International Journal of Hematology (2019) 109:214–220
https://doi.org/10.1007/s12185-018-2561-9

CASE REPORT

A high titer of acquired factor V inhibitor in a hemodialysis patient who developed arterial thrombosis

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Received: 3 February 2018 / Revised: 12 November 2018 / Accepted: 13 November 2018 / Published online: 16 November 2018

Abstract

An 87-year-old man with diabetes mellitus was admitted to control recurrent bleeding from hemodialysis puncture sites. He was a smoker and had been diagnosed with arteriosclerosis obliterans. His PT and APTT were markedly prolonged, and all coagulation factors were markedly decreased (factor V [FV] activity < 1%) or below the measurement threshold, with the exception of fibrinogen and factor XIII. Neither PT nor APTT were corrected upon mixing with normal plasma. A high titer of FV inhibitor was found at 415 BU/mL, and anti-FV autoantibody was detected by both immunoblot assay and ELISA. Prednisolone administration and plasma exchange partially improved prolonged PT and APTT and decreased the FV inhibitor level. Five months later, he manifested symptoms of severe ischemia in both legs. Angiography revealed diffuse stenosis downstream of both common iliac arteries. Endovascular therapy was repeated four times, the prednisolone dose was reduced, and low-dose antiplatelet therapy was initiated. After the final successful endovascular therapy, arterial thrombosis was detected using ultrasound and angiography. Aspiration thrombectomy and thrombolytic therapy failed to achieve recanalization, and necrosis of the legs worsened. Despite the severe coagulation abnormalities, vascular interventions should have been performed with regular-dose antiplatelet therapy, as the patient exhibited multiple risk factors for atherothrombosis.

Keywords Anti-factor V autoantibody · Bleeding/hemorrhage · Thrombosis · False multiple factor deficiencies · False multiple factor inhibitors

Introduction

'Acquired hemophilia' is a category of rare autoimmune diseases characterized by 'the presence of autoantibodies directed against clotting factors [1]'. The incidence of the most frequently acquired hemophilia, acquired hemophilia A (AHA) due to anti-factor VIII (FVIII) inhibitors, has been estimated at 1.5 cases per one million population per year [2]. Fewer cases of acquired factor V (FV) inhibitor (AFV-I) or autoimmune-acquired FV deficiency due to anti-FV antibodies (so to speak, acquired parahemophilia) have been reported; their incidences are estimated at 0.09–0.29 cases per million person-years [3, 4]. AFV-I is likely under-recognized [5], as its clinical manifestations range from asymptomatic laboratory abnormalities to fatal exsanguination, or even to thromboembolic events [6]; however, most patients with AFV-I will exhibit some bleeding symptoms [3–6]. Historically, AFV-I has often developed in patients treated with bovine thrombin and is occasionally observed on an

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12185-018-2561-9) contains supplementary material, which is available to authorized users.

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idiopathic basis, as well as in association with antibiotics, malignancies, and autoimmune disorders.

Here, we report the case of a patient with AFV-I who developed arterial thrombosis in the left leg after long-term corticosteroid therapy against anti-FV autoantibodies.

Case presentation

An 87-year-old Japanese man with a longstanding history of type 2 diabetes mellitus (DM) was urgently admitted to our hospital to control recurrent bleeding from the hemodialysis puncture sites. An arteriovenous (AV) shunt had been created 3 years ago because of diabetic chronic renal insufficiency. On that occasion, there was no excessive bleeding and his prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT) were normal [PT, 11.7 s (reference range 10.5–14.6 s); PT activity, 100% (reference 70–140%); INR, 1.00 (reference 0.9–1.1); and APTT, 36.5 s (reference 25.0–40.0 s)]. In the past, he had undergone surgical revisions of the AV shunt 5 times and percutaneous transluminal angioplasty twice because of repeated stenosis and thrombotic occlusion, and thus, he was administered antiplatelet medicines: aspirin (100 mg/day) and clopidogrel (75 mg/day). Formerly, he did not experience any episode of excessive bleeding from the puncture sites after dialysis sessions with intra-circuit administration of un-fractionated heparin (2,500 units/session). The patient underwent uncomplicated prior surgical procedures for hemorrhoids in his twenties, prostate hypertrophy and cataracts in his seventies, and inguinal hernia and calcified cervical yellow ligament 3 years ago. To our best knowledge, the patient has never been exposed to bovine or human thrombin during these two recent surgeries. There was no family history of a bleeding diathesis. Two weeks before hospitalization, he developed bronchial pneumonia and underwent treatment with antibiotics: ceftriaxone (0.5 g/day on two dialysis days) and levofloxacin (250 mg/day). He was a regular smoker until his sixties (40 cigarettes/day) and was diagnosed with chronic obstructive pulmonary disease, as well as arteriosclerosis obliterans (ASO; Fontaine classification grade II).

He weighed 49.3 kg, and his height was 159 cm. Physical examination at the time of admission revealed pale palpebral conjunctiva and persistent oozing from two puncture sites of the AV shunt. He had mild dysesthesia and numbness in the lower extremities, suggesting the development of diabetic neuropathy. His ankle brachial pressure index (normal > 0.9) decreased bilaterally to 0.72 (right) and 0.78 (left), which was consistent with ASO. Laboratory studies showed that the patient's red blood cell (RBC) count was $3 \times 10^6/\mu L$ and hemoglobin was 9.7 g/dL. The remainder of the complete blood count was normal, as were electrolytes and liver function (Table S1). Increased levels of creatinine, blood urea nitrogen (BUN), fasting blood sugar, and glycated hemoglobin (HbA1c) were consistent with the parameters of diabetic nephropathy. His PT and APTT were markedly prolonged to 60 s and > 200 s, respectively, and INR increased to 4.98. Immediately, administration of antiplatelet medicines and ω-3 ethyl fatty acids (containing ethyl icosapentaenoate and ethyl decosa-hexaenoate) were discontinued. Neither PT nor APTT corrected after receiving 960 mL of fresh frozen plasma (FFP), as well as vitamin K (menatetrenone 20 mg × 3/day, iv) and protamine sulfate (40 mg iv).

Individual coagulation factor assays conducted by an external commercial laboratory revealed that all coagulation factors were drastically decreased (FV activity < 1%, reference 70–135%) or immeasurable (no clotting), with the exception of fibrinogen and factor XIII (FXIII), which were 417 mg/dL (reference 150–400 mg/dL) (Table S1) and 148% (reference 70–140%) (Table 1), respectively. Both factor VIII (FVIII) and factor IX (FIX) inhibitors were reported to be positive at > 5.1 Bethesda units (BU)/mL (reference < 0.5 BU/mL). Although lupus anticoagulant (LA) testing was also reported to be immeasurable (no clotting) based on diluted Russell's Viper venom time (dRVVT), results of anti-cardiolipin/β_2-glycoprotein I antibody, anti-cardiolipin immunoglobulin (Ig)G, and anti-phosphatidylserine-prothrombin complex (anti-PS/PT) antibody testing were negative (< 0.7 U/mL, < 8.0 U/mL, and < 5.0 U/mL respectively). Subsequently, experimental detailed analyses were carried out by the JCRG for the definite diagnosis of these multiple coagulation factor abnormalities. The patient's FVIII activity (which was assessed by employing a synthetic chromogenic substrate, Hyphen BioMed, Neuville-sur-Oise, France) and antigen (VisuLize™ FVIII Antigen Kit, Affinity Biologicals™ Inc., Ancaster, Ontario, Canada) levels were normal [90% and 1.5 IU/mL, respectively, (reference 50–200% and 0.64–1.89 IU/mL, respectively)]. He tested near the upper limit of gray zone for anti-FVIII autoantibody (26 IU/mL) using ELISA (Zymutest Anti FVIII IgG MonoStrip, Hyphen BioMed) either (12 < gray zone < 24 IU/mL) on day 27 of hospitalization. Thus, AHA was effectively excluded. Neither PT nor APTT were corrected upon mixing with normal plasma (0–2 h incubation) (Fig. 1), indicating the presence of a coagulation inhibitor, rather than a factor deficiency. In addition, a high titer of FV-I was found to be 415 BU/mL (Table 1); the presence of anti-FV autoantibody was confirmed by both an immunoblot assay and enzyme-linked immunosorbent assay (ELISA) employing purified human plasma FV (Fig. 1). Neither factor X (FX) inhibitor nor prothrombin (FII) inhibitor was detected by these experiments.

For inhibitor suppression, prednisolone (PSL) administration was initiated at 0.5 mg/kg daily. Slowly and partially, PT and APTT improved and the FV-I level decreased (Fig. 2a). When plasma exchange (PEX) was conducted three times

Table 1 Results of coagulation tests (abnormal values are underlined)

<Outside lab (hospital day 11)>	<Outside lab (hospital day 11)>	<JCRG (hospital day 27)>
FDP 3.5 μg/mL	F. II 1%	Total PAI-1 25 ng/mL
D-dimer 0.86 μg/mL	F. V < 1%	F. VIII < 1%
Fibrinogen* 417 mg/dL	F. VII 7%	1:1 mixing < 1%
antithrombin 91%	F. VIII not M	Control 47%
Protein C:Act** 91%	F. IX not M	Anti-PS/PT Ab < 5 U/mL
free Protein S:Ag 78%	F. X 1%	F. V inh 415 BU/mL
PIVKA-II < 1 μg/mL	F. XI not M	F. X inh not detected
TAT 1.1 ng/mL	F. XII not M	F. II inh not detected
PIC 0.6 μg/mL	F. XIII 148%	
<in-house>	F. VIII inh > 5.1 BU/mL	
Duke's bleeding time	F. IX inh > 5.1 BU/mL	
150 s		

Act activity, *Ag* antigen, *PIVKA* protein induced by vitamin K absence, *TAT* thrombin–antithrombin complex, *PIC* plasmin–plasmin inhibitor complex, *F. II* prothrombin, *not M*. not measurable (did not clot within 200 s), *inh* inhibitor, *PAI-1* plasminogen activator Inhibitor type 1, *PS/PT* phosphatidylserine/prothrombin, *Ab* antibody, *F.II* prothrombin

*Thrombin-based assay

**Chromogenic assay

in an attempt to enhance rapid elimination of FV-I [7] and to reduce PSL dosing, modest transient improvements in PT, APTT, and FV-I titer were observed during each PEX (Table S2). Manual compression for 20–30 min was still required to achieve hemostasis at puncture sites after hemodialysis sessions. Furthermore, persistent FV-I facilitated hemodialysis without anticoagulation with heparin. He was discharged 4 months after admission.

Three weeks after the discharge, he was readmitted for severe ischemic symptoms, including pain at rest and multiple ulcers in both legs. His ankle brachial pressure index worsened to 0.5 (right) and 0.86 (left). Because angiography revealed diffuse severe stenosis with calcification downstream of both common iliac arteries, endovascular therapy (EVT) was repeated 4 times. In addition, the dose of PSL was reduced and administration of the antiplatelet drug cilostazol was initiated at 100 mg/day (Fig. 2b). Five days after the last successful EVT of the left lower extremity, acute arterial thrombosis was detected using ultrasound and angiography in the initial portion of the left posterior tibial artery (Fig. 3). Aspiration thrombectomy and thrombolytic therapy with arterial urokinase injections (60,000 units, 3 times/day for 7 days) through an inserted Fountain™ catheter failed to achieve recanalization, and necrosis of the legs worsened (Fig. 2b). Unfortunately, the patient died of repeated aspiration pneumonia and general debility 4 months after the second hospitalization. His PT and APTT remained prolonged at around 35 s and 70 s, respectively. Nevertheless, enforced immunosuppressive treatment to eradicate FV-I was not selected throughout the clinical course, because the patient experienced no severe hemorrhage and was a compromised host who was an elderly individual, with DM, and on maintenance hemodialysis, thus, being vulnerable to infections.

Discussion

The present patient's medical history and clinical examination did not indicate the presence of typical risk factors of AFV-I, such as malignancies, autoimmune diseases, and bovine thrombin exposure. However, he was exposed to ceftriaxone and levofloxacin for the treatment of pneumonia; the former is an antibiotic specifically of the β-lactam group most frequently associated with the development of AFV-I [7, 8]. Discontinuation of the antibiotics, however, did not resolve the levels of anti-FV autoantibody in this patient. Alternatively, other unknown stimulants/precipitants may have predisposed the patient to developing FV-Is.

Importantly, this case showed false multiple coagulation factor inhibitors [5], as well as false multiple coagulation factor deficiencies, with the exception of fibrinogen, FXIII, and von Willebrand factor (VWF, ristocetin cofactor activity 118%; reference 60–170%). Because most coagulation factor assays are performed using clotting methods that employ specific coagulation factor-deficient plasma, FV in these plasma reagents would be completely neutralized by the extremely high-titer FV-I of this patient. Consequently, all coagulation factors, except for fibrinogen, FXIII, and VWF, in his plasma sample were completely deficient in appearance, resulting in pseudo-multiple coagulation factor deficiencies [3]. Because most LA assays also use clotting methods and plasma reagents, the high titer of the patient's FV-I made LA testing immeasurable (no

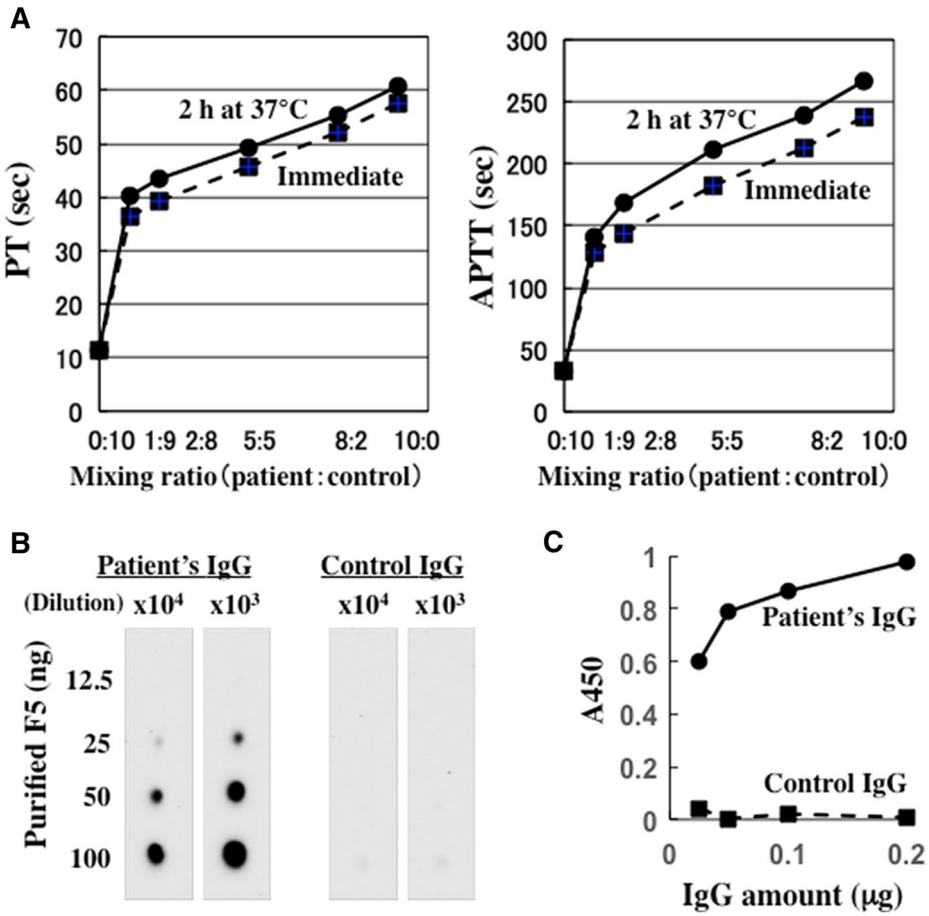

Fig. 1 JCRG's analyses for detection of anti-FV autoantibody. **a** Five-step dilution cross-mixing tests by PT and APTT. The mixed samples showed an inhibitor pattern both immediately (broken line and circles) and after 2 h of incubation at 37 °C (solid line and squares), because there was an upward deviation. **b** Immunoblot assays were performed using purified plasma-derived FV at the indicated amounts shown as antigen (ng). The results showed the presence of anti-FV antibody in an IgG fraction extracted from the patient's plasma using a protein A-Sepharose column. **c** ELISA for anti-FV autoantibody. The amount of patient's IgG is shown on the abscissa and the absorbance at 450 nm on the ordinate. Much more of the patient's IgG (solid line and squares) was bound to purified plasma-derived FV than the control IgG (broken line and circles). *JCRG* Japanese Collaborative Research Group on Autoimmune Coagulation Factor Deficiencies, *FV* factor V, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *IgG* immunoglobulin G, *ELISA* enzyme-linked immunosorbent assay

clotting). Accordingly, it is often difficult for physicians to make an early definite diagnosis with acquired FV-I, especially when its titer is high. It would be helpful to carry out the coagulation factor assays with synthetic enzymatic substrates that are specific to individual factors. In our patient, three anti-phospholipid antibodies were negative, and anti-FV autoantibody as well as FV-I was detected. LA (dRVVT) detected as negative 2 months after admission (Table S3), and all but FV of the coagulation factors returned to normal or subnormal levels 4 months after admission, as were FVIII and FIX inhibitors. With the benefit of hindsight, hepaplastin test (or Normotest) would be useful as a laboratory test for acquired FV deficiency because its patients present a discrepancy between results of PT (and APTT) and hepaplastin test [9].

The hemostatic treatment of symptomatic patients with FV-Is is mainly anecdotal and a few therapeutic options for bleeding are documented [3–6]. This patient's case presented a therapeutic dilemma between the newly developed coagulation abnormality (AFV-I) and the longstanding atherothrombotic tendency (ASO). In addition to the abnormal coagulation test results, the patient manifested mild bleeding, and thus, administration of antiplatelet medicines were discontinued and his maintenance hemodialysis was managed without anticoagulation during sessions, to avoid excessive bleeding. While FFP, vitamin K, and protamine sulfate were administered for hemostatic treatment at the initial clinical course before definite diagnosis, specific FV replacement therapy was not applied to the patient afterward, to avoid triggering possible thrombosis; moreover,

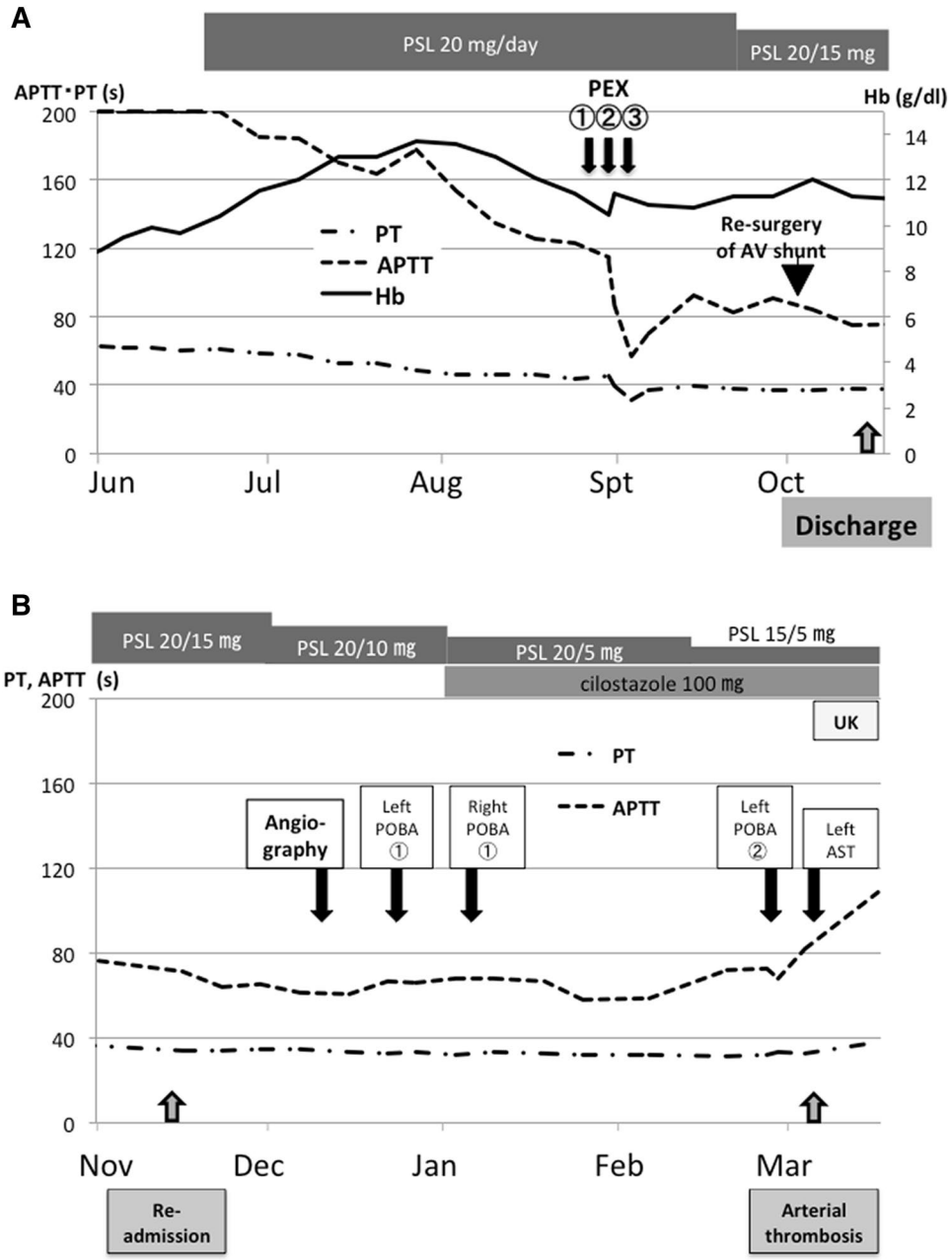

Fig. 2 Clinical course of the present case. **a** The patient underwent immunosuppressive therapy with oral PSL, and its dose was tapered later because bleeding symptoms improved. PEX (filled arrows) was also conducted three times to enhance rapid elimination of FV inhibitor and to reduce PSL dosing. PT (solid line), APTT (broken line), and hemoglobin levels (Hb; dotted line) were monitored to evaluate the therapeutic effect. Hb levels increased early after the initiation of corticosteroid therapy, and PT and APTT started to decrease gradually after a series of PEX, reflecting the decrease in FV neutralizing antibody. He was discharged after a re-surgery of AV shunt (filled arrowhead), because his clinical condition was stable. **b** Because pain in the patient's legs kept increasing and multiple ulcers were noted, EVT was repeated 4 times including AST (filled arrows). EVT by POBA2 achieved excellent dilatation of the left tibial arteries. However, the patient developed arterial thrombosis of the left posterior tibial artery, which was not reopened despite undergoing AST and thrombolytic therapy with UK. The patient died 4 months after readmission. *PSL* prednisolone, *PEX* plasma exchange, *FV* factor V, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *AV* arteriovenous, *EVT* endovascular therapy, *POBA* percutaneous old balloon angioplasty, *AST* aspiration thrombectomy, *UK* urokinase

commercial FV concentrates were unavailable. Platelet concentrates, which contain FV in their alpha-granules [10], were not used either.

We presented the case of a bleeding patient with a proven FV-I who developed arterial thrombosis 8 months after the discontinuation of anticoagulation for hemodialysis. Because the patient exhibited multiple risk factors for atherothrombosis, such as DM, smoking history, hypertension, dyslipidemia, chronic renal insufficiency, hemodialysis, and long-term corticosteroid therapy, his vascular interventions should have been performed with appropriate continuous anticoagulation to prevent postoperative thrombosis. At least two other cases with AFV-I have been reported to be complicated with arterial thrombosis [11, 12], as were 7 cases with venous thrombosis [13–19]. In FV-I patients associated with thrombosis, it is possible that FV-I may also inhibit the anticoagulant properties of FV [12, 15, 16, 18], e.g., FV-I can inhibit the FV's function as an activated protein C (APC) cofactor in the inactivation of activated factor VIII (FVIIIa) [20]. Alternatively, FV-I may inhibit directly the activated FV (FVa) inactivation by APC (the so-called APC resistance), and thus it may contribute to a thrombotic tendency. It has been reported that an anti-FV antibody(ies) isolated from a patient with thrombosis inhibited both FVa and FVIIIa inactivation by APC, but affected neither PT, APTT, nor FV activity [21].

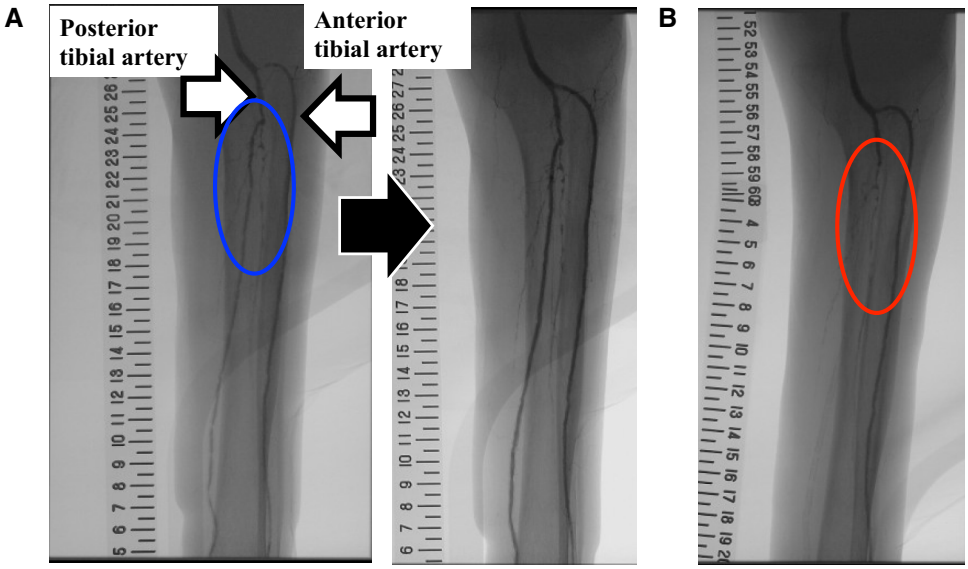

Fig. 3 Angiography of the left lower extremity on March 16 (**a**) and March 21 (**b**). **a** Angiography demonstrated stenosis of both anterior and posterior tibial arteries (left; open arrows and blue oval). EVT by plain old balloon angioplasty (left; POBA2 in Fig. 2b) achieved satisfactory dilatation of these arteries (right). **b** Angiography showed obstruction of the left posterior tibial artery (red oval). Recanalization was not obtained by AST and thrombolytic therapy with intra-arterial UK injection (180,000 units/day for 7 days), although a substantial amount of red and white thrombi was removed through the catheter

The risks and benefits of anticoagulation should be carefully accessed [18]. This unique issue may become common in super-aging societies, like in Japan, because AFV-I occurs mainly in elderly individuals [3].

Acknowledgements This study was supported in part by research aids from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Japanese Ministry of Health, Labor and Welfare (MHLW), and a research gran from Japan Agency for Medical Research and Development (AMED). We would like to thank all members of 'Japanese Collaborative Research Group (JCRG) on Autoimmune Coagulation Factor Deficiencies' and Ms. Yuriko Shibue and Ms. Eiko Ichinose for their cooperation in conducting a nation-wide survey in Japan from 2009 to 2018.

Author contributions HO carried out clinical studies and drafted the manuscript, MS, KK and TO performed experimental laboratory examinations and analyzed the results, SO, TK, and SW collected clinical data, KM reviewed the project and the manuscript, and AI designed the project and experiments, analyzed the results and wrote the manuscript. All authors have approved the submitted version.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interests in association with this study.

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