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 disease1-4). ABCA1 transports cholesterol at the plasma membrane and is expressed throughout the body5). In
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. 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 (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 nose bleeds. 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/m². 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. 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. 1H). 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).
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 disease10). We assumed that ABCA1 and cdc42 have intracellular colocalization11). 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 paper8) (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-

**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 deficiency9); 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

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**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.
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).

Fig. 3.
| age | gender | angina | other vascular disease | TCho | LDL-C | HDL-C | TG |
|-----|--------|--------|------------------------|------|-------|-------|----|
| 1   | 24     | M      | -                      | 53   | 16    | 0     | 284|
| 2   | 25     | F      | -                      | 63   | 30    | 0     | 351|
| 3   | 25     | F      | -                      | 46   | 38    | 4     | 72 |
| 4   | 29     | F      | -                      | 89   | 80    | 6     | 131|
| 5   | 72     | M      | +                      | 74   | 47    | 2     | 207|
| 6   | 48     | M      | +                      | 69   | 13    | 0     | 213|
| 7   | 37     | M      | -                      | 47   | 8     | 8     | 332|
| 8   | 25     | F      | -                      | 84   | 70    | 2     | 163|
| 9   | 33     | F      | -                      | 84   | 49    | 5     | 154|
| 10  | 40     | M      | -                      | 68   | 4     | 4     | 122|
| 11  | 3      | F      | -                      | 70   | 7     | 7     | 155|
| 12  | 5      | M      | -                      |       |       |       | 1971|
| 13  | 15     | F      | -                      | 59   | 47    | 2     | 207|
| 14  | 53     | F      | +                      | 95   | 9     | 9     | 180|
| 15  | 62     | M      | +                      | 60   | 0     | 0     | 230|
| 16  | 8      | F      | -                      | 83   | 5     | 5     | 105|
| 17  | 6      | F      | -                      |       |       |       | 1974|
| 18  | 10     | M      | -                      | 57   | 35    | 2     | 110|
| 19  | 7      | M      | -                      | 72   | 37    | 2     | 180|
| 20  | 56     | M      | +                      | 114  | 6     | 6     | 269|
| 21  | 2      | F      | -                      | 64   |       |       | 181|
| 22  | 56     | M      | -                      | 60   | 6     | 6     | 100|
| 23  | 53     | M      | -                      | 51   | 0     | 0     | 170|
| 24  | 56     | F      | -                      | 90   | 5     | 5     | 348|
| 25  | 56     | M      | +                      | 42   | 22    | 0     | 297|
| 26  | 14     | F      | -                      | 59   | 49    | 0     | 102|
| 27  | 69     | F      | -                      | 116  | 101   | 6     | 114|
| 28  | 19     | F      | -                      | 80   | 39    | 4     | 214|
| 29  | 20     | F      | -                      | 177  | 158   | 8     | 240|
| 30  | 26     | M      | -                      | 73   | 73    | 8     | 124|
| 31  | 19     | M      | -                      | 138  | 134   | 8     | 178|
| 32  | 29     | F      | -                      | 69   | 0     | 0     | 145|
| 33  | 31     | F      | -                      | 60   | 2     | 2     | 88 |
| 34  | 15     | M      | -                      |       |       |       | 1984|
| 35  | 62     | M      | +                      | 79   | 1     | 1     | 146|
| 36  | 28     | F      | -                      | 50   | 15    | 8     | 175|
| 37  | 26     | F      | -                      | 59   | 8     | 8     | 132|
| 38  | 38     | M      | -                      | 55   | 2     | 2     | 190|
| 39  | 53     | M      | -                      | 98   | 2     | 2     | 355|
| 40  | 36     | M      | -                      | 52   |       |       | 233|
| 41  | 65     | M      | -                      | 28   | 1     | 1     | 202|
| 42  | 61     | F      | -                      | 106  | 7     | 7     | 208|
| 43  | 62     | M      | -                      | 72   | 6     | 6     | 297|
| 44  | 27     | M      | -                      | 46   | 0     | 0     | 244|
| 45  | 55     | F      | +                      | 73   | 1.5   | 1.5   | 658|
| 46  | 50     | M      | -                      | 103  |       |       | 545|
| 47  | 14     | M      | -                      | 25   | 5     | 5     | 98 |
| 48  | 5      | M      | -                      | 23   | 1     | 1     | 40 |
| 49  | 30     | M      | -                      | 30   | 1     | 1     | 78 |
| 50  | 36     | M      | -                      | 127  | 9     | 9     | 124|
| 51  | 22     | M      | -                      | 35   |       |       | 89 |
| 52  | 43     | M      | -                      | 10   | 1     | 1     | 202|
| 53  | 47     | M      | +                      | 28   | 6     | 6     | 232|
| 54  | 46     | F      | -                      | 123  | 0     | 0     | 232|
| 55  | 61     | F      | -                      | 109  | 1     | 1     | 249|
| 56  | 48     | F      | +                      | 115  | 8.6   | 3     | 185|
| 57  | 52     | F      | +                      | 58   | 21    | 1     | 365|
| 58  | 37     | M      | +                      | 40   | 23    | 0     | 242|
| 59  | 40     | M      | -                      | 130  | 2     | 2     | 164|
| 60  | 56     | F      | -                      | 143  | 3.87  | 3.87  | 164|
| 61  | 29     | M      | -                      | 46   | 19    | 0     | 242|
| 62  | 40     | M      | -                      | 104  | 1     | 1     | 123|
| 63  | 36     | F      | -                      |       |       |       | 1997|
| 64  | 39     | F      | -                      | 89   | <10   | <10   | 487|
| 65  | 57     | F      | +                      |       |       |       | 98 |
| 66  | 8      | F      | -                      | 88.2 | 6.58  | 6.58  | 194|
| 67  | 1      | M      | -                      | 84.4 | 3.87  | 3.87  | 265|

Table 1. Clinical and laboratory features in Tangier disease
| age | gender | angina | other vascular disease | TCho | LDL-C | HDL-C | TG |
|-----|--------|--------|------------------------|------|-------|-------|----|
| 68  | 55     | M      | +                      | 36   | 2     | 143   | 2000 |
| 69  | 48     | M      | +                      | 28   | 6     | 232   | 2000 |
| 70  | 50     | F      | + +                   | 92.9 | 63.9  | 3.87  | 124  |
| 71  | 48     | M      | +                      | 96.3 | 56.8  | 5     | 75   |
| 72  | 20     | M      | -                      | 61   | 0     | 114   | 2002 |
| 73  | 69     | M      | -                      | 34   | 0.8   | 187   | 2002 |
| 74  | 57     | M      | +                      | 22   | 4     | 88    | 2002 |
| 75  | 56     | M      | +                      | 25   | 1     | 112   | 2002 |
| 76  | 54     | F      | -                      | 108  | absent| absent | 2003 |
| 77  | 32     | F      | -                      | 75.9 | 1.94  | 162   | 2003 |
| 78  | 29     | M      | -                      | 27   | 3     | 231   | 2003 |
| 79  | 36     | M      | -                      | 63   | not detectable | not detectable | 2004 |
| 80  | 52     | M      | -                      | 159  | 105   | 3.87  | 204  |
| 81  | 38     | M      | + +                   | 89   | 50.3  | 3.87  | 177  |
| 82  | 42     | F      | +                      | 147  | 108   | 3.87  | 228  |
| 83  | 42     | F      | -                      | 66   | 52    | 4     | 37   |
| 84  | 53     | M      | -                      | 41   |       |       |      |
| 85  | 72     | F      | -                      |       |       |       |      |
| 86  | 42     | F      | + 136                  | 108  | 1.55  | 177   | 2003 |
| 87  | 17     | M      | -                      |       |       |       |      |
| 88  | 24     | M      | -                      | 33   | 10    | 100   | 2006 |
| 89  | 65     | M      | + +                   | 70   | 29    | 299   | 2007 |
| 90  | 15     | F      | -                      | 127  | 5.79  | 166   | 2007 |
| 91  | 55     | F      | -                      | 81   | 4     | 384   | 2008 |
| 92  | 49     | M      | + +                   | 60   |       |       |      |
| 93  | 57     | M      | +                      | 78   | 37    | 178   | 2008 |
| 94  | 35     | F      | -                      |       |       |       |      |
| 95  | 31     | F      | -                      | 98   | 87    | 1     | 2009 |
| 96  | 74     | M      | -                      | 69   | 3.55  | 42    | 2009 |
| 97  | 44     | M      | + +                   | 64   | 2.5   | 272   | 2009 |
| 98  | 71     | F      | + +                   | 59   | 6     | 162   | 2009 |
| 99  | 54     | M      | + +                   | 35   | 0     | 395   | 2009 |
| 100 | 62     | M      | +                      | 65.8 | 19.4  | 1.93  | 274.6|
| 101 | 37     | M      | + +                   | 58   | 4     | 184   | 2009 |
| 102 | 40     | M      | -                      | 67   |       | 114.3 | 2010 |
| 103 | 55     | F      | -                      | 105  | 3     | 384   | 2010 |
| 104 | 53     | F      | + 141                  |      | 5     | 138   | 2010 |
| 105 | 43     | F      | -                      |       | 1.93  | 2012 |
| 106 | 52     | F      | -                      |       | 3.09  | 2012 |
| 107 | 39     | F      | + +                   |       | 1.16  | 2012 |
| 108 | 50     | M      | - +                   |       | 5.02  | 2012 |
| 109 | 22     | M      | -                      | 92   | 49    | 6     | 184  |
| 110 | 76     | F      | -                      | 34.8 | 19.3  | 0.38  | 283  |
| 111 | 33     | M      | + +                   | 108  | 46.4  | 5.41  | 283  |
| 112 | 6      | F      | 61.8 34.8 2.32 133     | 2012 |
| 113 | 32     | M      | -                      | 50.3 | not available | 1.16  | 2012 |
| 114 | 0      | M      | -                      | 96.7 | 22    | 5.03  | 133  |
| 115 | 69     | F      | - +                   | 143  | 104   | 11.6  | 133  |
| 116 | 37     | M      | -                      | 166  | not available | 5.41  | 1187 |
| 117 | 60     | F      | - +                   | 217  | 139   | 27.8  | 310  |
| 118 | 52     | M      | - +                   | 224  | 128   | 22    | 390  |
| 119 | 52     | M      | + +                   | 228  | 155   | 18.9  | 328  |
| 120 | 45     | F      | + +                   | 60   | 34    | unmeasurable | 103 |
| 121 | 59     | F      | + +                   | 57   | 31    | 2     | 2012 |
| 122 | 38     | F      | + +                   | 124  | 106   | <5    | 138  |
| 123 | 51     | M      | -                      | 48   | 8     | not detectable | 103 |
| 124 | 58     | F      | + +                   | 60   | 2     | 448   | 2014 |
| 125 | 12     | M      | -                      | 48   | 0     | 0.6   | 319  |
| 126 | 6      | M      | -                      | 40.4 | <3.1  | 2012 |
| 127 | 22     | F      | 50 27 3.1 108          | 2015 |
| 128 | 26     | M      | -                      | 65   | 34    | 7.7   | 2015 |
| 129 | 4      | F      | 49.9 14.7 5.41 151     | 2015 |
| 130 | 16     | M      | -                      | 86   | 49.8  | <5    | 2015 |
| 131 | 17     | M      | -                      | 59   |       | 2     | 107  |
| 132 | 43     | M      | +                      | 149  | 110   | 5     | 2016 |

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

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COI Statement

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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/m²  |                            |
| white blood cell   | 5,400 /µL   | 3,800 ~ 8,500 /µL          |
| red blood cell     | 3.67 x 10⁶ /µL | 4,00 ~ 5.00 x 10⁶ /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 x 10⁴ /µL | 10.0 ~ 40.0 x 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.