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Atypical Hemolytic Uremic Syndrome: An Unusual Complication of Activated Prothrombin Complex Concentrate

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INTRODUCTION: Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy characterized by thrombocytopenia, microangiopathic hemolytic anemia, and renal impairment.[1] It has a poor prognosis with greater than half of patients requiring dialysis or experiencing significant renal injury within the first year of diagnosis.[2] The underlying mechanism is thought to involve unregulated terminal complement activation.

Factor Eight Inhibitor Bypassing Activity (FEIBA) is an activated prothrombin complex concentrate (aPCC) composed of activated factor VII and inactivated factors II, IX, and X. It is FDA approved to control bleeding in those with hemophilia A or B with acquired inhibitors or non-hemophiliacs with inhibitors to factors VIII, IX, or XI.[3,4] More recently, data have shown its efficacy in off-label emergent need for anticoagulant reversal therapy.[5-8] Herein, we describe the first known case of atypical hemolytic uremic syndrome (aHUS) after administration of a large dose of FEIBA.

CASE REPORT: A 58-year-old man taking warfarin for an unprovoked deep vein thrombosis presented with one day abdominal and shoulder pain which progressed to non-radiating right upper quadrant abdominal pain. His past medical history was significant for hypertension for which he was taking Lisinopril. He was a 15-pack year smoker without alcohol or illicit drug use. Family history was significant for father with liver cancer.

On physical examination, vitals were stable with blood pressure of 130/87 mm Hg, heart rate of 67 beats/minute, respiratory rate of 16 breaths/minute, and body mass index of 48 kg/m2. He was in mild distress from pain. His lungs were clear to auscultation and cardiac examination demonstrated regular rhythm, no extra heart sounds or murmurs. On abdominal examination, he had mild right upper quadrant tenderness extending to the right flank. No rashes were found on skin examination. His neurologic exam showed no focal neurological deficits. Initial complete blood count and comprehensive metabolic panel were unremarkable. His INR was therapeutic at 2.8 with platelet count of 259x109/L, creatinine of 1.06 g/dL, and hemoglobin of 12.9 g/dL. An abdominal ultrasound and subsequent CT abdomen showed a 10 cm in diameter hepatic

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hematoma suggestive of active bleeding and rupture. Due to concern for potential decompensation, he was given 5mg of intravenous vitamin K and 14,150 Units of anti-inhibitor coagulant complex at 100 Units per kilogram infused over one hour for reversal of therapeutic anticoagulation and establishment of hemostasis. He was transferred to our institution for further management in the Intensive Care Unit.

Within 24 hours of admission he became oliguric and laboratory studies revealed potassium of 6 mmol/L and creatinine of 5.51 g/dL. Additional laboratory studies showed LDH 2618 IU/L, platelet count of 33x109/L, hemoglobin of 8.0 g/dL, haptoglobin of <30 g/dL, fibrinogen of 445 mg/dL, C3 of 110 mg/dL (ref 96-185 mg/dL), and C4 of 44 mg/dL (ref 18-53 mg/dL). Blood smear was significant for schistocytes, spherocytes, and anisocytosis. He was started on hemodialysis for acute renal failure.

Due to presumptive diagnosis of thrombotic thrombocytopenic purpura (TTP), he was begun on plasmapheresis and given IV corticosteroid. Further testing revealed normal ADAMTS-13 with 74% activity. Stool culture and antigen PCR were negative for E. Coli and Shiga toxins. He was then diagnosed with atypical HUS and given four weekly doses of intravenous Eculizumab. Following administration, his microangiopathic hemolytic anemia quickly resolved and his renal function improved allowing discontinuation of hemodialysis after two months. Given the temporal relationship and negative stool cultures, atypical HUS was deemed to be from FEIBA administration. Notably, he had no family history of atypical HUS and declined genetic testing. Follow-up over four years post hospitalization shows no evidence of recurrent atypical HUS.

DISCUSSION: This is the first report in the literature of atypical HUS secondary to administration of the aPCC FEIBA. Use of aPCCs has been gaining favor over component blood products when reversing vitamin K antagonists and direct oral anticoagulants. Several small trials have been conducted wherein they used small doses of 500-1000 Units FEIBA infused at 1-2Units per minute to achieve good reversal of vitamin K antagonist.[6,7] This range of fixed doses is much smaller than the therapeutic dose studied in those with hemophilia or

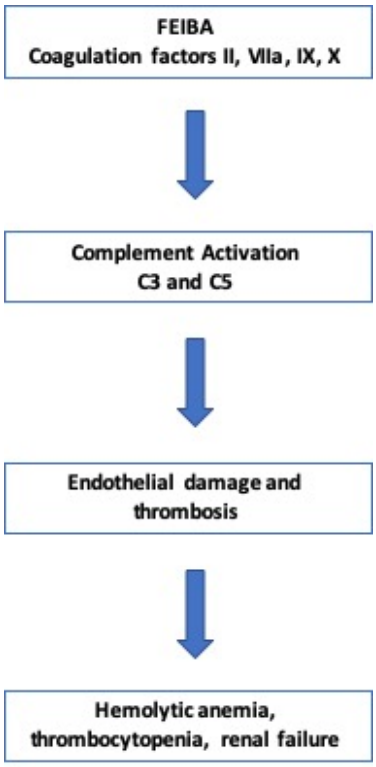

***Figure 1**. Proposed mechanism of FEIBA induced aHUS*

acquired inhibitors at 50-100 Units/kg. [C] Initial studies using FEIBA for hemophiliacs with joint and muscle bleeding[9] or as prophylaxis for bleeding in those with inhibitors[4] did not report thrombotic complications. However, post-marketing surveillance has revealed thrombotic complications in those receiving aPCC, particularly when administered at high doses or increased frequency.[3] Whereas

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microthrombotic complications are rarely described.

There is a single case report of the prothrombin complex concentrate K-Centra causing atypical HUS. This patient was treated in a similar fashion with HD and eculizumab to achieve a similarly good result.[2] The mechanism of aHUS is hypothesized to occur from impaired regulation of the terminal common complement pathway. Terminal complement activation leads to endothelial damage and development of thrombosis and the three features of aHUS: microangiopathic hemolytic anemia, thrombocytopenia, and renal injury.[1] This also explains the efficacy of eculizumab, a monoclonal antibody directed against complement protein C5[10], in achieving temporary or total remission of atypical HUS in other case reports and in our patient. Thus, the mechanism of FEIBA induced aHUS may be due to terminal complement activation.

The intricate interplay between the coagulation cascade and complement system is well known, however the specific physiologic mechanism remains elusive.[11] In vitro assays and in vivo mouse studies have shown the ability of thrombin to activate complement.[11,12] Furthermore, additional ex vivo studies have shown the ability of Factors IXa, Xa, XIa, thrombin, and plasmin have the ability to cleave C3 and C5 into their activated forms.[13,14] However, more recently in-vivo baboon studies have shown that supraphysiologic levels of factor ten are able to induce complement activation, but thrombin and plasmin did not activate complement in baboons.[15] Taken together this demonstrates the ability of coagulation factors to potentially activate terminal complement through both thrombin-dependent and thrombin-independent mechanisms. Herein, lies a possible mechanism of aHUS resultant of factor administration as in our patient.

Our patient, was treated with a very large dose of FEIBA containing coagulation factors II, VII, IX, and X.[16] Therefore, we hypothesize supraphysiologic dose of constituent coagulation factors induced terminal complement activation. The resultant terminal complement activation can serve as the impetus for the development of atypical HUS as illustrated in Figure 1, however, further research is needed to confirm this mechanism.

Debate remains concerning the optimal duration of Eculizumab treatment due to its financial burden. Recommendations based on limited case reports and data suggest for secondary aHUS caused by drugs, Eculizumab should be discontinued when hematologic remission is established.[17,18] In some cases of aHUS, Eculizumab has been recommended for indefinite use. However, the scarcity of outcomes data for drug induced aHUS outside the context of certain drugs like gemcitabine and tacrolimus universal recommendations cannot be made for all drug induced aHUS.[19] Our case report highlights the efficacy of a limited trial of Eculizumab treatment of FEIBA induced aHUS.

As FEIBA gains further clinical use this case report will serve as precaution for the potential development of aHUS as a complication of FEIBA administration. In addition, the potential mechanism discussed herein serves as a catalyst for future study and the short trial of Eculizumab shows its efficacy in treating aHUS secondary to FEIBA.

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