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Case Report

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Accelerated Atherogenicity in Tangier Disease

A Case Accompanied by Extensive Atherosclerotic Lesions, Leriche Syndrome and Bleeding Tendency, and Review of the Literature

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We report a case of Tangier disease with Leriche syndrome and bleeding tendency. In this male patient, nasal hemorrhage had been observed frequently throughout childhood. At 46 years old, he experienced effort angina, and coronary angiography demonstrated 75% stenosis in the right coronary artery. Orange-colored tonsils, mild hepatosplenomegaly and very low levels of serum high-density lipoprotein cholesterol (HDL-C) were observed, and the patient was diagnosed with Tangier disease. At 52 years old, effort angina recurred. Coronary angiography revealed 75% stenosis of the left main trunk, left anterior descending, and right coronary arteries. Stenosis of the brachiocephalic and right common iliac arteries was also recorded. Stents were implanted, and coronary artery bypass surgery was performed. At 53 years old, 15 months after surgery, the patient reported intermittent claudication, coldness of feet, and impotence. Aortic angiography showed progression of the stenosis at the bifurcation of the common iliac artery. The patient was diagnosed with Leriche syndrome, and aorta–left external iliac artery graft bypass surgery was performed. After surgery, oozing from subcutaneous tissue and leaking from the anastomotic region were observed. Additional analysis revealed two single-nucleotide polymorphisms (V825I and N935T) in the ATP-binding cassette transporter A1 (*ABCA1*) gene, and accumulation of small dense low-density lipoprotein together with low levels of HDL-C. In Tangier disease, HDL-C is markedly decreased because of ABCA1 deficiency. However, this is the first reported case to exhibit extensive atherosclerosis and bleeding tendency. This patient had atypical extensive and multiple atherosclerotic lesions, accompanied by Leriche syndrome and uncontrollable bleeding.

Key words: **Tangier disease, Leriche syndrome, Atherosclerosis, HDL, ABCA1**

Introduction

Tangier disease is characterized by orange-colored tonsils, mild hepatosplenomegaly, and a decline in high-density lipoprotein cholesterol (HDL-C) concentrations in the blood. A mutation of the ATP-binding cassette transporter A1 (ABCA1) gene has been indicated as the gene responsible for Tangier disease[1-4]. ABCA1 transports cholesterol at the plasma membrane and is expressed throughout the body[5]. In

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Tangier disease, it is believed that cholesterol is deposited in various tissues (vessel wall, β cells etc.), and we previously reported severely calcified coronary artery images by intravascular ultrasonography and impaired insulin secretion in ABCA1 deficiency[6, 7].

Here, we describe a case of Tangier disease with extensive atherosclerotic lesions, accompanied by Leriche syndrome and bleeding tendency. Although atherosclerosis is a characteristic of Tangier disease, its frequency and severity are unclear. Therefore, we analyzed 56 papers (78 cases) and a review paper[8] (54 cases) and investigated the frequency and severity of atherosclerosis and bleeding tendency in Tangier disease.

Case Presentation

A 53-year-old man was admitted to our hospital complaining of impotence, intermittent claudication, and a feeling of coldness in his lower extremities. He had a history of smoking from 17 to 52 years of age, 15 cigarettes per day (Brinkman Index: 525). The patient's father had type 2 diabetes. His mother had angina pectoris, type 2 diabetes, and renal insufficiency of unknown origin. His elder brother suffered a cerebral infarction at the age of 53. His younger sister died from sudden renal failure at 48 years of age.

From childhood, he often experienced nosebleeds. When he was 46 years old, he was diagnosed with effort angina. Coronary angiography revealed 75% stenosis in the right coronary artery #2 and a stent was implanted. At 52 years old, he again had chest pain on effort. Left coronary angiography revealed 75% stenosis in the left main trunk ostium (**Fig. 1A**) and moderate to severe diffuse stenosis from the ostium to the distal portion of the right coronary artery (**Fig. 1B**). Because of the severe coronary artery stenosis, including the left main trunk and right coronary artery, he was scheduled for coronary artery bypass graft (CABG) surgery in our hospital. He was administrated aspirin, ethyl icosapentate, and pitavastatin. At that time, because he had profound systemic atherosclerosis, we re-evaluated the atherosclerosis risk factors. His body mass index was 23.4 kg/m^2. Orange-colored swollen tonsils (**Fig. 2A**, **B**), and mild hepatosplenomegaly were observed. HDL-C was 2 mg/dL and apolipoprotein A-1 (ApoA1) was undetectable. In addition, low hemoglobin and platelet counts were observed, consistent with a previous report[7]. Mean platelet volume was indicative of larger platelets (**Fig. 3A**). In addition, activated partial thromboplastin time was prolonged. Bleeding time was over 10 minutes (**Supplemental Table 1**). Among the risk factors for atherosclerosis, HDL-C was 2 mg/dL. The patient was diagnosed with Tangier disease. Fasting blood sugar level was 121 mg/dL, fasting insulin 5.9 μU/mL, and hemoglobin A1c (NGSP) was 4.9%. A 75 g oral glucose tolerance test was not performed.

We evaluated the patient's systemic condition, especially the peripheral arteries. Irregular and eccentric stenosis of the brachiocephalic artery was observed (**Fig. 1C**). The lesion was treated with stent implantation (8 × 27 mm) (**Fig. 1D**). In addition, severe stenosis was found in the left subclavian artery (**Fig. 1E**) and was also treated with stent implantation. Angiography of the abdominal aorta and lower limbs revealed severe stenosis in the right common iliac artery (**Fig. 1F**), whereas the right internal iliac artery was not contrasted (**Fig. 1G**). In addition, severe stenosis was found in the left internal iliac artery (**Fig. 1G**). In the right common iliac artery, stenosis with dissection was observed (**Fig. 1H**) and treated with stent implantation (10 × 60 mm) (**Fig. 1I**). After treating the peripheral arteries, we performed CABG (right internal thoracic artery-posterior descending branch, AV node branch, and left internal thoracic artery-left anterior descending branch #8). At 5 days after surgery, cardiac tamponade occurred and was successfully controlled by platelet transfusion and pericardial drainage.

Six months later, the patient again suffered from effort angina. On coronary angiography, the radial artery graft between posterior descending branch #4 and AV node branch #4 was completely obstructed. We implanted a drug-eluting stent in the proximal right coronary artery to relieve the unprotected ischemic area.

Thirteen months later, at 53 years old, 1 year after the previous CABG, the patient was admitted to hospital complaining of impotence, intermittent claudication and a feeling of coldness in his lower extremities—a symptom of Leriche syndrome. The ankle–brachial pressure index was 0.79 on the right and 0.66 on the left, respectively. Angiography revealed severe stenosis at the bifurcation of the common iliac artery and dissection of the abdominal aorta (**Fig. 1J**). Three-dimensional computed tomography (CT) angiography showed incremental detritus stenosis with calcification at the ostium of the left renal artery and near the bifurcation of the common iliac artery (**Fig. 1K**, **L**). The patient was diagnosed with Leriche syndrome and underwent aorta–external iliac artery bypass surgery and replacement of the abdominal aorta with a blood vessel prosthesis. Histology of tissue obtained from the abdominal aorta indicated an aggregation of foam cells (**Fig. 5A**, **B**). On the following day, difficulty in hemostasis was again observed after surgery. As in the previous bypass surgery, we transfused plate-

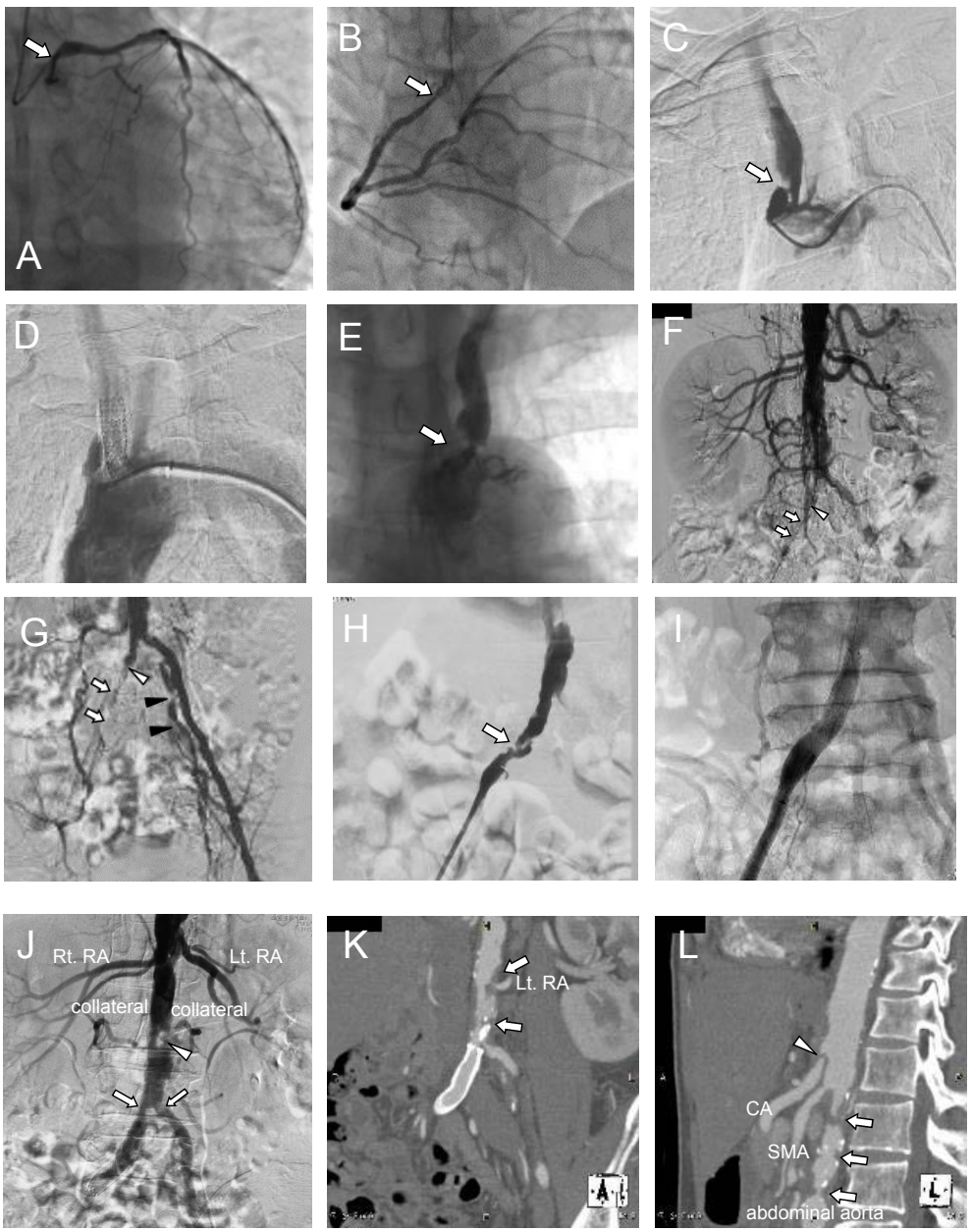

Fig. 1. Coronary and aortic angiography before and after coronary artery bypass graft surgery at the age of 52

In the left coronary artery (LCA), 75% stenosis was observed in the left main trunk ostium (A). In the right coronary artery ostium (RCA), moderate to severe diffuse stenosis was observed (B). In addition, multiple severe calcified lesion were observed in both the LCA and RCA on coronary angiography.

Angiography of the aortic arch revealed irregular and eccentric stenosis of the brachiocephalic artery (C). This lesion was treated with stent implantation (8 × 27 mm) (D). A huge lesion was observed in the left subclavian artery (E).

Angiography of the abdominal aorta and lower limbs showed severe stenosis in the right common iliac artery (open arrow) (F, G), whereas the right internal iliac artery was not contrasted (open arrowhead). In addition, severe stenosis was found in the left internal iliac artery (closed arrowhead). Angiography of the right lower limb revealed stenosis with dissection in the right common iliac artery (H). This lesion was treated with stent implantation (10 × 60 mm) (I).

Abdominal aortic angiography, 2 years after coronary artery bypass graft surgery, when the patient was 53 years old. During angiography of the aortic arch, newly developed multiple severe stenoses were observed at the bifurcation of the common iliac artery. The arrowhead indicates the dissection of the abdominal aorta, which had not been observed 2 years previously (Fig. 1-F)) (J). Three-dimensional CT angiography of the coronal section showed severe stenosis with calcification at the ostium of the left renal artery and near the bifurcation of the common iliac artery (K). Three-dimensional CT angiography in the sagittal view showed multiple severe irregular stenoses of the abdominal aorta (open arrow) and dissection of the celiac artery (open arrowhead) (L).

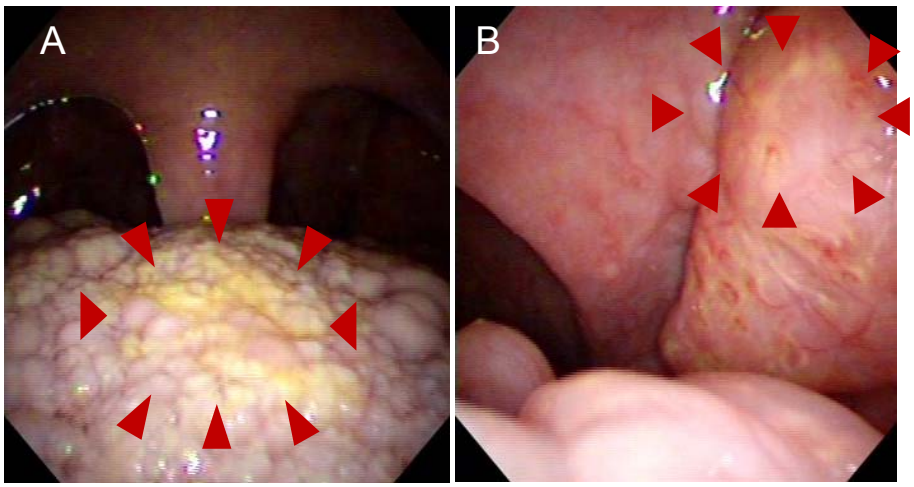

Fig. 2. Photos of tonsils of the proband. The lingual tonsil (A) and pharyngeal tonsil (B) were orange-colored and swelling, which is a typical characteristic in Tangier disease

let and managed to achieve hemostasis. However, internal bleeding could not be controlled; he suffered from compartment syndrome and died from rhabdomyolysis of the lower extremities.

To evaluate the etiology of the progressive atherosclerosis, we performed additional analyzes. Polyacrylamide gel electrophoresis (**Fig. 3B**, **C**) revealed a mid-band and increased peak of small dense low density lipoprotein (LDL). A mid-band suggested an increase of remnants, and small dense LDL were known as pro-atherogenic lipoproteins. However, an α-band (HDL) was not detected.

In terms of *ABCA1* gene mutation, this patient had compound heterozygosity for V825I and N935T. V825I has been previously reported and is located in the 6th transmembrane domains. N935T is a novel mutation, located between 6th transmembrane domain and ATP-hydrolyzing domain (**Fig. 3D**).

Discussion

Unfortunately, our case died from uncontrollable bleeding. On admission, we observed a prolonged bleeding time, which indicated platelet dysfunction, thrombocytopenia, and giant platelets in peripheral blood (**Fig. 1L**). There is one previous study that investigated impaired platelet activation in ABCA1 deficiency[9]; the authors concluded that impaired release of the content of dense bodies may explain the defective activation of ABCA1-deficient platelets by collagen and low concentrations of thrombin. In other hypoalphalipoproteinemic diseases such as apolipoprotein A1 deficiency and lecithin-cholesterol acyltransferase deficiency, there have been no case reports about bleeding tendency. To examine whether this conclusion might be universal among Tangier patients, we reviewed all previously published case reports. However, there was no clear report of bleeding tendency. On the other hand, we previously reported decreased expression of the Rho GTPase family, cdc42, in Tangier disease[10]. We assumed that ABCA1 and cdc42 have intracellular colocalization[11]. Interestingly, in a recent report of a patient with *de novo* cdc42 mutation[12], the patient had macrothrombocytopenia, which is completely consistent with our case (**Fig. 3A**). Although the precise molecular mechanism has not been completely elucidated, we are assuming that our patient might have had impaired or dysfunctional interaction between ABCA1 and cdc42, inducing macrothrombocytopenia and bleeding tendency in addition to defective HDL-C.

Atherosclerosis is a characteristic of Tangier disease; however, its frequency and severity are unclear. Therefore, we analyzed 56 papers (78 cases) and a review paper[8] (54 cases) and investigated the frequency and severity of atherosclerosis and bleeding tendency in Tangier disease. From our analysis, we were not able to find any patient with such extensive atherosclerotic lesions as in our case. The literature search also revealed that angina was observed in 33 cases (24.8%) and other vascular diseases in 29 cases (21.8%) of total 133 cases of Tangier disease (**Table 1**, **2**). It has been considered that Tangier patients might have a pro-atherogenic profile, due to very low levels of HDL-C, which is actually not common. In contrast, our Tangier disease case had extensive severe atherosclerosis. Furthermore, this is the first case of Tangier disease accompanied by Leriche syndrome. Schae-

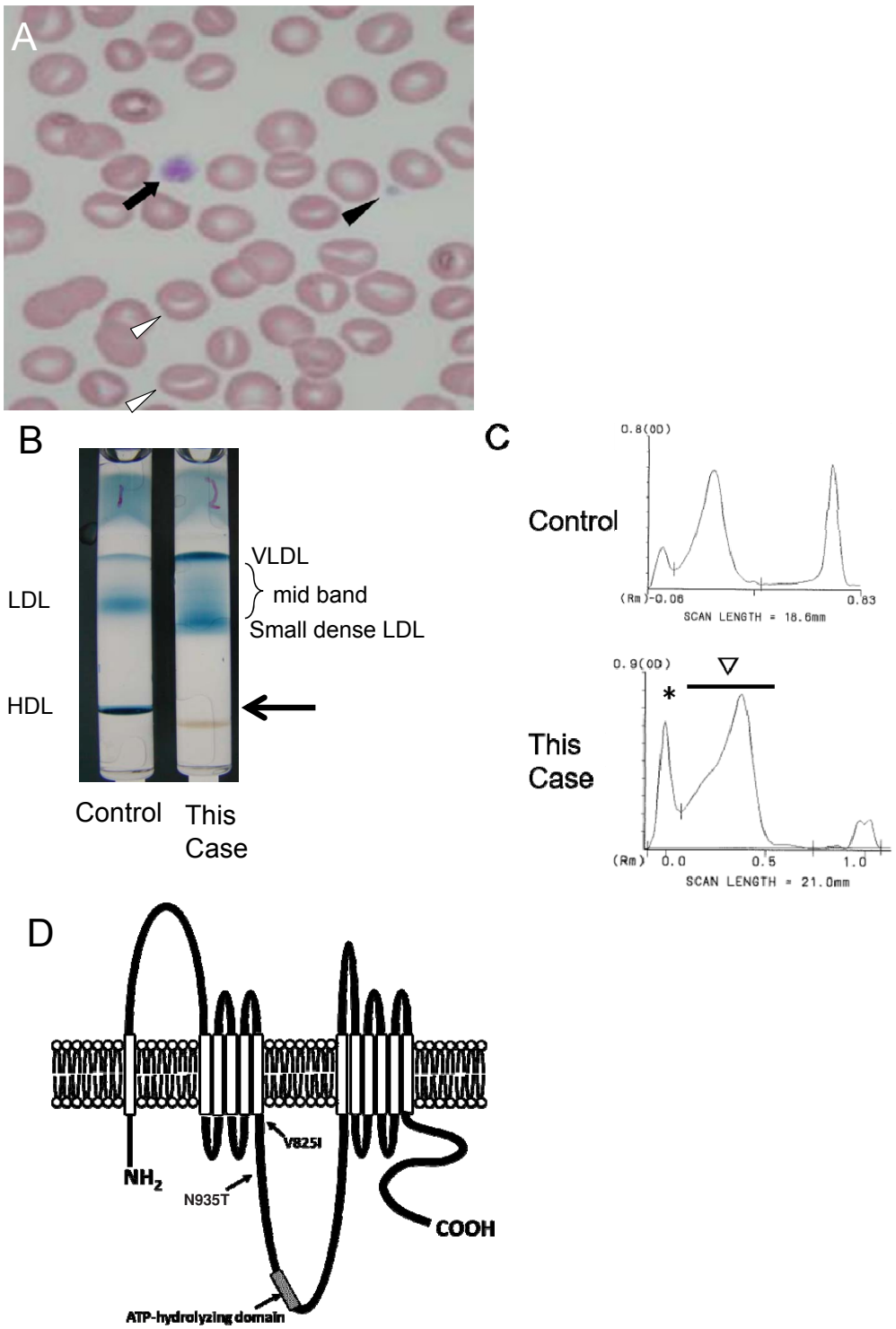

Fig. 3.

Peripheral blood was stained by Giemsa (×1000). Both normal platelets (closed arrow) as well as abnormal giant ones (closed arrowhead) were observed. In addition, erythrocytes with numerous stomatocytes (arrowhead) were observed (A).

Lipoprotein agarose gel electrophoresis was carried out. In this case, HDL was not observed at the arrow (B). The peak of VLDL (*) was high, and a mid-band was observed between VLDL (*) and LDL, suggesting accumulation of remnant. In this case, the second peak (arrow) was moved to the right, indicating accumulation of small-sized LDL (C). A putative model of ABCA1 mutation, V825I and N935T (D).

Table 1. Clinical and laboratory features in Tangier disease

	age	gender	angina	other vascular disease	TCho	LDL-C	HDL-C	TG		
1	24	M	-	-	53	16	0	284	1961	Fredrickson DS *et al.*
2	25	F	-	-	63	30	0	351	1961	Fredrickson DS *et al.*
3	25	F	-	-	46	38	4	72	1964	Fredrickson DS *et al.*
4	29	F	-	-	89	80	6	131	1964	Fredrickson DS *et al.*
5	72	M	+	+	74	47	2	207	1965	Hoffman HN *et al.*
6	48	M	+	+	69	13	0	213	1965	Hoffman HN *et al.*
7	37	M	-	-	47		8	332	1967	Kocen RS *et al.*
8	25	F	-	-	84	70	2	163	1967	Engel WK *et al.*
9	33	F	-	-	84	49	5	154	1967	Engel WK *et al.*
10	40	M	-	-	68		4	122	1968	Kummer H *et al.*
11	3	F	-	-	70		7	155	1970	Kracht J *et al.*
12	5	M	-	-					1971	Bale PM *et al.*
13	15	F	-	-	59	47	7	136	1971	Bale PM *et al.*
14	53	F	+	+	95		9	180	1972	Lindeskog GR *et al.*
15	62	M	+	+	60		0	230	1974	Haas LF *et al.*
16	8	F	-	-	83		5	105	1974	Greten H *et al.*
17	6	F	-	-					1974	Stanios W *et al.*
18	10	M	-	-	57	35	2	110	1975	Fetrans VJ *et al.*
19	7	M	-	-	72	37	2	180	1975	Fetrans VJ *et al.*
20	56	M	-	+	114		6	269	1975	Utermann G *et al.*
21	2	F	-	-	64			181	1976	Assman G *et al.*
22	56	M	-	-	60		6	100	1976	Assman G *et al.*
23	53	M	-	-	51		0	170	1976	Assman G *et al.*
24	56	F	-	-	90		5	348	1976	Assman G *et al.*
25	56	M	-	+	42	22	0	297	1977	Brook JG *et al.*
26	14	F	-	-	59	49	0	102	1978	Herbert PN *et al.*
27	69	F	-	+	116	101	6	114	1978	Dyck PJ *et al*
28	19	F	-	-	80	39	4	214	1982	Suarez BK *et al.*
29	20	F	-	-	177	158	8	240	1982	Frith RW *et al.*
30	26	M	-	-	73	73	8	124	1982	Frith RW *et al.*
31	19	M	-	-	138	134	8	178	1982	Frith RW *et al.*
32	29	F	-	-	69		0	145	1983	Ohtaki *et al*
33	31	F	-	-	60		2	88	1983	Ohtaki *et al*
34	15	M	-	-					1984	Dechelotte P *et al*
35	62	M	+	+	79		1	146	1984	Vergani CG *et al*
36	28	F	-	-	50	15	8	175	1984	Tarao K *et al*
37	26	F	-	-	39		8	132	1984	Tarao K *et al*
38	38	M	-	-	55		2	190	1985	Gibbels E *et al*
39	53	M	-	-	98		2	355	1985	Pietrini V *et al*
40	36	M	-	-	52			233	1986	Clerc M *et al*
41	65	M	-	-	28		1	202	1987	Pressly TA *et al*
42	61	F	-		106		7	increased	1987	Schmalbruch H *et al*
43	62	M	-	-	72		6	297	1987	Frohlich J *et al*
44	27	M	-	-	46		0	244	1988	Bracco G *et al*
45	55	F	+		73		1.5	658	1989	Reinhard W.H. *et al*
46	50	M	-	-	103			545	1989	Leal Luna A *et al*
47	14	M	-	-	25		5	98	1990	Lo W.D. *et al*
48		M	-	-	23		1	40	1990	Kunitake S.T. *et al*
49		M	-	-	30		1	78	1990	Kunitake S.T. *et al*
50	36	M			127			124	1990	Schmitz G *et al*
51	28	M			35			89	1990	Schmitz G *et al*
52	43	M	-				10		1991	Dumon MF *et al*
53	47	M	+		28		6	232	1991	Matsuzawa Y *et al*
54	46				123		0		1991	Antoine JC *et al*
55	61	F			109		1	249	1993	Fazio R *et al*
56	48	F	+				2		1993	Cheung MC *et al*
57	52	F	+	+	115	8.6	3	185	1994	C. Serfaty-Lacrosniere *et al*
58	37	M	+	+	58	21	1	365	1994	C. Serfaty-Lacrosniere *et al*
59	40	M	-	-	40	23	0	242	1994	C. Serfaty-Lacrosniere *et al*
60	56	F			130		2		1994	Frosini G *et al*
61	29	M	+	-	143		3.87	164	1994	Burnett JR *et al*
62	40	M	-	-	46	19	0	242	1994	Barnard GF *et al*
63	36	F			104			123	1996	No authors listed
64	39	F		-	89		<10	487	1996	Mentis SW *et al*
65	57	F		+					1998	Neuman M *et al*
66	8	F			88.2		6.58	194	1998	Lachaux A *et al*
67	1	M			84.4		3.87	265	1998	Lachaux A *et al*

(Cont Table 1)

	age	gender	angina	other vascular disease	TCho	LDL-C	HDL-C	TG		
68	55	M	+		36		2	143	2000	Ohnishi M *et al*
69	48	M	+		28		6	232	2000	Komuro R *et al*
70	50	F	+	+	92.9	63.9	3.87	124	2001	Bertolini S *et al*
71	48	M	+		96.3	56.8	5	75	2002	Ishii J *et al*
72	20	M	-		61		0	114	2002	Guo Z *et al*
73	69	M	-		34		0.8	187	2002	Guo Z *et al*
74	57	M	+		22		4	88	2002	Guo Z *et al*
75	56	M	+		25		1	112	2002	Takami H *et al*
76	54	F	-	-	108	absent	absent		2003	Zuchner S *et al*
77	32	F	-	-	75.9		1.94	162	2003	Kolovou GD *et al*
78	29	M	-	-	27		3	231	2003	Grobusch MP *et al*
79	36	M	-	-	63	not detectable	not detectable		2004	Sinha S *et al*
80	52	M	-	-	159	105	3.87	204	2004	Hovingh GK *et al*
81	38	M	+	+	89	50.3	3.87	177	2004	Hovingh GK *et al*
82	42	F	+		147	108	3.87	228	2004	Albrecht C *et al*
83	42	F	-	-	66	52	4	37	2004	Guan JZ *et al*
84	53	M			41		4		2004	Morchen M *et al*
85	72	F							2004	Herrmann WA *et al*
86	42	F		+	136	108	1.55	133	2006	Slatter TL *et al*
87	17	M							2006	Cai Z *et al*
88	24	M	-		33	10	1	100	2006	Espinel J *et al*
89	65	M	+	+	70	29	5.5	299	2007	Imai R *et al*
90	15	F	-	-	127		5.79	166	2008	Theaudin M *et al*
91	55	F			81		4	384	2008	Sperti C *et al*
92	49	M	+	+	60		0		2008	Schippling S *et al*
93	57	M	+		78	37	5	178	2008	Bektas M *et al*
94	35	F	-	-					2009	Miyachi K *et al*
95	31	F			98	87	1	66	2009	Maekawa M *et al*
96	74	M	-		69		3.55	42	2009	Koseki M *et al*
97	44	M	+		64		2.5	272	2009	Koseki M *et al*
98	71	F	+		59		6	162	2009	Koseki M *et al*
99	54	M	+		35		0	395	2009	Koseki M *et al*
100	62	M	+		65.8	19.4	1.93	274.6	2009	Hooper AJ *et al*
101	37	M	+	+	58		4	184	2009	Sampietro T *et al*
102	40	M	-	-	67		2.32	114.3	2010	Cameron J *et al*
103	55	F				105	3	384	2010	Pichit P *et al*
104	53	F	+			141	5	138	2010	Pichit P *et al*
105	43		-	-			1.93		2012	Zyss J *et al*
106	52		-	-			3.09		2012	Zyss J *et al*
107	39		+	+			1.16		2012	Zyss J *et al*
108	50	M	-	+			5.02		2012	Zyss J *et al*
109	22	M	-	-	92	49	6	184	2012	Rader DJ *et al*
110	76	F	-	-	34.8	19.3	0.38	283	2012	Fasano T *et al*
111	33	M	+	+	108	46.4	5.41	283	2012	Fasano T *et al*
112	6	F			61.8	34.8	2.32	133	2012	Fasano T *et al*
113	32	M	-	-	50.3	not available	1.16	186	2012	Fasano T *et al*
114	0	M			96.7	22	5.03	133	2012	Fasano T *et al*
115	69	F	-	+	143	104	11.6	133	2012	Fasano T *et al*
116	37	M	-		166	not available	5.41	1187	2012	Fasano T *et al*
117	60	F	-	+	217	139	27.8	310	2012	Fasano T *et al*
118	54	M	-	+	224	128	22	390	2012	Fasano T *et al*
119	52	M	-	+	228	155	18.9	328	2012	Fasano T *et al*
120	45	F	+	+	60	34	unmeasurable	103	2012	Pervaiz MA *et al*
121	59	F	+	+	57	31	2		2012	Feng W *et al*
122	38	F	-	+	124	106	<5	138	2013	Negi SI *et al*
123	51	M	-	-	48	8	1	not detectable	2014	Lucchi T *et al*
124	58	F		+	60		2	448	2014	Sechi A *et al*
125	12	M	-	-	48	0	0.6	319	2014	Sahiner N *et al*
126	3	M			60	41.4	<3.1		2014	Ravesloot *et al*
127	22	F			50	27	3.1	108	2015	Brunham LR *et al*
128	26	M		-	65	34	7.7	114	2015	Brunham LR *et al*
129	4	F			49.9	14.7	5.41	151	2015	Brunham LR *et al*
130	16	M	-	-	86	49.8	<5	86	2015	Per H *et al*
131	17	M	-	-	59		2	107	2016	Murano T *et al*
132	43	M		-	149	110	5		2016	Nagappa M *et al*

Abbreviations: The same cases were described with preference to the latest report. TCho, total cholesterol (mg/dL); LDL-C, low density lipoprotein-cholesterol (mg/dL); HDL-C, high density lipoprotein-cholesterol (mg/dL); TG, triglycerides (mg/dL).

Table 2. Clinical characteristics and lipid profiles of Tangier patients divided by presence or absence of atherosclerosis

male	CVD(+) (n=26)	CVD(−) (n=41)	p-value
age	51.1 ± 10.3	34.9 ± 17.7	<0.001
TCho (mg/dL)	65.8 (42.0, 89.0)	58.0 (46.3, 72.0)	0.347
LDL-C (mg/dL)	52.1 ± 44.4	46.9 ± 40.9	0.377
HDL-C (mg/dL)	3.87 (1.00, 5.31)	2.00 (1.00, 5.00)	0.555
TG (mg/dL)	231 (173, 286)	184 (112, 242)	0.110
female	**CVD(+) (n=17)**	**CVD(−) (n=26)**	**p-value**
age	54.2 ± 9.71	28.8 ± 18.1	<0.001
TCho (mg/dL)	105 (63.3, 130)	73.0 (59.8, 89.0)	0.049
LDL-C (mg/dL)	85.9 ± 44.7	53.9 ± 37.7	0.038
HDL-C (mg/dL)	3.87 (2.00, 6.00)	5.00 (1.97, 7.00)	0.932
TG (mg/dL)	150 (133, 217)	159 (131, 206)	0.709

These statistical analyses were performed using the STATA version 11.0 (Stata, College Station, TX, USA) statistics software package. Data are expressed as mean ± s.d. or median (interquartile range; 25–75%) because of histogram. All participants were using t-tests or Wilcoxon's signed rank tests appropriately.
TCho, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglycerides.

fer EJ *et al*. indicated that LDL-C levels were typically lower than normal in Tangier disease[13]. This was explained by a twofold increase in LDL-C catabolism. However, it was also reported that the low levels of LDL-C in Tangier patients were rich in small dense LDL[13]. In our case, small dense LDL was markedly elevated, and this could have been involved in the extensive atherosclerosis.

Regarding the mutational analysis of *ABCA1* gene, there is a report that V825I was associated with coronary artery disease while having no effect on HDL-C or ApoA1 levels[14]. In addition, the V825I mutation is located in the transmembrane domain[15]. Frikke-Schmidt *et al*. genotyped single-nucleotide polymorphisms of 69,259 individuals and found that V825I affected the risk of coronary artery disease[16]. On the other hand, Yin *et al*. suggested that there was no significant association between the V825I polymorphism and the risk of atherosclerosis[17]. Thus, the association between V825I and cardiovascular disease is controversial. In our case, the other mutation, N935T is a novel mutation, located between 6th transmembrane domain and ATP-hydrolyzing domain. We consider that the feature of this novel mutation might be associated with transportation of cholesterol.

There still remain many unknown points regarding the pathophysiology of Tangier disease. Further investigation is required to assess the incidence and the mechanism of atherosclerosis and bleeding tendency in Tangier patients.

COI Statement

The authors have no conflicts of interest to declare in association with this study.

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Supplemental Table 1. Clinical characteristics and Hemostasis Coagulation Tests of this case

	Proband		Normal range
Height	160 cm		
Weight	60.0 kg		
BMI	23.4 kg/m^2		
white blood cell	5,400 /μL		3,800～8,500 /μL
red blood cell	3.67×10^6 /μL		4.00～5.00×10^6 μL
Hemoglobin	12.3 g/dL	↓	13.0～16.80 g/dL
Hematocrit	35.6%	↓	38.0～52.0%
total cholesterol	98 mg/dL		130～219 mg/dL
HDL-C	2 mg/dL	↓↓↓	40～70 mg/dL
LDL-C	89 mg/dL		61～139 mg/dL
triglyceride	67 mg/dL		35～149 mg/dL
lipoprotein (a)	2 mg/dL		～40 mg/dL
apoprotein A-1	＜5 mg/dL	↓↓↓	119～155 mg/dL
Platelet counts	6.3×10^4 /μL	↓↓	10.0～40.0×^{4} /μL
MPV	12.9 fL	↑	7.5～11.0 fL
PDW	17.8%	↑	15.2～17.2%
PCT	0.081%	↓	0.1～0.3%
PT	90%		80～120%
PT-INR	1.07		0.87～1.11
APTT	40.8 sec	↑	24.1～35.3 sec
Bleeding time	＞10 minute	↑↑	1.0～5.0 minutes

Abbreviations: HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; MPV, mean platelet volume; PDW, platelet distribution width; PCT, plateletcrit.