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CASE REPORT

Successful initiation of hemodialysis for a hemophilia A patient with factor VIII inhibitor: a case report and literature review

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Abstract

We report the first case of hemophilia A with factor VIII (FVIII) inhibitor who received hemodialysis via an arteriovenous (AV) fistula. Hemophilia A is a congenital deficiency of blood coagulation FVIII that is characterized by prolonged bleeding. Approximately 30% of patients with hemophilia develop allogeneic antibodies of FVIII. The inhibitors decrease the hemostatic effect of replacement therapy; thus, the prophylaxis strategy should be well designed. Prophylactic treatment with invasive procedures is needed to prevent excessive bleeding in patients with hemophilia undergoing hemodialysis. On the contrary, hemodialysis requires attention to the development of intracircuit coagulation during dialysis. Peritoneal dialysis or hemodialysis with a long-term tunneled central venous catheter has mainly been selected as the dialysis modality for patients with hemophilia and end-stage renal disease requiring renal replacement therapy because hemodialysis with an arteriovenous fistula may result in bleeding from the puncture site after each hemodialysis session. In our patient, hemodialysis was safely performed without any anticoagulant agents, and replacement therapy with FVIII concentrates prevented bleeding after puncture of the AV fistula.

Keywords Hemophilia A · Factor VIII inhibitor · Hemodialysis · Hemostasis · Coagulation factor replacement

Introduction

Patients with hemophilia A present with prolonged bleeding, spontaneously or after minor trauma, due to a congenital deficiency of blood coagulation factor VIII (FVIII). They can live an almost normal life as long as they receive the standardized therapies, including replacement of clotting factor concentrates [1]. Accordingly, the prevalence of chronic kidney disease (CKD) in patients with hemophilia has increased, along with the aging of the patients. Some patients with CKD and hemophilia require renal replacement therapy (RRT). Because of the high risk of bleeding, it is important to choose the renal replacement modality according to the patient's condition. Several reports have shown the efficiency of peritoneal dialysis (PD), hemodialysis (HD) treatment using catheters, and renal transplantation in patients with hemophilia [2–5]. However, patients without these indications are receiving HD via vascular access without the use of catheters with coagulant factor replacement. One of the most important issues in the management of patients with hemophilia A is development of FVIII inhibitors. The inhibitors are associated with the morbidity, considerably decreasing the patients' quality of life (QOL). Here, we report a hemophilia A patient with FVIII inhibitor who was treated with HD via an arteriovenous (AV) fistula with replacement of FVIII.

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Case report

The patient was a 71-year-old Japanese man who was diagnosed with congenital severe hemophilia A at the age of 20 and received replacement therapy with a clotting factor concentrate. At age 61, he developed chronic kidney dysfunction, renal biopsy was not performed because of the risk of bleeding due to hemophilia. He was treated mainly with conservative management of chronic renal failure, but his renal function gradually declined. At the age of 65, he presented with end-stage renal disease of unknown cause. He was administered PD as a RRT with low bleeding risk. During the course of his treatment, he developed multiple episodes of peritonitis, but was able to undergo PD treatment for 5 years. Five years later, the patient had no choice but to switch to HD due to decreased peritoneal function. Considering that he had experienced various types of bacterial infection sepsis several times, we supposed that an AV fistula would be better than catheters for vascular access to HD. The patient underwent AV fistula surgery. Although the patient was receiving regular administration of factor VIII, he had frequent episodes of anemia due to bleeding tendency caused by hemophilia. Each time, a close examination of the anemia, including gastrointestinal bleeding, was performed, the cause of the anemia was unknown. When an arteriovenous shunt was created, the patient developed a FVIII inhibitor (the titer was 0.8 B.U./mL). Thus, 2000 Units each of rurioctocog alfa, as a factor VIII preparation, was administered on the day of surgery and the day after, and hemostasis was achieved without any postoperative problems. However, before HD initiation, a FVIII inhibitor was further elevated (the titer was 2.0 B.U./mL) and his blood examination revealed decreased FVIII coagulant activity (FVIII:C) (2.3%), prolonged activated partial thromboplastin time (APTT) (66.5 s), and prolonged activated clotting time (ACT, 226 s). HD was initiated without anticoagulant in the dialysis circuit and the patient was given recombinant FVIII concentrates (Lonoctocog Alfa, 3000–6000 Units/10 mL slowly administered from the venous) at the end of dialysis, which enabled hemostasis within 10 min. Prior to the initiation of HD, our case had been treated with emicizumab prophylaxis. He had been receiving subcutaneous injections of emicizumab 390 mg as a factor VIII drug, once every 4 weeks. However, lonoctocog alfa was used at the end of HD because emicizumab would overly shortened APTT and ACT to monitor the extracorporeal circuit. The dose of FVIII concentrate was adjusted by body weight, hematocrit, and inhibitor (INH) periodically. ACT was measured at the start of dialysis and 30 min after each session, and the time elapsed was 150 to 230 s. There was no clot in the dialysis circuit, and HD was performed safely. The patient was able to maintain HD therapy via an AV fistula with the standard replacement of FVIII concentrates. The patient underwent a total of 12 HD treatments at this hospital and was then discharged and continued HD at a maintenance dialysis hospital. He was able to continue dialysis without bleeding problems.

Discussion

Hemophilia A is a hereditary bleeding disorder caused by FVIII deficiency. Occasionally, coagulant factor infusions are required for severe hemorrhage or invasive procedures, including surgery and AV fistula puncture during HD. Hemophilia A is categorized as severe if the residual factor VIII activity is < 1%, moderate (1–5%), and mild (> 5% of normal) [6]. Approximately 30% of patients with hemophilia develop allogeneic antibodies of FVIII [7], and Zheng et al. [3] reported that inhibitors were detected in 25% of patients with hemophilia treated with peritoneal dialysis. The survival duration of HD patients with hemophilia has not been reported in most case reports. The inhibitors decrease the hemostatic effect of replacement therapy; thus, the prophylaxis strategy should be well designed. There have been scattered reports of HD in patients with inhibitor-negative hemophilia [8, 9] and in each case, hemodialysis could be safely performed with replacement therapy with FVIII concentrate or activated prothrombin complex concentrates (APCC) products, or FVII products or non-factor products (emicizumab) (Table 1). The required infusion dose (Unit) of FVIII products at the time of arterial puncture is calculated using the formula = body weight (kg) × target peak factor level × 1/2 (A target peak factor level; within 20–40%). Furthermore, hemophilia A patients with FVIII inhibitor need an additional loading dose to neutralize the inhibitor according to the following formula [body weight (kg) × 40 × {(100-hematocrit (%))/100} × antibody titer (BU/mL)] [10]. There are several types of therapies for the bleeding management of hemophilia A with inhibitors; (1) neutralization therapy using more FVIII products to neutralize the inhibitors, (2) bypass therapy using activated prothrombin complex concentrate(APCC) or FVII products, and (3) non-factor products (emicizumab). Since the inhibitor level in our patient was low (titer < 5 B.U.), neutralization therapy was chosen instead of bypass therapy. If the inhibitor level is higher than 5 B.U., FVIII products are not sufficient to neutralize the inhibitor; therefore, bypass therapy such as FVII product or APCC should be used. The patient had been previously treated with non-factor products (emicizumab) for bleeding before hemodialysis induction. However, emicizumab influences the monitoring of the coagulation state; thus, infusion of FVIII products (lonoctocog alfa) could be the preferred therapy during hemodialysis. In our patient

Table 1 Summary of anticoagulants and coagulant state during hemodialysis in hemophilia patients with hemodialysis

References	Hemophilia Type	Inhibitor	Anticoagulant drugs	Dose	ACT	Coagulation factor activity (%)	Intracircuit coagulation	FVIII products
[19]	A	–	Dalteparin sodium	1000U (beginning)	Not described	20	None	500
[20]	A	–	Local heparinization	–	Not described	< 1	None	Not described
[21]	A	–	None	–	145 s (During dialysis)	20–30	None	1000
[22]	A	–	None	–	Not described	10–20	None	1000
[23]	B	+	Nafamostat mesylate	30 mg/h	Not described	< 0.1	Rarely	none
[13]	B	–	Low-molecular-weight heparin	800 → 400U/h	Not described	18	None	1000
[24]	B	–	Low-molecular-weight heparin	500U (Beginning)	Not described	5–23	None	500
[25]	B	–	None	–	Not described	8.60	None	Not described
[26]	A	–	None	–	150–180 s (when dialysis starts)	10–20	Rarely	500
[27]	A	–	None	—	Not described	< 1	None	1000

(body weight; 62 kg, hematocrit; 36.3), the required dose was within 3779–4399 Unit (required dose as hemophilia; 620–1240 Unit, the inhibitor neutralizing dose; 3159 Unit) and 4000 Units of FVIII were administered before needle removal after each dialysis session. Body weight, hematocrit, and INH were measured periodically, and the dose was adjusted accordingly. About 3000–6000 Units of FVIII were administered before needle removal after each dialysis session. The peak of coagulation factor activity after coagulation factor administration is 10–15 min. Timing of coagulation factor product administration is considered appropriate at the end of dialysis to coincide with hemostasis at the peak of coagulation factor activity. Prior to the initiation of HD, our case had been treated with emicizumab prophylaxis. However, lonoctocog alfa was used at the end of HD because emicizumab would overly shortened APTT and ACT to monitor the extracorporeal circuit. He continued safe HD with appropriate replacement. Some cases of hemodialysis in patients with inhibitor-negative hemophilia have used nafamostat mesylate [11], dalteparin [12], and low-molecular-weight heparin [13, 14], while others have reported no anticoagulant use [9, 15–17]. The ACT during dialysis was prolonged to about 200 s without anticoagulant, and dialysis was performed in the absence of anticoagulant. No intracircuit coagulation was observed, and hemostasis time was approximately 5 to 10 min. In a previous report, hemophilia B patient with an inhibitor who required the extracorporeal ultrafiltration method (ECUM) received APCC, and continued ECUM without difficulty in hemostasis [11]. There is no accepted consensus for the selection of renal replacement therapy in patients with hemophilia. However, induction of HD with an AV fistula has been difficult for patients with hemophilia because of concerns regarding bleeding at the puncture site of the AV fistula. Therefore, PD or HD with a long-term tunneled central venous catheter is indicated for most patients with hemophilia who need renal replacement therapy. Although there are scattered reports of cases of patients with inhibitor-negative hemophilia receiving hemodialysis via AV fistula [12–18], to the best of our knowledge, we report the first case of inhibitor positive hemophilia A patient receiving HD via AV fistula. Over the past decades, the life expectancy of patients with hemophilia has improved with replacement therapy [1]; however, older patients may have aging-related disorders, including renal failure. Therefore, it is important to have several options for RRT according to the patient's condition, and our report indicates that HD is an executable therapy for severe hemophilia.

Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal participant rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Tagliaferri A, Rivolta GF, Iorio A, Oliovecchio E, Mancuso ME, Morfini M, Rocino A, Mazzucconi MG, Franchini M, Ciavarella

N, Scaraggi A, Valdrè L, Tagariello G, Radossi P, Muleo G, Iannaccaro PG, Biasoli C, Vincenzi D, Serino ML, Linari S, Molinari C, Boeri E, La Pecorella M, Carloni MT, Santagostino E, Di Minno G, Coppola A, Rocino A, Zanon E, Spiezia L, Di Perna C, Marchesini M, Marcucci M, Dragani A, Macchi S, Albertini P, D'Incà M, Santoro C, Biondo F, Piseddu G, Rossetti G, Barillari G, Gandini G, Giuffrida AC, Castaman G. Mortality and causes of death in Italian persons with haemophilia, 1990–2007. Haemophilia. 2010;16:437–46.
2. El Bakkouri J, Mamdouh A, Faez S, Medkouri G, Ramdani B, Benchemsi N. Kidney transplantation in a patient with haemophilia A. Transfus Clin Biol. 2009;16:471–3.
3. Zheng H, Wang H, Zhou Z, Cai H, Liang J, Qin Y, Xia P, Chen L. End stage renal failure patients with hemophilia treated with peritoneal dialysis: a case series. Kidney Int Rep. 2022;7:2639–46.
4. Páramo L, Enciso Olivera LJ, Noreña I, Amaya MA, Santacruz JC. First case of acquired hemophilia B in a patient with HIV infection: case report and literature review. Cureus. 2019;11: e4179.
5. Solak Y, Turkmen K, Atalay H, Turk S. Successful peritoneal dialysis in a hemophilia A patient with factor VIII inhibitor. Perit Dial Int. 2010;30:114–6.
6. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. 2014;12:1935–9.
7. de Biasi R, Rocino A, Papa ML, Salerno E, Mastrullo L, De Blasi D. Incidence of factor VIII inhibitor development in hemophilia A patients treated with less pure plasma derived concentrates. Thromb Haemost. 1994;71:544–7.
8. Ishii H, Miyoshi C, Hirai K, Morino J, Minato S, Kaneko S, Yanai K, Matsuyama M, Kitano T, Shindo M, Aomatsu A, Shimoyama H, Miyazawa H, Ito K, Ueda Y, Kaku Y, Hoshino T, Ookawara S, Morishita Y. Induction of hemodialysis with an arteriovenous fistula in a patient with hemophilia A. CEN Case Rep. 2020;9:225–31.
9. Lambing A, Kuriakose P, Lanzon J, Kachalsky E. Dialysis in the haemophilia patient: a practical approach to care. Haemophilia. 2009;15:33–42.
10. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A. Guidelines for the management of hemophilia. Haemophilia. 2013;19:e1-47.
11. Takahashi S, Satomura A, Maruyama T, Fujita Y, Nakura Y, Matsumoto K, et al. Successful treatment of anasarca in a patient with steroid-resistant nephrotic syndrome complicated with severe hemophilia B treated by the extracorporeal ultrafiltration method (in Japanese). J Jpn Soc Dial Ther. 2005;38(1):51–6.
12. Koike H, Hatori M, Nitta T, Kashiwagi B, Suzuki K, Yamanaka H, et al. A case of hemophilia A treated with maintenance hemodialysis. J Jpn Soc Dial Ther. 2004;37:91–4.
13. Magari T, Hatori M, Ono Y, Shiono A, Shimizu N, Kurokawa K, et al. A case of hemophilia B associated with chronic renal failure and renal pelvis tumor treated with hemodialysis and surgery. J Jpn Soc Dial Ther. 2003;36:1731–6.
14. Fujii T, Takata N, Saito S, Naito T, Kimura A. Management of haemostasis during haemodialysis in a patient with haemophilia B. Haemophilia. 2008;14:1135–7.
15. Shino T, Okada T, Matsumoto H, Han M, Hidaka H, Yoshino M, et al. A case of hemophilia A complicated with chronic renal failure treated with maintenance dialysis. J Jpn Soc Dial Ther. 1999;32:1091–4.
16. Kusztal M, Kuzniar J, Weyde W, Klinger M. Haemodialysis in a patient with haemophilia B. Nephrol Dial Transplant. 2008;23:424–5.
17. Izumi H, Goto S, Fujii H, Yoshiya K, Hashimura Y, Katayama Y, et al. A case of a patient with hemophilia A requiring factor VIII replacement and anticoagulant adjustment at the time of hemodialysis induction. J Soc Dial Ther. 2016;49(12):847–52.
18. Ohzono S, Yasumoto Y, Toyama M, Uruta Y, Yamashita W, Ohsaki K, et al. A case of hemophilia A complicated with acute renal failure. J Jpn Soc Dial Ther. 1990;23:163–6.
19. Koike H, Hatori M, Nitta T, et al. A case of hemophilia A treated with maintenance hemodialysis. J Jpn Soc Dial Ther. 2004;37:91–4.
20. Oizono F, Yasumoto Y, Toyama M, et al. A case of hemophilia A complicated with acute renal failure. J Jpn Soc Dial Ther. 1990;23:163–6.
21. Shino A, Okada T, Matsumoto H, et al. A case of hemophilia A complicated with chronic renal failure treated with maintenance dialysis. J Jpn Soc Dial Ther. 1999;32:1091–4.
22. Lambing A, Kuriakose P, Lanzon J, et al. Dialysis in the haemophilia patient: a practical approach to care. Haemophilia. 2009;15:33–42.
23. Takahashi S, Satomura A, Maruyama T, et al. Successful treatment of anasarca in a patient with steroid-resistant nephrotic syndrome complicated with severe hemophilia B treated by the extracorporeal ultrafiltration method (in Japanese). J Jpn Soc Dial Ther. 2005;38(1):51–6.
24. Fujii T, Takata N, Saito S, et al. Management of haemostasis during haemodialysis in a patient with haemophilia B. Haemophilia. 2008;14:1135–7.
25. Kusztal M, Kuzniar J, Weyde W, et al. Haemodialysis in a patient with haemophilia B. Nephrol Dial Transplant. 2008;23:424–5.
26. Izumi H, Goto S, Fujii H, et al. A case of a patient with hemophilia A requiring factor VIII replacement and anticoagulant adjustment at the time of hemodialysis induction. J Soc Dial Ther. 2016;49(12):847–52.
27. Koene RA, Gerlag PG, Jansen JL, et al. Successful haemodialysis and renal transplantation in a patient with haemophilia A. Proc Eur Dial Transplant Assoc. 1977;14:401–6.