



Case Report

A case of fibromuscular dysplasia related intracerebral hemorrhage without angiographically cerebral abnormal vessels

Gaku Fujiwara¹, Daisuke Maruyama¹, Hidetoshio Okabe², Yujiro Komaru³, Mamoru Murakami³, Kanade Katsura⁴, Nobukuni Murakami³, Naoya Hashimoto¹

¹Department of Neurosurgery, Kyoto Prefectural University of Medicine, ²Department of Diagnostic Pathology, Nishinotoin Bukkoji Clinic, Departments of ³Neurosurgery, ⁴Pathology, Japanese Red Cross Society, Kyoto Daini Hospital, Kyoto, Japan.

E-mail: *Gaku Fujiwara - gaku Fujiwara@hotmail.com; Daisuke Maruyama - d.maru1214@gmail.com; Hidetoshio Okabe - okabe@belle.shiga-med.ac.jp; Yujiro Komaru - marco-07@koto.kpu-m.ac.jp; Mamoru Murakami - mmurakami@kyoto2.jrc.or.jp; Kanade Katsura - katsurak@kyoto2.jrc.or.jp; Nobukuni Murakami - nobukuni-m@hera.eonet.ne.jp; Naoya Hashimoto - hashimotonaoya@me.com



*Corresponding author:

Gaku Fujiwara,
Department of Neurosurgery,
Kyoto Prefectural University of
Medicine, Kyoto, Japan.

gakufujiwara@hotmail.com

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ABSTRACT

Background: Fibromuscular dysplasia (FMD) can cause cerebral aneurysms and dissection, which can lead to stroke. Angiographic findings are important in the diagnosis. We report a case of FMD in which the cause of hemorrhage could not be determined by angiography.

Case Description: A 73-year-old woman suffered from intracerebral hemorrhage (ICH) associated with FMD without abnormal angiography cerebral vessels. She presented with headache and nausea. Subsequent head-computed tomography-revealed ICH in the left frontal lobe, and contrast-enhanced magnetic resonance imaging revealed a gadolinium-enhancing lesion in the perihematoma area and in the genu of the corpus callosum. Although cerebral angiography revealed a string of beads appearance in the bilateral extracranial internal carotid arteries, no abnormality explaining the hemorrhage was identified. The hematoma was removed and the pathological diagnosis was FMD. In the pathological specimen, various patterns of vulnerable vessels, such as aneurysmal dilatation and obstruction, were observed, which could easily collapse and result in hemorrhage. In the case of ICH of unknown origin, microscopic vessel disruption due to FMD should also be considered.

Conclusion: FMD can cause ICH in microscopic vascular lesions that are undetectable on angiography.

Keywords: Fibromuscular dysplasia, Intracerebral hemorrhage, Stroke

INTRODUCTION

Fibromuscular dysplasia (FMD) is a noninflammatory and nonatherosclerotic vascular disorder that leads to arterial tortuosity, stenosis, occlusion, aneurysm, and dissection of the middle and distal arterial segments of the human body.^[7,17] FMD mainly affects the media of arteries, and the most common histological characteristic is medial fibroplasia, which results in an artery with an appearance of “string of beads.”^[9] FMD appears commonly occurs in the renal arteries, extracranial internal carotid artery (ICA), and the vertebral artery. Most patients with FMD have a good clinical course; however, some of them with cerebrovascular disorders, called cerebrovascular FMD, including cerebral aneurysm or dissection, have a high risk of stroke

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and death;^[10,11] thus, their outcome is worse.^[8] Here, we experienced a case with intracerebral hemorrhage (ICH) due to FMD without findings of culprit aneurysm or dissection in cerebral arteries and presented with characteristic pathological findings.

CASE REPORT

A 73-year-old Japanese woman with a history of hyperlipidemia, diabetes mellitus, and malignant lymphoma of mucosa-associated lymphoid tissue (MALT) presented to our hospital complaining of headache and nausea for 10 days. MALT lymphoma had been treated with chemotherapy 10 years ago and was in complete remission. The patient had no antithrombotic medications. The patient was fully alert and had no neurological deficits on initial physical examination. Brain computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated subacute subcortical hematoma mainly in the left superior to middle frontal gyrus ($43 \times 18 \times 44$ mm) with gadolinium enhancement in the perihematoma area and in the genu of the corpus callosum [Figure 1]. Cerebral angiography detected neither vascular abnormalities nor feeder-like arteries of tumors in the left ICA, although it revealed an aneurysm in the contralateral ICA. A string of beads appearance was also detected in the bilateral extracranial ICA [Figure 2]. Abdominal three-dimensional CT angiography performed for examination of hematuria 10 years previously also revealed a string of beads sign in the right renal artery. These studies indicate that FMD existed in the background.^[5] The abnormal vessels explaining the bleeding source were not disclosed on angiography; thus, we could not diagnose the apparent cause of hemorrhage. Craniotomy biopsy and removal of the hematoma were performed for diagnosis and decompressive treatment 10 days after admission. With a left frontal craniotomy, a xanthochromic capsule was observed on the surface of the hematoma. Although no

specific findings were observed in the intraoperative frozen section diagnosis, the final permanent pathology specimen revealed FMD predominantly involving small- to medium-sized arteries distributed in the hemorrhagic necrotic brain tissue and overlying meninx. Many of the affected segments had stenoses with obliterations due to fibroplasia spreading into the intima and recanalization was observed in some of the obliterated vessels [Figure 3a]. In addition, aneurysmal dilatations were formed in the segments with severe medial lesions [Figures 3b and c]. Immunostaining revealed that the most of the endothelium of thin-walled blood vessels and capillaries due to aneurysm had only CD31 without CD34 [Figures 3d and e]. The patient was discharged 27 days after surgery. She was followed up in the outpatient clinic, and we recommend intervention for an aneurysm of the right ICA.

DISCUSSION

ICH due to FMD without obvious angiography abnormal vessels is an extremely rare entity and characteristic pathological findings are presented in this case. First, ICH associated with FMD has been reported in some reports [Table 1]. Mettinger *et al.*^[6] reported that 8.1% of cerebrovascular FMD patients had a history of ICH, and Krittanawong *et al.*^[5] reported that 0.01% of all FMD patients had a history of ICH. Kadian-Dodov *et al.*^[4] reported that 1.2% of FMD patients with neither aneurysm nor dissection experienced subarachnoid hemorrhage, although the frequency of the history of ICH was not mentioned.^[4] Since few cases of ICH due to FMD and few SAH without vascular abnormalities in FMD have been reported, we can conclude that this case is very rare. This could be because pathological examination is the only way to diagnose such an entity. Further examinations are needed to explore the incidence and clinical implications of this rare ICH.

According to the previous pathological reports of FMD, it was reported that FMD has lesions in small- and medium-

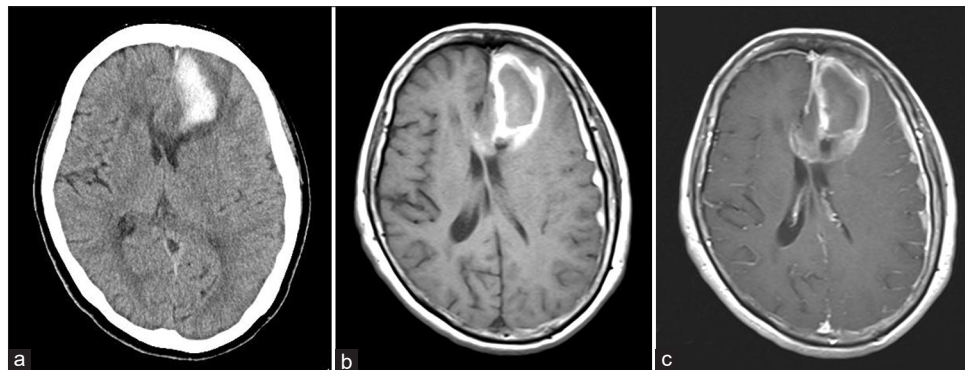


Figure 1: CT showed high-density lesion in the left frontal lobe (a). MRI images on admission showed the high intensity around hematoma and in genu of corpus callosum in T1WI (b and c), enhanced lesion around hematoma and in the genu of the corpus callosum in gadolinium enhancing T1WI (c).



Figure 2: On cerebral angiography, strings of beads appearance, was observed in the left extracranial carotid artery (a and b) and no abnormal vessel in the left carotid artery was detected (c and d).

sized vessels that cannot be captured on imaging.^[1,2,12] In the present case, there was a mixture of medial and intimal lesions and the intramedullary lesion with ICH was thought to be caused by the obstruction of small vessels associated with FMD. Microscopic vascular breakdown, presumably due to vulnerability, was seen in the present case. Therefore, we conclude that ICH is related to FMD without abnormal vessel findings on angiography. Moreover, in the present case, the immunostaining findings showed that most of the endothelium of thin-walled blood vessels and capillaries due to aneurysmal dilatation had only CD31 without CD34. This is a novel finding that has not been reported in other FMD cases: only CD31 positive endothelium without CD34 is usually seen in the sinusoid of the liver and spleen, which are highly permeable and have several large pores that penetrate the sporophyte.^[14] The cause of the endothelium being positive only for CD31 in the lesion is unknown; nevertheless, functional abnormalities in endothelial cells have been suggested. In this case, we consider that these changes may be secondary to wall degeneration and may also cause functional abnormalities in the endothelium, which consists of the blood-brain barrier (BBB).^[19] The irregular spreading of the lesion around the hematoma and in the genu of the corpus callosum seen on gadolinium-enhancing MRI may be interpreted as those seen in subacute or chronic hematoma,^[3,13,15,16,18] although we hypothesize that it could be associated with dysfunction of the endothelium associated with the breakdown of the

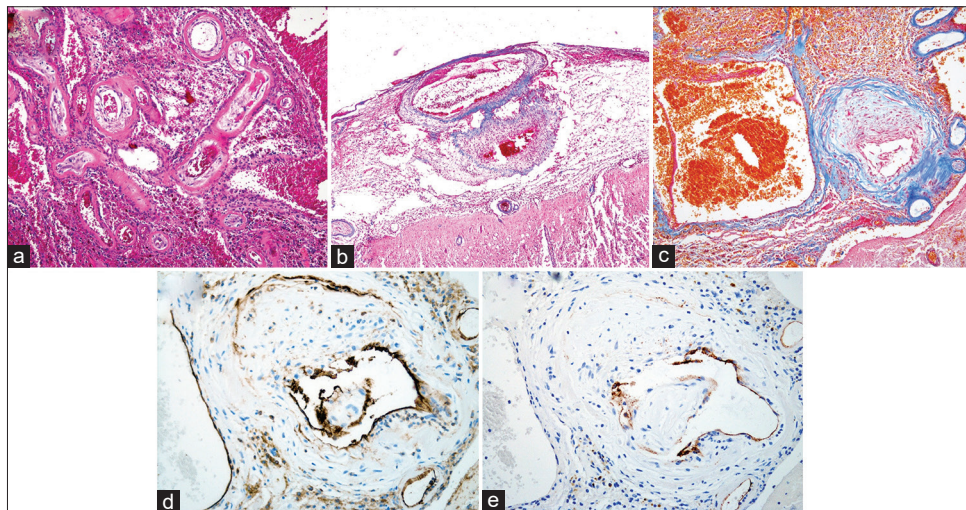


Figure 3: Continuous stenosis with multifocal obliterations in the segment of small arterial fibromuscular dysplasia (FMD) affecting media to intima (a), and recanalization was shown in some of these obliterations. Consecutive two aneurysms occurring within the arterial wall with characteristic medial FMD (b) and markedly expanded aneurysm with quite thin residual wall locating nearby the artery with stenosis due to FMD (c). Areas of wall thickening and greatly dilated vessel endothelium are CD31-positive (d), whereas the endothelium of the thin-walled aneurysm is CD34-negative (e). (Original magnifications $\times 40$ (a-c), $\times 100$ (d and e)).

Table 1: The characteristics and proportion of intracranial hemorrhage in FMD patients of the previous literatures.

Author	Year	Registry	Participants	Number	Mean age (y)	Female (%)	SAH (%)	ICH (%)
Mettinger <i>et al.</i>	1982	single-center	cerebrovascular FMD	37	47.8	81	48.6	8.1
Pasquini <i>et al.</i>	2015	single-center	cerebrovascular FMD	36	57	88.6	5.6	N/A
Kadian-Dodov <i>et al.</i>	2016	US registry	all FMD	921	48.1	93.5	2.8	N/A
Krittanawong <i>et al.</i>	2019	NIS database	all FMD	2,420	62.25	86.2	N/A	0.01
Pappacogli <i>et al.</i>	2020	Euro Registry	all FMD	1,022	45.8	81.5	3.2	N/A

FMD: Fibromuscular dysplasia, N/A: Not applicable, SAH: Subarachnoid hemorrhage, ICH: Intracerebral hemorrhage, NIS: National inpatient sample, Euro: The European/international FMD registry

BBB. The pathological findings described above led to the diagnosis of ICH due to microscopic vascular disruption.

CONCLUSION

We encountered a rare case of FMD that caused ICH without angiography cerebral abnormal vessels and showed marked pathological findings in the small vessel wall. It should be considered that FMD can cause ICH due to microscopic obstruction or aneurysmal dilatation caused by vessel wall vulnerability.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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