

Case Report

Recurrence of FVIII Inhibitor during Surgery in a Patient with Severe Hemophilia A Receiving Emicizumab Prophylaxis

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Emicizumab, a bispecific monoclonal antibody, benefits patients with severe hemophilia A. It alters laboratory assessments of coagulation activity, requiring anti-idiotypic monoclonal antibodies for accurate monitoring. A 64-year-old man, receiving emicizumab regularly, was admitted for laminoplasty. We planned to use FVIII replacement during the perioperative period after confirming the disappearance of inhibitors, monitoring coagulation activity with anti-idiotypic monoclonal antibodies. Activated partial thromboplastin time was prolonged on postoperative day 2, prompting an immediate switch to eptacog alfa. The patient recovered without bleeding. This case underscores the necessity of anti-idiotypic monoclonal antibodies for accurate monitoring.

Key words: emicizumab, eptacog alfa, hemophilia A, inhibitor, anti-idiotypic monoclonal antibodies to emicizumab

Hemophilia A, an X-linked recessive bleeding disorder, results from a deficiency of factor VIII (FVIII). To prevent bleeding in deep tissues, patients periodically receive plasma-derived or recombinant FVIII. However, about 30% of patients with severe hemophilia A develop FVIII inhibitors, a complication of replacement therapy. These patients are treated with immune tolerance induction (ITI) or bypass agents such as activated prothrombin complex concentrate and recombinant activated factor VII [1-4]. ITI is ineffective in 30% of patients [5], and bypass agents require frequent administration due to their short half-lives [6-8].

Emicizumab has recently emerged as the new standard of care for hemophilia A patients with inhibitors. It has a long half-life (approximately 1 month) and can

be administered subcutaneously once a week to once every 4 weeks to prevent bleeding [9,10]. Its use for prophylaxis significantly reduces the bleeding rate in hemophilia A patients without inhibitors [11,12]. However, managing major surgery with emicizumab alone is challenging due to bleeding risks, necessitating additional coagulation factors, and no established protocol exists for this scenario [13,14]. Furthermore, emicizumab excessively shortens the activated partial thromboplastin time (APTT) *in vitro* because it mimics FVIIIa by bridging FIXa and FX. Therefore, anti-idiotypic monoclonal antibodies to emicizumab are essential for accurately measuring APTT, FVIII activity, and FVIII inhibitors [15].

This report presents the case of a 64-year-old man with severe hemophilia A treated with emicizumab who underwent laminoplasty for cervical spondylosis with

Received January 25, 2025; accepted July 4, 2025.

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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

FVIII replacement. On postoperative day (POD) 2, we detected the FVIII inhibitor using anti-idiotype monoclonal antibodies to emicizumab, prompting an immediate switch to a bypass agent. This case highlights the importance of anti-idiotype monoclonal antibodies to emicizumab during the perioperative period for patients receiving emicizumab.

Case

A 64-year-old man with severe hemophilia A sought treatment for cervical spondylosis at our hospital. He had been receiving plasma-derived factor VIII (FVIII) replacement since age 15. At 58, he underwent bilateral total knee arthroplasty for osteoarthritis and switched to rurioctocog alfa pegol (extended half-life recombinant FVIII) after the surgery. At 59, he underwent total hip arthroplasty for osteoarthritis in his right hip. At 60, he was diagnosed with hepatocellular carcinoma (HCC) and had high-titer inhibitors (10 BU/ml). He underwent laparoscopic hepatic segmentectomy for HCC, with perioperative bleeding controlled using eptacog alfa. On POD2, however, computed tomography (CT) revealed intramuscular bleeding around the surgical site, which improved with continued eptacog alfa

administration. After surgery, FVIII inhibitors were detected, and he was started on emicizumab (3 mg/kg every 2 weeks) as a replacement for FVIII prophylaxis. The inhibitors resolved spontaneously within 3 months after detection.

At 64, the patient was admitted for laminoplasty. Upon admission, he presented with joint contractures in his wrists and elbows, as well as numbness in both upper limbs. His clinical course is shown in Fig.1. Blood samples were tested before and after surgery; to neutralize them, anti-idiotype monoclonal antibodies to emicizumab were used as described previously [15]. Emicizumab was administered 7 days prior to surgery as baseline prophylaxis. We had repeatedly confirmed the absence of FVIII inhibitors before admission. He received a bolus infusion of plasma-derived FVIII 3,000 U (40 U/kg), which was expected to increase FVIII activity to 80% [16]. Two hours later, FVIII activity was 78%, and APTT normalized to 33.3 sec following the infusion. These results indicated that the FVIII inhibitor had spontaneously disappeared during emicizumab use. Given the patient's previous postoperative bleeding despite eptacog alfa, we decided to use plasma-derived FVIII replacement therapy to prevent excessive bleeding. Just before surgery, he received a bolus infusion of

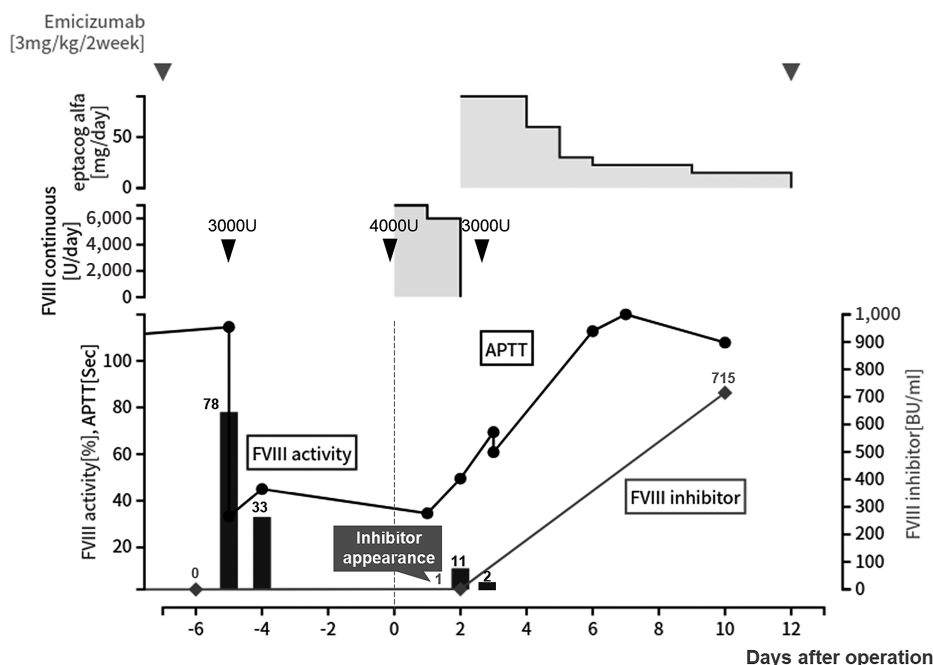


Fig. 1 Clinical course of this case.

plasma-derived FVIII 4,000 U (55 U/kg), followed by a continuous infusion at 7,000 U/day (4 U/kg/h) to maintain 100% FVIII activity [16]. The laminoplasty was successfully completed without any major complications. On POD1, with no signs of bleeding and APTT within the normal range (34.6 sec), we reduced the plasma-derived FVIII dose to 6,000 U/day to maintain FVIII activity at 80%. However, on POD2, APTT lengthened to 49.5 sec and his FVIII activity dropped to 11%. Suspecting a recurrence of FVIII inhibitors, we switched from plasma-derived FVIII to eptacog alfa every 2 h. On POD3, a test dose of 3,000 U was again administered, but FVIII activity remained at 2%. We deemed FVIII replacement ineffective and continued with eptacog alfa. After confirming the absence of bleeding via CT scan, we gradually weaned him off eptacog alfa and restarted emicizumab. He was discharged on POD12 without any obvious bleeding or thrombotic events. After discharge, the inhibitor increased to 1 BU/ml on POD2 and to 715 BU/ml on POD10. Nonetheless, the patient has remained free of bleeding and thrombotic symptoms while receiving emicizumab.

Ethics approval. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Discussion

We describe a patient with severe hemophilia A who underwent perioperative FVIII replacement therapy due to inhibitors that spontaneously disappeared with emicizumab use. However, these inhibitors recurred post-surgery, necessitating an immediate switch from FVIII replacement to eptacog alfa. The patient was discharged without complications. This case highlights three key points. First, the perioperative use of anti-idiotypic monoclonal antibodies to emicizumab is essential for accurately measuring APTT, FVIII activity, and FVIII inhibitors in patients treated with emicizumab who are also receiving FVIII replacement. Second, even transient inhibitors can reappear after FVIII replacement. Finally, when planning to use FVIII replacement therapy perioperatively for patients treated with emicizumab, it is crucial to have eptacog alfa readily available in case of inhibitor recurrence,

facilitating a safe switch from FVIII replacement therapy.

Emicizumab is a humanized bispecific monoclonal antibody that functions similarly to FVIIIa by binding to and bridging FIXa and FX. It does not require activation by thrombin. Two anti-idiotypic monoclonal antibodies bind to the FIXa or FX Fab of emicizumab, neutralizing the activity of the bispecific antibodies. Thus, adding these antibodies *in vitro* allows accurate measurement of APTT, FVIII inhibitors, and FVIII activity in samples involving emicizumab [15]. Without these antibodies, APTT appears shortened because emicizumab binds FIXa and FX *in vitro*, leading to incorrect calculations of FVIII activity and inhibitors. Hence, anti-idiotypic monoclonal antibodies to emicizumab are necessary during its use [15,17-19]. Alternative methods such as thrombin generation assay (TGA) or thromboelastography (TEG) can also assess coagulation function [20,21]. TGA evaluates hemostatic balance through continuous and simultaneous measurement of thrombin formation and inhibition [20]. TEG measures the viscoelastic properties of a clot from the enzymatic phase through the fibrinolytic phase, quantifying fibrinolysis, coagulability, and the effects of antithrombotic and anticoagulant therapy [21]. Therefore, TGA and TEG are recommended for coagulation assessment in patients receiving emicizumab [18]. In our case, however, accurate APTT monitoring was crucial to assess the effectiveness of plasma-derived FVIII, prompting us to prepare the anti-idiotypic monoclonal antibodies. After surgery, we measured APTT daily using these antibodies and detected prolonged APTT on POD2. Suspecting recurrent FVIII inhibitor development, we promptly switched from plasma-derived FVIII to eptacog alfa.

In some hemophilia A patients, FVIII inhibitors spontaneously disappear without ITI [2,22]. In our case, transient inhibitors were found. The patient did not receive ITI as he experienced no bleeding events after starting emicizumab, resulting in spontaneous inhibitor disappearance. To determine the perioperative treatment strategy, we tested for inhibitors multiple times before surgery, with none detected. Moreover, they were not found during treatment with plasma-derived FVIII but appeared after the switch to recombinant factor VIII. Indeed, recombinant FVIII is associated with a higher rate of inhibitor development than plasma-derived FVIII [23]. Based on these factors, we

decided to use plasma-derived FVIII replacement. To confirm its efficacy, we administered it 5 days before surgery. As expected, FVIII activity increased [16]. Nonetheless, the inhibitors recurred.

Reports indicate that FVIII inhibitors can recur after FVIII administration in patients who tested negative for inhibitors during ITI [24,25]. However, few discuss inhibitor recurrence when FVIII is reintroduced after spontaneous disappearance with emicizumab. With the recent development of bypassing agents and emicizumab, bleeding events in hemophilia A patients with inhibitors have decreased, allowing management without FVIII replacement. Consequently, reduced exposure to FVIII in these patients may contribute to an increased frequency of spontaneous inhibitor disappearance. In such instances, inhibitors may recur, as seen in our case, necessitating frequent coagulation factor monitoring.

Emicizumab alone is insufficient for major surgeries, such as joint procedures, requiring additional treatment to prevent excess bleeding in the perioperative period [13]. Treatment strategies are more complex in patients with a history of inhibitor development. First-line drugs for bleeding control in hemophilia A patients with high-titer inhibitors are bypassing agents [4]. In addition to eptacog alfa, FEIBA and Byclot® are also utilized. Previous studies have reported complications, including thrombosis, when using FEIBA or Byclot® concurrently with emicizumab; thus, eptacog alfa is recommended for use with emicizumab [3, 10, 13, 14]. In this case, thrombosis did not develop when eptacog alfa was administered. We will use it again if the patient experiences any events during future surgeries or bleeding episodes.

Emicizumab is beneficial for patients with hemophilia A, regardless of FVIII inhibitor development, and has become widely used [11, 12]. It is important to prepare anti-idiotypic monoclonal antibodies to emicizumab for accurate coagulability assessment, with monitoring needed to confirm whether inhibitors develop. More cases and data are needed to ascertain how often such inhibitors recur after spontaneous disappearance during emicizumab use.

Acknowledgments. The authors thank the patients and medical staff for their contributions to this case report.

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