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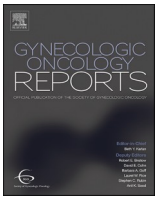

Case report

Acquired factor VIII inhibitor caused by solid tumor malignancy

Olivia de Bear [a,*], Karen McLean [b], Jean Siedel [a], Aimee Rolston [a]

[a] Gynecologic Oncology Division, Department of Obstetrics and Gynecology, Michigan Medicine, 1500 East Medical Center Drive, Ann Arbor, MI 48109, United States
[b] Department of Gynecologic Oncology and Department of Pharmacology & Therapeutics, Roswell Park Comprehensive Cancer Center, Elm & Carlton Streets, Buffalo, NY 14263, United States

1. Introduction

Acquired factor VIII (FVIII) inhibitor is a rare immunological production of alloantibodies against coagulation FVIII also known as acquired hemophilia A (Riitta Lassila, 2019). Normally, the coagulation cascade is triggered in response to tissue injury resulting in primary and secondary hemostasis. However, FVIII antibodies disrupt this cascade and instead cause inadequate clotting (Fig. 1). This results in a severe, life-threatening bleeding condition typically requiring hospitalization and hematology input for both diagnosis and management (Knoebl et al., 2012). The overall cause of FVIII inhibitor syndrome is idiopathic (51.9%), followed by an association with autoimmune diseases (13.4%) and malignancy (11.8%). It is marginally more common in men (53.1%) than women (46.9%) with median age of diagnosis being 73.9 years. Prostate and lung make up the majority of solid tumors (40%) while lymphoproliferative disorders are most common amongst hematologic cancers (66.7%) (Napolitano et al., 2018). The affected female population has a bimodal curve distribution; younger women will typically acquire this condition as it relates to pregnancy-associated events and the postpartum period (8.4%) (Knoebl et al., 2012). Those older than 60 years will commonly develop this in association with a malignancy versus unknown etiology (Riitta Lassila, 2019). To our knowledge, the only documented cases of acquired FVIII inhibitor in gynecologic malignancies were in the context of uterine and cervical cancer (Napolitano et al., 2018) (Hauser, 1999). Malignancy-associated acquired hemophilia A cases are typically diagnosed simultaneously with initial cancer diagnosis, but they can also present on a more delayed timeline (Sallah, 2001) (Hauser, 1999).

Although acquired FVIII inhibitor is a rare condition, the purpose of this report is to bring awareness of the phenomenon to gynecologic oncologists as a potential cause of bleeding of unknown etiology postoperatively or during cancer treatment. In this case study, we discuss a patient who developed acquired FVIII inhibitor associated with her gynecologic malignancy, with a focus on presentation as well as diagnosis and management.

2. Case report

A 54-year-old female with recurrent mucinous carcinoma of the ovary on bevacizumab, capecitabine and oxaliplatin presented with abdominal pain and nausea. Abdominal x-ray showed concerns for bowel perforation. She was started on intravenous piperacillin/tazobactam and urgently transferred to the operating room with gynecologic oncology and general surgery teams, where she underwent exploratory laparotomy, lysis of adhesions, loop ileostomy, and primary closure of colonic perforation with drain placement.

On postoperative day two, the patient's intraperitoneal drain and surgical incision bandage became saturated with blood. Prothrombin time (PT), international normalized ration (INR) and partial thromboplastin time (PTT) were critically elevated at 69.6 s, 7.9, and 66.4 s, respectively. Other pertinent laboratory values were hemoglobin 7.3 g/dL, hematocrit 20.6 %, platelets 282 K/uL, and fibrinogen 471 mg/dL. The patient's care teams hypothesized the cause was dysfunctional liver metabolism from severe malnutrition, prealbumin 5 mg/dL and albumin 1.9 g/dL, causing decreased synthesis of clotting factors. One unit of fresh frozen plasma and intravenous phytonadione (vitamin K1) 10 mg for three days were ordered to acutely correct the coagulopathy. She was started on parental nutrition to address the malnutrition and intravenous desmopressin (DDAVP) to decrease bleeding time and shorten the prolonged PTT. Repeat coagulation studies showed improvement with PT 13.0 s and INR 1.2, though with ongoing prolongation of PTT at 44.5 s. She also developed new rectal bleeding. The hospital course was additionally complicated by postoperative ileus and intra-abdominal abscesses requiring infectious disease consult, additional drain placement for source control, and intravenous antibiotics.

Over the subsequent days, she continued to have oozing blood from the abdominal surgical incision site with newly developed ileostomy site bleeding. The bleeding location and pattern continued to reinforce concern for anatomic causes of blood loss. Coagulation studies were repeated with the following results: PT 12.5 s, INR 1.2, and PTT 48.7 s. On hospital admission day sixteen, she became unresponsive,

* Corresponding author at: 1500 East Medical Center Drive, L4000 UH South, Ann Arbor, MI 48109, United States.
E-mail address: kwiatkoa@med.umich.edu (O. de Bear).

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hypotensive with blood pressure of 73/57, tachycardic heart rate of 115 and desaturated to 83% on room air. She was transferred to a critical care medical unit and found to have active extravasation of blood into a left upper quadrant abdominal hematoma. Interventional radiology urgently performed coiling of the left inferior epigastric artery. Gastroenterology and hematology were consulted to evaluate for causes of bleeding. Gastroenterology ruled out gastrointestinal bleed with upper endoscopy and ileoscopy which showed a single, non-bleeding ulcer thought unlikely to be the source of the bleed. Hematology assessed that previous interventions should had corrected PT/INR and PTT, and hence recommended workup for prolonged PTT. FVIII assay revealed a value of 0.52% (reference range 50–150%), a positive mixing study indicating a specific coagulation protein inhibitor, and factor 8 inhibitor assay 4.8 Bethesda units (BU) (reference range < 0.5 BU). These results collectively led to the conclusion of a factor 8 inhibitor diagnosis.

With the assistance of hematology, the patient was started on coagulation recombinant activated factor VII (rFVIIa) for acute coagulopathy control due to poor hemostasis requiring transfusing 1–2 units of packed red blood cells daily. This approach allows the coagulation cascade inhibition that results from FVIII inhibitor to be circumvented (Fig. 1). Per hematology, long term treatment would require a prolonged course of intravenous steroids, intravenous activated prothrombin complex concentrates (APCC), and weekly rituximab for 4 weeks while hospitalized (Riitta Lassila, 2019) (Knoebl et al., 2012). The goals of this multimodal treatment approach were to inhibit antibody function and decrease new antibody production. She continued to have fluctuating oozing from the surgical incision, ostomy and intraperitoneal drain site which required frequent adjustments of the APCC dose. During this treatment, she was given inhaled pentamidine for pneumocystis pneumonia prophylaxis given the high dose steroids. The patient was discharged on hospital admission day fifty-two when hematology felt her bleeding was stable and trended lab values for FVIII assay and FVIII inhibitor assay were improving towards normal range. She received a total of seventeen units of packed red cells and two units of fresh frozen plasma during her hospitalization.

Upon discharge, the patient was followed closely in an outpatient hematology clinic with weekly FVIII labs and prolonged taper of oral prednisone. The patient had a significant improvement in her factor VIII level and factor VIII inhibitor (520% and 0.7 BU, respectively) but had ongoing intermittent bleeding. She ultimately died because of cancer progression approximately four months after diagnosis of acquired factor VIII inhibitor.

3. Discussion

In this case report, we highlight a rare paraneoplastic syndrome involving spontaneous formation of an autoantibody against factor VIII post-operatively in a patient with an ovarian malignancy. To our knowledge, there are only a few reported cases of acquired FVIII inhibitor in uterine and cervical gynecologic malignancies (Napolitano et al., 2018) (Hauser et al., 1999). Diagnosis is generally prompted by a bleeding event that does not resolve with common interventions (Knoebl et al., 2012). A screening PT and PTT will result in a normal PT and prolonged PTT. Further workup with PTT mixing study will reveal decreased levels of FVIII activity and elevated FVIII inhibitor titers (Riitta Lassila, 2019). It is recommended to consult expert hematologists for ongoing evaluation and treatment (Tiede et al., 2020).

Initial treatment of FVIII inhibitor requires achieving hemostasis during the active bleeding phase. This can be done by bypassing FVIII with the utilization of APCC, recombinant activated FVII (rFVIIa), or porcine-derived FVIII (Riitta Lassila, 2019). It is recommended that hemostatic treatment be initiated regardless of inhibitor titer or FVIII activity level because heavy bleeding can continue up to five months after diagnosis of FVIII inhibitor (Tiede et al., 2020). It is important to avoid any iatrogenic injury to prevent further bleeding. Invasive procedures, including arterial sticks or surgical interventions, should be delayed or discussed with expert hematology advice.

The standard treatment is to achieve remission by inducing the body into immunosuppression and creating long-term tolerance for FVIII (Riitta Lassila, 2019) (Alvarado et al., 2007). This is done with the use of

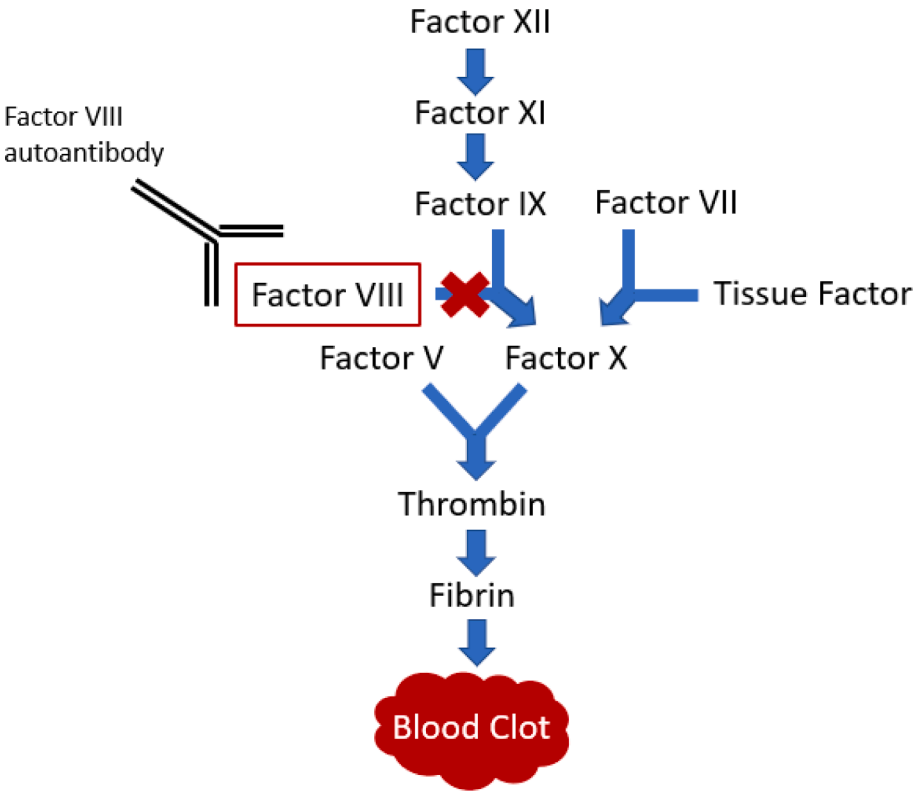

Fig. 1. Demonstration of factor VIII inhibitor disrupting hemostasis in the coagulation cascade.

steroids and cytotoxic agents, such as cyclophosphamide or rituximab (Knoebl et al., 2012). FVIII inhibitor autoantibodies are produced by B cells; rituximab, a monoclonal antibody against CD20, causes apoptosis and complement-mediated lysis against $CD20^{+}$ B cells (Alvarado et al., 2007). An alternative treatment called the modified Bonn-Malmö Protocol (MBMP) utilizes immunoadsorption, FVIII substitution, intravenous immunoglobulin and immunosuppression therapy with cyclophosphamide and prednisolone. It can be effective for very high inhibitor titers but requires a complex protocol and results in a higher rate of side effects, therefore is recommended only in refractive cases (Alvarado et al., 2007) (Tiede et al., 2020). According to the 2020 Haematologica international recommendation regarding immunosuppressive therapy in patients with acquired hemophilia A, patients can be given corticosteroids alone for 3–4 weeks (for patients with FVIII $\geq$ 1% and $\leq$ 20 BU/mL) or a combination of corticosteroids with a cytotoxic agent for 3–4 weeks (for patients with FVIII $<$ 1% or $>$ 20 BU/ml) (Tiede et al., 2020). Despite our patient's levels qualifying her for steroid only treatment for 3–4 weeks, hematology chose to initiate steroids with rituximab, due to her tenuous hospitalization with significant continued bleeding and multiple postoperative complicating factors. Treatment is continued until the inhibitor is below detection level (0.6 BU/mL) and PTT and FVIII levels have normalized for a few weeks (Riitta Lassila, 2019). Close follow-up is highly recommended because relapse can occur within six months in 12–18% of patients (Tiede et al., 2020).

It is important to review that 22% of patients with early-stage or potentially curative malignancy had complete response and eradication of inhibitor when treated with chemotherapy, hormones, or surgical resection in addition to the above regimens. Conversely, advanced or end-stage disease correlated with unfavorable prognosis due to reduced response to cancer-directed treatment and hence ongoing, persistent inhibitor (Sallah, 2001).

4. Conclusion

FVIII inhibitor is an extremely rare condition. Early diagnosis and urgent treatment are required to prevent life threatening bleeding. When a gynecologic cancer patient presents with ongoing bleeding despite routine hemostatic interventions, FVIII inhibitor should be considered in the differential diagnosis.

Consent

Written consent was obtained from the patient's family.

CRediT authorship contribution statement

Olivia de Bear: Conceptualization, Investigation, Writing – original draft. **Karen McLean:** Supervision. **Jean Siedel:** Supervision. **Aimee Rolston:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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