Effectiveness of plasma exchange for acquired type A hemophilia

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Abstract An 80-year-old man was treated at our hospital for chronic kidney disease, diabetes mellitus and hypertension. He presented a bleeding tendency over the past several weeks. When he was admitted to our hospital with a consciousness disturbance, he had irregular 10–20 cm patches of subcutaneous bleeding. Laboratory findings showed prolonged activated partial thromboplastin time (APTT) but normal platelet count and prothrombin time. The administration of fresh frozen plasma did not control the bleeding tendency and the result of APTT cross-mixing test suggested the presence of factor VIII inhibitor. The diagnosis of acquired hemophilia A was made by a marked decrease in factor VIII activity levels ($<1\%$) and a high titer of factor VIII inhibitor (11 Bethesda units). To remove the factor VIII inhibitor and suppress its production, plasma exchange was performed and methylprednisolone was administered. Thereafter, the bleeding tendency could be controlled with APTT measurement normalization. Plasma exchange does not have a first priority in the treatment but our case findings suggested that plasma exchange is an effective method for eliminating factor VIII inhibitor and alleviating acquired hemophilia A severity.

Keywords Acquired hemophilia A · Factor VIII inhibitor · Plasma exchange

Introduction

In patients with acquired hemophilia A, factor VIII levels are usually decreased due to the synthesis of factor VIII inhibitors. These patients present with a bleeding tendency and prolonged activated partial thromboplastin time (APTT) with normal platelets and prothrombin time. Although the mechanisms of acquired hemophilia A remained unclear, disorders of immune system which is related to postpartum state, autoimmune diseases, malignancy, infection, drug-induced adverse effects, and aging would have associations with the development of this disease [1]. Immunosuppressive therapy is thought to be an important strategy in addition to the hemostatic therapy. Furthermore, mainly in Europe, several reports have indicated the effectiveness of blood purification, including plasma exchange and plasma absorption, to remove its inhibitor from the circulating plasma [2–4]. Here, we report a case of acquired hemophilia A caused by the presence of factor VIII inhibitor, which was dramatically improved by plasma exchange with methylprednisolone administration. Although plasma exchange is not the first-line therapy for acquired hemophilia A [5–9], we found it an effective method for removing factor VIII inhibitor and alleviating the severity of acquired hemophilia A.

Case report

Our patient was an 80-year-old man who was treated in our hospital with end stage kidney disease, diabetes mellitus,

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hypertension, hyperlipidemia, hyperuricemia, atrial fibrillation for over 10 years in each disease, and a past history of angina pectoris with a surgical history of coronary artery bypass graft at the age of 78. His medications included: cilnidipine 10 mg/day, doxazosin mesilate 0.5 mg/day, furosemide 60 mg/day, aspirin 100 mg/day, lansoprazole 15 mg/day, carvedilol 2.5 mg/day, spironolactone 25 mg/day, febuxostat 20 mg/day, atorvastatin calcium hydrate 10 mg/day, sennaride 12 mg/day, insulin aspart 20 units/day and insulin glargine 8 units/day. The above medications had not been changed for >1 year.

The patient had noticed the bleeding tendency with subcutaneous bleeding induced by shaving and scratching for several weeks prior to admission. When he admitted to our hospital complaining of disturbed consciousness and the bleeding tendency, he had 10–20 cm irregular patches of subcutaneous bleeding on his forearms and purpura inside his thighs. On his physical examination, his conjunctiva appeared anemic but not icteric. A rectal examination showed no bloody or tarry stool. He had no abnormal neurological signs except slight drowsiness. His body temperature was 37.5 °C, heart

rate was 87 bpm, blood pressure was 123/49 mmHg, and oxygen saturation was 97 % on room air. We did not find any abnormalities on his chest x-ray, electrocardiography, or head computed tomography.

The patient's laboratory data on admission are shown in Table 1. In particular, a blood coagulation test showed a prolonged APTT (96.5 s), whereas the platelet count ($19.3 \times 10^4/\mu\text{L}$) and prothrombin time (14.6 s) were within the normal range. Factor VIII activity was markedly decreased to <1 % (normal range 60–150 %), whereas von Willebrand factor level was within the normal range and lupus anticoagulant was negative. The APTT cross-mixing test, which is useful for the rapid distinction between factor VIII deficiency and the presence of factor VIII inhibitors, revealed that APTT linearly declined (Fig. 1). Accordingly, the existence of factor VIII inhibitor was suspected and factor VIII inhibitor titer was further examined. The titer increased at 11 Bethesda units, so he was diagnosed with acquired hemophilia A. Although fresh frozen plasma (FFP) was administered to control his bleeding tendency, the APTT did not improve at all.

Table 1 The patient's laboratory data on admission

Complete blood count		Biochemistry		Immunological examination	
WBC	9850/ μL	TP	6.4 g/dl	LA	1.11
RBC	$201 \times 10^4/\mu\text{L}$	Alb	3.7 g/dl	ANA	$\times 40$
Hb	6.2 g/dl	T-Bil	0.51 mg/dl	RF	≤ 10 IU/mL
Hct	18.6%	D-Bil	0.22 mg/dl	Anti ds-DNAAb	<10 IU/mL
MCV	92.5 fl	AST	17 IU/l	Anti SmAb	–
MCHC	33.3 g/dl	ALT	8 IU/l	IgG	1300 mg/dl
Plt	$19.3 \times 10^4/\mu\text{L}$	LDH	320 IU/l	IgA	351 mg/dl
Ret	2.7 %	ALP	337 IU/l	IgM	90 mg/dl
Coagulation test		γ -GTP	15 IU/l	C3	61 mg/dl
PT	66.2 %	BUN	86 mg/dl	C4	19 mg/dl
PT-INR	1.15	Cr	6.13 mg/dl	CH 50	29.4 U/ml
PT-s	14.6 s	UA	6.7 mg/dl	VW factor	155 %
APTT	96.5 s	Na	132 mEq/l	Factor VIII	≤ 1 %
D-dimer	3.3 $\mu\text{g/ml}$	K	3.7 mEq/l		
Fibrinogen	494 mg/dl	Cl	101 mEq/l		
FDP	8.6 $\mu\text{g/ml}$	CRP	1.92 mg/dl		
AT-3 activity	105 %	BS	215 mg/dl		
Coombs test		Ammonia	15 $\mu\text{g/dl}$		
Direct	–	Fe	63 $\mu\text{g/dl}$		
Indirect	–	UIBC	154 $\mu\text{g/dl}$		
		Haptoglobin	18 mg/dl		

WBC white blood cell, RBC red blood cell, Hb hemoglobin, Ht hematocrit, MCV mean corpuscular volume, MCHC mean corpuscular hemoglobin concentration, plt platelet, Ret reticulocyte, PT prothrombin time, APTT activated partial thromboplastin time, FDP fibrinogen degradation products, AT-3 antithrombin-III, TP total protein, Alb albumin, T-Bil total bilirubin, D-Bil direct bilirubin, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, ALP alkaline phosphatase, γ -GTP γ -glutamyltransferase, BUN blood urea nitrogen, Cr creatinine, UA uric acid, Na sodium, K potassium, Cl chlorine, CRP C reactive protein, BS blood sugar, Fe iron, UIBC unsaturated iron-binding capacity, LA lupus anticoagulant, ANA antinuclear antibody, RF rheumatoid factor, Anti ds-DNA Ab anti double strand DNA antibody, Anti Sm Ab anti smith antibody, CH50 serum complement level, VW factor von Willebrand factor

As soon as the diagnosis of acquired hemophilia A was made, methylprednisolone (0.6 mg/kg/day) was administered and plasma exchange was performed to remove the factor VIII inhibitor and suppress its production. With regard to the manner of plasma exchange, Plasmaflo OP (Asahi Medical, Tokyo, Japan) that contains a polyethylene membrane was used as a plasma separator, and 45 mL/kg $\times$ body weight (kg) of FFP was used as the substitution fluid. As an anticoagulant, 30 mg/h of nafamostat mesilate was used to prevent further bleeding tendency in this case. Plasma exchange was performed every alternate day and three times in total. Thereafter, the APTT was normalized and bleeding tendency was alleviated (Fig. 2). Thereafter, factor VIII activity improved to 86 % and the titer of its inhibitor decreased to 1 Bethesda unit.

This patient was discharged after being fully recovered and has been treated successfully on an outpatient basis since then.

Fig. 1 The activated partial thromboplastin time (APTT) results in a cross-mixing test showed that APTT linearly decreased and suggested the presence of factor VIII inhibitor

Fig. 2 The patient's clinical course. After initiation of the combination therapy of plasma exchange and methylprednisolone administration, factor VIII activity improved to 86 % and titer of its inhibitor decreased to only 1 Bethesda unit

Discussion

In patients with acquired hemophilia A, the synthesis of factor VIII inhibitor, which is induced by immunological abnormalities, reduced the quantity of factor VIII. Although the precise mechanisms of inhibitor synthesis remain unclear, various factors are thought to be associated with it [1]. The frequency of acquired hemophilia A was reported to be 1–1.5 in per million persons per year [5–10], and in the United Kingdom, the incidence of acquired hemophilia increases with age and the median patient age was 78 years [7]. In this case, there were no abnormalities with autoimmune diseases, malignancy, infection, and drug-induced adverse effects, and therefore, only age would be a possible cause of factor VIII inhibitor synthesis.

In the treatment of acquired hemophilia A, it is important to adequately correct the immunological disorders and control the bleeding tendency. Under the condition of moderate or severe bleeding, recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (APCC) are recommended for by-passing concentrates [6]. If the titer of factor VIII inhibitor is low (<5 Bethesda Units), the infusion of factor VIII concentrates would be effective as same as rFVIIa or APCC, even in the presence of factor VIII inhibitor [9]. However, all of these coagulation factor concentrates are extremely expensive, making their use difficult in the clinical setting. In this case, considering the bleeding severity, patient age and cost effectiveness, a plasma exchange with methylprednisolone administration was initiated instead of treatment with coagulation factor concentrates.

The Modified Bonn/Malmö protocol (MBMP), which includes large volume absorption 2.5–3 times the total plasma volume with a double column system comprising Sepharose-coupled anti-human immunoglobulin G (IgG) sheep antibodies in combination with immunosuppression, IgG administration, and high-dose factor VIII substitution, was recently reported in Europe [2, 3]. In the Nordic Guidelines for Diagnosis and Treatment of Acquired hemophilia, plasmapheresis or immunoabsorption followed by factor VIII concentrates administration is recommended only if the other alternative treatments have failed [6]. In the United Kingdom Haemophilia Centre Doctors Organization's guideline and international recommendations on the diagnosis and treatment of patients with acquired hemophilia A, the use of immunotolerance regimens with immunoabsorption was recommended in the case of life-threatening bleeding [5, 8]. However, in Japan, the absorption column that is used in the MBMP cannot be obtained in the clinical setting, and therefore, plasma exchange was performed instead of plasma adsorption in this case.

The use of plasma exchange for treating acquired hemophilia A has several benefits. First, in a patient with acquired hemophilia complicated by lung tuberculosis, plasma exchange without immunosuppressive therapy was previously reported effective [3]. To prevent various complications such as infection due to excessive immunosuppression in patients who are elderly, have immunocompromised status, or have active infection, the administration of plasma exchange would be favorable. Second, plasma exchange would be also effective as well as plasma adsorption because of pathological and physiological mechanisms by removing factor VIII inhibitors from the patient's circulating plasma. Factor VIII inhibitors are polyclonal autoantibodies to FVIII, which usually belong to IgG1 and IgG4 subclasses, and have molecular weights of about 150,000 Da. The sieving coefficient in this separator for IgG was previously reported to be from 0.94 to 1.0, and furthermore, this value was well maintained even after 3L plasma perfusion [11].

Finally, plasma exchange is much more cost-effective. For example, the cost of rFVIIa is about 99,000 yen per 1 mg. Following pharmaceutical references, at least 36 mg per day rFVIIa is used (3,564,000 yen) in 50 kg patient. On the other hand, the cost of plasma exchange is about 272,000 yen per session. Therefore, in Japan, the administration of coagulation factor concentrates is more expensive than that of plasma exchange.

In conclusion, we experienced an elderly case of acquired hemophilia A. Plasma exchange with methylprednisolone administration is an effective method for removing factor VIII inhibitor and alleviating acquired hemophilia A severity.

Conflict of interest All the authors have declared no competing interest.

References

1. Nihon Kessenshiketsu Gakkai Koutensei Ketsuyubyo A shinryo Gaidorain Sakusei Iinkai. Kotensei Ketsuyubyo A shinryo Gaidorain. <http://www.jsth.org>. Accessed 21 Oct 2014.
2. Zeitler H, Ulrich-Merzenich G, Hess L, Konsek E, Unkrig C, Walger P, Vetter H, Brackmann HH. Treatment of acquired hemophilia by the Bonn-Malmö Protocol: documentation of an in vivo immunomodulating concept. *Blood*. 2005;105:2287–93.
3. Zeitler H, Ulrich-Merzenich G, Marquardt N, Oldenburg J, Goldmann G. immunoabsorption for pregnancy associated severe acquired haemophilia A. *Ther Apher Dial*. 2014;18:103–10.
4. Ogata H, Sakai S, Koiwa F, Tayama H, Kinugasa E, Ideura T, Akizawa T. Plasma exchange for acquired hemophilia A. *Ther Apher*. 1999;3:320–2.
5. Hay CR, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol*. 2006;133:591–605.
6. Working Group on Acquired Haemophilia of the Nordic Haemophilia Centres. Acquires haemophilia: Nordic Guidelines for diagnosis and treatment. http://www.Medfak.lu.se/pdf/medkirortpdf/koagulation/nordic_guidelines. Accessed 21 Oct 2014.
7. Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, Keeling DM, Liesner R, Brown SA, Hay CR; UK Haemophilia Centre Doctor's Organisation. Acquired haemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors Organisation. *Blood*. 2007;109:1870–7.
8. Huth-Kühne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Lévesque H, Castellano ME, Shima M, St-Louis J. International recommendation on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. 2009;94:566–75.
9. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol*. 2003;121:21–35.
10. Collins PW, Percy CL. Advances in the understanding of acquired haemophilia A: implications for clinical practice. *Br J Haematol*. 2010;148:183–94.
11. Nagano T, Nakazono K, Iwamoto H, Sato T, Shizume Y, Take-naka Y, Mune-kata K, Koga N. Comparative study of polyethylene plasma separator sterilized by ethylene oxide and gamma rays. *Jpn J Apheresis*. 1997;16:297–8.