Received: 11 April 2021 | Revised: 14 June 2021 | Accepted: 4 July 2021

DOI: 10.1002/ccr3.4788

CASE REPORT

Clinical Case Reports Open Access WILEY

Recombinant activated factor VII in a patient with intracranial hemorrhage and severe thrombocytopenia

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Abstract

Hemorrhage in patients with hematologic malignancies is often difficult to manage as many of these patients also have coagulopathy and thrombocytopenia of varying severity. Recombinant factor VIIa is a FDA-approved agent for management of bleeding in hemophilia patients with inhibitors. Use of recombinant FVIIa has also been used as a last resort in various clinical settings such as trauma, alveolar hemorrhage, gastrointestinal bleeding, and intracranial hemorrhage for control of bleeding with variable outcomes. This paper presents a case of recombinant FVIIa administration in a patient with multiple myeloma and profound transfusion refractory thrombocytopenia suffering from traumatic subdural hematoma.

KEYWORDS

intracranial hemorrhage, multiple myeloma, platelet transfusion refractoriness, recombinant activated FVII, thrombocytopenia

1 | INTRODUCTION

Recombinant activated factor VII (rFVIIa) is a universal hemostatic agent, which has traditionally been utilized in the treatment and prevention of bleeding in hemophilia patients with factor inhibitors and qualitative platelet disorders.[1,2] At physiologic levels, FVIIa mediates its effects via interaction with endogenous tissue factor (TF) ultimately leading to thrombin generation.[1] When administered at pharmacologic doses, rFVIIa binds to the surface of activated platelets in a TF-independent manner and promotes factor X activation and thrombin generation on the activated platelet surface.[2,3] Recombinant FVIIa's direct effect on platelet function can reduce the bleeding time by 50%.[4,5]

Recombinant FVIIa has been shown to be effective in securing hemostasis following massive trauma, major surgery, and warfarin overdose.[1] Several case reports have also demonstrated its effectiveness in the treatment of bleeding in patients with severe thrombocytopenia, including in those with intracranial hemorrhage (ICH), for which limited hemostatic treatment options are available.[6,7] Herein, we present a case of rFVIIa use in a patient with ICH and severe thrombocytopenia complicated by platelet transfusion refractoriness (PTR).

2 | CASE REPORT

A 51-year-old female patient presented with a history of IgG kappa multiple myeloma and extramedullary plasmacytomas with pelvic, liver, and oral mucosal involvement. She had previously been treated with two cycles of daratumumab, bortezomib, thalidomide, dexamethasone and 3 cycles of bortezomib, dexamethasone,

cisplatin, doxorubicin, cyclophosphamide, etoposide, without significant disease response. Salvage treatment for refractory disease was administered, using intermediate dose melphalan 70 mg/m^2 given intravenously (i.v.). Her admission laboratory testing was significant for pancytopenia with a hemoglobin of 5.1 grams per deciliter (g/dL), white blood cell count of 2.9 × 10^9 per liter (L^{-1}), and a platelet count of 11 × 10^9 L^{-1}, normal prothrombin time (PT) of 14.8 seconds (sec), prolonged activated prothrombin time (aPTT) of 45 sec and a normal fibrinogen of 232 mg/dL. Her hospital course was significant for severe thrombocytopenia complicated by platelet transfusion refractoriness. An alloantibody screen was performed and confirmed the presence of antibodies directed against HLA allo-antibodies. She received cross-matched platelet units and was started on aminocaproic acid due to her increased bleeding risk. Unfortunately, on day 20, she acutely developed confusion after suffering minor trauma to the head. A computed tomography of her head demonstrated bilateral subdural hematomas measuring 6 millimeters (mm) on the right side and 4 mm on the left with no midline shift. Aminocaproic acid was stopped, and an infusion of rFVIIa was immediately given, at a dosage of 90 micrograms per kilogram (μg/kg), every 2 hours (×3 doses) followed by every 4 hours (×5 doses) for a total of 8 doses. A factor VII (FVII) activity assay was not performed prior to the first infusion, but FVII levels two hours following the infusion were found to be >800%. Despite the absence of a platelet count increment, immediately before and following her ICH, there was a considerable increase in her FVIIa plasma levels. This resulted in a significant reduction of her PT levels from 16 sec to less than 10 sec (Figure 1), and stabilization of her intracranial bleed. This was evident on serial imaging of her head, which revealed bilateral subdural hematomas stable in size with no new areas of cerebral hemorrhage seventy-two hours following the initial event (Figure 2). An electroencephalogram demonstrated abnormal generalized periodic discharges consistent with worsening encephalopathy, for which she was started on i.v. levetiracetam. Despite stability of her ICH, her liver function continued to worsen. There was interval development of multiple hepatic masses on CT imaging (Figure 3) and laboratory studies showed worsening transaminitis, hypoalbuminemia, hypofibrinogenemia, and a prolonged PT. Unfortunately, her mental status would continue to deteriorate as a result of rapidly progressive myeloma with circulating plasma cells. She died of progressive myeloma on day 44 following chemotherapy.

3 | DISCUSSION

Severe bleeding is a common and potentially fatal complication in patients with hematologic malignancies. Platelet transfusion, along with correction of coagulopathies, is the cornerstones of managing bleeding in these patients. However, patients may develop platelet transfusion refractoriness (PTR) during their disease course, which limits treatment options for achieving hemostasis. PTR is defined as a failure to achieve a post-transfusion platelet count increment of greater than 10,000 microL^{-1} on more

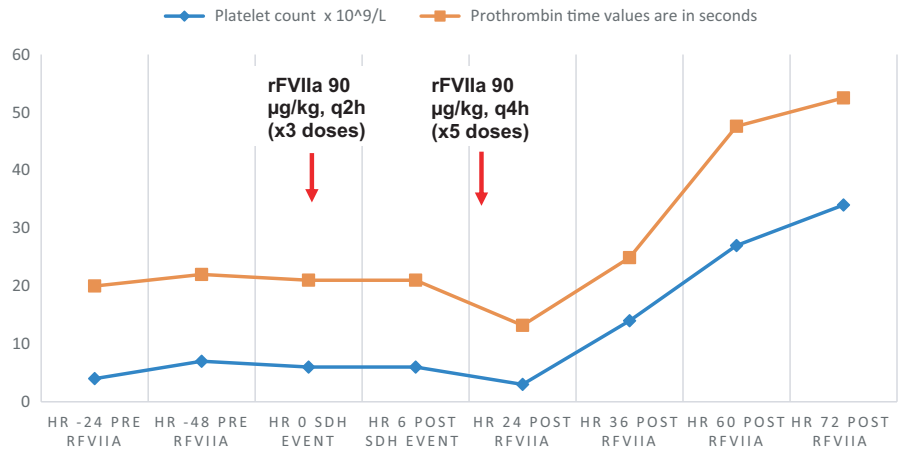


FIGURE 1 Levels of prothrombin time (orange line) and platelet count (blue line) were measured at the associated time points listed above. Recombinant FVIIa was initially given at a dosage of 90 μg/kg every 2 hours (q2h) for 3 doses. Twelve hours following subdural hemorrhage (SDH), our patient was given rFVIIa every 4 hours (q4h) for 5 doses. Prothrombin time decreased significantly to less than 10 seconds immediately following rFVIIa infusion but was prolonged thereafter. Fibrinogen levels also decreased during this time period, consistent with worsening liver function. Platelet count reached a nadir of 6 × 10^9 per L, followed by a fourfold increase at 72 hrs post-rFVIIa infusion. This significant platelet count response in our patient, perhaps reflected better hemostasis and reduced platelet consumption .

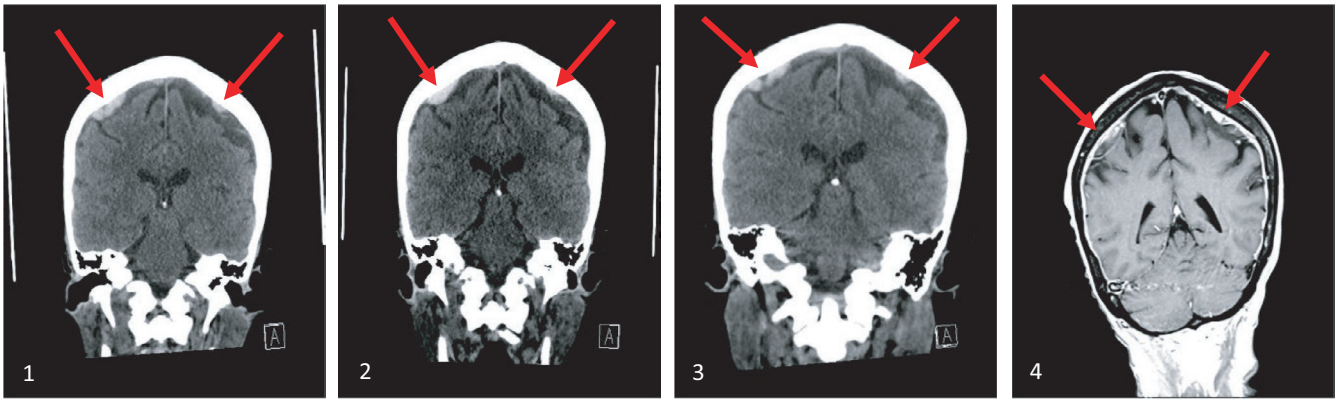
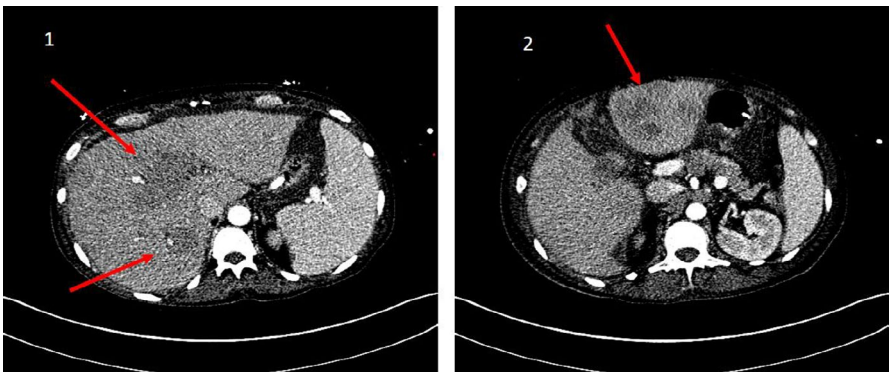


FIGURE 2 CT non-contrast head of initial event (A) showing acute bi-temporal subdural hemorrhages (SDH), prior to administration of rFVIIa. Serial non-contrast CT head scans performed at 12 hours (B), 24 hours (C), and MRI brain with and without contrast performed 72 hours post-SDH (D) demonstrating stability of the bi-temporal SDH, following infusion of rFVIIa.

FIGURE 3 CT scan of abdomen and pelvis with contrast showing multiple hypo-attenuating lesions in the right (A) and left hepatic lobes (B), consistent with disease progression and worsening liver dysfunction.



than one occasion.[8] PTR may be a result of non-immune factors such as DIC, sepsis, and splenomegaly, or immune factors including alloimmunization against human leukocyte antigen (HLA) and/or human platelet antigen (HPA) systems.[9,10] Management of PTR in patients with alloimmunization includes the use of HLA-matched or cross-match compatible platelet units. Anti-fibrinolytic agents and rFVIIa may also be utilized in the treatment of active bleeding and PTR.[11,12]

Recombinant FVIIa has also been investigated in several settings including in the control of bleeding following major trauma, liver transplantation, cardiac surgery, and intracranial hemorrhage.[13] Intracranial hemorrhage (ICH) is complicated by high morbidity and mortality, with approximately, 40% of patients dying within 30 days. Baseline hematoma size and rate of expansion of bleeding have been demonstrated to influence prognosis.[14] Treatment for ICH is generally supportive, including blood pressure control and possible surgical removal of intracranial clot. Hemostatic therapy, including rFVIIa, may reduce ongoing bleeding and improve outcomes in patients with ICH.[1]

The use of rFVIIa has been extensively studied in patients with ICH. Benefits of rFVIIa administration include its ability to be given immediately without any need for confirmation of blood group or thawing of blood products as well as its small volume which is important in the setting of raised intracranial pressure. Limitations of rFVIIa therapy include its high cost, very short half-life, and its risk for thrombotic adverse events.[1] In the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, it was noted that patients given the 80 μg/kg dose of rFVIIa experienced an increase in arterial thromboembolism compared to placebo (4 versus 9 percent; $p = 0.04$). There were no significant differences observed in rates of venous thromboembolism.[14]Previous studies of rFVIIa have demonstrated mixed efficacy results with respect to morbidity and mortality in patients with life-threatening bleeding. While rFVIIa was found to reduce the growth of ICH when administered within 4 hours of symptom onset, it did not improve clinical outcomes such as functional recovery or survival in the FAST trial participants.[14] Another retrospective study of over 3400 patients with hematologic and solid organ malignancies reported improved survival in rFVIIa responders along with reduced need for platelet, red cell, cryoprecipitate, and plasma transfusions following the first dose of rFVIIa at 90 μg/kg.[15] In this

study, a majority of patients (70%) received only one dose of rFVIIa. The survival rate was 57% with median follow-up of 28 days post-discharge. Overall, the morbidity and mortality rate in patients receiving rFVIIa as treatment remains high and this is likely due to severity of the underlying disease. For instance, Shah et al, demonstrated a 24-hour survival of 80%, but a 30-day survival rate of only 40% in a mixed surgical and medical group of patients, when rFVIIa was given as a last resort for life-threatening bleeding.[16] Our patient had persistent severe thrombocytopenia and PTR, with new ICH which prompted our use of rFVIIa therapy. Despite the absence of a platelet count increment, immediately before and following her bleeding episode, the use of rFVIIa resulted in a significant reduction of her PT levels, and successful hemostasis of her ICH.

Furthermore, as shown in Figure 1, our patient's PT levels became significantly prolonged, beginning thirty-six hours post-rFVIIa infusion. This was consistent with worsening liver dysfunction as evidenced by new liver masses on CT imaging as well as laboratory studies which showed hypoalbuminemia and hypofibrinogenemia. Given these findings, we recommend frequent monitoring of fibrinogen levels and cryoprecipitate repletion in patients who experience bleeding complicated by severe hepatic dysfunction.

The appropriate dosage and duration of rFVIIa therapy remains unclear. Previous literature suggests a range of 1 to 17 doses at 40 to 120 μg/kg in cancer patients with life-threatening bleeding.[17] Our patient received a dosage of 90 ug/kg, every 2 hours (×3 doses) followed by every 4 hours (×5 doses) for a total of 8 doses for her ICH. Following rFVIIa treatment, serial imaging of her head performed over the next three days showed stability in size of her ICH, suggesting achievement of hemostasis.

Finally, while rFVIIa may represent an effective therapeutic option in cancer patients with major hemorrhage refractory to conventional therapies, it is important to recognize the potential futility of this therapy in patients with far advanced disease. In the patient reported here remission induction was being attempted, justifying the use of recombinant FVIIa, nevertheless, the case illustrates the importance of concurrent treatment of a patient's underlying malignancy. For instance, in cancer patients with acquired hemophilia, where rFVIIa is used for treatment of the bleeding episodes, successful treatment of the underlying malignancy has been associated with eradication of the antibody against FVIII.[18] Therefore, rFVIIa treatment should be reserved for cancer patients who are likely to benefit from further disease-modifying therapy and avoided in patients with end-stage disease in which the adverse effects and high cost of treatment may outweigh any potential clinical benefit.

4 | CONCLUSION

This case highlights the use of rFVIIa in the context of severe thrombocytopenia and ICH complicated by PTR. In addition to the use of cross-matched platelets, our patient also received rFVIIa therapy. While our patient ultimately did not survive her ICH, her hemorrhages remained stable in size and there was no evidence of other sites of intracranial bleeding seventy-two hours following rFVIIa therapy. We conclude use of rFVIIa may be an effective hemostatic agent in the setting of life-threatening ICH.

ACKNOWLEDGMENTS

There are no acknowledgments for this case report.

CONFLICTS OF INTEREST

All contributing authors declare no conflicts of interest.

AUTHORS CONTRIBUTIONS

AMA and AK: performed the literature search, acquired relevant clinical data, designed figures, and drafted the manuscript. AF: prepared neuroimaging and provided expertise regarding radiographic findings. AAT: conceived topic for manuscript, supervised, and critically reviewed manuscript for important intellectual content.

ETHICAL STATEMENT

This work has been conducted in accordance with the Declaration of Helsinki (1964).

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Ansari AM, Khorasanchi A, Faghihimehr A, Toor A. Recombinant activated factor VII in a patient with intracranial hemorrhage and severe thrombocytopenia. *Clin Case Rep*. 2021;9:e04788. https://doi.org/10.1002/ccr3.4788