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LETTER TO THE EDITOR

A Pathologically Verified Case of Peripheral Intracranial Aneurysmal Formation With Massively Infiltrating Meningioma Cells

Tatsuki Kimura, MD[1], Taichi Ikedo, MD, PhD[1], Keiko Ohta-Ogo, MD, PhD[2], Eika Hamano, MD[1], Tsuyoshi Ohta, MD, PhD[1], Hisae Mori, MD[1], Tetsu Satow, MD, PhD[1], Masatake Sumi, MD[1], Naoki Hashimura, MD[1], Takeshi Hara, MD[1], Koji Shimonaga, MD, PhD[1], Yuji Kushi, MD[1], Yoshihiko Ikeda, MD, PhD[2], Kinta Hatakeyama, MD, PhD[2], Koji Iihara, MD, PhD[1], and Hiroharu Kataoka, MD, PhD[1]

[1]Department of Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
[2]Department of Pathology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

Correspondence to: Taichi Ikedo, Department of Neurosurgery, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan; E-mail: taichi.ikedo@gmail.com

To the Editor:

The prevalence of peripheral cerebral aneurysms is estimated to be 1%–9% of middle cerebral aneurysms (1). Common etiologies of peripheral cerebral aneurysms include bacterial infection, trauma, and autoimmune diseases. Invasion of vessel walls by tumor cells is also reported to be another cause of peripheral cerebral aneurysms (1, 2). This entity has been termed, "neoplastic cerebral aneurysm" (NCA) and in previous reports it has been caused by various tumors including cardiac myxoma, choriocarcinoma, lymphoma, and metastatic brain tumor (2). NCAs are usually attributed to migration and invasion of the intima from the luminal side of the artery by a detached tumor cell embolus that results in weakening of the arterial wall (3).

There is, however, no previous report of aneurysmal formation caused by the direct infiltration of tumor cells from the outer side of the cerebral arteries. We describe the first case of a fusiform aneurysm in the peripheral middle cerebral artery (MCA) in a patient with an invading recurrent meningioma. Pathological examination revealed a rare phenomenon of aneurysmal formation with massive meningioma cells infiltrating all layers of the artery.

A 67-year-old man had undergone surgical resection of a left parasagittal atypical meningioma 8 years earlier. Subsequently, 3 stereotactic radiosurgeries and a second tumor resection were performed for the recurrent meningioma. The patient gradually developed aphasia and was immediately brought to our hospital. On arrival, he was completely awake and alert but had aphasia. Magnetic resonance imaging revealed a recurrent (Fig. 1A) and de novo meningioma in the left frontal region with extensive perifocal edema. Contrast-enhanced T1-weighted images showed a well-defined solid tumor with homogeneous enhancement (Fig. 1A). This was not present in the cerebral angiography study performed 1 year previously (Fig. 1B), the preoperative cerebral angiography revealed a fusiform aneurysm 4.5 mm × 3.0 mm in size in the left central artery (Fig. 1C).

We surgically resected both the de novo and recurrent meningiomas along with the fusiform aneurysm. Intraoperative findings showed a white spindle-shaped fusiform aneurysm on the peripheral MCA encased in the tumor with a tiny blood clot, suggesting minor bleeding from the aneurysm (Fig. 1D). As planned before the operation, the proximal side of the aneurysm was temporarily clipped. Indocyanine green video angiography revealed backflow on the distal side of the fusiform aneurysm (Fig. 1E). We confirmed leptomeningeal anastomosis and no visualization of the aneurysm by cerebral angiography. Based on these findings, we decided to trap and resect the fusiform aneurysm without bypass surgery, followed by tumor resection. Although the aphasia persisted, the patient experienced no additional neurological deficits during the postoperative period.

The meningioma was characterized by hypercellularity, sheet-like growth, prominent nucleoli, necrosis, and more than 4 mitoses per 10 high-power fields (Fig. 1F). The histopathologic diagnosis was an atypical grade II meningioma with a Ki-67 labeling index of 13% (Fig. 1G). The aneurysm was 5 mm × 3 mm in size, forming a double-humped dilatation (Fig. 2A–C). The internal elastic lamina (IEL) was disrupted at the boundary between the aneurysm and intact artery (Fig. 2D, E). The aneurysmal wall was characterized by thinning with decreased smooth muscle cells (Fig. 2F). Massive meningioma cells stained with anti-vimentin antibody and antiepithelial membrane antigen (EMA) invaded the intima and disrupting the IEL in the aneurysmal wall (Fig. 2G–I). Thickening with hyperplasia of the intima and nuclear atypia of fibroblasts were consequences of multiple radiation therapies (Fig. 2J). Infiltrating inflammatory cells, including CD68-positive macrophages

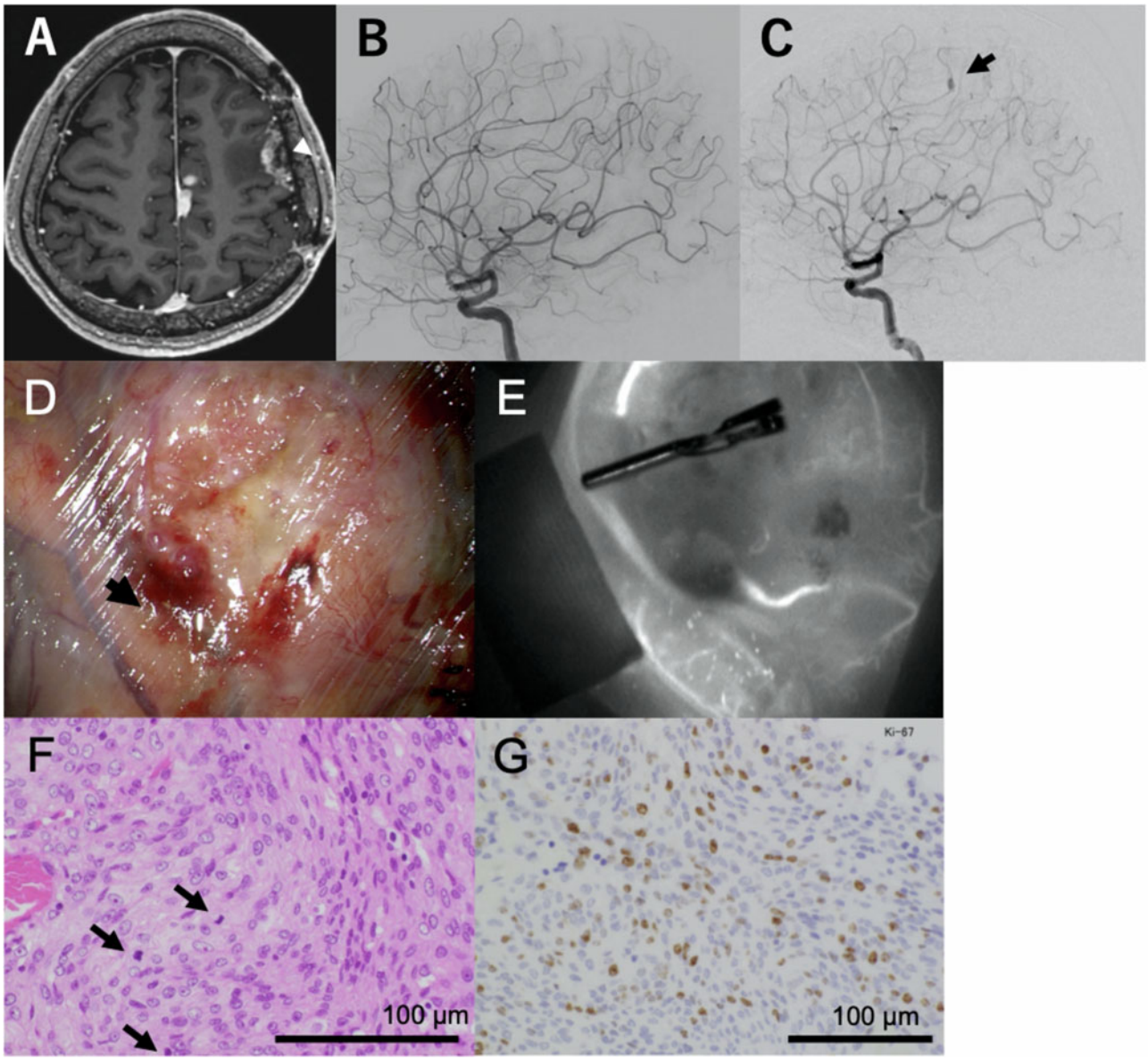

FIGURE 1. Preoperative images and intraoperative findings of meningiomas and a peripheral fusiform aneurysm. **(A)** Contrast-enhanced T1-weighted image showing a recurrent meningioma in the left frontal region **(**white arrowhead**)**. **(B, C)** Conventional cerebral angiography 1 year **(B)** and 1 week **(C)** before the surgery. Black arrow indicates the peripheral fusiform aneurysm in the left middle cerebral artery **(C). (D)** A spindle-shaped fusiform aneurysm (black arrow) formed on the peripheral middle cerebral artery encased in the tumor with a tiny blood clot. **(E)** Indocyanine green video angiography show backflow in the distal side of the fusiform aneurysm. **(F, G)** The resected recurrent meningioma stained with hematoxylin and eosin **(F)** and anti-Ki-67 antibody **(G)**. Arrows indicate mitotic figures in tumor cells. Scale bars: 100 μm.

and CD3-positive T cells, were observed at the point where red blood cells penetrated the disrupted aneurysmal wall (Fig. 2K–N).

There are previous reports of direct invasion of the arterial walls by intracranial tumors but without forming intracranial aneurysms. Aoki et al (4) described a case of arterial dissection in the MCA caused by infiltration of malignant glioma cells. Microscopic examination revealed glioblastoma multiforme cells invading the media and disrupting the IEL without aneurysmal formation. Meningioma cells sometimes infiltrate the dura mater and venous sinus but usually do not invade arteries. Although cavernous meningiomas rarely invade the adventitia and media of the cavernous portion of the internal carotid artery, the intima is never infiltrated in such cases (5). In an exceptional case of MCA invasion by a sphenoid ridge meningioma, intraoperative findings showed a soft tumor tightly adhering to the arterial wall with perforation of the MCA bifurcation and subsequent subarachnoid hemorrhage (6). However, the report lacked pathological analysis to prove the infiltration of meningioma cells into the arterial

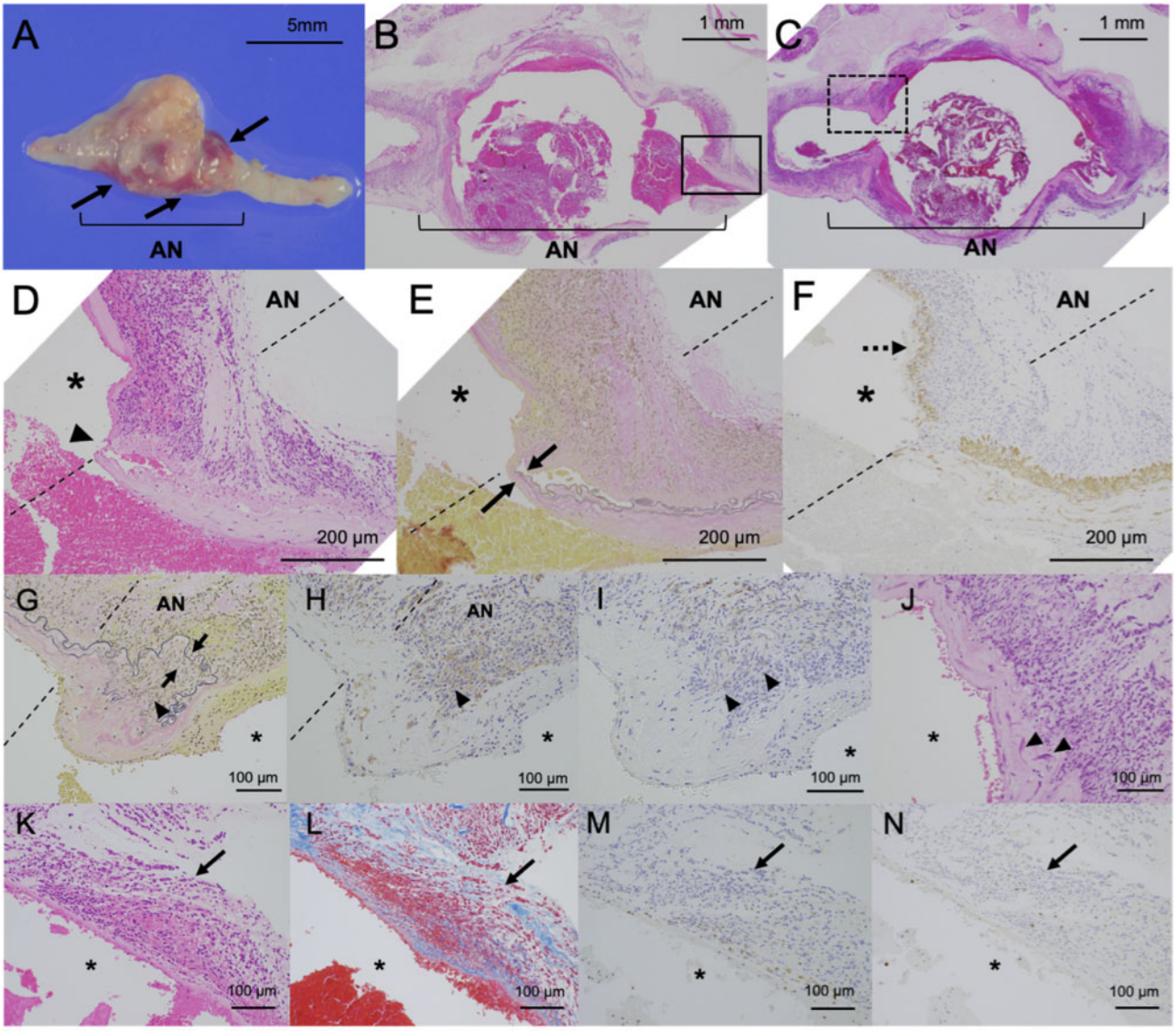

FIGURE 2. Pathological images of the resected peripheral aneurysm. **(A)** A macroscopic view of the double-humped fusiform aneurysm. Black arrows indicate minor bleeding. Scale bar: 5 mm. **(B, C)** Two cross-sectional views of the resected aneurysm with hematoxylin and eosin (H&E) staining. Scale bars: 1 mm. **(D–F)** Magnified views of the bold square in **(B)** stained with H&E **(D)**, Elastic van Gieson (EVG) **(E)** and with antismooth muscle actin (SMA) antibody **(F)**. **(D)** Intimal thickening change discontinued at the boundary between the aneurysm and intact artery (arrowhead) **(E)** Internal elastic lamina (IEL, arrows) was disrupted at the boundary. **(F)** The number of SMA-positive cells decreased in the aneurysmal wall (dotted arrow). Scale bars: 200 μm. **(G–I)** Magnified views of the dotted square in **(C)** stained with EVG **(G)**, antivimentin antibody **(H)**, and antiepithelial membrane antigen **(I)**. Meningioma cells are shown infiltrating into the intima (arrowheads, **H, I**), in the area of disrupted IEL (arrows, **G**) in the aneurysmal wall (arrowheads). **(J)** Thickening change with hyperplasia of the intima and nuclear atypia of fibroblasts (arrowheads) caused by multiple radiation therapies in the aneurysmal wall. **(K–N)** Magnified views where red blood cells were penetrating the disrupted aneurysmal wall (black arrows). Staining with H&E **(K)**, Masson trichrome **(L)**, anti-CD 68 antibody **(M)**, and anti-CD3 antibody **(N)**. Scale bars: 100 μm. Asterisks indicate the luminal side of the aneurysm. AN, aneurysm.

wall. Our case provides a detailed pathological examination that verified massive meningioma cells invading the arterial wall with aneurysmal formation.

To prove that the infiltrating cells were meningioma cells, the meningioma and the aneurysmal wall were stained with anti-EMA and antivimentin antibodies. EMA immunostaining was not strong but was diffusely positive in the tumor. Previous reports have indicated that increased tumor malignancy was associated with decreased EMA expression and increased vimentin expression (7). The high Ki-67 labeling index of 13% and multiple recurrences in the present case indicate the aggressiveness of the tumor reflected in the

low EMA expression. Disruption of the IEL and accumulation of inflammatory cells have been hypothesized to promote arterial wall weakness, leading to aneurysmal formation (8). Although it is not known whether the tumor cells disrupted the IEL directly, the EMA-positive meningioma cells infiltrating the aneurysmal wall into the intima and the macrophage accumulation support the likelihood that tumor cell invasion contributed to the aneurysmal formation in the present case.

Important pathological features of radiation-induced aneurysms include irregular thickening of the media and intima by poorly cellular fibrous tissues (9, 10). Because the present case also had intimal hyperplasia and nuclear atypia of fibroblasts in the parent arteries, multiple radiotherapies may have influenced on aneurysmal formation. However, the aneurysmal wall was characterized not by thickening but rather by thinning changes, suggesting different mechanisms from previously reported radiation-induced aneurysms (9, 10).

The incidence rate of intracranial hemorrhage is reported to be 0.5%–2.4% in all patients with meningiomas (6, 11). Previously reported mechanisms include bleeding from proliferating blood vessels, direct vascular invasion of tumor cells, tumor infarction, and stretched subdural veins. Bleeding from intracranial aneurysms formed by tumor invasion has not previously been considered as a possible cause (6, 11). In the present case, we successfully detected rare aneurysmal formation in the preoperative period and safely resected both the aneurysm and meningioma.

In conclusion, aneurysmal formation associated with infiltrating tumor cells and subsequent intracranial hemorrhage are potential complications in patients with malignant recurrent meningiomas.

COMPETING INTERESTS

The authors have no duality or conflicts of interest to declare.

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