Intracranial Multiple Berry Aneurysms associated with Fibromuscular Dysplasia and Mixed Connective Tissue Disease

—Case Report—

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Abstract

A rare case of multiple intracranial berry aneurysms associated with fibromuscular dysplasia (FMD) and mixed connective tissue disease (MCTD) is reported together with a review of the literature, particularly that of Japan.

The patient was a 59-year-old woman who had a subarachnoid hemorrhage during the course of MCTD. Angiographically, multiple intracranial aneurysms and "string of beads" were demonstrated in both cervical internal carotid arteries. The three aneurysms of the left internal carotid and middle cerebral arteries were treated surgically, and the remaining aneurysms in the right middle cerebral artery and at the top of the basilar artery were to be treated at a later date. Although the immediate postoperative course was uneventful, 1 month after surgery the patient died suddenly of sepsis with disseminated intravascular coagulation. At autopsy, FMD involving medial fibroplasia with aneurysms was found in the internal carotid and renal arteries. The intracranial aneurysms showed features typical of saccular aneurysms related to the arterial fork. Other than the aneurysms, no changes due to FMD were noted in the cerebral arteries. Although characteristic MCTD lesions were present in the visceral organs, no specific changes due to MCTD were seen in the brain.

Among the 29 patients with cervico-cephalic FMD reported in Japan, 15 had intracranial aneurysms. These included four cases of multiple aneurysms and 11 cases of rupture. No association between FMD and MCTD has been reported in the world literature.

Key words: mixed connective tissue disease, fibromuscular dysplasia, intracranial multiple aneurysms, subarachnoid hemorrhage, cerebral angiography

Introduction

Since the first description of renoarterial fibromuscular dysplasia (FMD) by Leadbetter and Burkland in 1938,²⁶⁾ its clinical importance in renovascular hypertension has been emphasized. Evidence of extra-renal FMD, including that of the cervical internal carotid artery, was reported by Palubinskas and Ripley in 1964.³⁹⁾ A close correlation between cervico-cephalic FMD and intracranial aneurysms has been well established by a large number of studies.^{6,18,30-32,38,46,47)} However, only 28 cases of cervico-cephalic FMD have been recorded in the Japanese literature, including 14 cases associated

with cerebral aneurysms.^{1,13,16,20,23,33-36,50)}

Mixed connective tissue disease (MCTD) is a recently described syndrome that shares various features of systemic lupus erythematosus, polymyositis, and progressive systemic sclerosis.⁴¹⁾ The disease is characterized by a high titer of antibody specific for the ribonuclear protein (RNP) component of extractable nuclear antigen (ENA).⁴²⁾ Although several associated central nervous system disorders have been found, to our knowledge there have been no reports of intracranial aneurysm or subarachnoid hemorrhage in patients having both MCTD and FMD or MCTD alone. In this paper we describe the clinical course and autopsy findings in a 59-year-old woman with bilateral cervical FMD who had a subarachnoid hemorrhage during the course of MCTD.

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Case Report

A 59-year-old woman who had been diagnosed as having MCTD at the age of 47 was referred to our department with a diagnosis of subarachnoid hemorrhage based on lumbar puncture and computed tomography (CT) scan (Fig. 1). Her hypertension had been controlled with an antihypertensive drug.

Raynaud's phenomenon with sclerodactyly, puffiness of the hands and fingers, polyarthralgia, and sicca syndrome was verified. Laboratory studies yielded the following values: ESR, 115 mm/hr; RA test, positive; CRP, 5+; LE test, negative; anti-nuclear factor, positive; anti-DNA test (RIA), 75.5 units/ml; ENA antibody titer, 1:81,920 (RNP+); and test for antibody to the ribonuclease-resistant component of ENA, negative.

On admission to our department on December 10, 1984, the patient exhibited interstitial pneumonitis, pulmonary edema, cardiomegaly, congestive heart failure, mild disturbance of consciousness, and nuchal rigidity. Her four-vessel cerebral angiograms demonstrated multiple intracranial aneurysms and "string of beads" within the bilateral cervical internal carotid arteries (Fig. 2A). The aneurysms were located at the junction of the left internal carotid and posterior communicating arteries, at the bifurcation

Fig. 1 Precontrast CT scan shows high-density areas of subarachnoid hemorrhage in the subarachnoid space and basal cisterns. No ventricular shift and dilatation are noted.

of the left internal carotid artery, at the trifurcations of both middle cerebral arteries (M_1 and M_2 portion) (Figs. 2B and 3), and at the top of the basilar artery (Fig. 4). There was no evidence of hydrocephalus or infarction on the CT scan. After waiting for nearly 1 month for her condition to improve, on February 7, 1985, through a left osteoplastic craniotomy, we clipped the left internal carotid bifur-

Fig. 2 Anteroposterior views of right internal carotid angiograms. A: A "string of beads" appearance is evident at the right cervical internal carotid artery (arrows). B: A berry aneurysm is visible at the trifurcation of the right middle cerebral artery (arrow).

Fig. 3 Anteroposterior (A) and lateral (B) views of left internal carotid angiograms show a large berry aneurysm at the bifurcation of the left internal carotid artery (*arrowhead*), a medium-sized berry aneurysm at the trifurcation of the left middle cerebral artery (*double arrow*), and a small aneurysm at the junction of the left internal carotid and the posterior communicating arteries (*arrow*).

Fig. 4 Anteroposterior view of left vertebral angiogram. A berry aneurysm is seen at the top of the basilar artery (*arrow*).

cation and left middle cerebral aneurysms and wrapped the left internal carotid and posterior communicating aneurysm. The aneurysm of the left inter-

nal carotid bifurcation was thought to have been responsible for the subarachnoid hemorrhage. Postoperatively, her course was uneventful and we hoped to eventually clip the untreated aneurysms. However, on February 24, 1985, 17 days after the initial operation, the patient died suddenly of sepsis with disseminated intravascular coagulation. An autopsy was performed.

Autopsy: The brain weighed 1,190 g. There was mild hemosiderosis around the surgically treated aneurysms. In addition, there were untreated berry aneurysms, the largest of which was located at the bifurcation of the right middle cerebral artery (M_1 – M_2 portion). It was dumbbell-shaped and was composed of nodules $8 \times 5 \times 4$ mm and $4 \times 4 \times 4$ mm in size. The aneurysm at the top of the basilar artery was $2 \times 2 \times 4$ mm in size. Another aneurysm, 2 mm in diameter, was noted at the right M_2 – M_3 portion; this aneurysm had not been detected by angiography. Histologically, all aneurysms showed features typical of saccular aneurysms related to the arterial fork. The tunica media was attenuated and merged with the fibromuscular tissue of the aneurysmal wall. The internal elastic lamina was lost at the neck of the aneurysm (Fig. 5A). Focal mural necrosis with mild hemosiderosis was noted in the wall of the aneurysm at the top of the basilar artery. Extensive calcium deposition was observed in the vascular walls of the globus pallidus. Other intracranial arteries were normal except for mild atherosclerosis.

Fig. 5 A: A saccular aneurysm at the right M₂-M₃ portion. The internal elastic lamina is lost at its neck and no media is seen in most of the aneurysmal wall. Elastica van Gieson stain, $\times 25$. B: Longitudinal section of the left internal carotid artery showing typical features of FMD. Fibromuscular ridges alternating with areas of mural thinning are visible. The internal elastic lamina is interrupted and absent at the foci of mural thinning. Mallory's azan stain, $\times 40$.

In the bilateral cervical internal carotid arteries, fibromuscular ridges alternating with areas of mural thinning were evident in the longitudinal sections (Fig. 5B). The internal elastic lamina was discontinuous and disappeared in the areas of mural thinning. These histological findings are those of FMD of the type involving medial fibroplasia and aneurysm. The same histological features, although to a milder degree, were found in both renal arteries and in the external iliac and lienal arteries.

Pathological changes of MCTD were present in various organs. There were many central nuclei and irregularities of fiber size in the skeletal muscles. Marked round cell infiltration was noted in the salivary glands. Onion skin-like lesions were seen in the spleen. Diffuse mural fibrosis of the alimentary tract, especially of the lower esophagus, was identified. Subpleural fibrosis with honeycombing was revealed in the lungs and was associated with fibrous

intimal lesions of the arteries; it was not observed outside the fibrotic lesions, in the kidneys, or in other organs.

Discussion

FMD is a segmental, non-atheromatous abnormality of intermediate-sized arteries. The etiology of FMD has been ascribed to microtrauma due to stretching of arteries,²⁷⁾ mural ischemia caused by thrombotic or mechanical obliteration of the vasa vasorum,⁴⁰⁾ hormonal, metabolic, and immunologic factors,^{15,22)} ergotamine medication,⁸⁾ unknown connective tissue disorder,⁴⁰⁾ and hereditary vascular disease.³¹⁾

A histopathological classification of FMD was developed based on the renal arterial layer — intimal, medial, or adventitial — in which the lesions predominate.¹⁴⁾ The most frequently observed pattern is that of medial FMD. Medial lesions are classified into four subgroups according to the predominant histopathological features: (a) medial fibroplasia with mural aneurysm, showing multistenosis due to thickened fibromuscular ridges alternating with areas of marked mural thinning (aneurysm) and producing "string of beads" arteriograms; (b) medial hyperplasia; (c) perimedial fibroplasia; and (d) medial dissection. The lesions of the internal carotid artery in our patient corresponded to medial fibroplasia with aneurysm.

FMD of the internal carotid artery, angiographically characterized by "string of beads," was first described by Connett and Lansche,⁵⁾ and then by others. The angiographic incidence of cervico-cephalic FMD was less than 1% in several series of cerebral angiograms: less than 0.32% in that of Houser and Baker,¹⁸⁾ 0.6% in that of Corrin *et al.*,⁶⁾ 0.53% in that of So *et al.*,⁴⁶⁾ and 0.9% in that of Mettinger and Ericson.³¹⁾

Of clinical importance is the association between intracranial berry aneurysms and FMD. Aneurysms were found in 19 of 37 patients (51%) in Mettinger and Ericson's series³¹⁾ and in 27 of 70 patients (39%) in that of Manelfe *et al.*²⁷⁾ Frens *et al.*⁹⁾ reported 23 intracranial aneurysms diagnosed angiographically in 109 reported cases of FMD of the cervical arteries.

In the literature limited to Japanese patients, only 29 patients with cervico-cephalic FMD have been reported^{1,12,13,16,19-21,23,33-36,43,44,49,50,52)} (including our patient) (Table 1), of whom 19 (66%) were female. The female-to-male ratio is similar to that reported in the Western literature.³⁰⁾ The females' ages ranged from 20 to 67 years (average, 49.3 years) and the males' ages from 20 to 72 years (average, 45.3 years). Of 24 patients with the description of blood pressure, six

(25%) had arterial hypertension, three of whom with pathological changes (dilatation, "string of beads," stenosis) on renal angiograms. Eighteen (75%) were normotensive, four of whom with pathological changes ("string of beads," stenosis) on renal angiograms. Five of the 29 patients had transient ischemic attack and five had cerebral infarction. Ten of 15 patients (67%) with bilateral cervical or vertebral FMD had a marked tendency to develop intracranial aneurysms. Of the nine patients having bilateral cervical FMD with intracranial aneurysms, three had multiple aneurysms. FMD of the internal carotid artery was accompanied by aneurysms in the anterior half of Willis's ring, whereas FMD of the vertebral artery was associated with aneurysms in the posterior half of the ring.¹⁶⁾ Fifteen (52%) had intracranial cerebral aneurysms; these ruptured in 11 patients and included multiple aneurysms in four. In three cases these aneurysms were located on the

anterior communicating artery³³⁻³⁵⁾ and, in one case each, on the internal carotid artery,²³⁾ on the middle cerebral artery,²⁰⁾ the anterior cerebral artery,¹³⁾ the junction of the internal carotid and posterior communicating arteries,⁵⁰⁾ the true posterior communicating artery,¹⁶⁾ the junction of the vertebro-posterior inferior cerebellar artery,¹⁾ the posterior cerebral artery,³⁴⁾ and the basilar artery³⁶⁾ (Table 1). In three of four cases of multiple intracranial aneurysms, angiograms demonstrated the characteristic "string of beads" appearance in the bilateral cervical internal carotid artery. The multiple aneurysms were distributed on the anterior cerebral artery in the first case,³³⁾ on the right ophthalmic artery and junction of the internal carotid and posterior communicating arteries in the second,³³⁾ on the left anterior cerebral, middle cerebral, and basilar arteries in the third,³⁶⁾ and on the left internal carotid bifurcation, the junction of the left internal carotid and

Table 1 Summary of 29 cases of cervico-cephalic FMD in Japanese patients

Author (Year)	Age & sex	Location of FMD	Angiographic "string of beads" appearance	Intracranial aneurysm (*ruptured)	Renal angiography	Hypertension	Autopsy or FMD histology
Handa <i>et al.</i> (1970) ¹³⁾	50M	bil. ICA	+	*rt. ACA	dilatation	+	
Hamaguchi <i>et al.</i> (1976) ¹²⁾	43F	lt. ICA	irregular stenosis	TIA	"string of beads"		histology
Tsumuraya <i>et al.</i> (1978) ⁵⁰⁾	54M	lt. ICA	+	*rt. IC-PcomA		—	
Shindo <i>et al.</i> (1978) ¹⁴⁾	52F	bil. ICA	+	acoustic neurinoma			
Abdul-Rahman <i>et al.</i> (1978) ¹⁾	72M	rt. ICA	irregularity	*lt. VA-PICA		—	autopsy, histology
Ishii <i>et al.</i> (1979) ²¹⁾	47F	rt. CCA	+	infarction			
Shimojo <i>et al.</i> (1979) ⁴³⁾	68M	rt. ICA	+	TIA			histology
Nishimoto and Onbe (1979) ³³⁾	43F	bil. ICA	+	multiple: ACA	"string of beads"	—	
"	57F	bil. ICA	+	TIA		—	
"	66F	lt. ICA	+	*AcomA	normal	—	
"	45F	bil. ICA	+	multiple: rt. OphA, rt. IC-PcomA	single stenosis	—	
"	43F	rt. ICA	+	seizure	"string of beads"	—	
Yamamoto <i>et al.</i> (1979) ⁵²⁾	33M	lt. ICA	+	infarction		—	
Teraura <i>et al.</i> (1979) ⁴⁹⁾	20F	multiple constrictions and dilatations in intracranial arteries		seizure, rubella infection	"string of beads"	—	histology (STA)
Kobayashi <i>et al.</i> (1980) ²³⁾	20M	rt. ICA (including carotid siphon)	+	*rt. ICA (fusiform)	normal	—	

Contd.

posterior communicating arteries, the bilateral middle cerebral arteries, and the basilar artery in the fourth (our patient).

In contrast to Mettinger and Ericson's report,³¹⁾ the intracranial aneurysms described in the Japanese literature were not most often found on the same side as the most affected extracranial carotid artery. Among Japanese FMD patients, only one-fourth had hypertension and no cerebral hemorrhage (apart from aneurysmal rupture) was reported. Further, only five of 15 patients with intracranial aneurysms had hypertension. Mettinger and Ericson³¹⁾ did not consider intracranial aneurysms to be a secondary effect of hypertension, as Stehbens⁴⁸⁾ described, because only nine of their 19 patients with aneurysms were hypertensive.

Although central nervous system involvement is extremely rare in MCTD, some neurological abnormalities have been reported: psychosis, aseptic men-

ingitis, convulsion, and cerebellar ataxia.^{2,3)} There have been no reports of MCTD associated with subarachnoid hemorrhage or intracranial aneurysms. Subarachnoid hemorrhage has occasionally been reported in patients with systemic lupus erythematosus, but it has not been determined whether the hemorrhage had been caused by ruptured aneurysms.^{4,11,29,37)} No reports are available concerning MCTD associated with FMD or vice versa.

Histologically, the blood vessel walls in MCTD demonstrate various changes. In the branches of the pulmonary arteries^{7,28)} and in the renal interlobular arteries,²⁵⁾ the walls are markedly narrowed by intimal proliferation. Proliferative intimal lesions in medium- to large-sized arteries have also been reported.⁴⁵⁾ Postmortem histological examinations of MCTD patients have uncovered no remarkable changes in the brain or its vessels.^{24,28)} This was also true in our case.

Table 1, page 2

Author (Year)	Age & sex	Location of FMD	Angiographic "string of beads" appearance	Intracranial aneurysm (*ruptured)	Renal angiography	Hypertension	Autopsy or FMD histology
Nishimoto <i>et al.</i> (1981) ³⁴⁾	37F	bil. ICA	+	TIA	normal	+	
"	41F	rt. ICA	+	infarction		—	
"	49F	bil. ICA	+	*AcomA		—	
"	50F	bil. ICA, lt. VA	+	*rt. PCA	not done	+	
"	64F	rt. ICA	+	infarction	not done	—	
Ikari <i>et al.</i> (1981) ¹⁹⁾	20M	rt. ICA	+	infarction			
Nishimoto <i>et al.</i> (1982) ³⁵⁾	65F	bil. VA	+	TIA		—	
"	67F	bil. ICA	+	facial spasm		—	
"	72M	bil. ICA	+	*AcomA		—	
Ohuchi <i>et al.</i> (1984) ³⁶⁾	34F	rt. ICA	—	multiple (SAH+): lt. ACA (1), lt. MCA (2), BA (4)	"string of beads"	+	autopsy, histology
"	30M	bil. ICA	complete occlusion	BA	stenosis	+	
Hasue and Miwa (1985) ¹⁶⁾	34M	bil. VA	+	*true PcomA		—	histology (OA)
Imaya <i>et al.</i> (1985) ²⁰⁾	54F	bil. ICA, bil. VA	+	rt. MCA	normal	—	
Present case	59F	bil. ICA	+	multiple: *lt. IC bifurcation, lt. IC-PcomA, bil. MCA, BA	not done	+	autopsy, histology

ICA: internal carotid artery, CCA: common carotid artery, VA: vertebral artery, ACA: anterior cerebral artery, PcomA: posterior communicating artery, PICA: posterior inferior cerebellar artery, AcomA: anterior communicating artery, OphA: ophthalmic artery, PCA: posterior cerebral artery, MCA: middle cerebral artery, BA: basilar artery, STA: superficial temporal artery, OA: occipital artery, TIA: transient ischemic attack, SAH: subarachnoid hemorrhage. The blank columns indicate that there was no mention of the matter in the published report.

The location of aneurysms and absence of hypertension in many patients with FMD suggests that the aneurysms are manifestations of the morphological process of FMD itself rather than secondary effects of hypertension.³⁰⁾ Some reported autopsy cases have provided evidence of histopathological changes of FMD in intracranial aneurysms and adjacent cerebral arteries.^{1,17,51)} The postmortem examination of our patient showed no pathological changes, including those of MCTD and/or FMD, in the cerebral arterial walls outside of the aneurysms.

Both intracranial aneurysms and FMD of the medial fibroplastic type are characterized by degeneration or focal absence of the tunica media and disruption and loss of the internal elastic membrane.⁵²⁾ The weak points in the walls of predisposed cerebral arteries are considered responsible for the development of intracranial aneurysms even in the absence of a diseased renal artery or hypertension.¹⁰⁾ Abdul-Rahman *et al.*¹⁾ observed a 50-year-old woman in whom an intracranial aneurysm and cervical internal carotid FMD lesion developed that had not been revealed on the first angiogram 8 years previously. Cervical FMD is a dynamic and progressive disease in some cases.⁵²⁾ Undetected connective tissue disorders are probably responsible for the development of arterial lesions in fibromuscular dysplasia.⁴⁰⁾

The histological similarities between intracranial aneurysms and other types of aneurysms in patients with FMD, the frequency of intracranial aneurysms in patients with extracranial FMD, and the similar worldwide sex and age incidences suggest a common etiology.⁵¹⁾

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