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Case Report

Perioperative therapeutic plasma exchange in a patient with rare Factor XIII inhibitor

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ABSTRACT

Introduction: Factor XIII deficiency is a rare bleeding disorder which could be severe if inherited or less severe if acquired. We report a case of acquired Factor XIII inhibitor in a 75-year-old male with a suspicious left renal mass treated perioperatively with therapeutic plasma exchange (TPE).
Patient and method: To perform kidney biopsy and ablation of the renal mass, six daily TPE treatments were performed before and after biopsy to minimize bleeding risk because the patient did not respond to drug therapy. Both thromboelastography (TEG) and laboratory-based coagulation tests were performed to assess coagulation status prior to and after TPE.
Results: The biopsy indicated oncocytoma which was removed by surgical procedure. Factor XIII activity remained below 15 % throughout TPE treatments, but Factor XIII inhibitor titer reduced from initial positive value of 1:40 to negative following the third TPE and remained negative through the sixth TPE. Unfortunately, the inhibitor titer was positive at 1:20 in the fifth month and 1:5 in the sixth month during follow-up.
Conclusions: TPE is useful in removing XIII inhibitory factor, but the effects are only short term.

1. Introduction

Inherited Factor XIII deficiency is a rare autosomal recessive bleeding disorder with a prevalence of one per 1–3 million people depending on geographic region and is higher in areas where consanguineous marriage is common [1]. Acquired Factor XIII deficiency is even rarer than inherited factor XIII deficiency. If acquired deficiency is due to the presence of an immune-mediated inhibitor (very rare), this disorder may cause spontaneous or delayed post-operative bleeding. However, the majority of acquired Factor XIII deficiencies are non-immune modulated and patients are often asymptomatic. In immune-mediated acquired Factor XIII deficiency, a neutralizing antibody may be present that significantly reduces the effect of Factor XIII, or a non-neutralizing antibody may significantly increase clearance of Factor XIII. Non-immune modulated acquired Factor XIII deficiency may result from decreased synthesis (hematological disorder or liver dysfunction) or increased consumption (thrombotic events and hemostasis challenges such as surgery and disseminated intravascular coagulation). Factor XIII deficiency should be considered in the bleeding patient with normal screening coagulation studies and no evidence of platelet deficiency/dysfunction [2].

Treatment of Factor XIII deficiency is based on the nature of the defect. Congenital deficiency requires administration of Factor XIII concentrates [3]. However, if inhibitor to XIII is present due to autoantibody, then immunosuppression therapy with a drug such as steroids, cyclophosphamide, cyclosporine, mycophenolic acid, intravenous immunoglobulin (IVIG) or anti-CD20 monoclonal antibody may be helpful [4]. Case reports of acquired Factor XIII inhibitors describe mixed results with these options and patients often require more than one treatment. Given the rarity of this bleeding disorder, there is no standard treatment algorithm and management is tailored to patient response [5].

2. Case presentation

A 75-year-old male with Factor XIII inhibitor had a history of significant bleeding, hematoma, and splenic rupture. His Factor XIII activity (ARUP laboratory, Utah, USA) remained below 15 % with

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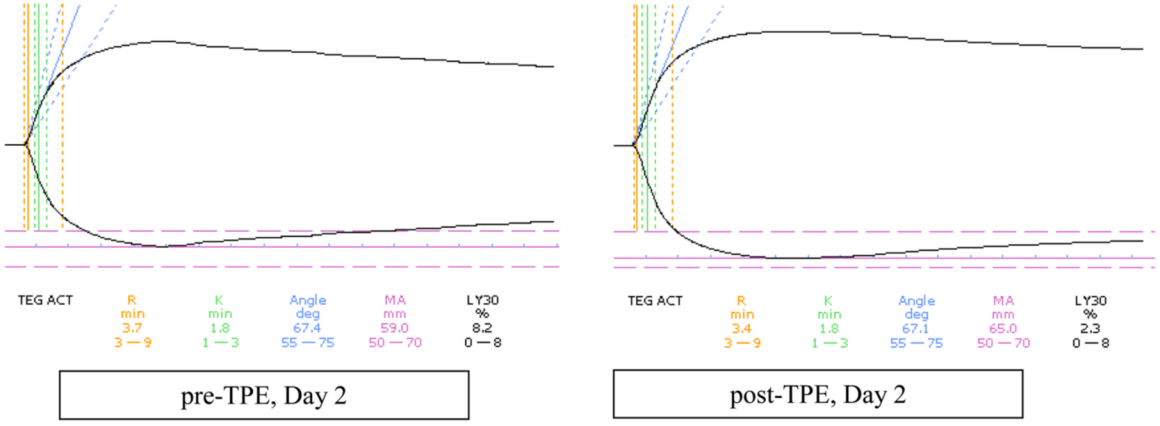

Fig. 1. TEG diagrams on Day 2, pre- and post- TPE (Ly30 declined post-TPE while rest of the parameters were within reference ranges).

Table 1
TEG results before (B) and after (A) TPE.

TEG	Reference range	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6	
		B	A	B	A	B	A	B	A	B	A	B	A
Ly60	< 15 %	9.9	3.3	14.2	7.3	5.2	6.6	9.4	5.4	9.3	6.7	5.9	9.9
Ly30	< 8.1 %	3.1	0.3	8.2	2.3	1.0	2.6	3.6	1.9	4.0	2.7	1.2	2.8
MA	> 49.9 mm	57.8	67.1	59.0	65.0	54.0	63.8	56.2	65.4	60.0	63.8	58.6	60.9
R	< 9.1 min	3.6	2.8	3.7	3.4	4.3	5.1	5.2	3.8	4.4	2.4	4.2	5.5
K	< 3.1 min	1.4	1.6	1.8	1.8	2.1	1.6	2.2	1.3	2.1	1.4	2.1	1.7
Angle	> 54.9 deg	70.3	68.3	67.4	67.1	64.0	68.3	60.2	70.7	62.1	69.3	63.5	66.6

Table 2
Factor XIII activity and inhibitors peri- and post-operation.

	Reference range	Day 1*	Day 3*	Day 6*	5 month	6 month
Factor XIII activity	69–143 %	< 15 %	< 15 %	15 %	< 15 %	< 15 %
Factor XIII Inhibitor screen	Negative	Positive	Negative	Negative	Positive	Positive
Factor XIII Inhibitor titer#		1:40			1:20	1:5

#Although Factor XIII inhibitor titers were significantly increased after five months, p value cannot be established because titer measurements were performed only once but not in triplicate.

* Factor XIII activity and Inhibitor samples were collected right before TPE.

persistent Factor XIII inhibitor despite treatment with rituximab, prednisone, IVIG, and cyclophosphamide. He had a renal mass concerning for a primary malignancy and suspicious as a potential source of paraneoplastic syndrome producing Factor XIII antibody. Since the patient did not respond to drug therapy, daily TPE with 100 % plasma was planned to mitigate his bleeding risk before and after his procedure. Pre- and post-TPE Kaolin TEG tests (TEG 5000 Hemostasis Analyzer system, Haemonectics, USA) were used to monitor coagulation, especially clot lysis (Ly30 and Ly60). Prior to initiating therapy and following the third and sixth exchanges, we also measured partial thromboplastin time (PTT), international normalized ratio (INR), platelet count, fibrinogen activity, Factor XIII inhibitor profile including Factor XIII activity, Factor XIII inhibitor screen and Factor XIII antibody titer (Labcorp, North Caroline, USA), euglobin clot lysis time (ECLT), tissue plasminogen activator (tPA) antigen, alpha-2 anti-plasmin activity, and plasminogen activator inhibitor-1 (PAI-1) antigen. The patient consented to all procedures and the Institutional Review Board (IRB) of the University of Kansas Medical Center considered this treatment as "exempt".

Six daily TPE procedures with 100 % plasma were performed. Ablation of renal mass was done on Day 3 and the biopsy report indicated a low-grade oncocytic neoplasm, favoring oncocytoma. Ly30 and Ly60 were either within reference range or borderline elevated throughout treatments. However, Ly30 and Ly60 values declined post-TPE in 4 out of the 6 treatments, especially those on Day 2 (Fig. 1). Angle, K and R time and maximum amplitude were within reference ranges (Table 1). Factor XIII inhibitor titer, initially positive at 1:40 prior to the treatments, was negative following the third plasma exchange and remained so following the sixth exchange but Factor XIII activity remained below 15 % throughout treatments (Table 2). Declined Ly30 and Ly60 (i.e., decrease of fibrinolysis) probably resulted from the removal of Factor XIII inhibitor by TPE. Results for PTT, INR, platelet count, ECLT, plasminogen activity, tissue plasminogen activator antigen, alpha-2 antiplasmin activity, and PAI-1 antigen remained within their reference ranges throughout treatments. The patient's elevated fibrinogen activity (529 mg/dL, Reference Range: 200–400 mg/dL) was normalized to 282 mg/dL following the first TPE due to normal Fibrinogen level in the replacing donor plasma. Fibrinogen activity was maintained within normal range during all six TPE treatments by 100 % plasma as replacement solution. The biopsy and ablation were performed without incident. The patient was discharged without any bleeding or other complications. Subsequent testing in the fifth and sixth months showed the inhibitor returned at titer of 1:20 and 1:5 respectively without bleeding events and immune suppression treatment (Table 2).

3. . Discussion

Acquired Factor XIII deficiency is caused by autoantibodies that

inhibit Factor XIII and can result in bleeding despite normal routine coagulation test results. Given the rarity of this disease, large clinical studies have not been conducted. Tone et al. reviewed 36 case reports and 3 case series meeting eligibility criteria (63 patients in total) for acquired Factor XIII deficiency due to inhibitors. Clinical improvement in bleeding was seen in patients receiving Factor XIII concentrate (13/17 patients), cryoprecipitate (5/8), and plasma (10/18). Inhibitor reduction was seen in patients who received rituximab (6/6 patients), plasma exchange (2/2), intravenous immunoglobulin (4/5), steroid (15/20), and cyclophosphamide (10/15) [6]. Interestingly, in one report, the authors concluded that TPE may cause acquired Factor XIII deficiency since routine coagulation tests remain unaltered. It might cause major bleeding, particularly in patients with a recent history of surgery like kidney transplants [7]. Therefore, treating such patients is very challenging.

Factor XIII activity remaining below the reference range is unexpected in our patient, especially with the significant drop of inhibitor titer after three exchanges. However, the stable fibrinolytic activity and absence of major bleeding events suggest perioperative TPE could offer temporary but effective protection to patients with refractory acquired Factor XIII deficiency who need invasive procedures.

4. . Conclusions

In our patient therapeutic intervention failed to dimmish Factor XIII inhibitor and correct the coagulopathy but TPE was very effective in removing the inhibitor and the operation was safely performed. TPE could be the last resort to enable surgical procedures with high bleeding risk in patients with refractory acquired Factor XIII deficiency.

CRediT authorship contribution statement

Joshua Smith: Data collection and analysis, Writing – original draft. Jared S. Bodine: Data collection and analysis. Mark T. Cunningham: Methodology. Kathleen Gooley: Investigation. Frederick V. Plapp: Conceptualization, Methodology. Amitava Dasgupta: Writing – review & editing. Zhan Ye: Conceptualization, Methodology, Supervision, Data curation, Writing – review & editing.

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