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A 66-year-old woman was admitted to our hospital with acute inferior myocardial infarction. She had a history of hypertension, hyperlipidemia, and surgical replacement of the descending aortic aneurysm with a prosthetic graft at 59 years of age. Emergent coronary angiography showed 90% stenosis in the middle right coronary artery. The lesion was successfully dilated with the deployment of a bare metal stent.

Physical examination revealed an absence of pulsation of the left popliteal artery and a slight swelling above the left popliteal fossa without pulsation and tenderness. The ankle-brachial pressure indexes of her right and left extremities were 1.08 and 0.58, respectively. Regardless of our careful history taking, she had no history of claudication, traumas, surgery, or acupuncture around the left knee joint. A computed tomography revealed a huge mass (65×70×50 mm) above the left knee joint (Figure 1A) and ruled out adjacent osteochondroma. Her left popliteal artery was obstructed just behind the mass (Figure 1B). Abundant collateral arteries were observed running around the mass and connecting into the distal part of popliteal artery. The mass had 2 high-density enhanced areas surrounded by an outer low-density area without enhancement (Figure 1C and 1D).

An aneurysmectomy was performed (Figure 2A), and the left popliteal artery was repaired with a 7-mm-diameter Dacron graft. A resected specimen had 2 internal solid thrombi surrounded by extensive thick blood with capsule (Figure 2B). The arterial perforation communicating with the aneurysmal sac was covered by the thrombus. Histologically, the wall of aneurysm lost elastic tissues in the media that were replaced by collagen fibers, indicating a pseudoaneurysm (Figure 2C). Rich capillary channels were observed in an old mural thrombus inside the aneurysm (Figure 2D).

A pseudoaneurysm of the popliteal artery is rare and mostly reported in association with penetrating trauma, adjacent osteochondroma, or iatrogenic complications such as total knee arthroplasty, arthroscopic meniscectomy, and acupuncture.[1–3] In this case, none of the conceivable reasons listed above applied. However, spontaneous dissection of the arterial wall of patients with arteriosclerosis could be an initial trigger leading to repeated bleeding from the membranous capsule into the closed sac. Consequently, such a giant pulseless aneurysm may be formed with internal thrombus. To the best of our knowledge, this is the largest case of an asymptomatic popliteal pseudoaneurysm reported to date.

Disclosures

None.

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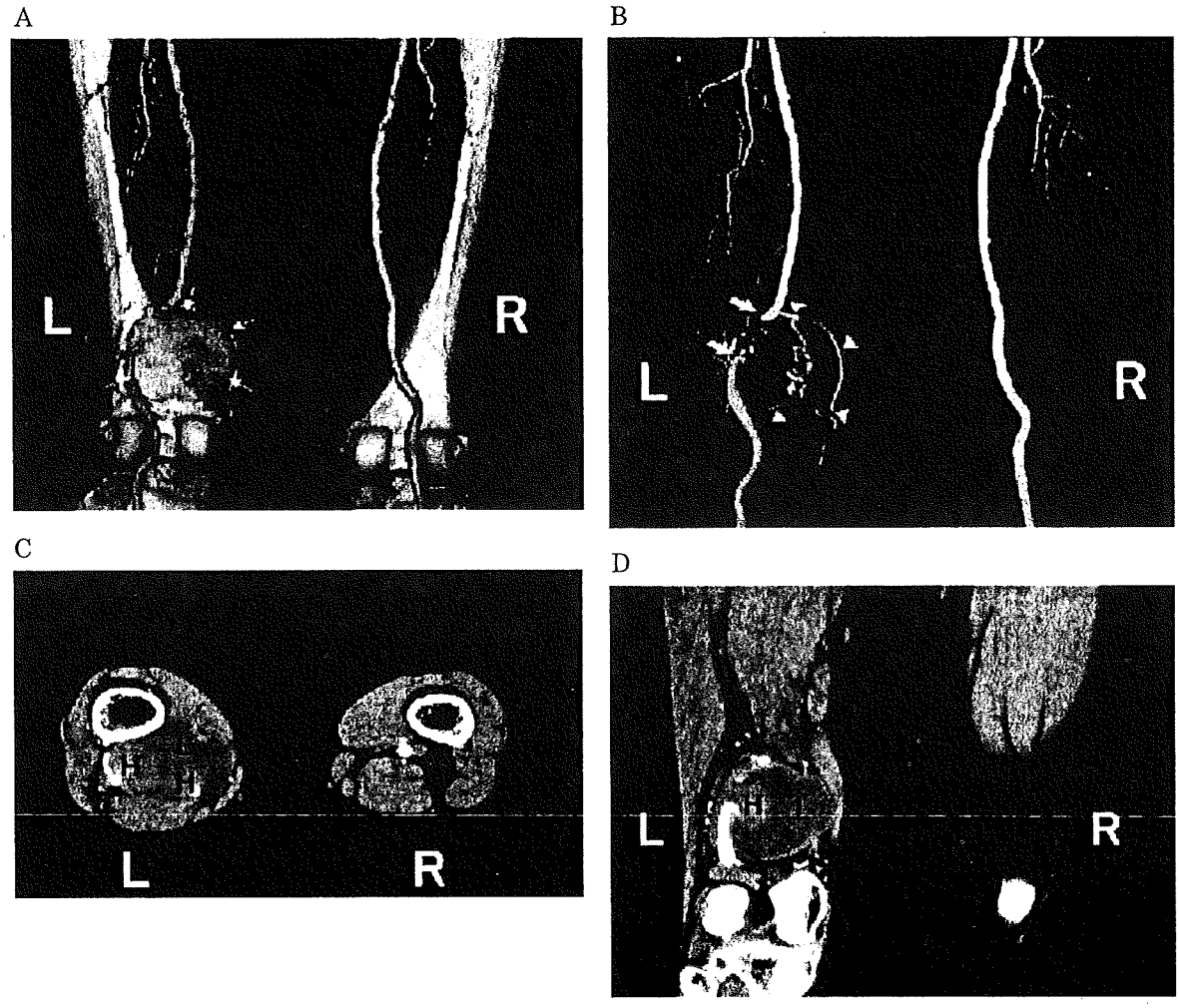

Figure 1. Three-dimensional reconstruction image of an enhanced computed tomographic scan of lower limbs revealed huge 65×70×50-mm mass above the left knee joint (A; thin white arrow). Computed tomographic angiogram showed an obstruction of the left popliteal artery just behind the mass (B; thick white arrow). Abundant collateral arteries were observed running around the mass and connecting into the distal part of popliteal artery (B; arrowheads). A horizontal section (C) and oblique vertical section (D) of the mass revealed 2 internal high-density enhanced areas (H) surrounded by an outer low-density area (L) with capsule.

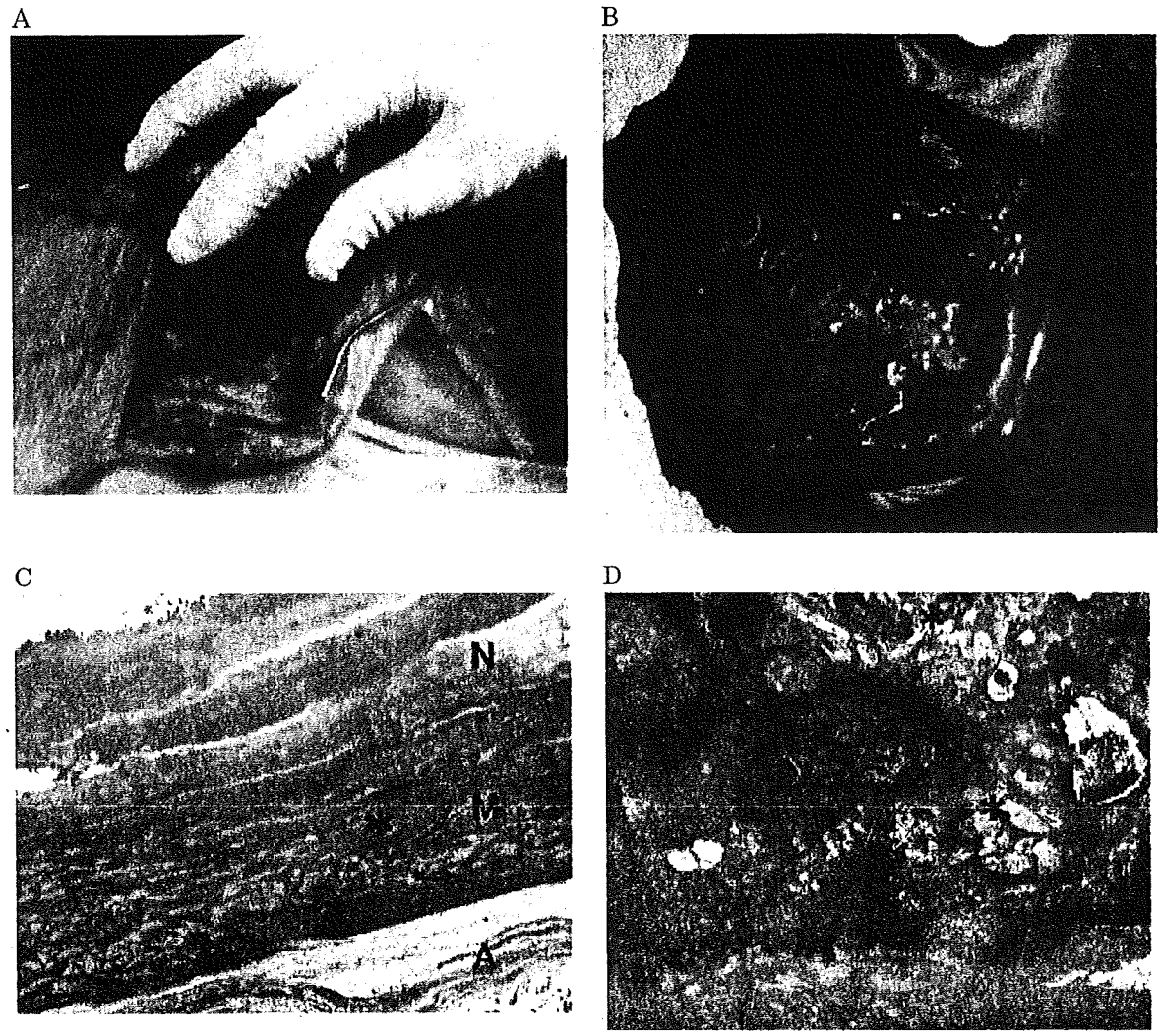

Figure 2. The mass had 2 internal solid thrombi (T) surrounded by extensive thick blood with capsule (A, B). Histopathological examination showed the disappearance of elastic fibers in the tunica media replaced by collagen fibers (asterisk) in the wall of aneurysm (C; Masson's trichrome stain; magnification ×12.5) and rich capillary channels (asterisk) in an old mural thrombus (D; elastica van Gieson stain; magnification ×12.5). N indicates neointima; M, media; and A, adventitia.

A Case of Acute Type B Aortic Dissection: Limited Role of Laboratory Testing for the Diagnosis of Mesenteric Ischemia

Koichi Akutsu, MD, Hitoshi Matsuda, MD, Hiroaki Sasaki, MD,
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Yuiichi Tamori, MD, Naoyuki Yokoyama, MD, Hiroshi Nonogi, MD, and
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Case Report

A Case of Acute Type B Aortic Dissection: Limited Role of Laboratory Testing for the Diagnosis of Mesenteric Ischemia

Koichi Akutsu, MD,[1] Hitoshi Matsuda, MD,[2] Hiroaki Sasaki, MD,[2] Kenji Minatoya, MD,[2] Hitoshi Ogino, MD,[2] Satoshi Kasai, MD,[1] Yuiichi Tamori, MD,[1] Naoyuki Yokoyama, MD,[1] Hiroshi Nonogi, MD,[1] and Satoshi Takeshita, MD[1]

A 30-year-old man with severe back and abdominal pain was referred to our hospital because of a recurrence of acute type B aortic dissection. A computed tomography scan showed a 3-channel dissection and a severe narrowing of the true lumen of the descending aorta to the abdominal aorta because of the expansion of the newly formed second false lumen. Although laboratory testing, including creatine phosphokinase, lactate dehydrogenase, and lactate levels, indicated no visceral ischemia, abdominal pain requiring narcotics treatment had to be continued for more than 1 week. Based on the symptoms and computed tomography findings, the patient finally underwent aortic replacement, fenestration, and a reconstruction of the inferior mesenteric artery, after which the abdominal pain disappeared. Operative findings confirmed a pale shrunken intestine, indicative of mesenteric ischemia. The present case is a good demonstration revealing that mesenteric ischemia still remains a diagnostic challenge, and suggests that currently available laboratory markers are not sensitive enough to detect the presence of ischemia. A strong clinical suspicion for mesenteric ischemia may be the only key to preventing a catastrophic outcome in this condition. (Ann Thorac Cardiovasc Surg 2007; 13: 360–364)

Key words: acute aortic dissection, mesenteric ischemia, mesenteric necrosis, surgical repair

Introduction

Acute aortic dissection (AAD) is a lethal condition affecting the aorta. Without appropriate treatment, approximately 75% of patients with AAD die within 2 weeks of the disease onset.[1)] The principal cause of early death, particularly in patients with proximal dissection, is aortic rupture. However, dissection also involves the branches of the aorta and could obstruct the branch ostia. When malperfusion affects the central nervous system or abdominal viscera, the mortality rate increases dramatically. The reported mortality rates of patients presenting with mesenteric ischemia are 45%–87%.[2–4)] According to the International Registry of Acute Aortic Dissection (IRAD) data, 15% of all the deaths of patients with type B dissection were related to mesenteric ischemia.[5)] Although surgical therapy is required for patients with visceral ischemia, the repair is often delayed, and organ necrosis may develop. This is mainly because mesenteric ischemia is extremely difficult to diagnose before necrosis develops. Herein we describe the case of an AAD presenting with mesenteric ischemia in which repetitive laboratory testing failed to indicate it.

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Case Report

A 30-year-old man was referred to our hospital for acute type B aortic dissection. He had no family history of aor-

Table 1. Clinical course

		Arrival ↓								Surgery ↓	
Days after onset	0	1	2	3	4	5	6	7	8	9	10
Dose of pentazocine (mg)				15	15	15		30	30	30	
Computed tomography scan	∇	∇								∇	
Intestinal gas on abdominal X-ray		–	–	–	–	–	–	–	–	–	
Occult blood in stool		+						–			
Blood tests:											
D-dimer (normal: <1.0 μg/mL)		16.0	12.5		10.8				6.2		
CRP (normal: <0.3 mg/dL)		1.3	1.7		13.9				14.9		
Lactate (normal: <17 mg/dL)		25	12		8		14		12		
Base excess (normal: –3.0 – +3.0 mmol/L)		–3.4	0.7	0.1	0.4	1.3	0.2	2.5	2.7	2.7	
CPK (normal: 62–287 IU/L)		84	73		74		72		43	40	

∇, performed computed tomography scan; +, present; –, absent. CRP, C-reactive protein; CPK, creatine phosphokinase.

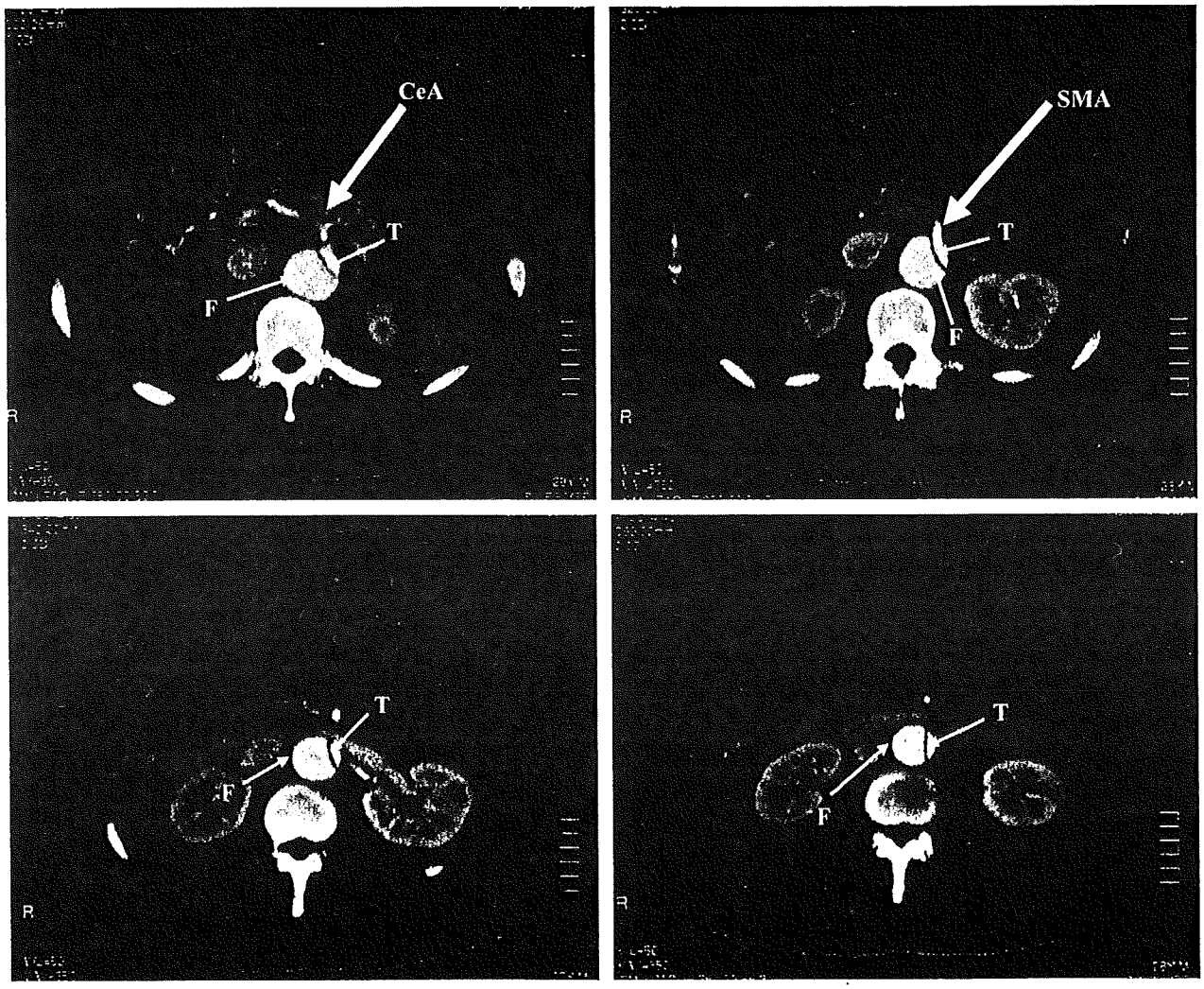

Fig. 1. A computed tomography (CT) scan obtained 12 months after the first occurrence of aortic dissection shows a true lumen (T) compressed by false lumen extending from the distal arch to the right common iliac artery. The celiac arteries (CeA), the superior mesenteric arteries (SMA), and the left renal arteries originate from the true lumen, whereas the right renal artery originates from the false lumen.

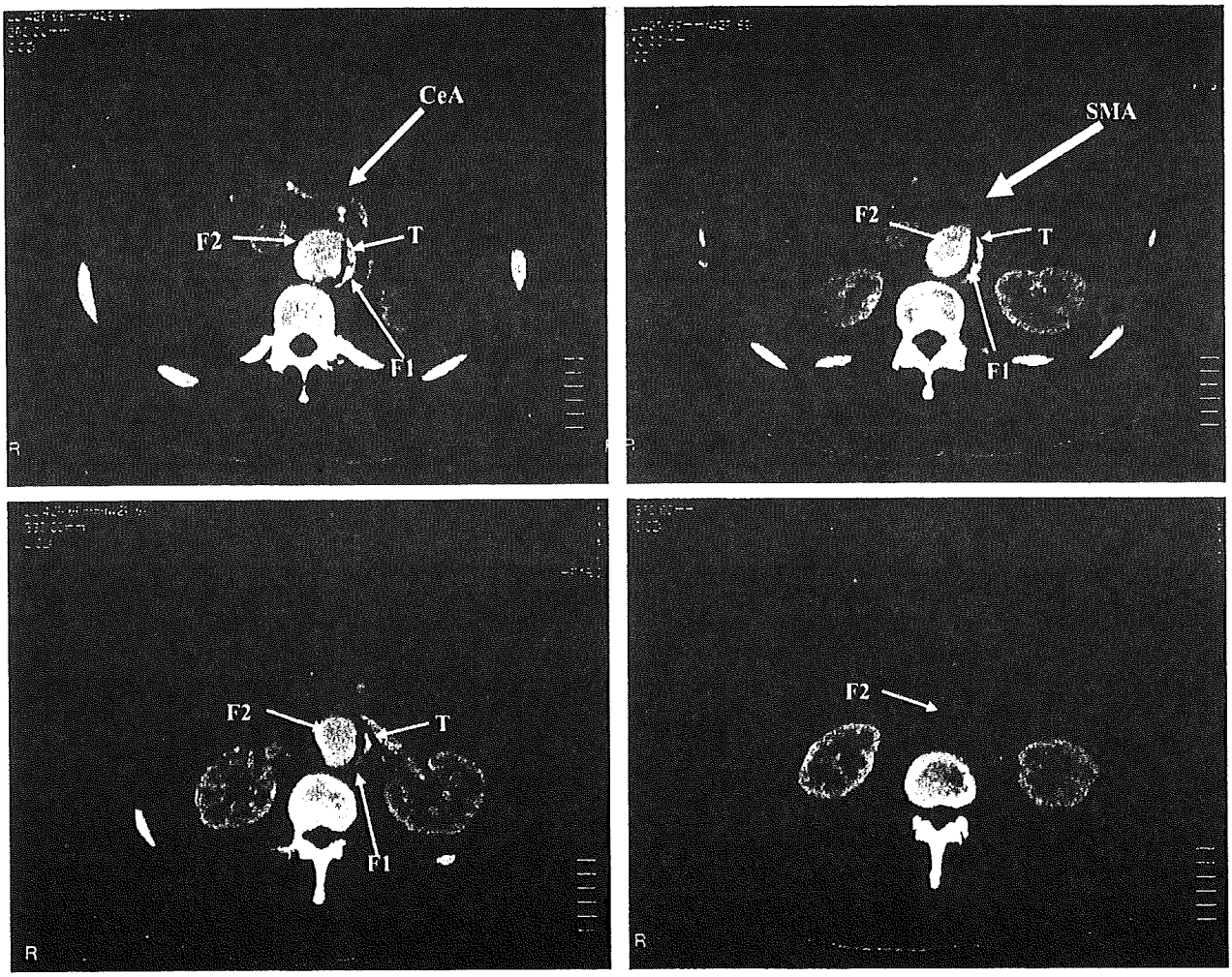

Fig. 2. A computed tomography (CT) scan obtained upon arrival (2 years after the first occurrence of aortic dissection) shows a 3-channel dissection. A newly formed false lumen (second false lumen: F2) is seen anterior to the true lumen (T). The first false lumen (F1), which developed at the time of the first occurrence of aortic dissection, is difficult to identify because of the compression by the second false lumen. The true lumen, from which the celiac and the superior mesenteric arteries arise, is also compressed by the second false lumen.

tic disease and did not meet the diagnostic criteria for Marfan syndrome. He had a history of hypertension and hyperlipidemia.

The patient first had acute type B aortic dissection 2 years earlier. A computed tomography (CT) scan at the time of the first occurrence of aortic dissection revealed an enlarged false aortic lumen, originating from the proximal descending thoracic aorta and extending to the right common iliac artery. The false aortic lumen had compressed the true lumen, from which the celiac, the superior mesenteric, and the left renal arteries originated. The right renal artery arose from the false lumen (Fig. 1).

At this second occurrence of aortic dissection, the patient suffered a severe tearing pain that migrated from his chest to his back and then to his abdomen. The next day he was referred to our hospital. Physical examination upon arrival revealed blood pressure of 182/78 mmHg and abdominal tenderness around the navel. The pulsation in the lower limbs was decreased, which soon resolved on the day of admission.

A CT scan obtained upon arrival revealed a 3-channel dissection (Fig. 2). The newly formed false lumen (second false lumen, F2), originating from the level of tracheal bifurcation and extending down to the right common iliac artery, was completely thrombosed below the level of the renal arteries. Above this level, the expanded second false lumen severely compressed the true lumen (T), from which the celiac and superior mesenteric arter-

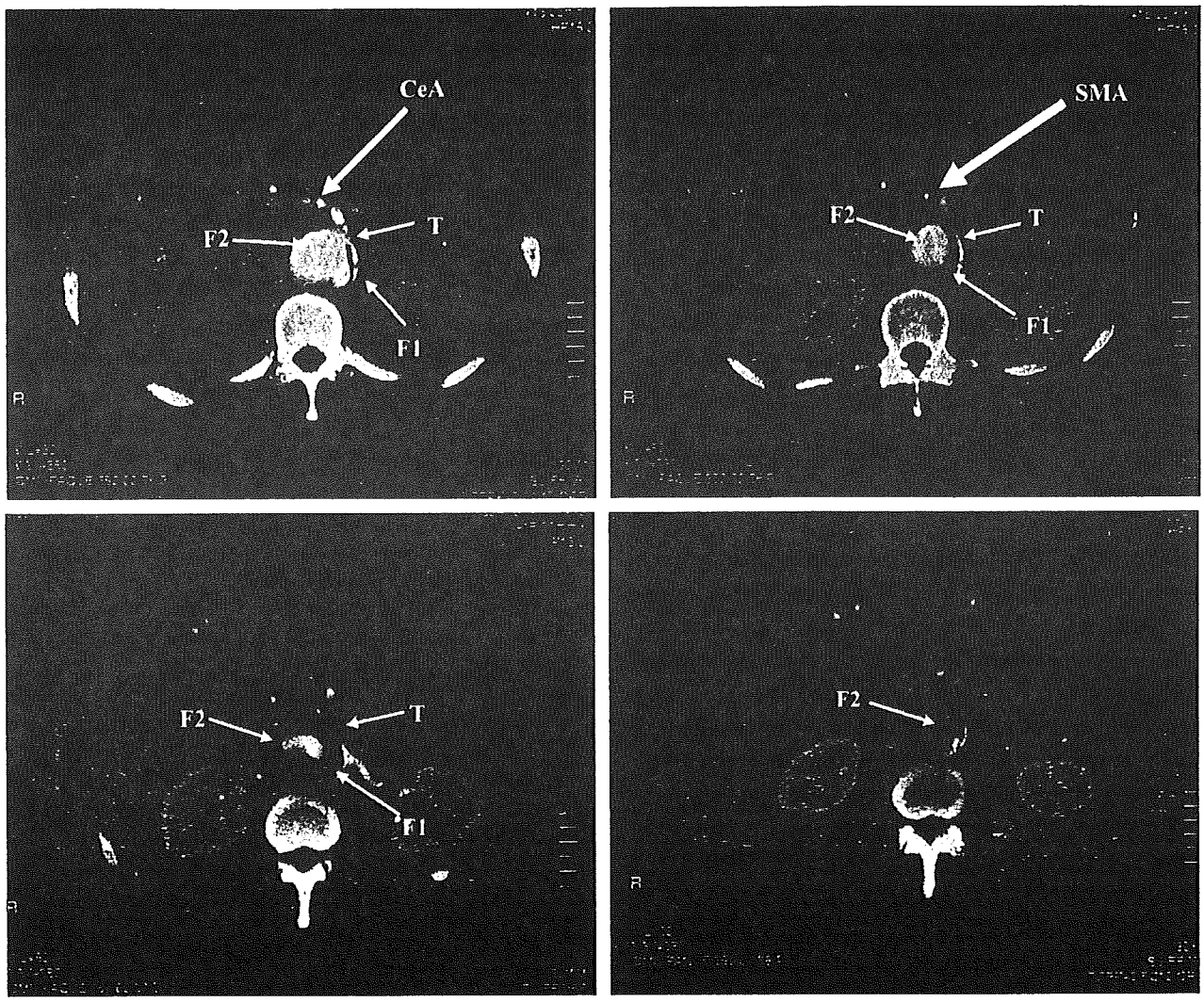

Fig. 3. A CT scan obtained 9 days after the onset of symptoms shows that the second false lumen (F2) is further expanded and that thrombosis has developed in it. The true lumen (T) is more severely compressed.

ies arose. The first false lumen (F1) that had developed with the first occurrence of aortic dissection was also severely compressed by the second false lumen and was difficult to identify. At the time of his arrival, despite these CT findings suggestive of severely disturbed abdominal flow, laboratory results, including creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels, stayed within the normal limits. Slight acidemia (pH 7.38; base excess –3.2) and a slightly elevated lactate level (25 mg/dL; normal range: <17 mg/dL) that were observed upon arrival resolved soon after the admission (Table 1). With the administration of a β-blocking agent and a calcium channel blocker, the patient's systolic blood pressure decreased to 100–120 mmHg, and his pain was alleviated. However, severe abdominal pain recurred on the second day and continued for more than 1 week. The patient required 15–30 mg of pentazocine per day for pain relief. Laboratory tests were performed repeatedly but showed no sings of mesenteric ischemia/necrosis. Abdominal X-ray examination was also performed repeatedly, but showed no intestinal gas or niveau formation, which would have been indicative of ischemic colitis. Although occult blood was detected once in his stool, another test was negative.

Nine days after the onset of symptoms, a follow-up CT scan was performed (Fig. 3). The second false lumen (F2) had expanded further, and as a result the true lumen (T) had become more severely compressed. Although during the admission, no definitive signs of mesenteric ischemia had been observed by laboratory testing, surgical repair was undertaken on the next day based on a strong clinical

suspicion.

A pale shrunken intestine was found during the surgery, indicative of mesenteric ischemia. The aorta was opened just below the renal arteries, and the thrombi inside the false lumens were removed. Two flaps were widely resected, and proximal anastomosis was performed with a knitted Dacron graft (GelsoftPlus, Vascutek, UK). Bilateral distal anastomoses were performed on the common iliac arteries, and the inferior mesenteric artery was attached to the left limb of the graft. The surgical repair alleviated the patient's abdominal pain. He started taking meals on postoperative day 12 and was discharged on postoperative day 27.

Discussion

Previous studies have indicated that medical therapy provides an excellent outcome for patients with uncomplicated distal dissection of the aorta. The 30-day survival rate for patients with distal dissection treated medically is as high as 92%.[5] Therefore medical therapy is preferred to surgical therapy for patients with uncomplicated distal dissection. However, the outcome of medical therapy may be poor when distal dissection is complicated by abdominal visceral ischemia, uncontrolled pain, and rapid expansion of the dissected aorta. Mesenteric ischemia and necrosis, for example, are potentially lethal complications of distal dissection seen in 3%–5% of cases.[2,3,6,7] The operative mortality rates for patients with mesenteric ischemia or necrosis are 45%–87%.[2-4] Despite successful visceral vascular reconstruction, death often results from the sequela of mesenteric necrosis.[2] In fact, mesenteric ischemia is also recognized as an independent risk factor for surgical death.[8] Thus it is strongly recommended that when patients with distal dissection are treated medically, they should be carefully monitored for any evidence of branch arterial malperfusion, particularly mesenteric ischemia. The clinical features of mesenteric ischemia, however, may be subtle and therefore can go unrecognized.

Laboratory testing, including the measurement of CPK[9] and lactate[10,11] levels, has been reported as a good diagnostic tool for mesenteric ischemia. When CPK and lactate levels are elevated, however, small intestine or colon necrosis may be in progress. By the time mesenteric ischemia is clinically obvious, irreversible organ damage may have already occurred. Thus it appears that these markers could be markers of necrosis rather than ischemia.

In this patient, lasting abdominal pain requiring analgesics and narrowing the true lumen on CT scan were clinical signs suggesting mesenteric ischemia. However, through the entire clinical course, repetitive laboratory testing showed no abnormalities. In this regard, the present case is a good demonstration that mesenteric ischemia still remains a diagnostic challenge and suggests that currently available laboratory markers are not sensitive enough to detect the presence of ischemia. Physicians cannot rely heavily on these markers; a strong clinical suspicion for mesenteric ischemia may be the only key to preventing a catastrophic outcome in this condition.

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Phenotypic Heterogeneity of Marfan-Like Connective Tissue Disorders Associated With Mutations in the Transforming Growth Factor-β Receptor Genes

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Phenotypic Heterogeneity of Marfan-Like Connective Tissue Disorders Associated With Mutations in the Transforming Growth Factor-β Receptor Genes

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Background Mutations in the genes for transforming growth factor-β receptor (TGFBR) have been identified in patients with Marfan syndrome (MFS) and Marfan-like connective tissue disorders. There are several syndromes associated with mutations in TGFBR genes, including Loeys-Dietz syndrome (LDS), MFS2, Furlong syndrome, and Shprintzen-Goldberg syndrome. However, with the exception of the first report by Loeys et al, the phenotypic features of patients with TGFBR gene mutations have not been precisely reported.

Methods and Results A total of 18 patients suspected of having MFS were recruited and 7 were diagnosed with MFS and mutations in *FBN1*. Among the remaining 11 patients, 1 patient had mutations in *TGFBR1*, 2 had mutations in *TGFBR2*, and 1 had mutations in *COL3A1*. The clinical manifestations of the 3 patients with TGFBR gene mutations were examined according to the list of 36 clinical features described in the first report by Loeys et al. The clinical manifestations of these 3 patients differed from those previously observed in patients with MFS2, Furlong syndrome, and Shprintzen-Goldberg syndrome. Thus, the most probable diagnosis of these 3 patients was LDS, despite the fact that they presented with only a fraction of the 36 clinical features associated with LDS.

Conclusions Although the number of the patients was limited, the findings support the notion that mutations in the TGFBR gene may be associated with greater phenotypic heterogeneity than previously reported. (*Circ J* 2007; **71:** 1305–1309)

Key Words: Loeys-Dietz syndrome; Marfan-like connective tissue disorder; Marfan syndrome; Transforming growth factor-β receptor genes

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder associated with acute aortic dissection (AAD) and annulo-aortic ectasia (AAE). The diagnosis of MFS depends on manifestations in multiple organ systems, primarily the skeletal, ocular, and cardiovascular systems, and on family history. However, many patients with young-onset AAD or AAE fail to meet the diagnostic criteria for MFS and are not characterized by a mutation of the fibrillin-1 gene (*FBN1*). These cases have therefore been classified as Marfan-like connective tissue disorders.

Recently, mutations in the genes for transforming growth factor-β receptor (TGFBR) have been found in patients with MFS or Marfan-like connective tissue disorders[1,2] and several distinct syndromes have been proposed that are associated with such mutations, including MFS type 2 (MFS2)[1] Loeys-Dietz syndrome (LDS)[2,3] Shprintzen-Goldberg syndrome[4] and Furlong syndrome[5] With the exception of the first report by Loeys et al[2] however, none of these reports present precise clinical characteristics of each patient.

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We describe here the clinical features of 3 patients with Marfan-like connective tissue disorders associated with TGFBR gene mutations in accordance with the 36 clinical features proposed by Loeys et al[2]

Methods

Patients

Between March 2004 and February 2006, a total of 21 patients with suspected MFS were referred to us. Patients were suspected of MFS because of presentation of young-onset AAD (<40 years) (n=8), AAE (n=5), and patient background (n=8); that is, family history, physical findings, and the presence of mitral valve prolapse. Among the 21 patients, 3 were excluded because they had relatives in the study group. The current study thus included 18 patients.

All 18 patients underwent genetic analysis as well as careful assessment including physical examination, computed tomography scanning, magnetic resonance imaging, echocardiography, and slit-lamp examination. These assessments covered all the diagnostic criteria for MFS[6] as well as the 36 clinical features of LDS[2] (Table 1).

The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the National Cardiovascular Center (Osaka, Japan). All patients gave written informed consent to participate in this study.

Table 1 Clinical Characteristics of the Patients With Mutations in the TGFBR Gene

	Patient 1	Patient 2	Patient 3	Loeys et al	Singh et al
Individual					
Age (years)	44	35	33		
Gene mutation	TGFBR2	TGFBR2	TGFBR1		
Craniofacial					
*Hypertelorism**	+	–	–	36/40 (90%)	1/7 (14%)
Cleft palate or abnormal uvula,††*	+	–	–	36/40 (90%)	1/7 (14%)
Malar hypoplasia	+	–	–	24/40 (60%)	5/7 (71%)
Rentrognathia	–	–	–	20/40 (50%)	
Craniosynostosis	–	–	–	19/40 (48%)	0/9 (0%)
Exotropia	–	+	–	7/13 (54%)	
Proptosis	–	–	–	6/13 (46%)	
Blue sclerae	–	–	–	16/40 (40%)	1/7 (14%)
Ectopia lentis†	–	–	–	0/40 (0%)	0/9 (0%)
Cardiovascular					
*Aortic root aneurysm**	+	+	+	39/40 (98%)	10/11 (91%)
Patent ductus arteriosus	–	–	–	14/40 (35%)	0/7 (0%)
*Arterial tortuosity**	–	+	–	21/25 (84%)	0/2 (0%)
Bicuspid aortic valve	–	–	–	2/12 (17%)	
Bicuspid pulmonary valve	–	–	–	1/9 (11%)	
Mitral valve prolapse	–	–	–	4/14 (29%)	
Pulmonary artery aneurysm	–	–	–	9/13 (69%)	
Descending aortic aneurysm	+	+	–	3/9 (33%)	
Ductal aneurysm	–	–	–	3/12 (25%)	
Subclavian artery anerurysm	–	–	–	2/7 (29%)	
Superior mesenteric artery aneurysm	–	–	+	1/8 (13%)	
Cerebral aneurysm	–	NE	NE	2/9 (22%)	
Atrial sptal defect	–	–	–	9/40 (22%)	0/7 (0%)
Aneurysm of other vessels,†*	–	–	+	21/40 (52%)	1/9 (11%)
Skeletal					
Dolichostenomelia	–	–	–	7/40 (18%)	7/9 (78%)
Arachnotactyly	–	–	–	28/40 (70%)	6/8 (75%)
Pectus deformity	–	+	+	27/40 (68%)	7/9 (78%)
Camptodactyly	–	–	–	6/14 (43%)	
Scoliosis	–	–	–	20/40 (50%)	6/9 (67%)
Postaxial polydactyly	–	–	–	2/14 (14%)	
Talipes equinovarus	–	–	–	18/40 (45%)	
Camptodactytly	–	–	–	15/40 (38%)	2/9 (22%)
Joint laxity	–	–	–	27/40 (68%)	6/9 (67%)
Cervical spine instability†	–	–	–	7/40 (18%)	
Cutaneous					
Velvety skin	–	–	–	11/40 (28%)	
Translucent skin	–	–	–	13/40 (32%)	
Nervous system					
Chiari malformation	–	–	–	2/10 (20%)	
Hydrocephalus	–	–	–	2/13 (15%)	0/11 (0%)
Developmental delay	–	–	–	3/14 (21%)	0/11 (0%)
Dural ectasia	–	–	–	1/2 (50%)	

**Defined as typical by Loeys et al (2006).*
TGFBR, transforming growth factor-β receptor; NE, not examined.
†Ectopia lentis, aneurysm of other vessels, and cervical spine instability were not listed in the first report by Loeys et al[2] of the 36 clinical features of Loeys-Dietz syndrome.
††Cleft palate and abnormal uvula were listed as separate 2 items in the first report by Loeys et al[2]

Genetic Analysis

Genetic analysis was performed to screen for mutations in the *FBN1* and TGFBR genes. Genomic DNA was isolated from the peripheral blood leukocytes of patients by an NA-3000 Nucleic Acid Isolation System (Kurabo Industries Ltd, Osaka, Japan) and amplified by polymerase chain reaction (PCR). Primers and conditions for PCR were as described previously[1,2,7] Genetic variants were screened with a denaturing high-performance liquid chromatography method in which the PCR products were analyzed with a WAVE DNA Fragment Analysis System (Transgenomic Inc, Omaha, NB, USA) according to the manufacturer's protocol. All detected variations were further confirmed by direct sequencing with an ABI 3700 Autosequencing System (Applied Biosystems, Foster City, CA, USA).

Results

Genetic Analysis

The median age of the patients at the time of blood sampling for genetic analysis was 33 years (range: 9–58). Among the 18 patients with suspected MFS, 7 fulfilled the diagnostic criteria of MFS, including 2 patients with AAD and 3 with AAE. Each of these 7 patients had mutations in *FBN1*. Eleven of the 18 patients were not diagnosed with MFS according to the criteria, and these patients were instead classified as having a Marfan-like connective tissue disorder. Among the latter, 1 patient had mutations in type I TGFBR gene (*TGFBR1*), 2 had mutations in type II TGFBR gene (*TGFBR2*), 1 had mutations in *COL3A1* and 7 did not have any mutations in the *FBN1* and TGFBR genes.

These 7 patients showed only reported polymorphisms in *FBN1*, *FBN2*, *TGFBR1*, and *TGFBR2*. Details of the 3 patients with TGFBR gene mutations are described below.

Clinical Course of the Patients With TGFBR Gene Mutations

Patient 1 Patient 1 was a 44-year-old woman (height, 157 cm; weight, 43 kg). She suffered the first episode of AAD (DeBakey IIIb) at the age of 29 years. Her identical twin sister also developed AAD at the same age. Surgical replacement of the proximal descending aorta for expansion of a false lumen was performed when the patient was 31 years of age. At 33 years of age, she suffered a recurrence of the AAD (IIIb), which was associated with expansion of the false lumen in the distal descending aorta to the abdominal aorta. At the age of 35 years, she suffered a third episode of AAD (II), for which emergency surgery, including total arch replacement, aortic root remodeling, and reconstruction of the right coronary artery, was performed. At 43 years of age she underwent surgical replacement of the thoracoabdominal aorta to correct expansion of the distal descending to abdominal aortic aneurysm and she also underwent the Bentall procedure for AAE with aortic regurgitation at 44 years of age. She did not show any of the following phenotypic manifestations of MFS: wrist sign, thumb sign, pectus carinatum, pectus excavatum, ectopia lentis, pneumothorax, mitral valve prolapse, striae distensae, or dural ectasia. The arm span to height ratio was <1.05. The clinical manifestations did not fulfill the diagnostic criteria for MFS, and Marfan-like connective tissue disorder was thus diagnosed. Although the patient had hypertelorism, bifid uvula, and aneurysm of aortic root, she had neither aneurysms of other vessels nor a tortuous aorta, which are typical clinical features of LDS? Mutations were not detected within the *FBN1*. However, we did detect a mutation in exon 7 of *TGFBR2*, leading to an Arg-to-Cys substitution at residue 537.

Patient 2 Patient 2 was a 35-year-old man (height, 179 cm; weight, 69 kg). His mother had died from AAD and his first episode of AAD (DeBakey IIIb) occurred at 34 years of age. Replacement of the descending aorta was performed when he was 35 years of age. Although he had moderate-grade pectus excavatum, he did not show any of the following phenotypic manifestations of MFS: wrist sign, thumb sign, pectus carinatum, ectopia lentis, pneumothorax, mitral valve prolapse, striae distensae, or dural ectasia. The arm span to height ratio was <1.05. The clinical manifestations did not fulfill the diagnostic criteria for MFS, and therefore he was classified as having a Marfan-like connective tissue disorder. Although the patient had aortic root aneurysm and a tortuous aorta, he did not have hypertelorism, cleft palate, abnormal uvula, or aneurysms of other vessels, which are typical clinical features of LDS. In addition, he had exotropia. Genetic analysis detected a nonsense mutation in exon 6 of *TGFBR2* that caused a stop codon instead of an Arg at amino acid position 495. We did not detect mutations in *FBN1* responsible for MFS.

Patient 3 Patient 3 was a 33-year-old man (height, 181 cm; weight, 56 kg). He did not have a family history suggestive of heritable connective tissue disorders or aortic disease. At 16 years of age, he developed AAD (DeBakey II) and underwent a modified Bentall procedure. At 27 years of age, he underwent surgeries to repair right pneumothorax and then left pneumothorax. Also at age 27 years, he had a second episode of AAD (DeBakey II) originating from the

Table 2 Clinical Characteristics of the 8 Patients Without Mutations in *FBN1* or TGFBR Genes

Age (years)	Sex	Height (cm)	Skeletal involvement	Cardiovascular involvement	Ocular involvement	Family history related to cardiovascular events	Reasons for genetic analysis	Clinical diagnosis at the time of genetic analysis
33	M	168	–	–	–	AAA: brother (21 yo), SAH: sister (19 yo), TAA: father (42 yo)	Family history	Ehlers-Danlos syndrome (COL3A1 mutation)
32	M	176	–	AAE, MVP	–	–	AAE	Post Bentall for AAE and AR (bicuspid aortic valve)
58	F	160	Pes planus	AD (IIIb, 58 yo)	–	AD: brother (54 yo)	Family history	Acute AD
28	M	168	–	–	NE	AD: father (30 yo), brother (25 yo)	Family history	NP
55	F	161	–	AD (I, 54 yo)	–	–	AD	Chronic AD, post TAR
31	F	174	Thumb sign, scoliosis, pectus excavatum	MVP	–	–	Physical examination	MR
20	F	156	–	MVP	–	–	MVP	MR, AR
44	F	159	–	AAE	NE	–	AAE	Post Bentall for AAE and AR

FBN1, fibrillin-1 gene; AAA, abdominal aortic aneurysm; yo, years old; SAH, subarachnoid hemorrhage; TAA, thoracic aortic aneurysm; AAE, annulo-aortic ectasia; MVP, mitral valve prolapse; AR, aortic regurgitation; AD, aortic dissection; NP, nothing particular; TAR, total arch replacement. Other abbreviations see in Table 1.

distal portion of the previously replaced ascending aorta, and replacement of the aortic arch was performed by the elephant trunk method. At 33 years of age, he presented with ectasia of the ostias of both coronary arteries, as well as an aneurysm of the superior mesenteric artery. He underwent another Bentall procedure and reconstruction of the left coronary artery. Although he had moderate grade pectus excavatum and a history of pneumothorax, he did not show any of the following phenotypic manifestations of MFS: wrist sign, thumb sign, pectus carinatum, ectopia lentis, mitral valve prolapse, striae distensae, or dural ectasia. The arm span to height ratio was <1.05. The clinical features did not fulfill the diagnostic criteria for MFS, and therefore a diagnosis of a Marfan-like connective tissue disorder was made. Although some features characteristic of LDS, including aortic root aneurysm and superior mesenteric artery aneurysm, were observed, other features such as hypertelorism, cleft palate, abnormal uvula, and tortuous aorta were absent. Genetic analysis detected a mutation in exon 9 of *TGFBR1*, resulting in an Arg487Gln substitution. Mutations of *FBN1* associated with MFS were not detected.

Comparison of the Present Clinical Features With Those in Previous Reports

The clinical features of these 3 patients are summarized and compared with those described by Loeys et al[2,3] and Singh et al[8] (Table 1). Loeys et al proposed 36 clinical features of LDS, of which the median number of features examined in each patient was 31, with a median number of positive features of 13, and a median positive ratio of 46%. In the present study, the number of these 36 features examined was 36 in patient 1, 35 in patient 2, and 35 in patient 3. The number of positive features in these 3 patients was 5 in patient 1, 5 in patient 2, and 3 in patient 3, with a positive ratio therefore of 14% (5/36), 14% (5/35), and 9% (3/35), respectively, which is much less than the ratio reported by Loeys et al.

Clinical Features of Patients Without FBN1 or TGFBR Gene Mutations

The clinical features of the 8 patients without *FBN1* or TGFBR gene mutations are shown in Table 2. Among them, 1 patient had mutations of *COL3A1* and was diagnosed as having Ehlers-Danlos syndrome. The remaining 7 patients showed reported polymorphisms only in *FBN1*, *FBN2*, *TGFBR1*, and *TGFBR2*. They were associated with several phenotypes of MFS such as pes planus, thumb sign, scoliosis, pectus excavatum, mitral valve prolapse, aortic dissection, and annuloaortic ectasia, but did not fulfill the criteria for MFS (Table 2).

Discussion

The diagnostic criteria for MFS were first established in 1986[9] and were based solely upon phenotypic abnormalities of the skeletal, ocular, and cardiovascular systems. The observation that mutations in *FBN1* were linked to this syndrome required that these classic criteria be revised to include genetic factors.[6] However, mutations in *FBN1* have been detected in only 66–91% of MFS patients![10,11] Some patients who present with Marfan-like skeletal and cardiovascular phenotypes, but who lack or exhibit only mild ocular involvement and who do not exhibit mutations in the *FBN1* locus have been classified as MFS2![12] Chromosome 3p25–p24.2 has been identified as a second locus for MFS[13] in lineages in which MFS2 was shown. This locus is also known as TAAD2 and is thought to be responsible for familial TAA and AAD![14] Subsequent studies by Mizuguchi et al[1] identified mutations in *TGFBR2* as a cause of MFS2. More recently, Loeys et al reported that mutations in *TGFBR1* or *TGFBR2* are responsible for the development of a Marfan-like connective tissue disorder in certain patients, and proposed a new disease entity, named LDS? LDS is characterized by widely spaced eyes (hypertelorism), bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection. Although the phenotype overlaps somewhat with that of MFS, LDS does not fulfill the diagnostic criteria for MFS.

There is clear evidence in the literature for the existence of at least 4 syndromes associated with mutations in *TGFBR1* or *TGFBR2*; that is, LDS? MFS2! Shprintzen-Goldberg syndrome[4] and Furlong syndrome[5] LDS has been subdivided into types 1 and 2[3] LDS type 1 is associated with craniofacial involvement consisting of cleft palate, craniosynostosis, or hypertelorism, whereas type 2 is associated with Ehlers-Danlos syndrome. Shprintzen-Goldberg syndrome is characterized by craniosynostosis and mental retardation, and Furlong syndrome is characterized by only craniosynostosis.

We report 3 cases of young-onset AAD associated with mutations in *TGFBR1* and *TGFBR2*. Diagnoses of MFS and MFS2 were excluded because the patients did not fulfill the diagnostic criteria for MFS. In addition, because the patients exhibited neither craniosynostosis nor mental retardation, diagnoses of Shprintzen-Goldberg or Furlong syndromes were excluded. We also did not observe characteristics associated with Ehlers-Danlos syndrome, such as skin hyperextensibility, fragile and soft skin, delayed wound healing with formation of atrophic scars, and generalized joint hypermobility. Thus, LDS type 2 was also ruled out. Consequently, the most probable diagnosis of these 3 patients was LDS type 1. However, these 3 patients presented only a fraction of the features associated with LDS type 1;[2] only 9–14% of the 36 reported clinical features of LDS, which is far less than that reported by Loeys et al (median 46% of the 36 features). It should be also pointed out that patient 3 had repetitive pneumothorax, which is not listed in the features of LDS. These observations support the notion that TGFBR gene mutations may give rise to greater phenotypic heterogeneity than previously reported.

Finally, as described above, several syndromes have been linked to TGFBR gene mutations. Although the phenotypic manifestations of these syndromes overlap, the extent of this remains to be determined more precisely, mainly because the precise clinical features have not been evaluated and/or reported in most patients with TGFBR gene mutations. In fact, to our knowledge, the study performed by Loeys et al[3] is the only one in which as many as 36 clinical features associated with TGFBR gene mutations have been evaluated, although there are some published reports of mutations of TGFBR genes![15–19] Given the current incomplete understanding of the clinical features associated with TGFBR gene mutations, more detailed clinical studies should be performed in patients who present with these mutations.

Conclusions

We described 3 cases of Marfan-like connective tissue disorder associated with TGFBR gene mutations. The clini-

cal features differed from those of previously reported cases of Marfan-like connective tissue disorder associated with TGFBR gene mutations. Although the number of patients was limited, our findings support the notion that these mutations may give rise to greater phenotypic heterogeneity than previously reported.

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血行動態異常の評価法と左心不全/治療

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心筋梗塞急性期の予後はCCUの開設，冠動脈再灌流療法の確立により改善してきた。しかし，左心不全，心原性ショックなどのポンプ失調による死亡率は高く，いかに迅速に診断・治療するかが現在のCCUの大きな課題である。

心筋梗塞急性期におけるポンプ失調の病態は生存心筋量の減少により左室収縮機能障害を生じて全身の需要に見合うだけの血液が駆出できなくなり，その代償機序によって末梢血管の収縮や左室充満圧の上昇，さらには肺うっ血をきたし，重症例では心原性ショックに移行するというものである。急性心筋梗塞では，心筋壊死量が20%を超えると心拍出量が低下し，肺うっ血などの心不全症状が出現し，40%を超えると心原性ショックに陥るとされている。したがって，急性心筋梗塞における左心不全の治療は急性心筋梗塞発症早期に再灌流療法を行い，梗塞壊死心筋量を最小限にすることから始まるが，再灌流療法の詳細については別項を参照されたい。

血行動態異常の評価法

心筋梗塞急性期の血行動態の評価はポンプ失調重症度判定やそれに基づく治療方針の決定，さらには治療効果の評価に不可欠である(図1)[1]。

◇理学所見

Killip分類

特に肺野の聴診は重要である。肺野のうっ血の有無によりKillipらは急性心筋梗塞の重症度を分類している(表1)。Killip 1型は心不全なし，Killip 2型は軽症ないし中等症の左心不全，Killip 3型は重症の左心不全（肺水腫），Killip 4型は心原性ショックである。さらに心音で3音，4音の有無を確認し，僧帽弁閉鎖不全，心室中隔穿孔の合併を示唆するような収縮期雑音についてもチェックする。

◇胸部X線写真 (図2)

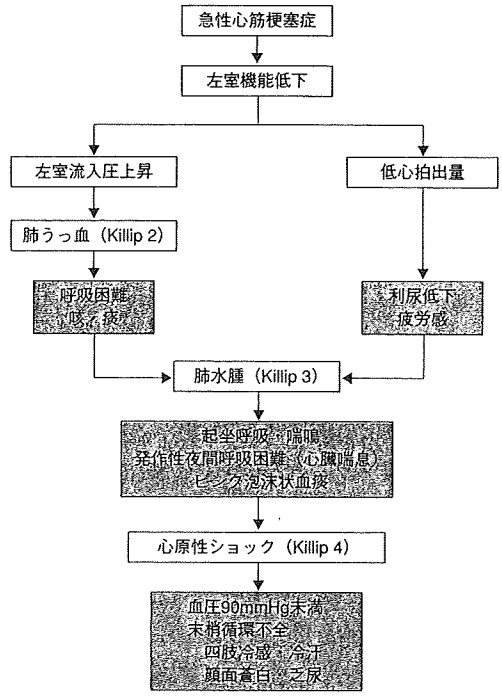
胸部X線写真

スリガラス様陰影

butterfly shadow

急性左心不全では心拡大が著明でないことがある。肺静脈圧が高値になるとまず上葉肺静脈の拡大を認める。肺静脈圧が25mmHgを超えてくると肺間質性の水腫が生じ肺門部陰影が不鮮明(hilar haze)となり，肺野全体がスリガラス様陰影に覆われる。またカーリーA線，カーリーB線がみられる。肺静脈圧が20～35mmHgを超えてくると肺胞性の水腫をきたし，典型的には肺野陰影の内側2/3を中心に斑状，雲状陰影(蝶形陰影：butterfly shadow)がみられる。

図1 ▶ ポンプ失調の病態と症状



（文献1より引用）

表1 ▶ Killip分類

症状	原著死亡率（%）
1型：心不全徴候なし	6
2型：軽～中等度の心不全（肺ラ音聴取域：全肺野の50%未満）	17
3型：肺水腫（肺ラ音聴取域：全肺野の50%以上）	38
4型：心原性ショック	81

（Killip T 3rd, Kimball JT : Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol 20 : 457-464, 1967.）

心エコー・ドプラ法

◇心エコー・ドプラ法

心エコー法は非侵襲的検査であるためベッドサイドで繰り返し心機能，血行動態の評価が行える。左室局所壁運動異常の部位，広がりを確認し，左室拡張期末期径，収縮期末期径を計測し収縮性の指標である左室内径短縮率を測定する。三尖弁逆流血流速度から収縮期右室右房間圧格差を求めることができるので，右房圧がわかれば右室収縮期圧を推定することができる。肺動脈弁逆流血流速度から拡張末期肺動脈右室間圧較差を求めることができるので，右室拡張期圧と右房圧に大差ないとすれば右房圧がわかれば肺動脈拡張末期圧が類推できる。右房圧は下大静脈の径が15mm以下であれば10mmHg以下で，下大静脈径が15mm以上で呼吸性変動が50%以下であれば10mmHgを越えるとされている。ここで併せて弁膜疾患あるいはシャント疾患の有無，評価も行う。

肺動脈拡張末期圧の類推

Swan-Ganzカテーテル法

◇Swan-Ganzカテーテル法

ベッドサイドで右心系の圧，心拍出量，血管抵抗，混合静脈血酸素飽和度などが計測できる。表2に圧の正常値を示す。ForresterらはSwan-Ganzカテーテルから得られる血行動態の指標から急性心不全を4つのサブセットにわけている（図3）。肺

Forrester分類

図2 ▶ 心原性ショックの胸部X線写真

84歳の女性。心原性ショックにて緊急搬送され緊急外来にてカテコラミン点滴，気管内挿管，PCPS挿入された。引き続いてカテ室でIABP挿入後右橈骨動脈より冠動脈造影施行され，左主幹部完全閉塞に対してPCI施行された。

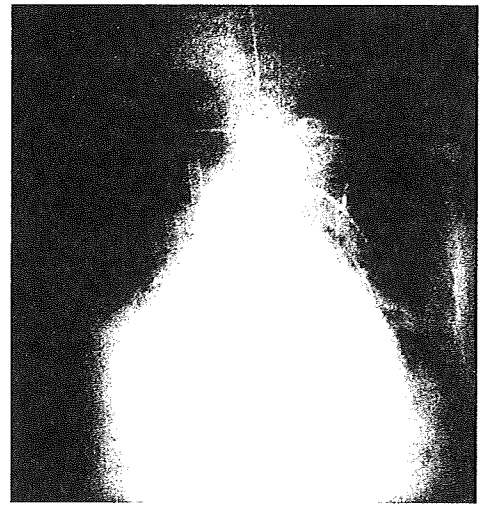


表2 ▶ 右心カテーテル検査により求められる圧の正常値

右房圧	平均	1～5mmHg
右室圧	収縮期	15～30mmHg
	拡張末期	1～5mmHg
肺動脈圧	収縮期	15～30mmHg
	拡張期	1～12mmHg
	平均	9～18mmHg
肺動脈楔入圧	平均	1～12mmHg

うっ血の指標として肺動脈楔入圧を，末梢循環不全の指標として心係数を用いて分類し，そのサブセットに応じた治療法が記され，血行動態の把握のみならず治療法を考えるうえで参考になる。

治療の実際

◇一般的処置

酸素吸入し，静脈路確保，心電図などをモニターする。呼吸困難が強いときには塩酸モルヒネを静注する。塩酸モルヒネは交感神経緊張による動静脈の収縮を解除し，直接の血管拡張作用はないものの前負荷と後負荷の軽減をきたす作用がある。ただし，呼吸抑制と血圧低下には十分な注意が必要である。十分な酸素投与にもかかわらず，酸素分圧を60mmHg以上に維持できない場合には気管内挿管を行い人工呼吸器管理とするが，吸入気酸素濃度(FiO_2)が50%以上必要なときは呼気終末陽圧(PEEP)を5～10mmHgにして陽圧呼吸を開始する。Swan-Ganzカテーテルを用いて血行動態を観察しながら適切な薬物とその使用量を決定する(**図3，表3**)。

人工呼吸器管理

呼気終末陽圧(PEEP)

◇利尿薬

Forrester分類のII群，IV群に対して速効性のフロセミドを使用するのが一般的である。利尿作用により肺うっ血が軽減するとともに，呼吸困難が軽減，左室容量の減少に伴う左室壁張力低下に伴う心筋酸素需要の減少，後負荷軽減により駆出特性

利尿薬

図3 ▶ Forrester分類と各サブセットの治療法

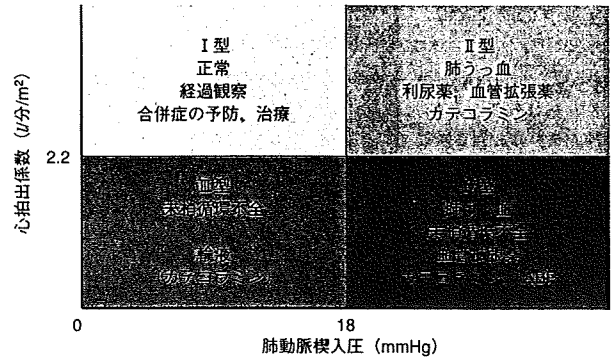


表3 ▶ ForresterⅣ群における適応薬剤の選択

収縮期血圧	適応薬剤の選択
＞120mmHg	血管拡張薬 または PDE阻害薬
120～90mmHg	ドブタミンand/orドパミン＋血管拡張薬 または PDE阻害薬
＜90mmHg	ドブタミンand/orドパミン ↓ PDE阻害薬 ↓ ノルアドレナリン ↓ 補助循環

の改善が得られる。時間尿量を観察しながら静注，あるいは持続点滴で使用する。

◇血管拡張薬

血管拡張薬

Forrester分類のII群，IV群に対して末梢血管を拡張し前負荷および後負荷を減少させ，うっ血による症状を軽減，心筋酸素消費の低下による心筋虚血の改善に有効である。

■ニトログリセリン

ニトログリセリン

硝酸薬は主に静脈系の血管平滑筋を直接弛緩させ，前負荷を軽減，左室充満圧の低下により肺うっ血を改善する。血圧低下作用により後負荷の軽減，心筋酸素消費量を減少させる。持続点滴静注で0.1～0.2μg/kg/分から開始し，最大2～3μg/kg/分まで用いる。

■ホスホジエステラーゼ(PDE)阻害薬

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サイクリックAMP分解酵素であるホスホジエステラーゼ(PDE)-IIIを阻害することにより，細胞内のサイクリックAMP濃度を上昇させ，心筋細胞では強心作用をきたし，血管平滑筋細胞では弛緩作用を生じ血管拡張をきたす。この薬剤も前負荷・後負荷軽減作用により，心筋酸素消費量の増加が抑制され心エネルギー効率が改善され急性心不全に有効である。急性期には不整脈誘発に注意が必要である。