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Rapid development of lower leg compartment syndrome following firearm injury in a patient with moderate hemophilia B

TO THE EDITOR: Hemophilia is the most common inherited bleeding disorder caused by factor VIII (hemophilia A) or factor IX (FIX) (hemophilia B) deficiency. The incidence of hemophilia A is 1 in 5,000, and that of hemophilia B is 1 in 30,000 live male births. Increased bleeding tendency is the main clinical manifestation of the disease; however, the bleeding pattern may be highly variable depending on the residual activity of the missing factor. In patients with a severe form of the disease (residual activity <1 IU/dL), spontaneous joint and muscle bleeding are common. In patients with residual factor activity >1 IU/dL, prolonged bleeding after trauma or surgery may predominate in clinical presentation [1].

Firearm injuries in patients with hemophilia, even if treated immediately, undoubtedly have uncertain outcomes. Only two cases of firearm injury in patients with hemophilia have been reported, with one being fatal [2, 3]. Therefore, the clinical course and treatment of these injuries in patients with hemophilia are unknown.

Herein we present a patient with moderate hemophilia B who sustained a gunshot wound to the right lower leg that was complicated by acute limb compartment syndrome (ACS) development.

The patient, born in 1983, was diagnosed with moderate hemophilia B at the age of 10 years after prolonged bleeding following tooth extraction. In the initial finding, the FIX level was 4 IU/dL. The patient never experienced significant spontaneous hemorrhage and received FIX replacement therapy on one occasion in 2015 for pilonidal sinus surgery.

The patient was brought to the emergency department of our institution on January 6, 2019, with a penetrating gunshot wound in the right lower leg, which was sustained after a bullet from a 7.65 mm caliber pistol backfired.

Immediately after the injury, the bleeding was intense, so the patient pressed the wound with gauze to stop the bleeding, as he did not have FIX concentrate at home. Emergency medical personnel were called, and they continued to apply pressure, which was enough to control the bleeding. Owing to harsh winter conditions, it took approximately 3 h until the patient was brought to the emergency

department.

Physical examination revealed a young, healthy male with an elevated blood pressure of 150/90 mmHg and a pulse rate of 90/min. On the lateral side of the distal right lower leg, 5 cm above the lateral malleolus, there was a round entrance wound surrounded by an abrasion ring with a minor irregular exit wound on the opposite side. No bleeding from the injury was observed. The entire right calf was painful, pale, and swollen. Measured to the greatest extent, the difference between the right and left calves was 4 cm. The muscles were taut, and stretching intensified the pain. A tibialis posterior and a dorsalis pedis were not palpable on the right side, while they were present on the left leg. Radiography and computed tomography (CT) scans excluded bone lesions but showed transection of the tibial artery and vein. Laboratory results were as follows: hemoglobin 123 g/L (normal range, 119–157 g/L), white blood cell count 10.7×10^9/L (normal range, $3.4–9.7\times10^9$/L), platelet count 173×10^9/L (normal range, $156–424\times10^9$/L), fibrinogen 4.2 g/L (normal range, 2–4 g/L), prothrombin time 10.9 s (normal range, 10.7–12 s), activated prothrombin time 43.7 s (normal range, 22–32 s), and FIX 4 IU/dL. Owing to the finding of the tibial artery and vein transection and the clinical picture of ACS, the patient was scheduled for urgent surgery.

Surgery was started 5 h after the injury. Immediately before the operation, the patient received 80 IU/kg of plasma-derived FIX concentrate. The incision on the lateral side of the right calf and fasciotomy revealed extremely swollen muscle peroneus longus and brevis and muscle tibialis anterior, with signs of devitalized muscular tissue of the distal part of the musculus tibialis anterior. Transection of the tibial artery and vein was visible with active bleeding. Vascular structures were ligated, which stopped the bleeding. Decompressive fasciotomy of the right calf was performed and left to heal per secundam. The total blood loss during surgery was 150 mL. In the first 3 d after surgery, the FIX trough level was maintained at approximately 80 IU/dL, and for the next 7 d at approximately 60 IU/dL (Fig. 1). The patient continued to receive FIX concentrate (20 IU/kg) once daily without any pharmacological thromboprophylaxis. The patient was transferred to the plastic surgery ward for skin grafting. Four weeks after the injury, the skin graft was placed on the right calf using a split-thickness homologous graft harvested from the right thigh. Immediately before surgery, the patient received 50 IU/kg FIX concentrate and continued to receive 20 IU/kg for the next 7 d. After prolonged physical therapy, the patient regained muscle function in the right leg and recovered completely (Fig. 2).

DISCUSSION

Only few reports of gunshot wounds in patients with hemophilia are available in the literature [2, 3]. Here, we report the case of a patient with moderate hemophilia B who developed ACS due to a firearm wound to the right calf.

ACS is a limb-threatening and even life-threatening surgical emergency caused by bleeding or edema in a closed muscle compartment surrounded by unyielding fascial membranes, leading to muscle and nerve ischemia [4]. ACS diagnosis is mainly based on clinical findings and is confirmed by measuring compartment pressure. ACS is likely if the pressure is >30 mmHg [4]. However, ACS is still a clinical diagnosis, and appropriate handling should not be delayed by measuring the pressure.

ACS most commonly develops due to trauma associated with long bone fractures of the extremities, particularly

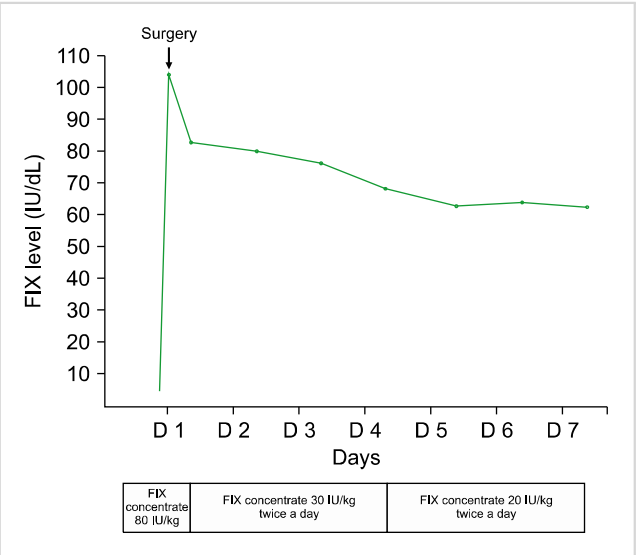

Fig. 1. Factor IX level at the time of the surgery and the trough levels in the first 7 d after surgery.

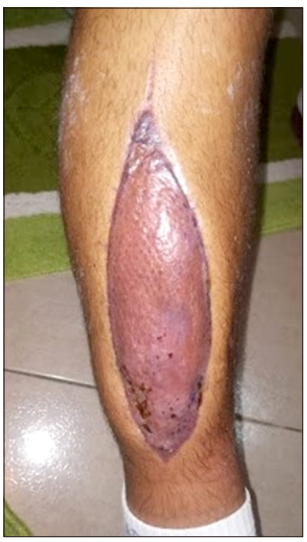

Fig. 2. Right lower leg after autologous skin grafting.

proximal tibial fractures [5]. However, the incidence varies with the trauma mechanism, and patients who sustained a combined arterial and venous injury have a 41.8% likelihood of developing ACS, whereas the probability is 5.9% for open fractures and 2.2% for closed fractures [6]. In a recent meta-analysis, gunshot wounds with a fracture or vascular injury yielded the highest odds ratio for developing ACS [odds ratio, 12.5; 95% confidence interval (CI), 5.69–27.46] [7]. Gonzalez *et al.* [8] reported that no patients with distal below-the-knee penetrating injuries developed ACS, whereas 27% of those with proximal below-the-knee penetrating injuries eventually required fasciotomy. In contrast to the general population, our patient developed ACS after a distal below-the-knee injury, which may be attributed to heavy bleeding in the muscle compartment caused by the combined effects of trauma and coagulation defects.

Therefore, early treatment of ACS is essential. Increased pressure in the muscle compartment, even for a few hours, may result in irreversible tissue ischemia and neuromuscular damage. In patients without hemophilia, urgent decompression of the involved compartments with fasciotomy is the method of choice for ACS treatment [4]. Rorabeck and Macnab [9] underlined the importance of timely diagnosis of ACS and reported almost complete recovery of limb function if fasciotomy was performed within 6 h. Normal limb function was recovered in only 68% of patients when fasciotomy was performed in the first 12 h, whereas after 12 h, only 8% regained normal function [9, 10].

However, the treatment of ACS in patients with hemophilia remains controversial, mainly because literature data are based on scattered case reports and small case series. If it occurs spontaneously, care should focus on early recognition and factor concentrate replacement therapy. In this setting, fasciotomy is reserved for recalcitrant cases with an imminent threat to limb viability [1]. Lancourt *et al.* [11] and Dumontier *et al.* [12] reported the most extensive case series involving 34 and 12 patients with ACS, respectively. Fasciotomy was performed in only two patients, and skin grafting was necessary for one patient, but both were associated with spontaneous ACS development, late diagnosis, and treatment [11, 12]. There are no guidelines for ACS treatment for hemophilia that occurs after trauma.

In our patient, significant muscle ischemia developed only a few hours after the injury owing to intense intracompartmental bleeding resulting from the combination of vascular injury and congenital bleeding disorder. Interestingly, there was no substantial wound bleeding upon admission, probably because the fully developed ACS led to bleeding tamponade, which slowed down the hemorrhage. However, this could easily be misleading with regard to the severity of the injury.

Skin grafting following fasciotomy in patients with hemophilia has been reported in a few case studies [11-14]. However, there are no data on how these patients are treated from a hematological point of view. Our patient received prophylactic FIX therapy until the skin graft was placed and 7 d afterward, aiming for a FIX trough level of approximately 30 IU/dL. The application of this regimen was not complicated by bleeding and led to successful skin graft implementation.

In conclusion, patients with hemophilia with leg trauma, especially those with firearm injuries, should be closely monitored for signs of ACS that may develop rapidly due to the injury and associated hemostasis defect. Cessation of wound bleeding without replacement therapy may be misleading and may herald ACS development. Correction of coagulation defects by replacement therapy is critical for bleeding control and should be achieved as soon as possible. However, surgical management of ACS, including fasciotomy, may be necessary and should not be delayed if indicated.

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Comparison of serum and urine free light chain analysis in clinical diagnosis

TO THE EDITOR: Serum protein electrophoresis (sPEP) and serum immunofixation electrophoresis (sIFE) are the gold standards for diagnosing monoclonal gammopathies (MGs) [1]. However, the PEP and IFE results may vary depending on the method, expertise of the laboratory personnel, and differences between laboratories [2]. Urine protein electrophoresis (uPEP) and urine IFE (uIFE) can be used with high sensitivity [3]; however, the results can be affected by renal function [4]. The free light chain (FLC) assay is an alternative method for diagnosing and monitoring MGs, and has several advantages [3]. First, owing to its short half-life, the FLC assay can be used for real-time monitoring of disease progression or response to treatment in patients with MG [5, 6]. Second, the FLC assay is more sensitive than the PEP and IFE [7]. They are immensely useful, especially in the follow-up of patients with low levels of monoclonal proteins, which account for 20% of MGs [5]. The analytical performance and clinical usefulness of serum FLC (sFLC) assays have been evaluated and compared in previous studies. However, data on urinary FLC (uFLC) assays are limited [8]. Therefore, this study aimed to evaluate and compare the usefulness of sFLC and uFLC assays for diagnosing MGs and other related diseases, and to determine their application in clinical practice.

DATA COLLECTION AND ASSAY METHODS

From June to November 2021, the remaining pairs of serum and 24-h urine samples were collected from patients whose samples were submitted for sPEP, sIFE, uPEP, and uIFE tests as routine examinations. Serum samples were stored at -70°C, thawed, and assayed on the same day. However, urine samples were assayed on the day of collection to prevent the degeneration of urine proteins. We retrospectively reviewed patients' electronic medical records and collected the following data: age, sex, clinical diagnosis, whether the sample was collected at initial diagnosis or follow-up, response to treatment, bone marrow study results (if available), and estimated glomerular filtration rate (eGFR). The eGFR value was calculated using the Modification of Diet in Renal Disease 4-variable formula (isotope dilution mass spectrometry traceable), whereas the body surface area was calculated using the Dubois formula.

Protein electrophoresis and immunofixation were performed using the Sebia Capillarys 2 Flex Piercing System (Sebia, Lisses, France) using the following reagents: Capillarys Protein (E) 6 Kit for sPEP, Capillarys/Minicap Urine Kit for uPEP, and Capillarys Immunotyping Kit for sIFE and uIFE. The detection limit was 0.1 g/dL for sPEP and 2.0 mg/dL for uPEP. sPEP and uPEP results were considered positive if the levels of monoclonal proteins detectable by laboratory personnel were above the detection limit. Total protein and creatinine levels in serum were determined using a colorimetric method, and serum immunoglobulin (sIg) heavy chain and urinary total protein levels were determined using an immuno-turbidimetric method (Cobas c 702 module, Roche Diagnostics, Switzerland). sFLC and uFLC levels were measured using the Freelite assay (The Binding Site Group Ltd, Birmingham, UK), a latex-enhanced immunonephelometric assay measuring free κ and λ light chains, on an automated Cobas 8000 platform (Roche). The sensitivity of this FLC assay has been reported to be <1 mg/L [9]. The reference interval of FLCs established by the manufacturers was as follows: 3.3–19.4 mg/L for serum κ, 5.7–26.3 mg/L for serum λ, 0.26–1.65 for the serum κ/λ ratio, <32.70 mg/L for urine κ, <4.99 mg/L for urine λ, and 2.04–17.78 for the urine κ/λ ratio.

This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (IRB No. CR321321), which waived the requirement for informed consent.

STATISTICAL ANALYSIS

The quantitative values of sFLC and uFLC were compared, and the sFLC and uFLC levels were compared according to the presence of MG [additionally subdivided into newly diagnosed/refractory or relapsed (ND/RR) or non-MD/RR]. In patients without MG, the sFLC and uFLC levels were compared according to the degree of renal insufficiency.