Case Report

Successful hemostasis in refractory alveolar hemorrhage using low-dose recombinant activated factor VII

John Selickman a, *, Jacob Fiocchi b, Hem Desai a, Kathryn M. Pendleton a

a Department of Medicine, Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, University of Minnesota, Minneapolis, MN, USA
b Department of Medicine, Division of General Internal Medicine, University of Minnesota, Minneapolis, MN, USA

ABSTRACT

Diffuse alveolar hemorrhage (DAH) is a life-threatening condition requiring prompt recognition. Conventional therapy, even when initiated early, may not have an immediate effect, and in severe cases, bleeding can persist despite treatment. We report the case of a previously healthy 33-year-old male who developed DAH secondary to granulomatosis with polyangiitis, resulting in respiratory failure and the need for mechanical ventilation. High-dose corticosteroids, plasma exchange, and remission induction with cyclophosphamide failed to control bleeding, leading to severely impaired gas exchange. 20 mcg/kg of systemic recombinant activated Factor VII (rFVIIa), a dose lower than previously reported for management of DAH, resulted in hemostasis and improved oxygenation after only three doses. No complications were observed, and our patient was liberated from ventilatory support eight days later. In the setting of DAH with refractory bleeding, hemostasis may be achievable with a lower dose of rFVIIa than commonly used, potentially mitigating the risk of dose-dependent side effects.

1. Introduction

Diffuse alveolar hemorrhage (DAH) is a life-threatening condition that manifests as a clinical constellation of hemoptysis, anemia, radiographic infiltrates, and hypoxemia. While no consensus exists regarding its classification, etiologies of DAH are commonly grouped in accordance with their histopathologic findings, which include pulmonary capillaritis, bland pulmonary hemorrhage, and diffuse alveolar damage [1]. Pulmonary capillaritis, which is typically mediated by autoimmunity, is the most common histopathologic finding, accounting for 88% of cases in one small study; among the causes of capillaritis in this study, systemic vasculitis was most common [2].

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, in particular granulomatosis with polyangiitis (GPA) and microscopic polyangiitis, are known for their association with pulmonary capillaritis [3], and alveolar hemorrhage may be the presenting manifestation. DAH, regardless of the etiology, is a life-threatening condition that warrants immediate and aggressive treatment. For patients with GPA presenting with acute, severe disease (including DAH), treatment consists of high-dose corticosteroids and remission induction with either cyclophosphamide or rituximab [4]. The role of plasma exchange for severe disease remains controversial following a clinical trial that showed no mortality benefit [5], although many experts still recommend its use [6].

In spite of appropriate and prompt treatment, the mortality rate for DAH remains high, particularly in patients requiring mechanical ventilation [7,8]. The effect of first-line therapies is not immediate: plasma exchange is a labor-intensive process requiring time to initiate, and the systemic effects of corticosteroids can take up to 8 hours [9]; in some cases, there may not be an initial response to ei-
ther. In the setting of refractory hemorrhage, adjunctive therapy is required to preserve gas exchange and minimize blood loss while waiting for immunosuppression to take effect. In this clinical scenario, recombinant activated Factor VII (rFVIIa) is a potential therapeutic option.

2. Case presentation

A 33-year-old otherwise healthy male presented to the emergency department with dyspnea, non-productive cough, myalgias, and fevers as high as 40 °C at home. On arrival, his blood pressure was 122/67 mmHg, heart rate 78 beats per minute, temperature 36.6 °C, respiratory rate 18 breaths per minute, and SpO2 96% while breathing ambient air. He appeared acutely ill but breathing at rest was non-labored. Physical examination was notable for the presence of scattered rhonchi and palpable purpura over the back and buttocks.

Initial laboratory evaluation was notable for a C-reactive protein of 184 mg/dL [0.0–8.0], hemoglobin of 13.7 g/dL [13.3–17.7], platelet count of 140 × 10^9/L [150–450], and creatinine of 0.85 mg/dL [0.66–1.25]. Chest radiograph initially demonstrated mixed interstitial and airspace opacities in the left mid-lung and right upper lobe (Fig. 1). Computed tomography of the chest revealed consolidation in the dependent portion of the lung bases and upper lobes (Fig. 2). Blood and sputum samples were collected for culture and empiric antibiotics were started.

Supplemental oxygen requirements increased throughout the first 48 hours of admission. Due to failure to respond to initial antibiotic therapy and concern for alveolar hemorrhage, bronchoscopy was performed on hospital day 3. Frothy, hemorrhagic secretions were observed throughout the proximal airways. Bronchoalveolar lavage of the posterior subsegment of the right upper lobe revealed progressively hemorrhagic return, consistent with a diagnosis of DAH.

Within several hours of bronchoscopy, the patient required transfer to the intensive care unit due to increased work of breathing and oxygen requirements. A repeat chest radiograph demonstrated significant interval increase in infiltrates bilaterally (Fig. 1). High-dose methylprednisolone (1 g daily) was initiated for treatment of DAH, but due to progressive respiratory distress, the patient required intubation shortly after transfer and plasma exchange was initiated. Serologic testing, obtained shortly after presentation, subsequently returned as positive for cytoplasmic-ANCA of 1:160 [< 1:10] and proteinase-3 IgG antibody of 2.3 AI [0.0–0.9], consistent with a diagnosis of GPA.

Alveolar hemorrhage persisted in spite of immunosuppression with steroids, remission induction with cyclophosphamide (750 mg/m^2 x 1), and plasma exchange, necessitating multiple transfusions of red blood cells. In the setting of persistent hemorrhage and severe hypoxemia, we elected to administer systemic rFVIIa (20 mcg/kg every 8 hours for three doses) on hospital day 5. Following

![Fig. 1. Initial chest radiograph demonstrating the presence of mixed interstitial and airspace opacities in the left mid-lung and right upper lobe (left panel). Subsequent chest radiograph prior to intubation demonstrating interval worsening (right panel).](image1)

![Fig. 2. Axial slice from computed tomography demonstrating consolidative opacities in the dependent portion of the upper lobes and adjacent areas of ground glass opacities.](image2)
the administration of rFVIIa, there was an appreciable decrease in the amount of bloody airway secretions and gas exchange improved significantly. Our patient was extubated five days later on hospital day 10.

3. Discussion

We present a case of life-threatening DAH, with refractory hemorrhage in spite of first-line therapies, in which hemostasis was successfully obtained using systemic rFVIIa. rFVIIa is an activated clotting factor approved for use in patients with hemophilia who have developed inhibitors of coagulation (antibodies to clotting factor), rendering standard treatment with Factor VIII and Factor IX concentrates ineffective [10]. It has also been used (‘off-label’) outside the realm of acquired or congenital Factor deficiencies in cases of severe or refractory bleeding, including DAH. No clinical trials have demonstrated the safety or efficacy of rFVIIa for treatment of DAH, and the optimal dose, frequency, and duration of therapy remain uncertain. The risk of side effects, most notably thrombosis [11], remains an important consideration.

In a single-center retrospective analysis of rFVIIa use for refractory hemorrhage, twenty-three patients with DAH received systemic rFVIIa over a ten-year period; patients with vasculitis had more favorable outcomes than those with other causes of DAH, with eight out of nine patients surviving [12]. Multiple case series have also reported successful treatment of refractory alveolar hemorrhage with intrapulmonary administration of rFVIIa (using a bronchoscope for delivery) [13,14]. Compared to the systemic route, lower doses of rFVIIa have been used successfully with intrapulmonary administration, potentially reducing the risk side effects.

A comprehensive review recently identified 111 cases of DAH treated with either systemic or intrapulmonary rFVIIa [15]. Among patients who received systemic rFVIIa, single or repeated doses ranging from 35 to 200 mcg/kg were used, with an average of 250 mcg/kg/episode. Patients receiving intrapulmonary rFVIIa, however, achieved hemostasis with considerably lower doses (50 mcg/kg/episode) and, unlike systemic administration, no thromboembolic events were reported.

While the mechanism underlying the increased efficacy of intrapulmonary rFVIIa is not known with certainty, a potential explanation may be the tissue factor (TF)-dependent activity of rFVIIa. rFVIIa affects hemostasis through two separate pathways: at pharmacologic doses, rFVIIa binds to activated platelets, leading to enhanced thrombin generation, downregulation of fibrinolysis, and formation of a fibrin-rich hemostatic plug. Alternatively, rFVIIa can bind to TF, leading to a thrombin burst at the site of injury [16]. In acute lung inflammation, expression of TF by alveolar epithelium is upregulated [17]. DAH may act similarly with respect to increased local expression of TF, resulting in enhanced interaction with TF (and by extension coagulation) when rFVIIa is administered via the intrapulmonary route.

However, lower doses of systemic rFVIIa have proven effective for other ‘off-label’ purposes, including management of bleeding after cardiopulmonary bypass [18]. In this case of refractory DAH, three doses of only 20 mcg/kg rFVIIa administered systemically—comparable to the lower doses used with intrapulmonary administration, resulted in a significant decrease in hemorrhage and improved oxygenation. This suggests that in some patients with DAH, lower doses of systemic rFVIIa than traditionally used may not only attenuate bleeding, but also avoid the risk of side effects typically associated with higher systemic doses while obviating the need for additional resources (i.e. bronchoscopy) required for intrapulmonary administration.

4. Conclusion

DAH is a life-threatening complication of GPA. In addition to supportive cares, first-line therapy includes high-dose corticosteroids, remission induction with either cyclophosphamide or rituximab, and potentially plasma exchange. First-line therapies can fail to achieve hemostasis, resulting in inadequate gas exchange and/or the need for large volumes of transfused blood cells. While higher doses of rFVIIa are often required when administered systemically, lower doses than previously reported may be effective for hemostasis, potentially reducing the risk of side-effects.

Funding

No funding was received.

Author contributions

JS, JP, HD, and KMP contributed to conceptualization of this manuscript. Original draft written by JS and JF. Review and editing performed by HD and KMP.

Declaration of competing interest

No conflicts of interest exist for any authors.

References

[1] A.R. Lara, M.I. Schwarz, Diffuse alveolar hemorrhage, Chest 137 (5) (2010) 1164–1171.
[2] W.D. Travis, T.V. Colby, C. Lombard, H.A. Carpenter, A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation, Am. J. Surg. Pathol. 14 (12) (1990) 1112–1125.
[3] J.C. Jennette, R.J. Falk, Small-vessel vasculitis, N. Engl. J. Med. 337 (21) (1997) 1512–1523.
[4] S.A. Chung, C.A. Langford, M. Maz, A. Abril, M. Gorelik, G. Guyatt, et al., American college of rheumatology/vasculitis foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis, Arthritis Rheumatol. 73 (8) (2021) 1366–1383 2021.
[5] M. Walsh, P.A. Merkel, C.A. Peh, W.M. Szpiro, X. Puechul, S. Fujimoto, et al., Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis, N. Engl. J. Med. 382 (7) (2020) 622–631.
[6] F.B. Cortazar, J.L. Niles, The fate of plasma exchange and glucocorticoid dosing in ANCA-associated vasculitis after PEXIVAS, Am. J. Kidney Dis. 76 (4) (2020) 595–597.
[7] K. Kanaoka, S. Minami, S. Ihara, K. Komuta, High neutrophils and low lymphocytes percentages in bronchoalveolar lavage fluid are prognostic factors of higher in-hospital mortality in diffuse alveolar hemorrhage, BMC Pulm. Med. 21 (1) (2021) 268.
[8] A. Mirosev, A. Parrot, V. Audigier, A. Demoule, J. Mayaux, G. Geri, et al., Severe diffuse alveolar hemorrhage related to autoimmune disease: a multicenter study, Crit. Care 24 (1) (2020) 231.
[9] D.M. Williams, Clinical pharmacology of corticosteroids, Respir. Care 63 (6) (2018) 655–670.
[10] U. Hedner, Recombinant coagulation factor VIIa: from the concept to clinical application in hemophilia treatment in 2000, Semin. Thromb. Hemost. 26 (4) (2000) 363–366.
[11] R. MacLaren, I.A. Weber, H. Brake, M.A. Gardner, M. Tanzi, A multicenter assessment of recombinant factor VIIa off-label usage: clinical experiences and associated outcomes, Transfusion 45 (9) (2005) 1434–1442.
[12] V. Pathak, J. Kuhn, D. Gabriel, J. Barrow, J.C. Jennette, D.C. Henke, Use of activated factor VII in patients with diffuse alveolar hemorrhage: a 10 Years institutional experience, Lung 193 (3) (2015) 375–379.
[13] M.S. Baker, K.J. Diah, W.G. Carlos, P. Mathur, Intrapulmonary recombinant factor VII as an effective treatment for diffuse alveolar hemorrhage: a case series, J Bronchology Interv Pulmonol 23 (3) (2016) 255–258.
[14] R. Diaz, P. Almeida, M. Alvarez, G. Ferrer, F. Hernandez, Life-threatening pulmonary hemorrhage responds to recombinant factor VIIa: a case series in south Florida hospitals, Cureus 11 (11) (2019) e6202.
[15] J.A. Park, Treatment of diffuse alveolar hemorrhage: controlling inflammation and obtaining rapid and effective hemostasis, Int. J. Mol. Sci. 22 (2) (2021).
[16] U. Hedner, Recombinant factor VIIa (NovoSeven) as a hemostatic agent, Dis Mon 49 (1) (2003) 39–48.
[17] J.A. Bastarache, L.B. Ware, G.R. Bernard, The role of the coagulation cascade in the continuum of sepsis and acute lung injury and acute respiratory distress syndrome, Semin. Respir. Crit. Care Med. 27 (4) (2006) 365–376.
[18] N.D. Andersen, S.D. Bhattacharya, J.B. Williams, E.L. Fosbol, E.L. Lockhart, M.B. Patel, J.G. Gaca, J.J. Welsby, G.C. Hughes, Intraoperative use of low-dose recombinant activated factor VII during thoracic aortic operations, Ann. Thorac. Surg. 93 (6) (2012) 1921–1928.