Renal Replacement Therapy

CASE REPORT Open Access

Oral tranexamic acid combined with low molecular weight heparin only during dialysis sessions successfully controlled chronic disseminated intravascular coagulation associated with aortic aneurysm and aortic dissection in a dialysis patient: a case report with literature review

Eriko Eguchi

Abstract

Background: Disseminated intravascular coagulation (DIC) is a relatively rare but important cause of bleeding diathesis in patients on maintenance dialysis. When the control of underlying disorders causing DIC is not achieved and anticoagulant therapy could not ameliorate the symptoms, other therapeutic options might be considered. While the use of antifibrinolytic agents, such as tranexamic acid, is generally not recommended in patients with DIC, the combined use of these agents with anticoagulants has produced good results in some cases with enhanced fibrinolytic-type DIC. Although the dose of tranexamic acid should be adjusted for patients with renal impairment to avoid neurotoxic complications, there are no widely accepted recommendations for dosage adjustment in dialysis patients. Therefore, the optimal indication and dosage of tranexamic acid in dialysis patients with hyper fibrinolytic type DIC remain unestablished.

Case presentation: We herein report a 94-year-old male patient on maintenance hemodialysis with hyperfibrinolytic DIC induced by chronic aortic aneurysm and aortic dissection. He suffered from hemorrhagic diathesis and was successfully treated with oral administration of 750 mg tranexamic acid per day combined with intravenous infusion of low molecular weight heparin (LMWH) every dialysis session. There were no apparent adverse events. Unintended dose reduction of tranexamic acid resulted in exacerbation of DIC along with alarming recurrence of blood flow in the previously thrombosed aortic false lumen, which was ameliorated soon after surely performing medication.

Conclusions: Combined use of oral tranexamic acid and minimum anticoagulant only during dialysis sessions successfully controlled aneurysm-induced DIC in a dialysis patient. Although the exact dosage and indication require further investigation, the treatment may be worth considering, even in dialysis patients, when other treatment options have failed to obtain good results.

Keywords: Tranexamic acid, Disseminated intravascular coagulation, Aortic aneurysm, Dialysis

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Background

Disseminated intravascular coagulation (DIC) is a relatively rare but important cause of bleeding diathesis in patients on maintenance dialysis. Clinical and laboratory manifestations are extremely variable among patients, highly depending on the underlying diseases [1]. When the control of underlying disorders causing DIC is not achieved, anticoagulant therapy may be indicated. This treatment frequently shows good results, whereas cautious use must be applied in patients with active bleeding. In this setting, other therapeutic options might be considered.

In some patients with enhanced fibrinolytic-type DIC, the combined use of antifibrinolytic agents, such as tranexamic acid, with anticoagulants has shown clinical effectiveness [2–4]. However, antifibrinolytic therapy is generally contraindicated in DIC [3, 5]. The dose of tranexamic acid should be adjusted for patients with renal impairment to avoid neurotoxic complications, while there are no widely accepted recommendations for dosage adjustment in dialysis patients. Therefore, the optimal indication and dosage of tranexamic acid in dialysis patients with hyperfibrinolytic-type DIC remain unestablished.

We herein report a dialysis patient with hyperfibrinolytic DIC induced by chronic aortic aneurysm and aortic dissection. He was successfully treated with oral administration of 750 mg tranexamic acid per day combined with intravenous infusion of low molecular weight heparin (LMWH) at 1250 anti-factor Xa (aXa) units every dialysis session without clinical adverse events.

Case presentation

A 94-year-old male with advanced dementia and a 3-year history of hemodialysis was admitted to our long-term care hospital because of his family circumstances. He was found to have inoperable thoracic and abdominal aortic aneurysms and aortic dissections 3 years before admission. The patient received maintenance hemodialysis with LMWH (dalteparin sodium) as an anticoagulant, using an initial bolus of 750 aXa units followed by a constant fixed infusion of 200 aXa units per hour without apparent hemostatic problems.

On admission to our hospital, laboratory measurements revealed a low platelet count (68,000/μL) and a slightly prolonged prothrombin time (PT; 15 s) with normal activated partial thromboplastin time (APTT) and normal liver function. Other coagulation assays were not performed. The time needed to achieve hemostasis after removing dialysis needles was extended (30–80 min) and gradually further lengthened (60–140 min) with developing delayed access site hemorrhage. The platelet count ranged from 55,000 to 100,000/μL. Despite a reduction in LMWH to a single bolus of 250 aXa units and the use of gelatin sponges on the puncture site after dialysis, the bleeding tendency was not controlled and resulted in the appearance of alarming hemorrhage, including hemoptysis, melena, and oral mucosal bleeding, requiring repeated blood transfusions. Oral tranexamic acid (250 mg per day) was started in an attempt to control hemorrhage, after which bleeding manifestation gradually disappeared over 1 month. While some reduction in time to hemostasis was obtained, this period was still extended (30–70 min) despite the appearance of occasional blood clotting in the dialysis circuits.

Fourteen months after admission, the author was appointed to the hospital. The patient still suffered from extended time to hemostasis following every dialysis treatment, despite occasional blood clotting in the circuits. Arteriovenous access dysfunction was not found. The platelet count ranged between 110,000 and 190,000/μL over months. Coagulation assays 3 weeks after the cessation of tranexamic acid revealed excessive levels of coagulation and fibrinolytic activation (fibrin and fibrinogen degradation product (FDP), 216 μg/mL (normal range < 5.0 μg/mL); thrombin-antithrombin complex (TAT), 18.1 ng/mL (normal range < 4.0 ng/dL); plasmin-α2 plasmin inhibitor complex (PIC), 5.5 μg/mL (normal range < 0.8 μg/mL)). The α2 plasmin inhibitor (α2-PI) (normal range 85–118%) was 82%. PT and APTT were 13.3 and 37.4 s, respectively. The fibrinogen level (161 mg/dL; normal range 150–340 mg/dL) was at the lower limit of normal. Antithrombin (AT; 70%; normal range 75–125%) was slightly decreased. D-dimer was not measured. Computed tomography (CT) scan demonstrated thoracoabdominal aortic aneurysms and dissections without any evidence of other underlying comorbidities. The above findings and the clinical course were compatible with chronic compensated DIC with enhanced fibrinolysis resulting from aortic aneurysms and dissections [1, 3].

An increment of LMWH to a single bolus of 1000 aXa units led to the further prolonged time to hemostasis with still recurring clot formation in the circuit. The oral administration of tranexamic acid 750 mg per day with increasing doses of LMWH up to a single bolus of 1250 aXa units finally achieved an improvement of laboratory findings (FDP, 4.3 μg/mL; TAT, 8.4 ng/mL; PIC, 0.7 μg/mL; fibrinogen, 256 mg/dL) and a reduction in time to hemostasis (average 10 min) with a disappearance of circuit clotting.

Subsequently, other therapeutic alternatives were considered in an attempt to avoid increasing the risk of adverse effects of tranexamic acid. Intravenous administration of 50 mg of nafamostat mesilate per every dialysis session was started in anticipation of an antifibrinolytic effect, with the cessation of tranexamic acid and unchanged LMWH regimen. This trial resulted in a

recurrence of extended time to hemostasis (40–50 min) and an exacerbation of laboratory data (platelets, 84,000/μL; FDP, 148 μg/mL; D-dimer, 73.6 μg/mL (normal range < 1.0 μg/mL); TAT, 30.7 ng/mL; PIC, 9.3 μg/mL; α2-PI, 69%; fibrinogen, 175 mg/dl; AT, 69%), which met the diagnostic criteria for overt DIC proposed by the Japanese Society on Thrombosis and Hemostasis [6]. Reinitiation of oral tranexamic acid with cessation of nafamostat mesilate promptly achieved both a reduction of time to hemostasis and an improvement of laboratory data (platelets, 113,000/μL; FDP, 5 μg/mL; D-dimer, 3.6 μg/mL; TAT, 7.7 ng/mL; PIC, 0.7 μg/mL; fibrinogen, 243 mg/dL; AT, 73.6%) without clinically evident adverse effects.

Nineteen months after admission, the patient developed a compression fracture at the first vertebra of the lumbar spine. Bed rest was followed by the development of delirium with decreased oral intake, poor medication adherence, actual body weight loss, and deterioration of blood pressure control. The actual dosage of tranexamic acid taken during the period was unclear, whereas the dosage was presumably at most 250 mg daily. Time to hemostasis was extended again, and laboratory test results showed a worsening of DIC (platelets, 95000/μL; FDP, 13.7 μg/mL; D-dimer, 3.8 μg/mL; TAT, 41.8 ng/mL; PIC, 9.5 μg/mL; fibrinogen, 129 mg/dL; AT, 71.0%). Unenhanced CT scan demonstrated the high attenuating crescent in the preexisting false lumen along the wall of the infrarenal abdominal aortic aneurysm without further increase in diameters (Fig. 1). The finding was interpreted as fresh thrombus resulting from recurrence of blood flow in the previously thrombosed false lumen [7, 8]. Confirming drug compliance with at least tranexamic acid and dry-weight reduction to lower blood pressure were performed. Within a week, both the lengthening of time to hemostasis and laboratory data (platelets, 149,000/μL; FDP, 2.7 μg/mL; D-dimer, 1.3 μg/ml; TAT, 15.2 ng/mL; PIC, 0.9 μg/mL; fibrinogen, 256 mg/dL; AT, 74.5%) were improved with some reduction in blood pressure (Fig. 2). Unenhanced CT images obtained a month later showed the same false lumen with decreased attenuation identical to that of intraluminal blood.

During the period of bed rest for 1 month, his ability to perform the activities of daily living remarkably declined. The patient eventually became bedridden and died of sepsis due to lower extremity infection in the 24th month after admission.

Discussion

DIC is characterized by continuous activation of both coagulation and fibrinolytic pathways [1, 3]. The range of fibrinolytic activation varies widely and highly dependent upon underlying diseases. Aortic aneurysm is one of the most typical causative diseases involved in highly activated fibrinolytic responses.

Aneurysm-induced DIC occurs in 2 to 4% of patients with aortic aneurysms and often follows a long course, described as compensated, low grade, nonovert, or chronic DIC [1, 5, 9–11]. The transformation into overt DIC may occur without identifiable reasons [1].

The most effective treatment for aneurysm-induced DIC is the surgical repair of the aneurysm, while different treatment options might be needed in patients with inoperable aneurysms [5]. Anticoagulation therapy is indicated to stop the intravascular clotting process and frequently shows good results [5, 11]. However, the safety of anticoagulation therapy is debatable in patients with active bleeding [1, 5, 11]. In this setting, the use of antifibrinolytic agents could be considered [1, 5].

Antifibrinolytic agents should not be routinely used for the treatment of DIC because of the potential for thrombotic complications, whereas concomitant use of these agents with anticoagulants could achieve beneficial results in some aneurysm-induced DIC patients, as presumably in whom hyperfibrinolysis predominates over coagulation activation [1–5, 12, 13]. Therefore, identifying enhanced fibrinolysis is recommended to avoid incorrect indications for antifibrinolytic therapy.

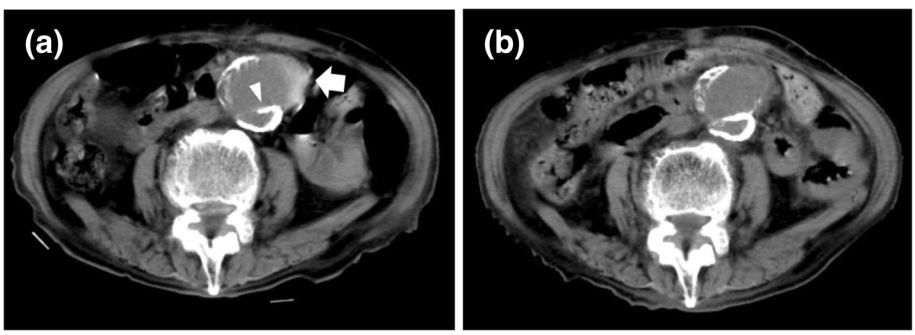

Fig. 1 Images of unenhanced computed tomography (CT) at 1 (**a**) and 2 (**b**) months after the lumbar compression fracture. **a** Internal displacement of intimal calcifications (arrowhead) and a hyperattenuating crescent (arrow) are shown in the enlarged abdominal aorta. **b** The hyperattenuating fluid collection shows attenuation almost identical to that of intraluminal blood

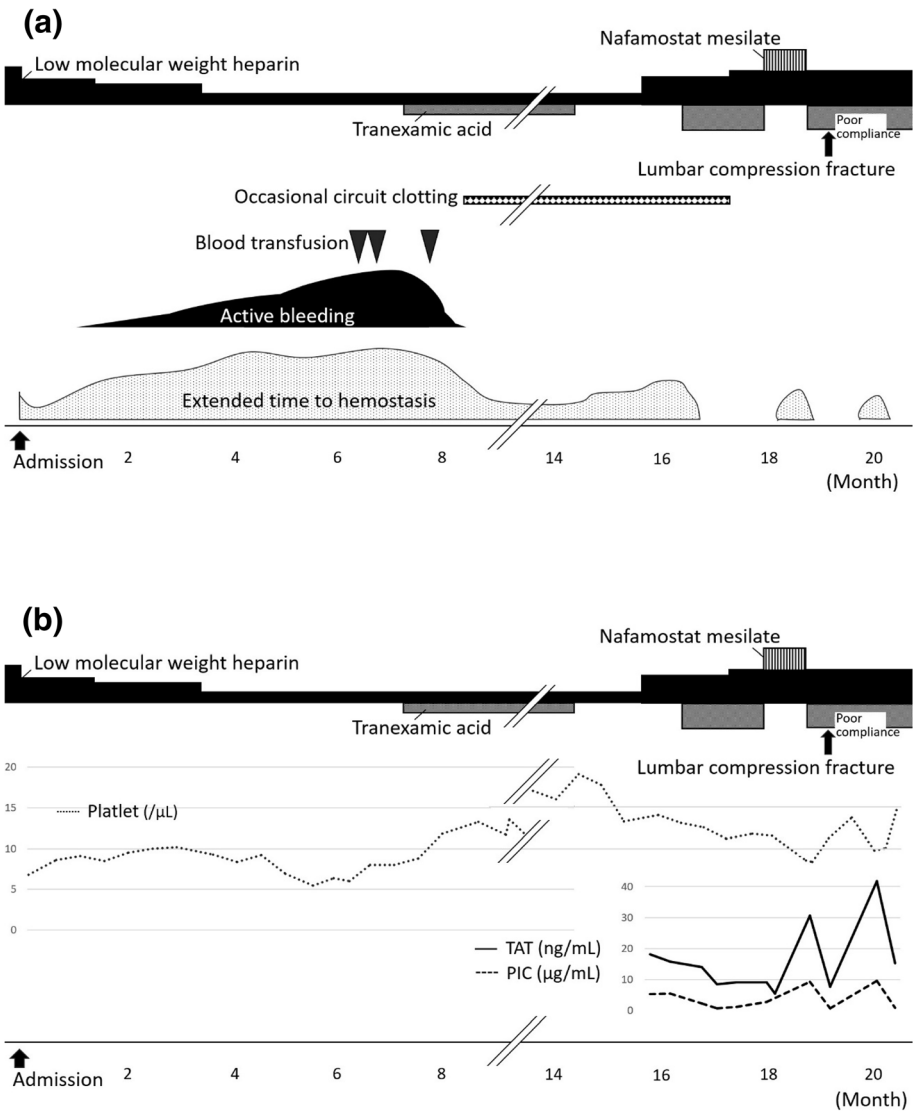

Fig. 2 Time course of treatment with clinical symptoms (**a**) and laboratory results (**b**) during 20 months after admission. TAT, thrombin-antithrombin complex; PIC, plasmin-α2 plasmin inhibitor complex

Monitoring molecular markers of coagulation and fibrinolysis is useful. Typically, the following results are obtained: marked elevation in both TAT and PIC, which are markers of coagulation system activation and fibrinolysis system activation; increased FDPs/D-dimer ratio; and decreased α2-PI activity [1, 3].

Synthetic proteinase inhibitors, such as nafamostat mesilate and gabexate mesylate, may also be effective for the control of bleeding in patients with aneurysm-induced DIC because of their antifibrinolytic effect [3, 14, 15]. On the other hand, the higher costs and short half-lives of these agents are not suitable for the maintenance of chronic DIC. Camostat mesilate, another synthetic proteinase inhibitor, is not available for the treatment of DIC in Japan despite being administered orally.

For patients with renal impairment, the dosage of tranexamic acid should be reduced in order to prevent adverse events, as urinary excretion is the main route of elimination [16, 17]. The most common adverse effect in those patients is neurotoxicity, such as seizures or visual impairment, whereas thrombotic complication is unexpectedly rare [18]. The following dose adjustments have been suggested for orally administered tranexamic acid in nondialysis-dependent chronic kidney disease patients: estimated glomerular filtration rate (eGFR) 60–89 mL/min/1.73 m^2, 15 mg/kg twice daily; eGFR 30–59 mL/min/1.73 m^2, 15 mg/kg daily; and eGFR < 29 mL/min/1.73 m^2, 7.5 mg/kg daily [17]. Dosage adjustments for intravenous administration vary depending on the clinical settings [17].

In contrast to dosing in nondialysis-dependent chronic kidney disease patients, there are no widely accepted recommendations for dosage adjustment in dialysis patients. This effect is presumably attributed to the lack of available data on the potential dialysis of tranexamic acid. On the other hand, the molecular weight of 157.2 Da, the volume of distribution of 1.0 L/kg, and the plasma protein binding of approximately 3% at therapeutic levels may suggest effective removal through dialysis [16, 17, 19].

Based on previous reports on the toxicity of tranexamic acid in maintenance dialysis patients, oral administration is less frequently associated with the appearance of adverse events than intravenous administration (Table 1). The lowest toxic dose of intravenous tranexamic acid was a mere 1 g single injection [18]. In the only known case of the adverse reaction associated with oral tranexamic acid, the dosage was 2 g daily, which is the upper limit of usual dosage, for 6 days [21]. The mode of renal replacement therapy was peritoneal dialysis in both cases. The lower bioavailability of approximately 40–50% for oral tranexamic acid may be related to the lower incidence rates of adverse events than intravenous tranexamic acid [16, 17].

Successful reports of tranexamic acid in aortic DIC patients on hemodialysis have shown good results, with orally 0.5–2.0 g tranexamic acid daily [2, 12]. In contrast to the abovementioned cases on peritoneal dialysis with the adverse reactions, no adverse effects were identified, despite the use of higher dosages than recommended for nondialysis-dependent chronic kidney disease patients with the same level of eGFR. This finding is presumably ascribed to the more effective removal of the drug by hemodialysis than peritoneal dialysis. These findings suggest the identification of the lowest effective dose of tranexamic acid in hemodialysis patients.

The present case had chronic DIC associated with inoperable aortic aneurysm and aortic dissection, and incorporation of tranexamic acid and LMWH achieved successful stabilization of the DIC with no apparent side effect. The intermittent systemic anticoagulation with LMWH during hemodialysis sessions might play a certain role in maintaining the DIC compensated before admission. This effect was eventually found to be insufficient. As an increment of LMWH led to further prolongation of time to hemostasis, higher-intensity anticoagulation alone was presumably implicated in an increased risk of hemorrhage. Therefore, the incorporation of antifibrinolytic therapy was considered. Oral tranexamic acid was employed because of the lower cost and ease of administration and produced a beneficial effect.

Conclusions

The combined use of oral tranexamic acid and minimum anticoagulant only during dialysis sessions successfully controlled aneurysm-induced DIC in a dialysis

Table 1 Previous reports on adverse events associated with tranexamic acid in patients on maintenance dialysis

Author	Patient age and sex	Mode of dialysis therapy	Dosage and route of administration (weight-based dosing)	Adverse events	Management	Days required for recovery	Outcome
Kitamura et al. [20]	56, male	Hemodialysis	2 g daily IV × approximately 2 weeks	Visual loss	Tranexamic acid discontinuation	2–3 days	Partial recovery with residual visual impairment in dark places
Hui et al. [21]	61, male	Peritoneal dialysis	2 g daily PO × 6 days	Multifocal myoclonus	Tranexamic acid discontinuation	4 days	Complete recovery
Ma et al. [18]	57, male	Peritoneal dialysis	1 g IV [< 15 mg/kg]	Disorientation, upper extremity myoclonus, and visual disturbance	Tranexamic acid discontinuation	3 days	Complete recovery
Ma et al. [18]	50, female	Peritoneal dialysis	6 g IV (4.5 g IV during operation and another 1.5 g IV postoperatively) [< 120 mg/kg within 12 h]	Disorientation, generalized tonic-clonic convulsion	Tranexamic acid discontinuation, continuous renal replacement therapy	1 week	Complete recovery
Ma et al. [18]	61, male	Peritoneal dialysis	3 g daily PO × 3 days [< 45 mg/kg per day]	Slurring of speech, upper extremity myoclonus, unsteady gait, and visual disturbance	Tranexamic acid discontinuation	3 days	Complete recovery
Fuah et al. [22]	65, male	Hemodialysis	2 g IV (1 g IV × 2 doses over 5 h)	Generalized tonic-clonic convulsion	Tranexamic acid discontinuation, intravenous diazepam 5 mg for the acute treatment of second seizure	1 day	Complete recovery

IV intravenous, *PO* per oral

patient. Although the exact dosage and indication require further investigation, the treatment may be worth considering even in dialysis patients, when other treatment options have failed to obtain good results.

Literature review

There are only few reported cases requiring hemodialysis with DIC induced by aortic aneurysm or aortic dissection, in which tranexamic acid was administered [2, 12, 23] (Table 2). No one received surgical procedures for aortic aneurysms or aortic dissections. In all cases, tranexamic acid was started because of difficulties in controlling the hemorrhagic diathesis by other treatment options such as anticoagulants and synthetic proteinase inhibitors. In case 3, the initiation of tranexamic acid treatment was during the pre-dialysis period, just after the creation of an arteriovenous fistula for hemodialysis. Other cases already received maintenance dialysis at the start of tranexamic acid. There were no apparent adverse events associated with administration of tranexamic acid. In every case, an improvement of hemorrhagic diathesis was achieved after the administration of tranexamic acid. On the other hand, case 3 alone experienced a relapse of hemorrhagic diathesis just before the initiation of hemodialysis. The hemorrhagic diathesis gradually ameliorated over 1 month after the start of hemodialysis using LMWH and the increment of camostat mesylate, off-label use, with the same regimen of tranexamic acid. In case 3, therefore, the

Table 2 Clinical features of previously reported cases requiring hemodialysis with DIC induced by aortic aneurysm/dissection, in which tranexamic acid was administered

	Case 1	Case 2	Case 3	Case 4
Author	Gatate et al. [2]	Kimura et al. [12]	Tanaka et al. [23]	Eguchi (the present case)
Patient age and sex	71, female	67, male	72, male	94, male
Cause of DIC	Aortic dissection	Aortic dissection	Aortic aneurysm	Aortic aneurysm and aortic dissection
Laboratory data on DIC				
Platelet counts (/μL)	98000	72000	46000	84000
FDP/D-dimer (μg/mL)	Not available/57.6	109.7/78.5	113.5/53.84	148/73.6
Fibrinogen (mg/dL)	< 50	110	113	175
PT-INR	1.37	Not available	1.14	1.14
Antithrombin (%)	Not available	89.9	88	69
TAT/PIC (ng, μg/mL)	60.0/9.1	60.0/9.8	Not available	30.7/9.3
α2-PI (%)	Not available	47	Not available	69
Treatment				
Surgical procedures	Not performed	Not performed	Not performed	Not performed
Anticoagulants	UH 4000 units every dialysis session	LMWH 4000 aXa units daily DIV ↓ Danaparoid 1250 units IV × 2 times/week	LMWH 300 aXa units/one shot and 150 aXa units/hour every dialysis session	LMWH 1250 aXa units/one shot every dialysis session
Dosage and route of administration of tranexamic acid (The duration of administration)	1500 mg daily PO ↓ 2000 mg daily PO (43 months)	1500 mg daily IV ↓ 1500 mg daily PO ↓ 500 mg daily PO (9 months)	150 mg PO × 3 times/week (2.5 months)	750 mg daily PO (15 months)
Synthetic proteinase inhibitors	Nafamostat mesilate 190 mg daily DIV (ineffective)	Not used	Camostat mesilate 300 mg daily PO ⟶ 900 mg daily PO	Nafamostat mesilate 50 mg every dialysis session (ineffective)
Outcome				
DIC	Well controlled	Well controlled	Well controlled	Well controlled
Alive/dead	Died of lower extremity infection	Died of cerebellar hemorrhage	Alive	Died of lower extremity infection
Adverse effects associated with tranexamic acid	None	None	None	None

aXa anti-factor Xa, *α2-PI* α2 plasmin inhibito, *DIC* disseminated intravascular coagulation, *DIV* drip infusion, *FDP* fibrin and fibrinogen degradation product, *IV* intravenous, *LMWH* low molecular weight heparin, *PIC* plasmin-α2 plasmin inhibitor complex, *PO* per oral, *PT-INR* prothrombin time international normalized ratio, *TAT* thrombin-antithrombin complex, *UH* unfractionated heparin

effect of tranexamic acid in controlling hemorrhagic diathesis appears insufficient. The finding is presumably ascribed to the lower dosage of tranexamic acid, 150 mg orally three times per week, than even recommended for nondialysis-dependent chronic kidney disease patients with the same level of eGFR. Of note, danaparoid used in case 2 is contraindicated in patients requiring hemodialysis in Japan, whereas the agent has been used in hemodialysis in Europe [24].

Abbreviations

APTT: Activated partial thromboplastin time; AT: Antithrombin; aXa: anti-factor Xa; CT: Computed tomography; DIC: Disseminated intravascular coagulation; eGFR: Estimated glomerular filtration rate; FDP: Fibrin and fibrinogen degradation product; LMWH: Low molecular weight heparin; PIC: Plasmin-α2 plasmin inhibitor complex; PT: Prothrombin time; TAT: Thrombin-antithrombin complex; α2-PI: α2 plasmin inhibitor

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Author's contribution

EE is corresponding author and wrote the whole manuscript. The author read and approved the final manuscript.

Availability of data and materials

The data and materials were all included in the manuscript.

Ethics approval and consent to participate

According to the Ethical Guidelines for Medical and Health Research involving Human Subjects in Japan, ethical approval is not required for case reports.

Consent for publication

Written informed consent was obtained from the son of the patient for the publication of this case report and any accompanying test results.

Competing interests

The author declares that he has no competing interests.

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