- (**A**), FLAIR T1- (**B**), T1-weighted (**C**) MRI with gadolinium enhancement (**D**), and coronal T1-weighted MRI with gadolinium enhancement (**E**) showing a mass lesion in the left frontal lobe with no peritumoral edema. The lesion was homogenously enhanced and not connected to the skull base. FLAIR = fluid attenuated inversion recovery.

our department and underwent resection of the tumor a month later. The tumor fit into the precentral sulcus, and the boundary between the normal brain and the tumor was relatively clear (Fig. 3A). Thus, complete resection of the tumor was achieved (Fig. 3B and C). Histopathological examination of the resected tumor revealed a mixture of cribriform and tubular patterns (Fig. 4A). Cribriform structures displayed variably sized pseudocysts filled with Alcian blue-positive mucinous material surrounding basaloid cells with hyperchromatic nuclei (Fig. 4B). Tumor cells were positive for AE1/AE3 (Fig. 4C), with a subset of cells stained for p63 (Fig. 4D), suggesting that the tumor was mainly composed of both epithelial and myoepithelial neoplastic cells. p53 (Fig. 4E) and Ki-67 (Fig. 4F) expression were detected in the tumor cell nuclei. Based on these pathological analyses, the patient was finally diagnosed with metastatic ACC tumor. He experienced no postoperative neurological complications and was discharged after 17 days. Although the patient had an uneventful course after the surgery without recurrence for 1.5 years, multiple brain metastases were found in September 2016, and his clinical neurological status deteriorated with worsening of his respiratory status due to lung metastases progression. Eventually, the patient's family opted for palliative care only and he was transferred to hospice.

Discussion

Observations

ACC typically arises from the salivary glands, and surgical resection is the radical treatment of choice, when feasible, followed by radiotherapy.[2,3] While ACC is generally known as an indolent tumor, the long-term survival rate is poor due to its high risk of recurrence, characterized by extensive perineural invasion and distinct metastasis, mostly to the lung (75%), followed by the bones (6.9%), the liver (6.9%), and other sites including the brain.[4,5]

Primary malignancies of the EAC are rare, with an incidence of approximately one per million people per year.[6] The most common type is squamous cell carcinoma (>80%), and ACC accounting for approximately 5% of cases.[7,8] Its morphological characteristics and genetic profiles are similar to those of ACC of the salivary glands.[9,10]

ACC of the EAC is also known as a slow-growing tumor, and recurrence after surgical resection is common. While the major pattern of recurrence is pulmonary metastasis, several studies have reported local recurrence with direct intracranial extension of the tumor.[11–13] However, a few cases of central nervous system metastases from the ACC of the EAC have been reported (Table 1). Only one study has reported distant metastasis to the brain of a patient with ACC of the EAC.[14] Another report showed intramedullary spinal cord metastasis from the ACC of the EAC.[15] The current case presents an extremely rare case of a patient with brain metastasis of ACC of the EAC who underwent surgical tumor resection with detailed imaging and pathological findings.

Histologically, ACC can be categorized into three types (cribriform, tubular, and solid), of which the solid subtype is considered to be associated with a poor prognosis. Although it has been conventionally agreed that an ACC prognosis is poor if the tumor contains >30% or >50% solid pattern,[16,17] recent studies have reported that the presence of any solid component is the most reliable prognostic factor.[2,5]

MRI features of ACC of the salivary glands are hypo- to isointense on T1-weighted images and hyperintense on T2-weighted images. Importantly, low-intensity lesions on T2-weighted MRI are correlated with high tumor cellularity (solid subtype) and a poor prognosis.[13] In our case, brain metastatic lesions exhibited a homogenously high signal on T2-weighted MRI, and pathological findings revealed that a major part of the tumor showed a mixture of cribriform and tubular patterns. These data are consistent with the characteristics of primary ACC.

We speculate that the mechanism of spread of this tumor is hematogenous metastasis, because the tumor in this case was a solitary metastasis with no evidence of leptomeningeal metastasis on MRI and intraoperative findings such as thickening of the dura mater or arachnoid membrane. Merchesini et al.[15] reported that in their case, the mechanism of dissemination of ACC of the EAC seemed to be direct invasion to the brain surface and subsequent spreading by cerebrospinal fluid seeding. The lesion we observed was inconsistent with direct invasion and the primary lesion in the EAC was stable. Therefore, this mechanism does not seem to apply to our case.

Important factors related to improved survival outcomes after surgery in patients with a single brain metastatic lesion are a good Karnofsky performance status and a limited number of extracranial metastases.[18] In our case, the patient had already been diagnosed with multiple progressive lung metastases and pleural dissemination of the ACC (Fig. 1C). It has been reported that surgery does not improve survival outcomes for intracranial solitary metastasis with

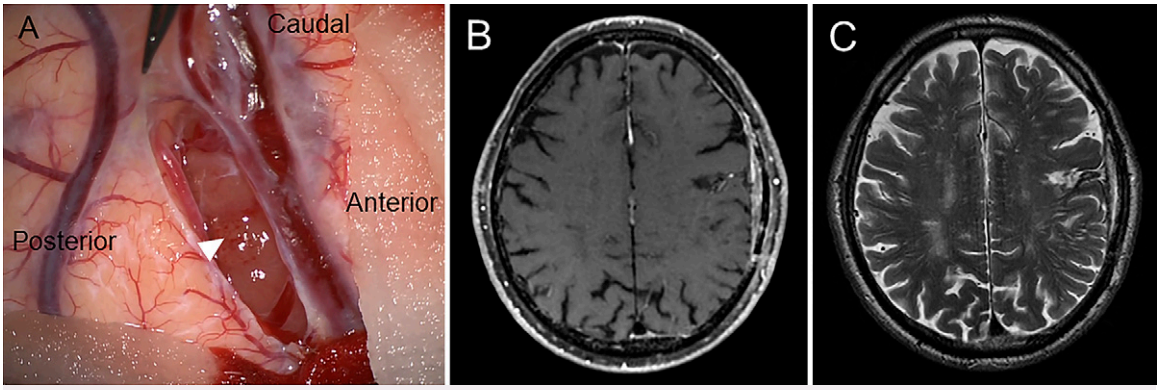

FIG. 3. Intraoperative photograph taken after opening the arachnoid membrane. **A:** The grayish tumor (*arrowhead*) fit into the precentral sulcus. **B:** Four-month postoperative images of axial T1-weighted MRI with gadolinium enhancement showed no enhanced lesion. **C:** T1-weighted MRI showed no edema.

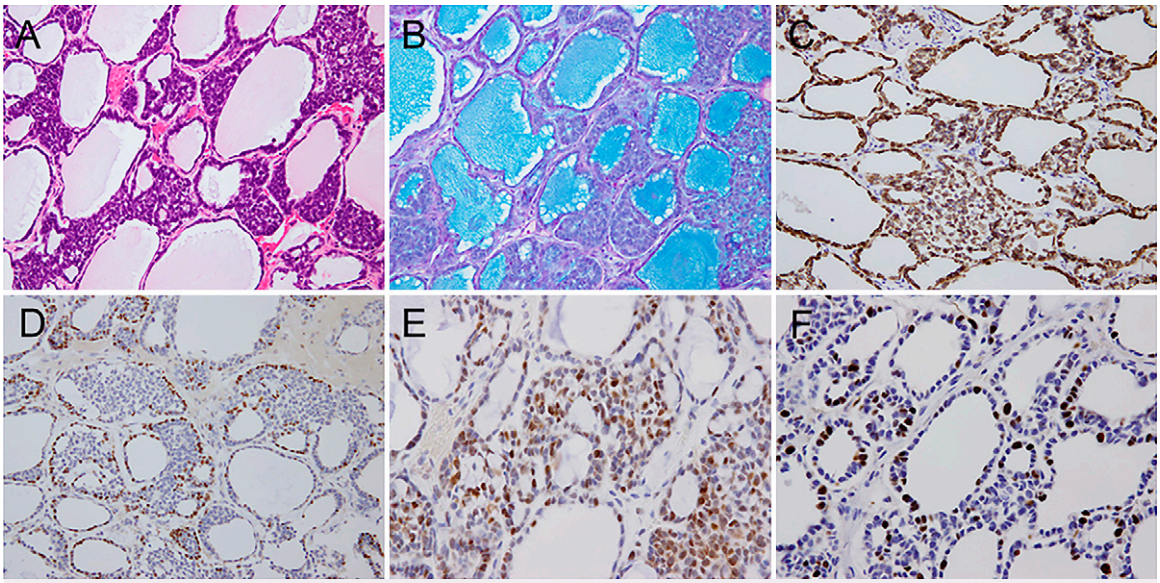

FIG. 4. Histopathological findings showing brain metastasis of ACC of the EAC. **A:** H&E staining ×200. **B:** PAS + Alcian blue ×200. **C:** AE1/AE3 ×200. **D:** p63 ×200. **E:** p53 ×200. **F:** Ki-67 ×200. H&E = hematoxylin and eosin; PAS = Periodic-acid-Schiff.

progressive and multiple extracranial metastases of other carcinomas, such as lung cancer and breast cancer.[19] Therefore, radiation therapy may be a good treatment option for these patients. Surgical resection is often not indicated for brain metastasis as a part of systematic metastases because it is considered a radical approach. However, ACC has an uncommon clinical course. Although data suggest that 40% of patients diagnosed with ACC of the EAC experience tumor recurrence in the protracted clinical course (median time to recurrence: 8 years), they survive for more than 2.8 years even after tumor recurrence; these unique characteristics of ACC therefore need to be considered when selecting therapeutic strategies.[8]

Marchesini et al.[15] recently reported intramedullary spinal cord metastases of the ACC of the EAC with multiple disseminated lesions in the brain. The patient underwent spinal cord tumor removal despite the advanced stage of the disease to improve their neurological symptoms. Our patient also underwent brain tumor resection even after multiple lung metastases had been detected. As a result, his neurological status improved after the surgery, and he survived 1.5 years without recurrence.

Lessons

We report a rare case of ACC of the EAC with a metastatic brain tumor. To date, there are no reports of brain metastasis of ACC of the EAC that provide detailed imaging and pathological findings due to the rarity of this tumor. It has thus not been clarified whether brain metastasis of ACC of the EAC can be managed the same way ACC of other origins is managed. Here, we show that the pathological and imaging characteristics of ACC of the EAC are

TABLE 1. Cases of central nerve system metastases from ACC of the EAC

Authors & Year	Age	Sex	Location	Other Distant Metastases	Main Histology	Previous Treatment	Time to CNS Metastases (yrs)	Symptoms	Therapy Following CNS Metastases Diagnosis
Conlin et al., 2002[14]	38	Male	Parietal lobe	None	Solid	Surgery	1	Headache	Biopsy
Marchesini et al., 2021[15]	54	Male	Cerebellum, parietal lobe, intramedullary conus	Lung, parotid gland	Cribriform	Surgery, radiotherapy (70 Gy), chemo (adriamycin/ cisplatin)	11	Gait disturbance sphincter impairment	Surgery (intramedullary conus lesion)
Current case	72	Male	Frontal lobe	Lung, parotid lymph node	Cribriform & tubular	Surgery, chemo (tegafur/ gimeracil/ oteracil)	7	Facial palsy & dysarthria	Surgery

chemo = chemotherapy; CNS = central nervous system.

similar to those of primary ACC or ACC originating from other sites. In this case, we showed the pathological and image characteristics are similar to those of primary ACC or ACC originating from other sites. Patients with ACC of the EAC often experience recurrence or distant metastasis in the long clinical course, but they survive for a relatively long period of time, even though an optimal treatment has not been established. Therefore, surgical resection for brain metastasis of ACC of the EAC to improve the patient's neurological symptoms is recommended.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: K Motomura, Kuramitsu, Kageyama. Acquisition of data: Kuramitsu, Tsujiuchi, A Motomura, Kageyama, Kojima, Ohno. Analysis and interpretation of data: Kuramitsu, Kageyama, Kojima. Drafting the article: K Motomura, Kuramitsu, Kageyama. Critically revising the article: Kuramitsu, Tsujiuchi. Reviewed submitted version of manuscript: K Motomura, Kuramitsu, Tsujiuchi, Kojima, Ohno, Saito. Administrative/technical/material support: Nakajima, Matsuo, Fukaya. Study supervision: K Motomura, Saito.

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