CASE REPORT

Squamous cell carcinoma invading peripheral cerebral blood vessels and causing repeated cerebral hemorrhage : A case report

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Abstract : Squamous cell carcinoma (SCC) is known to have less brain metastasis, but the reasons are not well established. Herein, we report the case of an 82-year-old man with recurrent cerebral hemorrhage of unknown cause ; upon brain biopsy, SCC was diagnosed infiltrating peripheral blood vessels of the brain and that it was state of micro-metastasis. It is possible that the blood-brain barrier blocked the infiltration of SCC into the brain parenchyma, and it did not form a mass in the brain parenchyma. In addition, because it did not form a mass, it could not be diagnosed as a metastatic brain tumor by contrast-enhanced magnetic resonance imaging or contrast-enhanced computed tomography. Among cases of recurrent cerebral hemorrhage of unknown cause in a short period, there may be cases of vascular infiltration without crossing the blood-brain barrier. Thus, if similar cases of recurrent cerebral hemorrhage of unknown cause is observed, it is necessary to distinguish metastatic brain tumors even if there is no evidence of suspected tumor on contrast-enhanced magnetic resonance imaging scan. J. Med. Invest. 70 : 276-280, February, 2023

Keywords **:** *brain metastasis, blood-brain barrier, hemorrhage*

INTRODUCTION

It is known that the frequency of brain metastasis (BM) varies depending on the primary tumor lesion and histological type. Among the histological types of lung cancer, squamous cell carcinoma (SCC) is known to have a lower frequency of BM than other histological types (1-5). According to a study by Wang *et al*., who retrospectively studied lung cancer patients, the frequency of BM was 5.7% in SCC, which was significantly lower than other histological types (6). The majority of BM originate from lung cancer (39%), breast cancer (17%), and malignant melanoma (10%) (7, 8). However, it is not clear why the frequency of BM varies depending on the histological type. We experienced repeated episodes of cerebral hemorrhage with unknown cause, and following brain biopsy, we confirmed that SCC, which is thought to be derived from lung cancer, was in a state of tumor embolization and micro-metastasis. Since there are few reports of repeated bleeding before forming a lesion that can be detected by contrast-enhanced magnetic resonance imaging (MRI) scan, we report this case.

CASE REPORT

An 82-year-old man was brought to our hospital due to a severe headache. At the time of the first medical examination, he was conscious and showed no abnormal neurological findings. However, computed tomography (CT) scan revealed multiple intracerebral hemorrhages (Figure 1). His initial blood pressure was 153/60 mm Hg, which was immediately controlled. Despite good blood pressure control, the number of cerebral hemorrhage sites increased every week on CT scan, and the consciousness level worsened to E3V2M5 on the Glasgow Coma Scale after 3 weeks (Figure 2). Contrast-enhanced MRI could not identify any obvious contrast-enhanced lesions, except for hemorrhagic lesions and no cerebral edema was found on MRI (Figure 3). Diffusion weighted imaging showed lesions showing cerebral hemorrhage, but no evidence of obvious cerebral infarction was seen (Figure 4). Cerebrovascular angiography was performed, but no

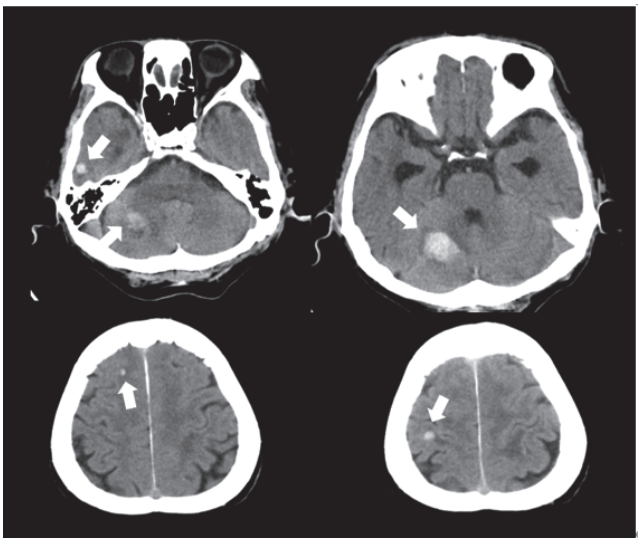

Figure 1. Computed tomography scan on admission revealed multiple intracerebral hemorrhage. White arrows indicate cerebral hemorrhage.

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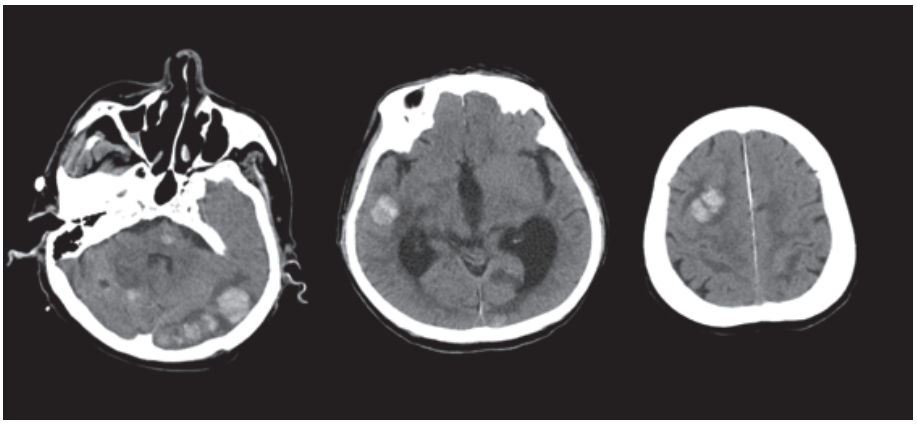

Figure 2. Computed tomography scan performed 3 weeks after admission revealed that the number of cerebral hemorrhages was increasing.

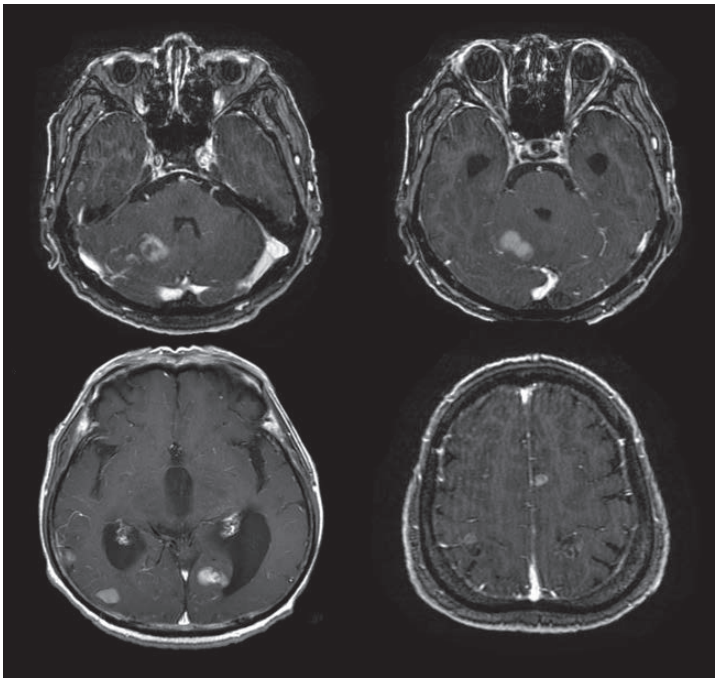

Figure 3. Contrast-enhanced magnetic resonance imaging performed 2 weeks after admission revealed intracerebral hemorrhage from multiple sites but could not identify any obvious contrast-enhanced lesions.

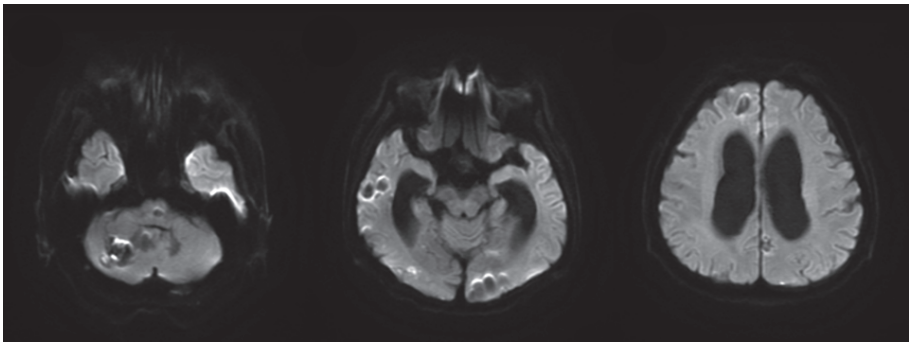

Figure 4. Diffusion-weighted imaging showed the lesions of cerebral hemorrhage, but no evidence of obvious cerebral infarction.

vascular malformation or microaneurysm was found. We measured tumor markers : NSE, SCC, CA19-9, CEA, AFP, CYFRA, ProGRP, and PSA in blood, but all were negative. Prothrombin time and activated partial thromboplastin time were within the normal range. D-dimer was only slightly increased to 2.4 ng/mL. On CT scan, a tumorous lesion was suspected in the right upper lung field, but transbronchial biopsy with bronchoscopy was negative. We had conducted a brain biopsy approximately a month after admission. Approximately 10 cm^3 of brain tissue around the bleeding site in the right temporal lobe was collected by the biopsy. Histopathological examination revealed numerous tumor emboli in arterioles and metastatic lesions of SCC along the vessel wall. (Figure 5A). The histopathological findings showed that tumor cells had infiltrated along the arterial wall, and a part was ruptured and in a state of tumor micro-metastasis. These pathological findings suggest that the cerebral hemorrhage was caused by the rupture and recanalization of peripheral arteries in the brain due to infiltration of tumor cells.

The epithelial markers CK (AE1/AE3) was positive and P40, a marker specific for SCC, was positive (Figure 5B, 5C). TTF-1, a marker specific for adenocarcinoma, was negative. Based on these histopathological results, the pathologist diagnosed a metastatic brain tumor derived from SCC. Six days after the biopsy, a decrease in consciousness level was observed, and CT of the head revealed a pontine hemorrhage. One week after the brain biopsy, we performed whole-brain irradiation on the patient with the schedule of 30 Gy in 10 fractions in order to suppress recurring cerebral hemorrhage. Although there was no increase in cerebral hemorrhage for 2 weeks after the inception of radiotherapy, he developed pneumonia and died 2 months after hospitalization. We could not obtain consent from the family to perform an autopsy.

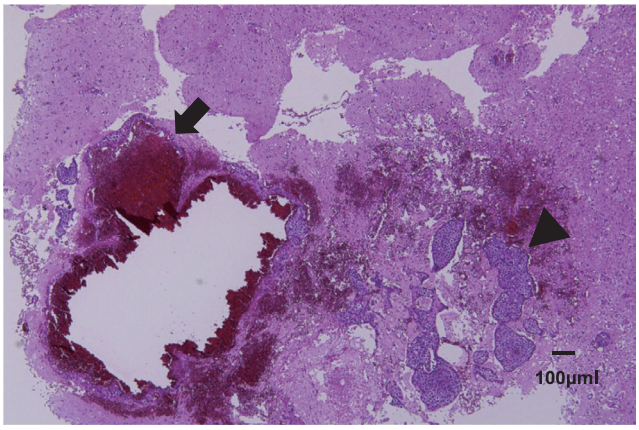

Figure 5A

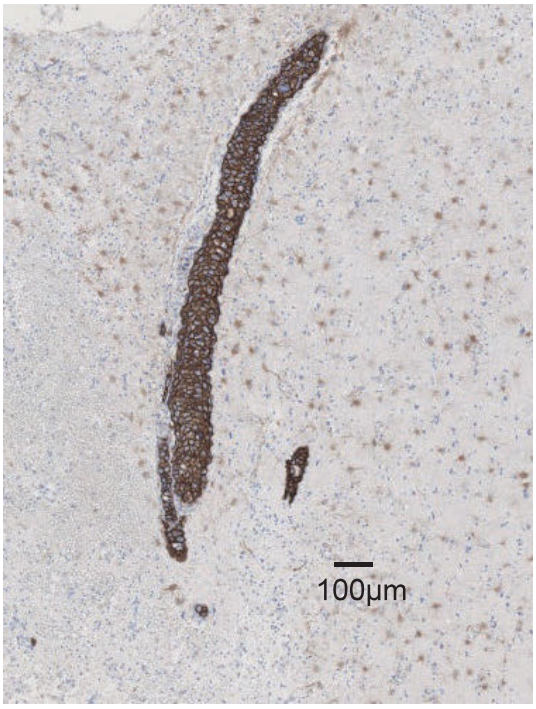

Figure 5B

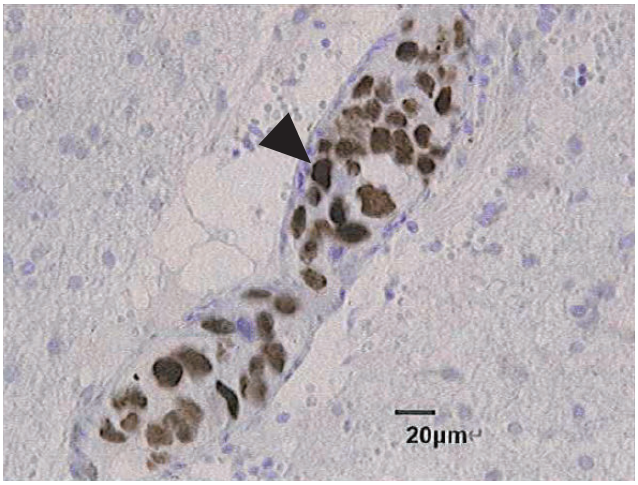

Figure 5C

Figure 5. A) Hematoxylin and eosin stain revealed that squamous cell carcinoma (SCC) invaded along the cerebral arteries and partially ruptured the blood vessel wall. The black arrowhead points at the tumor embolism. The black arrow points at a ruptured vessel. B) The epithelial marker CK (AE1/AE3) is positive, suggesting SCC. C) P40 staining ; the black arrowhead points towards the tumor embolism and indicates P40 SCC marker is positive.

DISCUSSION

The following two points were demonstrated in this case : SCC invades the peripheral arteries of the brain and can cause frequent cerebral hemorrhage in a short period of time ; and if it is in a state of micro-metastasis, contrast-enhanced MRI can't detect the neoplastic lesion.

Central nervous system (CNS) lacks a lymphatic system, therefore, the possibility for cancer cells to reach the brain is via the bloodstream or cerebrospinal fluid. BM can develop both in the parenchyma and the meninges (9). Leptomeningeal metastases resulting from solid tumors occur late and usually coexists with CNS parenchymal disease.

Metastatic cells invading the CNS parenchyma have to pass the blood-brain barrier (BBB). The majority of BM originate from lung cancer (40%–50%), breast cancer (15%–25%), and malignant melanoma (5%–20%) (7, 8). Among these tumors, melanoma has the highest frequency of metastasis : BM is diagnosed in 40%–50% of these cases, which, after autopsy, increases by an additional 30%–40% (10). Most studies of BM in non-small cell lung carcinoma suggest that SCC is associated with a lower incidence than adenocarcinoma (8, 11-13).

The tumor-derived factors such as adhesive molecules, chemoattractive factors, and proteolytic enzymes facilitate the migration of tumor cells in the extracellular matrix and through vessel walls (9). The cellular mechanisms that lead to BBB extravasation appear to be strictly related to cancer cell features and therefore linked to the primary tumor characteristics (14). In a transendothelial migration model, the migration of highly metastatic melanoma cells has been found to be mediated by the interaction of the $\alpha 4\beta 1$ integrin with its ligand vascular cell adhesion molecule-1 (VCAM-1) on the surface of activated endothelial cells. VCAM-1 is expressed by endothelial cells only upon activation by inflammatory stimuli like TNF-α or interferon-γ (15).

It was found that cyclooxygenase-2 (COX2)-mediated prostaglandin synthesis promotes proliferation of tumor-initiating cells by activating tumor-associated astrocytes followed by secretion of the chemokine CCL7 (16). Expression of matrix metalloproteinase is positively correlated to BM of breast cancer (16). COX2 is significantly overexpressed in patients with BM and that high expression of COX2 was significantly correlated to BM-free survival (16). COX2 is highly up-regulated in brain metastatic cells and that COX2-induced prostaglandins (16).

The process of transendothelial migration of melanoma cells has been further investigated by other in vitro studies showing that the ability of these cells to cross the BBB is related to melanotransferrin expression levels on the cell surface to the fibrinolytic system and to serine proteases released by melanoma cells (17-19). This accumulating evidence indicates that inflammatory stimuli contribute to the formation of breaches in the BBB. However, in contrast with these findings, other in vivo studies suggest that trasendothelial cancer cell migration does not necessarily imply a damage to vascular endothelial cells ; metastatic breast cancer cells in mice were found to cross the endothelium at sites where the vessel wall showed discontinuities without causing apoptosis or hypoxia in endothelial cells (20).

Thus, different tumor subtypes may have different BBB passage mechanisms and different susceptibilities for BM. SCC that infiltrated the vessel but did not form a mass in the brain parenchyma as in this case may not be detected by contrast-enhanced MRI.

The mechanism of neoplastic bleeding in metastatic brain tumors includes intratumoral necrosis, tumor vascular infiltration, venous compression by tumors, and hemorrhagic infarction due to tumor embolism (21-23). According to a study by Mandybur *et al*., the frequency of cerebral hemorrhage from BM was 14% and metastatic brain tumors derived from choriocarcinoma, malignant melanoma, lung cancer, and adrenal tumor are prone to bleeding (23). Several reports of repeated intracerebral hemorrhage were diagnosed as multiple metastatic brain tumors for the first time by autopsy without being diagnosed by imaging (22, 24).

Many routes have been suggested for metastatic tumors to reach the intracranial contents, including the dura mater, the leptomeninges, and the cerebral parenchyma. A generally accepted pathway is hematogenous metastasis (25, 26).

The difference in BBB passage between tumor subtypes may be related to the ease of BM, and tumors that do not easily pass through the BBB may cause vascular infiltration and tumor embolism, resulting in repeated intracerebral hemorrhage of unknown cause.

Currently, the most sensitive and commonly used imaging modality for the detection of BM is thin-slice contrast-enhanced MRI (27). Therefore, if it cannot be detected by contrast-enhanced MRI, it is difficult to detect the state of micro metastasis.

There are some limitations to this case report. Although the primary lesion was suspected in the lung field, it could not be diagnosed by bronchial biopsy because it was located in the periphery of the bronchus. Since pathological autopsy could not be performed, only fragmentary histopathological information could be obtained.

In summary, if recurrent cerebral hemorrhage of unknown cause is observed, it is necessary to distinguish metastatic brain tumors even if there is no evidence of suspected tumor on contrast-enhanced MRI scan.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FINANCIAL INTEREST

The authors have no financial conflicts of interest disclose concerning the case report.

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