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Case Report

Multiple hemorrhagic intraparenchymal tumors presenting with fatal intracranial hypertension: A rare manifestation of systemic epithelioid hemangioendothelioma

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Abstract

Background: Epithelioid hemangioendotheliomas (EHE) is an extremely rare tumor that can arise not only intracranially but also systemically. Its radiological characteristics and the mechanism underlying the multiple organ involvement in EHE are poorly understood.

Case Description: A 24-year-old woman with a 7-month history of coughing and blood-stained sputum complained of visual disturbance in the right eye that had persisted for 1-month. Magnetic resonance (MR) imaging revealed multiple intraparenchymal masses with low-intensity on MR susceptibility-weighted images with minimal enhancement with gadolinium. Systemic computed tomography revealed multiple nodules in both lungs and the liver. Because her neurological status rapidly deteriorated, brain biopsy of the right frontal mass was performed. The pathological diagnosis was EHE. Over the following 3 months, the patient gradually developed disturbance of consciousness. She died at 4 months after admission because of significant intracranial hypertension.

Conclusion: Although intracranial EHEs are extremely rare, they should be included in the differential diagnoses of multiple small-sized masses with low-intensity on MR susceptibility-weighted images. We also emphasize that the systemic involvement of this tumor was more compatible with multicentric development than metastasis.

Key Words: Epithelioid hemangioendothelioma, hemorrhagic brain tumor, liver tumor, multiple intracranial mass, pulmonary tumor

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INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is a rare tumor of vascular endothelial origin with an epithelioid appearance.[36] Lesions commonly arise in the lung, liver, bone, soft tissue, and skin. Previous studies reported 40 cases of this tumor arising intracranially.[2,3,5,7-10,13-15,17,18,21-26,29,31-35,38-40] Intracranial EHE most often occurs as a single lesion, and cases of multifocal lesions are extremely rare.[7] The tumor presents with pathological characteristics intermediate between benign and malignant, and their clinical courses

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vary widely, from cases remaining stable for years to cases with acute progression such as invasion, recurrence, and metastasis.[7-10,21]

We describe a case of a 24-year-old female who presented with myriad intracranial small lesions resembling hematomas on computed tomography (CT) scans and magnetic resonance images (MRIs). She was also found to have similar small lesions in the lungs and liver. Although the histology of the biopsied specimen showed benign features with a low proliferation index, her clinical course was very rapid due to intracranial hypertension caused by multiple intracranial masses.

CASE REPORT

A 24-year-old woman with no remarkable previous medical history had a 7-month history of coughing and blood-stained sputum. She also presented with a visual disturbance in the right eye occurring over 1-month. She visited a local ophthalmologist and was referred to an ophthalmologist at our hospital. Detailed examinations revealed no ophthalmological abnormality. Brain MRI showed multiple intracranial lesions and she was referred to us. On examination, she was awake and alert with no disorientation except for visual deficits rated as counting fingers in the right eye, whereas the left visual acuity was 30/50. There were no other focal neurological deficits. A brain CT scan revealed multiple 5–15 mm high-density nodules with perifocal edema in the bilateral cerebrum and cerebellum [Figure 1a]. The sulci appeared obscured, indicating the increased intracranial pressure. Emergency cerebral angiography ruled out vascular diseases such as sinus thrombosis. However, on angiography, the intracranial perfusion time of the contrast medium was prolonged, suggesting mild intracranial hypertension. MRI demonstrated that the signal of nodules was hypointense to isointense on T1-weighted images [Figure 1b] and hypointense on T2-weighted [Figure 1c]. Susceptibility-weighted images [Figure 1d] showed numerous low-intensity spots, indicating old hemorrhages. These lesions were accompanied by significant peritumoral edema. Postcontrast studies revealed little enhancement in most lesions, but a weak enhancement in some nodules [Figure 1e]. Under the suspicion of multiple brain metastasis from malignancies in other organs, chest CT scan was performed, which revealed multiple small nodules with bleeding in the lung [Figure 2a]. An abdominal CT scan showed a similar-sized mass without intralesional hemorrhage in the liver [Figure 2b]. The hepatic lesions were enhanced homogeneously [Figure 2c]. These findings were not typical of primary lung and hepatic cancers. Serum tumor markers including carbohydrate antigen 19-9, squamous cell carcinoma, and Sialyl LewisX were also negative. Sputum and bronchial lavage fluid cytology were class 1. Based on the MRIs and CT scans indicative of multiple hemorrhagic brain tumors, intracranial metastasis of melanoma, or choriocarcinoma were also included in the differential diagnoses. However, detailed dermatological inspection denied the presence of abnormal skin lesions. In addition, 5-S-cysteinyldopa, a serum tumor marker for melanoma, was negative. Gynecological examinations also excluded the possibility of any pelvic tumors. In addition, thallium scintigraphy indicated no abnormal uptake in any part of the body. The systemic and multiorgan nature of the disease led us to suspect other conditions such as metabolic, hematological, and infectious diseases.

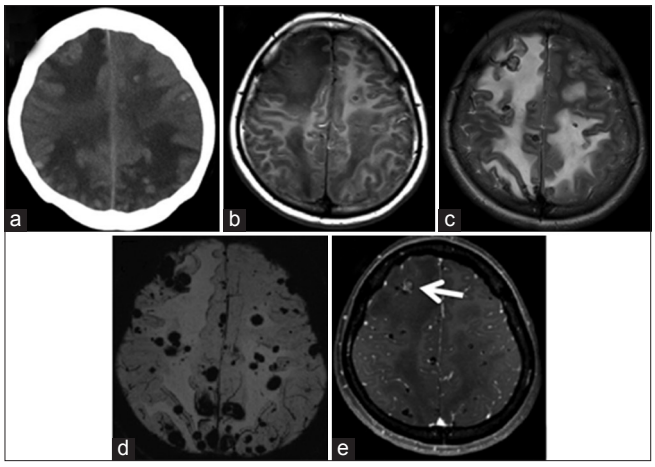

Figure 1: (a) Brain computed tomography scan showed multiple small intra-axial nodules with slightly high density. (b) Magnetic resonance imaging demonstrated that the signal of the nodules was hypointense to isointense on the T1-weighted image. (c) The magnetic resonance T2-weighted image revealed significant edema around multiple nodular lesions showing hypointensity. (d) The magnetic resonance susceptibility-weighted image showed numerous low-intensity spots, indicating old hemorrhages. (e) Magnetic resonance T1-weighted image with gadolinium enhancement demonstrated little enhancement in most lesions but a weak enhancement in some nodules (arrow)

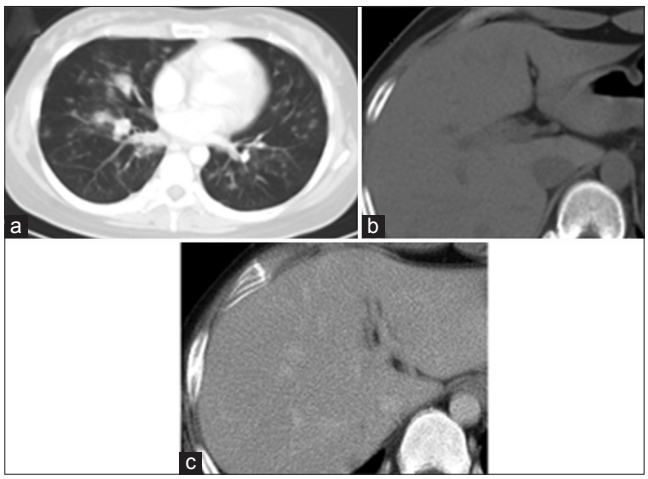

Figure 2: (a) Chest computed tomography scan showed multiple nodules with hemorrhage in the lung. (b) Abdominal computed tomography demonstrated hypodense nodules without intralesional hemorrhage in the liver. (c) Lesions in the liver were homogeneously enhanced with contrast medium

However, laboratory tests showed only mild anemia. The possibility of systemic amyloidosis was ruled out from the results of serum protein fractions and urinalysis. To eliminate the possibility of tuberculous lesions, bacterial cultures from the sputum and bronchial lavage fluid, acid-fast bacteria staining, *Mycobacterium tuberculosis* polymerase chain reaction, and interferon-gamma release assay were conducted; however, these examinations did not indicate tuberculosis.

During the course of these examinations, the patient's condition significantly progressed. Her bilateral visual acuity rapidly declined for 3 days after admission. She also had frequent general clonic seizures. The steroid, osmotic diuretics, carbamazepine, and levetiracetam were administered to control her seizures. Although her seizures were controlled over the following 3 days, her bilateral visual acuity had further declined to light perception. Because of the necessity of determining pathological diagnosis, a biopsy of the right frontal brain lesion was performed 14 days after admission. Increased intracranial pressure was observed intraoperatively. The lesion with slight enhancement on MRIs in the right frontal lobe was removed using a navigation guide. The tumor was moderately hemorrhagic, presenting a reddish-brown color [Figure 3]. The consistency of the tumor was elastic and hard.

Histopathological examination showed a diffuse cellular proliferation upon hematoxylin and eosin stain. Fine vascular channels, hemorrhage, and hemosiderosis were observed in the tissue [Figure 4a]. Cells contained a round and slightly coarse nucleus and a large volume of clear cytoplasm including large and small balloon-like lesions and erythrocytes [Figure 4b]. Immunohistochemical staining showed positivity for vimentin and CD31 of the cell membrane and cytoplasms [Figure 4c] and mild positivity for CD34 of the cytoplasm. Tumor cells were all negative for S-100, neurofilament, glial fibrillary acidic protein, IbaI, CD1a, CK AE1/3, epithelial membrane antigen, leukocyte common antigen, CD68, and alpha-smooth muscle actin. Mitotic nuclei were rare, and the MIB-1 labeling index was <3% in the tumor cells [Figure 4d]. Based on these histopathological findings and the multiplicity of lesions in the brain, lung, and liver, we finally determined the diagnosis as EHE.

The patient's conditions were stable for 3 months after biopsy. After a discussion about the treatment strategy with the patient and her family, we opted for conservative therapy comprising only rehabilitation on the basis of the low proliferation rate indicated by the histopathological findings. However, after 3 months, the patient gradually developed moderate disturbance of consciousness, headache, and vomiting. MRIs demonstrated aggravation of peritumoral edema without apparent enlargement of each nodule [Figure 5a]. The bilateral ambient

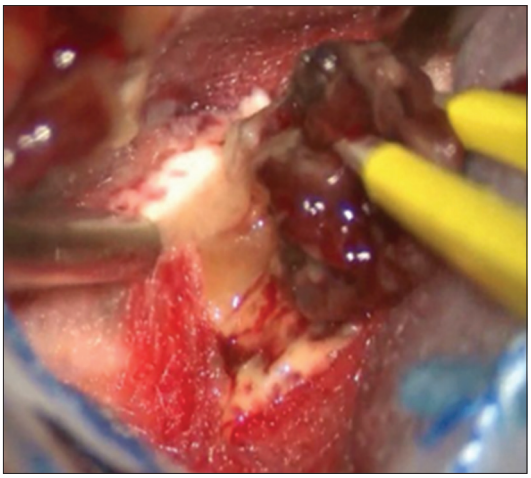

Figure 3: Intraoperative view. The tumor was elastic, hard, and moderately hemorrhagic

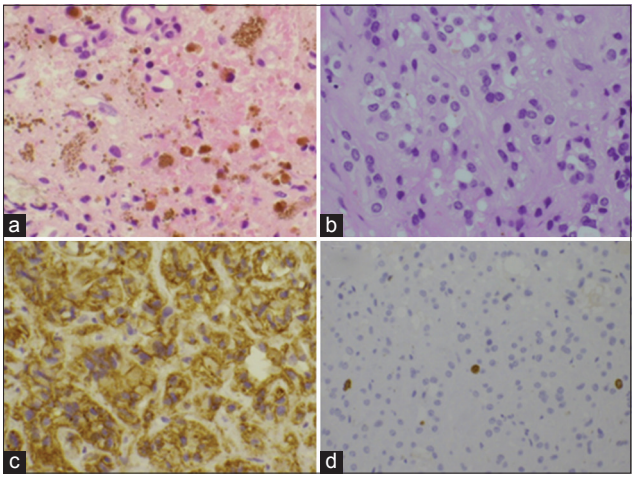

Figure 4: (a) Hematoxylin and eosin staining showing diffuse cellular proliferation, fine vascular channels, hemorrhage, and hemosiderosis. (b) Cells with a round and slightly coarse nucleus and a large volume of clear cytoplasm including large and small balloon-like lesions and erythrocytes were noted. (c) Immunostaining for CD31 revealed a significant staining of the cell membrane and cytoplasm. (d) The MIB-1 labeling index was <3% in the tumor cells

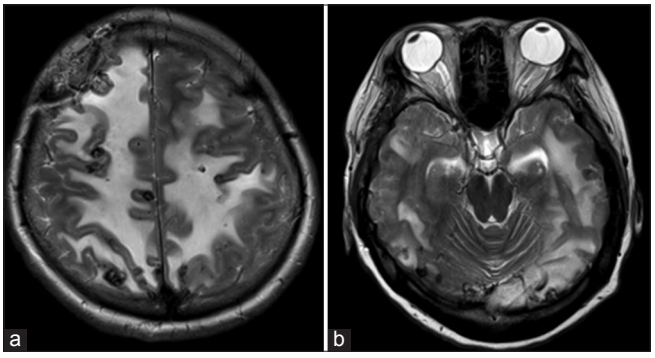

Figure 5: (a) T2-weighted image at 3 months after biopsy demonstrated aggravation of peritumoral edema without apparent enlargement of each nodule. (b) The bilateral ambient cisterns had narrowed, suggesting increased intracranial pressure

cisterns had narrowed, suggesting increased intracranial pressure [Figure 5b]. Steroid pulse therapy with osmotic diuretics improved her consciousness for 2 weeks, and she became able to eat. Palliative whole-brain radiation was initiated, but she did not respond to the treatment and developed diabetes insipidus requiring administration of desmopressin. Her consciousness continued to deteriorate. When she became comatose, her family hoped the termination of radiation and the provision of the best supportive care. She died after 4 months of hospitalization.

The autopsy revealed the cause of death as brainstem necrosis, possibly induced by brain herniation. In addition to the multiple intracranial, pulmonary, and hepatic lesions confirmed on diagnostic imaging, multiple white nodules were observed, including two in the spleen, two in the left kidney, one in the right kidney, and one in the third lumbar vertebra. All were confirmed as EHE.

DISCUSSION

The term EHE was coined by Weiss and Enzinger in 1982 to designate a vascular tumor with an epithelioid appearance.[36] This tumor usually develops in the lung, liver, bone, and soft tissue. There are 40 sporadic case reports in the literature on intracranial EHE,[2,3,5,7-10,13-15,17,18,21-26,29,31-35,38-40] for which Zheng *et al*. conducted an extensive review.[41] Of these reported intracranial lesions, only 5 (12.8%) cases presented with multiple lesions, similar to that in our case. While pulmonary EHE is more common in women,[7] intracranial EHE is more frequently seen among men.[41] The reported age ranges widely from the first to the eighth decade. No inherited case has been reported. Although several risk factors for hepatic EHE have been proposed, including oral contraceptives, vinyl chloride,[11] asbestos, alcohol, thorotrast, liver trauma, hepatitis virus, and chronic liver disease,[6] none has been reported to increase the risk of developing intracranial EHE.[20] Our patient had a history of chronic oral contraceptive use; however, whether this exposure actually caused EHE is unknown in this case.

On radiological examination, intracranial EHE can be extra- or intra-axial, with a variable size.[9,29] There are no typical radiological findings on CT or MRI for EHE.[1,4,8,13,28,41] Our case demonstrated numerous small nodules in the brain showing low-intensity on MR T2-weighted and susceptibility-weighted images, for which the patient underwent extensive workups covering vascular, tumorous, infectious, and metabolic diseases. In the present case, the results of biopsy and autopsy suggested that brain lesions were composed of hemorrhage and hemosiderin of different ages. This factor may account for the variety in radiological findings reported in the literature. Although it is rare, EHE should be carefully included in the differential diagnosis for multiple intracranial mass with previous hemorrhages. Previous reports have emphasized the difficulty in diagnosing EHE because of its rarity.[41] In particular, a manifestation of multiple small nodules, as observed in our case, is extremely rare. Díaz *et al*. reported only one case of radiological presentations similar to ours. They reported a case of pulmonary EHE, in which multiple small intracranial nodules were also found after treatment of a lung lesion.[7] They confirmed that the pathological diagnosis of tumors in the brain and lungs was EHE, and they suspected that the case was pulmonary EHE with synchronous central nervous system dissemination.

The mechanism underlying the multiple organ involvement in EHE is poorly understood. Two hypotheses have been proposed; metastasis[8,27,37] and multicentric tumors.[15,28] In our case, all the tumors found in multiple organs were approximately same in size, showing rather a latent progression. The patient's neurological symptoms were mild despite a large number of intracranial hemorrhagic nodules with significant edema on the initial MRIs, which appears to be incompatible with metastases of malignant tumors. We also performed thorough radiological and serological examinations on admission and simultaneously found multiple organ involvement. However, some of the studies advocating the metastasis theory failed to conduct sufficient screening of the whole body from the initial diagnosis. Because there has been no case of true metastasis radiologically confirmed in the literature, we believe that multicentric development theory is more plausible than metastasis.

The clinical course of EHE is also variable. Some reports describe cases with no progression after a long follow-up period,[3,23] whereas others describe cases with rapid aggravation.[7,8,10] We speculate that the aggressive course of EHE in our patient was attributable to the increased intracranial pressure, confirmed on the findings of MRIs, and autopsy. Temporary recovery obtained by administration of a steroid and diuretics was also consistent with the presumed intracranial hypertension. Pathologically, intracranial EHE has features of both angiosarcoma and hemangioma and is classified as a borderline brain tumor according to the fourth edition of the World Health Organization classification of tumors of the central nervous system.[19] It should be again stressed that the clinical course of intracranial EHE, despite the low proliferation indices, can be complicated, particularly in cases of multiple intracranial lesions.

Although the treatment strategy for EHE has not been well-established because of its rarity, most previous reports advocate surgical resection for intracranial lesions that are solitary and completely resectable.[4,12,14,22,41] However, cases have been reported in which the surgery was discontinued because of excessive bleeding.[5,13,17,24,26,29] Even intraoperative mortalities have occurred,[18] indicating that EHE carries a significant risk of bleeding. In addition, the surgical indication would be extremely limited for multiple intracranial lesions as observed in our case. Chemotherapy or radiotherapy has been administered in some cases, but the effectiveness of such treatments has not been proven.[4,13,30,31,34]

While conservative management can be an option for pulmonary EHE,[16] its significance for intracranial lesion remains unknown.

CONCLUSION

EHE is rare and can present as solitary or multiple intracranial masses. Although the diagnosis is not simple, radiological features indicating a mixture of old and new hemorrhages inside tumors are helpful. It should be included in the differential diagnoses, particularly when multiple intracranial, pulmonary, and hepatic lesions are observed. The systemic involvement of this tumor was more compatible with multicentric development than metastasis. The clinical manifestation of EHE can be rapid and aggressive regardless of a low proliferative potential.

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Conflicts of interest
There are no conflicts of interest.

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