

Primary Intracranial Malignant Epidermoid with Multiple Metastases in Internal Organs: A Rare Autopsy Case

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Primary intracranial malignant epidermoids are rare, with most cases developing from a pre-existing benign epidermoid cyst. We report a case involving a rare autopsy finding of a primary intracranial malignant epidermoid in the brainstem with cerebellopontine angle (CPA) involvement. A 53-year-old woman with double vision was diagnosed with right abducens palsy. At her visit to our hospital 3 months after the onset of the first symptom, she presented left hypoglossal nerve paralysis and truncal ataxia in addition to right abducens palsy. Magnetic resonance imaging (MRI) revealed a mass lesion (2-cm long and 3-cm thick) in the left CPA that exhibited gadolinium enhancement. Moreover, gadolinium-enhanced magnetic resonance imaging (MRI) revealed abnormal multiple brainstem and supratentorial mass lesions with partial enhancement. Whole-body computed tomography failed to identify any possible primary lesion. Following a tentative diagnosis of an epidermoid cyst with an assumption that the tumor was highly aggressive, we performed subtotal surgical resection of the CPA tumor. Histological findings revealed a malignant epidermoid in the CPA lesion. Although the patient underwent radiation and chemotherapy after the surgical resection, she died of respiratory failure 10 months after the onset of symptoms. Herein, we report the rare clinical course and autopsy data, and discuss the characteristic features of this rare condition.

Keywords: malignant epidermoid, cerebellopontine angle, methotrexate, radiation

Introduction

Intracranial epidermoid cysts account for approximately 0.2–1.8% of brain tumors and 7% of cerebellopontine angle (CPA) tumors; they develop from aberrant ectodermal embryonic tissues in the neural groove at 4 or 5 weeks of fetal development. These cysts are nearly always benign, slow-growing

tumors comprising only squamous epithelium. Here, we report a rare case of a patient diagnosed with disseminated and metastatic primary intracranial malignant epidermoid who died despite treatment efforts; diagnosis was confirmed based on autopsy findings. The rarity of the lesion prompted us to review the literature on the subject to analyze the clinicopathological findings that would explain the behavior of this tumor.

Case Report

Informed consent for research obtained, and the ethical committee of Nagaoka Red Cross Hospital approved this report, which was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

History and Neuroimaging

The patient, a 53-year-old woman, experienced double vision while driving a car. She visited a primary ophthalmology clinic and was diagnosed with right abducens palsy. Treatment with oral administration of prednisolone 20 mg was initiated, but the treatment was ineffective. She was referred to the neurology department. Plain computed tomography (CT) revealed no abnormalities, but brain magnetic resonance imaging (MRI) revealed a mass lesion in the left CPA. Thereafter, the patient developed dysgeusia, adversely affecting her eating habit. When she visited our hospital 3 months after the onset of symptoms, she presented right abducens palsy, left hypoglossal nerve paralysis, and truncal ataxia. CT revealed calcification on the ambient cistern in front of the left medulla, and dilatation of the left cerebellopontine cistern. Further, MRI revealed a mass lesion (2-cm long and 3-cm thick) in the left CPA with hypo and hyperintense signals on T₁- and T₂-weighted images, respectively, whereas diffusion-weighted MRI showed a hyperintense area in the left CPA (Figs. 1A–1C). The mass exhibited gadolinium enhancement and abnormal multiple supratentorial and brainstem mass lesions with partial enhancement after intravenous administration of gadolinium (Figs. 1D–1F). Laboratory tests revealed a normal blood count and C-reactive protein level and negative results for tumor makers. Whole-body CT failed to identify any possible primary lesion. Cerebrospinal fluid examination was positive for inflammatory cells, and cytology showed a few atypical cells (class III). Whole spine MRI and positron emission tomography image was not performed.

Operation

Following a tentative diagnosis of an epidermoid cyst with an assumption that the tumor was more aggressive one such as carcinoma, the patient underwent an operation for diagnosis

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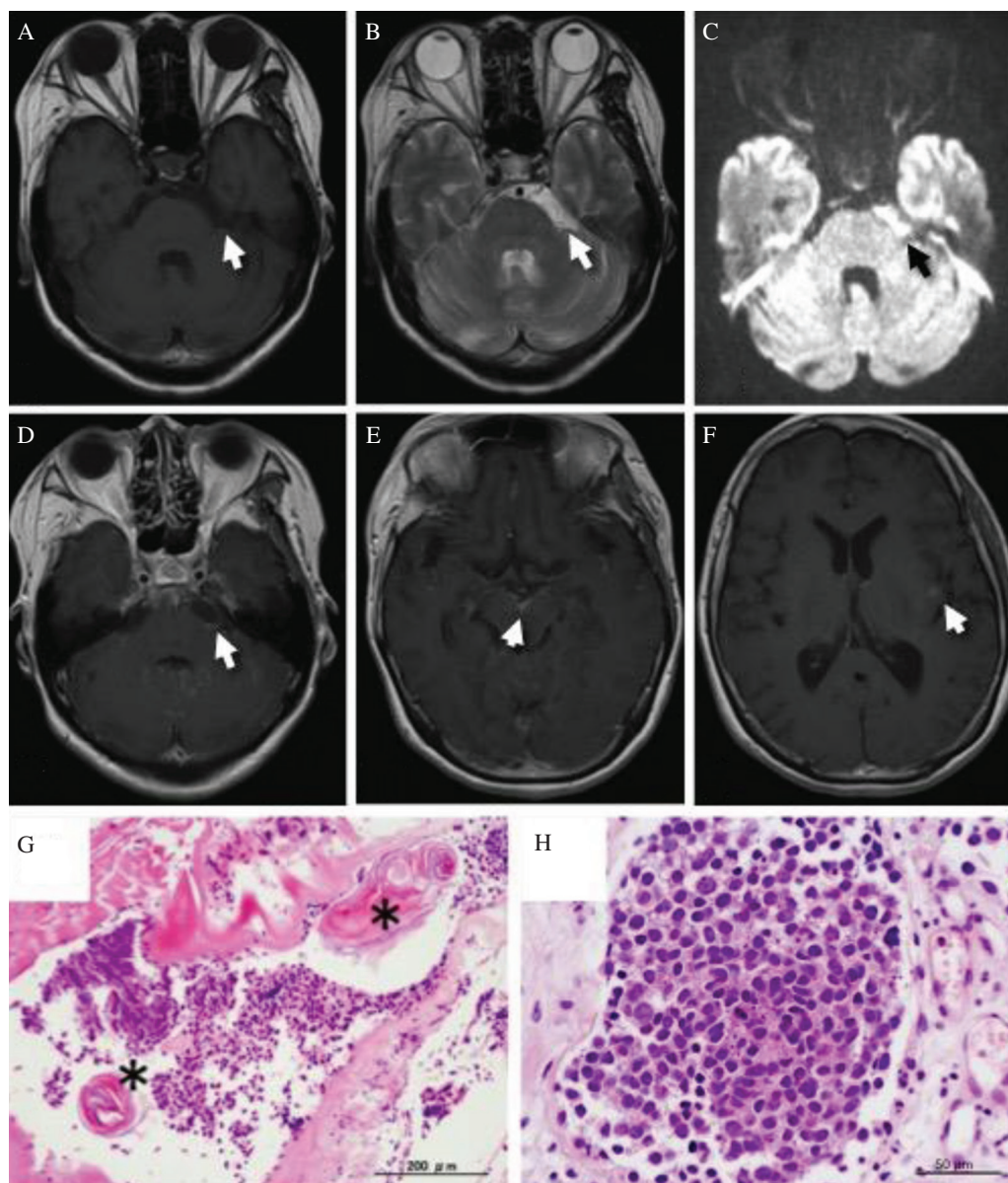


Fig. 1 Initial magnetic resonance imaging (MRI). (A–F) MRI shows a mass lesion in left cerebellopontine angle after gadolinium enhancement. The gadolinium-enhanced MRI also reveals abnormal multiple mass lesions with partial enhancement after intravenous administration of gadolinium (axial view: A, T₁-weighted image; B, T₂-weighted image; C, diffusion-weighted imaging; D–F, T₁-weighted image with gadolinium enhancement). Histopathology of the first operation (G and H). Anaplastic epithelioid tumor cells are observed with keratinized pearls (*) (G). Squamous cell-like tumor cells form highly cellular nests in the connective tissues (H). Hematoxylin–Eosin.

and therapy. First, a spinal drainage was inserted, and left suboccipital craniectomy was performed with the patient in the right lateral position. Retraction of the left cerebellar hemisphere exposed a large, pearly tumor in the CPA. However, the cyst contents were soft and could be aspirated easily; a part of the mass was tightly adhered to the lower cranial nerves and brainstem, and which bled easily. The cyst capsule was yellowish and very hard, making total resection impossible. Further, the tumor was tightly adhered to the facial and vestibulocochlear nerves. Although the cyst was carefully peeled off from the nerves as possible, the nerves were swollen.

Pathological Findings

The histological findings of the tumor showed an atypical cyst with a squamous cell-like epithelial lining and pleomorphic nuclei. There were several keratinized pearls in the specimen (Fig. 1G). The squamous cell-like tumor cells formed several nests in the connective tissues. The cellular

nests showed quite anaplastic features with necrosis and mitotic figures (Fig. 1H). The histological diagnosis was epidermoid carcinoma.

Postoperative Course

Multiple cranial nerve symptoms, multiple-enhanced lesions on MRI and cerebrospinal fluid cytology had suggested a possibility of meningeal dissemination preoperatively. Several spinal disseminations were revealed by whole spine MRI performed 6 days after the operations. Whole-brain 30-Gy and whole-spine 30-Gy radiotherapies were postoperatively administered, and an intrathecal infusion of methotrexate (10 mg × 10 days) was administered. The blood counts were monitored weekly for hematological toxicity in term of leukopenia and/or thrombocytopenia. After postoperative 1 month, percutaneous endoscopic gastrostomy was performed owing to dysphagia. After postoperative 5 months, the tumor decreased in size according to follow-up

intracranial gadolinium-enhanced MRI (Figs. 2A–2C). The MRI also revealed an absence of enhanced lesions in the spine. However, the symptoms of right abducens palsy, left hypoglossal nerve paralysis, and dysphagia remained unchanged. The patient was discharged after postoperative 2 months in a state in which she could independently perform her activities of daily living. However, within 3 months, her general condition worsened gradually, and she was rehospitalized with vomiting and nausea. She experienced pain in the right hypochondrium. Bone scintigraphy showed bone metastasis and, we prescribed radiotherapy at a dose of 24-Gy. After postoperative 6 months, CT revealed multiple liver metastases and hepatomegaly (Figs. 2F and 2G). The patient entered the final stage of the disease and died of respiratory failure after suffering for 10 months with the disease.

Post-mortem Examination

The brain weighed 1235 g after fixation, and was swollen. A whitish and membranous mass was present in the left CPA (Figs. 3A and 3B). Histologically, the mass comprised fibrous

connective and ossified tissue, but it lacked vivid tumor cell proliferation. Epithelial tumor cells covered the surface of the mass and outer surface of the adjacent arachnoid membrane, showing marked nuclear atypia and irregular stratification (Fig. 3C). Without forming a cyst, the tumor cells massively proliferated in the connective tissues. Immunohistochemically, these tumor cells demonstrated reactivity for cytokeratin (Fig. 3D), epithelial membrane antigen(EMA) (Fig. 3E), vimentin (Fig. 3F), and MIB-1 (Fig. 3G). The labeling index of MIB-1 was 50%. In several foci of the epithelial lining, the cellular features implied possible transformation of the non-malignant cells into anaplastic cells (Fig. 3H).

Massive subarachnoidal and intraventricular dissemination and parenchymal invasion were observed. The cells showed anaplastic features without specific cellular arrangement (Fig. 3I).

General autopsy showed numerous whitish nodules (up to 13 × 10 cm in size) throughout the liver (2795 g), marked lymphangitis carcinomatosa with vascular permeation, tumor emboli, parenchymal lung infiltration (left, 306 g; right, 332 g) (Figs. 3J and 3K), and marked osteolytic

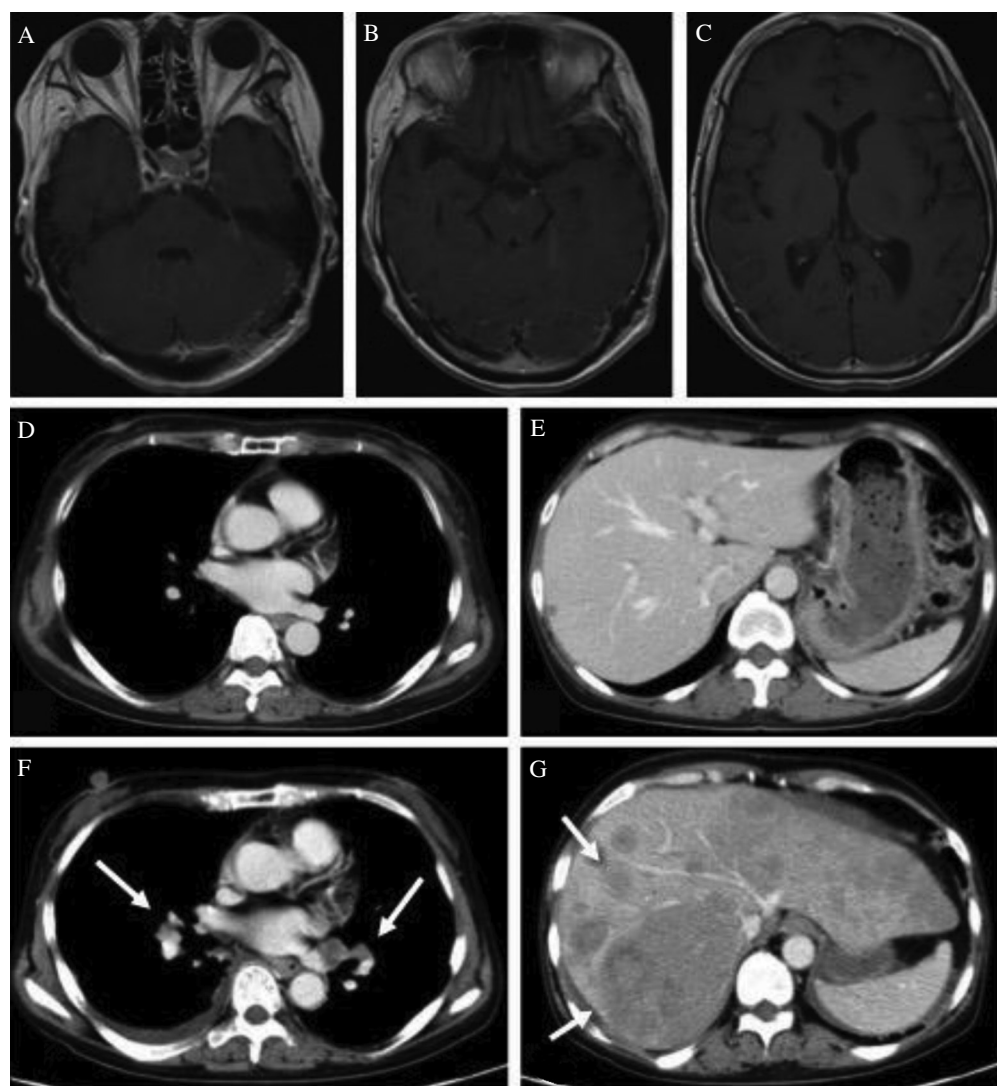


Fig. 2 Post radiation and chemotherapy (A–C) magnetic resonance imaging (MRI). After postoperative 5 months, the tumor decreased in size according to the follow-up intracranial gadolinium enhancement MRI (axial view: A–C, T₁-weighted image with gadolinium enhancement). Preoperative (D and E) and end-stage (F and G) trunk computed tomography (CT) demonstrating multiple liver metastases and hepatomegaly after postoperative 6 months (axial view: D and G, CT with enhancement).

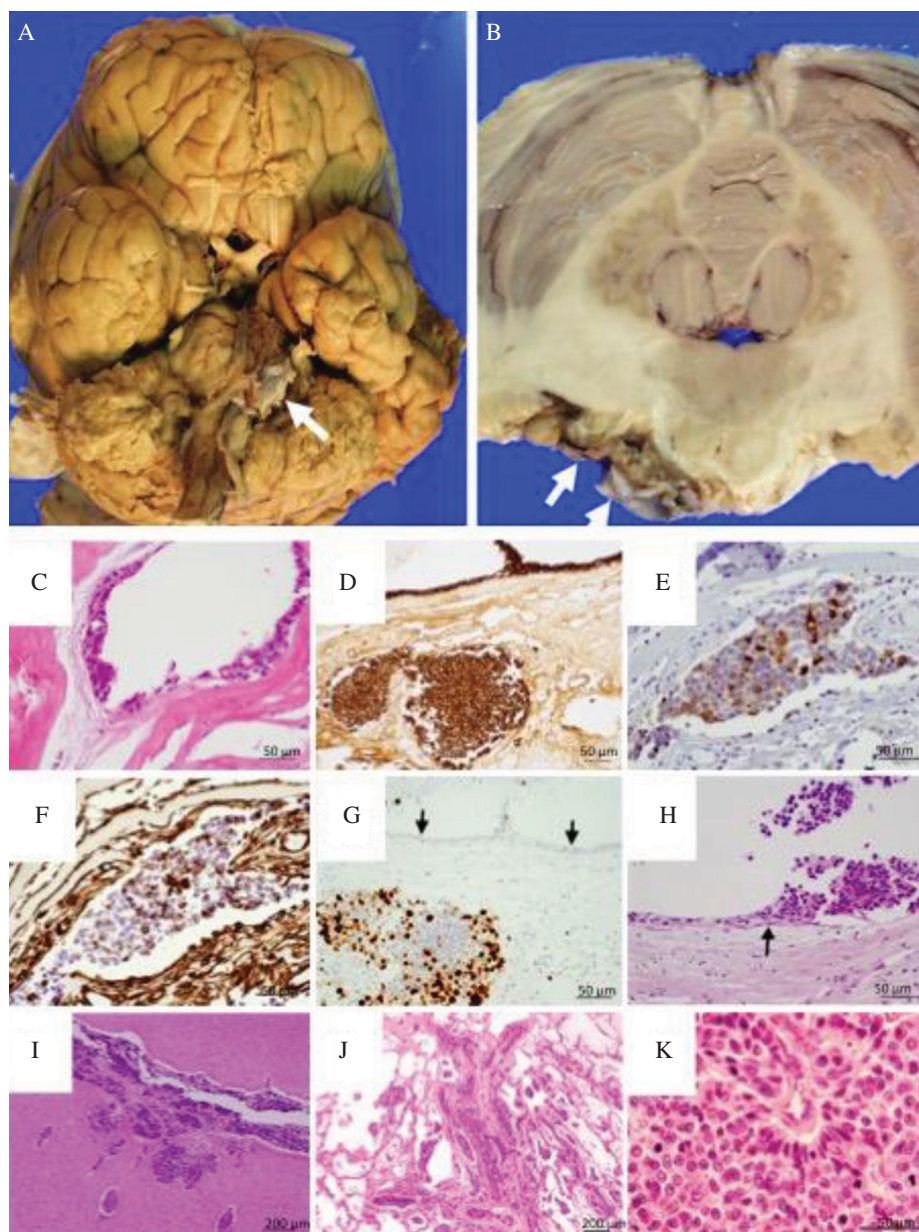


Fig. 3 Autopsy findings. Macroscopic findings of the brain (A and B). Basal view of the formalin-fixed brain (A). Membranous-whitish structures exist in the left cerebellopontine angle (arrow). Horizontal section of the cerebellum and middle pons (B). The whitish lesions are observed on the surface of left pontine base (arrows). Microscopic findings of the tumor (C–K). Tumor cells cover the cystic lesions (C) without forming keratinized pearls. The nest-forming tumor cells are positive to cytokeratin (D), EMA (E), vimentin (F), and MIB-1 (G). Note the monolayer cells have few MIB-1 positive nuclei (G, arrows). The monolayer cells show malignant transformation (H, arrow) in several places. The tumor cells invade in the brain parenchyma (I). The lung show lymphangitis carcinomatosa (J), and the metastatic tumor cells show many mitotic figures (K). C–K, hematoxylin-eosin; D, cytokeratin immunostaining; E, EMA immunostaining; F, vimentin immunostaining; G MIB-1 immunostaining.

metastasis in the examined ribs and vertebrae. Histologically, several cancer nests were found in a 1.5 × 1.0-cm follicular adenoma of the thyroid gland (16 g) and the cortices and medulla of the adrenal gland (left, 10; right, 8 g). Lymph nodes in the mediastinal pulmonary hilar and retroperitoneal areas were swollen and whitish (up to 2.0 × 1.5 cm in size). Although multiple metastases were present in internal organs, we found no evidence of a primary cancer in these organs.

Discussion

Some studies have reported malignant transformations of intracranial epidermoid cyst,^{1–4)} but primary intracranial malignant epidermoid cysts accompanied by leptomeningeal carcinomatosis are extremely rare.⁵⁾ Moreover, we have not encountered cases with metastases to internal organs, except this case (Table 1).^{1,2,5,6–22)}

Differences between malignant and benign epidermoids have been reported, with aggressive neurological symptoms related to tumor location (such as severe facial palsy, facial numbness, and gait disturbance) being pathognomonic of malignant epidermoid.^{2,23)}

In addition, a highly malignant epidermoid radiographically has lower signal intensity on diffusion-weighted imaging (DWI) than a benign epidermoid and presents a ring-like enhancement on T₁-weighted gadolinium-enhanced MRI, whereas benign epidermoid cysts have very high signal intensity on DWI.^{24,25)} Incomplete surgical resection of intracranial malignant epidermoids is common because the tumor strongly adheres to the brain parenchyma, cerebral vessels, and particularly to the brainstem. Pathologic malignant epidermoid cyst findings include cytologic atypia and stromal invasion. Primary intracranial epidermoids have poorly differentiated abnormal cells with pleomorphic

Table 1 Reported cases of intracranial malignant epidermoid with leptomeningeal carcinomatosis

Year	Authors	Age/Sex	Location	Treatment	Follow-up	Metastasis
1912	Ernest ⁶⁾	52/M	R CPA	Medical	Dead 12 mo	-
1955	Yamanaka et al. ⁷⁾	57/M	Base	Medical	Dead	-
1965	Fox and South ⁸⁾	50/M	L subtemporal	S	Dead 1.5 mo	-
1977	Kömpf and Menges ⁹⁾	57/F	Cerebellar	Medical	Dead	-
1982	Takado et al. ¹⁰⁾	34/F	Para pontine	B + Medical	Dead	-
1984	Bondeson and Fält ¹¹⁾	56/F	L CPA	Medical	Dead 0.6 mo	-
1986	Kubokura et al. ¹²⁾	60/F	Base	S	Dead 0.2 mo	-
1990	Gi et al. ¹³⁾	39/M	L CPA	S + Rx	Dead 15 mo	-
1996	Mohanty et al. ¹⁴⁾	20/M	Cerebellar	S + Rx	Dead 13 mo	-
2000	Ishikawa et al. ¹⁵⁾	65/M	CPA	Ch + Rx	Dead 10 mo	-
2001	Asahi et al. ¹⁾	55/F	R CPA	S	Dead 3 mo	-
2001	Khan et al. ¹⁶⁾	53/M	Pre pontine	Shunt	Dead 10 mo	-
2003	Shirabe et al. ¹⁷⁾	49/M	Ventral pons	B + Rx	Dead 42 mo	-
2005	Hamlat et al. ²⁾	62/F	Temporal	Ch	Dead 7 mo	-
2005	Michael et al. ¹⁸⁾	45/M	L CPA	S + Rx	Dead 12 mo	-
2007	Pagni et al. ¹⁹⁾	65/F	Pineal lesion	S	Unknown	-
2007	Kodama et al. ²⁰⁾	67/M	R CPA	S + Rx	Dead 13 mo	-
2010	Kano et al. ²¹⁾	64/F	L CPA	S + Rx	Dead 25 mo	-
2016	Raheja et al. ⁵⁾	54/F	Midbrain	S	Unknown	-
2016	Raheja et al. ⁵⁾	37/F	L CPA	B + Rx +Ch	Dead 17 mo	-
2018	Suematsu et al. ²²⁾	54/M	R CPA	S + R	Dead 12 mo	-
2019	This case	53/F	L CPA	S + Ch + Rx	Dead 10 mo	+

B: biopsy, Ch: Chemotherapy, CPA: cerebellopontine angle, F: female, L: left, M: male, Mo: month, R: right, Rx: Radiotherapy, S: Surgery.

nuclei.¹⁸⁾ Our patient had clinical, radiological, operative, and pathological features similar to those of malignant epidermoids at her first visit and during the operation. All her clinical features were explained by the primary malignant epidermoid carcinoma. Furthermore, extensive searches for the primary focus of the epidermoid carcinoma failed to reveal any lesions in the visceral organs or the skin at autopsy.

Primary intracranial epidermoids have been proposed to arise thorough malignant transformation of benign epidermoid cysts.²⁾ The potential transformation mechanisms include a chronic inflammatory response due to repeated cyst rupture or subtotal resection of the cystic wall. Because our case had presented malignant epidermoid features before the operation, we hypothesized that the malignant transformation mechanism underlying our case was due to chronic inflammatory stimulation by repeated epidermoid cyst rupture. However long-standing inflammation was not observed in the current case and, conclusive evidence of the cyst rupture was not obtained neuropathologically. A clinical course such as the one described here is extremely rare because our patient had multiple intracranial lesions already at her first visit and presented multiple internal

organ metastases a few months later during the end stage of the disease.

Reports have reviewed the management strategies for malignant transformation of epidermoid cyst.^{3,4,22)} Systematic analyses^{3,4)} have characterize and confirmed the added benefit of radiotherapy, stereotactic radiosurgery(SRS), chemotherapy, and multimodal adjuvant therapies. Although evidence on the management of primary malignant epidermoid is limited, maximal safe tumor resection and multimodal management are believed to provide the best prognosis of primary malignant epidermoids. Accumulation of cases can help define the optimal management of primary malignant epidermoids.

In conclusion, we encountered the case of a woman with a primary malignant epidermoid and leptomeningeal carcinomatosis and metastasis to internal organs confirmed by autopsy. The clinical data and neuropathological findings of this case provide valuable data on the characteristic features of this rare tumor.

Conflicts of Interest Disclosure

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

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