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A Hematological Menace: Multiple Venous Thrombosis Complicated by Acquired Factor VIII Deficiency

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Patient: Male, 21
Final Diagnosis: Acquired Factor VIII Deficiency
Symptoms: Abdominal hematoma • DVT • life threatening bleeding
Medication: —
Clinical Procedure: Life saving medical therapy
Specialty: Hematology

Objective: Rare disease

Background: Acquired hemophilia A (AHA) classically presents with spontaneous bleeding of mucosal sites, GI tract, and subcutaneous tissues, often leading to large hematomas and ecchymosis. Among documented cases, 50% are idiopathic and few have been associated with trauma or surgery. We present a case of life-threatening bleeding caused by AHA, following trauma and complicated by multiple venous thrombi.

Case Report: A 21-year-old man presented with multiple injuries secondary to trauma leading to extensive life-saving surgery. Two weeks post-operatively, he developed multiple deep venous thrombi and was started on anticoagulation. Twenty-four days post-operatively, he started bleeding from multiple mucosal sites and developed an abdominal hematoma. Anticoagulation was stopped, with administration of fresh frozen plasma and vitamin K. Diagnosis of AHA was made based on low factor VIII level and presence of factor VIII inhibitors after an appropriate battery of tests ruled out other possible diagnoses. He was started on steroids and recombinant factor VIIa, leading to immediate improvement. Once stable, Rituximab infusions resulted in decreasing factor VIII inhibitor levels, with gradual normalization of PTT.

Conclusions: AHA remains a diagnostic challenge because of its rarity, leading to delay in diagnosis and causing significant morbidity and mortality. Elevated PTT relative to PT/INR is a strong clue which should be followed by mixing studies. Very few cases have been associated with surgery or trauma and relatively few large, controlled trials have compared different treatment modalities for AHA. Growing evidence supports anti-CD20 (Rituximab) as an effective treatment option, as in this case.

MeSH Keywords: Factor VIIa • Hemophilia A • Venous Thrombosis

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/895316

Background

Acquired hemophilia A (AHA) is estimated to occur in 1–4 people per million. Due to its low incidence, a potentially high mortality rate, and the high prevalence of anticoagulation in patients today, AHA presents a diagnostic challenge.

AHA has a bi-modal peak, displaying prevalence in women ages 20–30 as a complication of pregnancy [1], and equally in men and women ages 60–67 [2–4]. In general, about 50% of all cases are associated with either peri/post-partum status, or rheumatological conditions. The other 50% of cases are idiopathic [1,5–7]. Post-partum hemophilia usually has a good prognosis, with favorable outcomes in up to 97% of cases [8,9] compared to post-operative bleeding in known AHA cases, which carries a 22% risk of fatality [1],

Of the rheumatologic conditions, acquired factor deficiency is most highly associated with rheumatoid arthritis and SLE [10–12], accounting for about 18% of cases [13]. Associations have also been reported with solid tumors and certain drugs, including Penicillin, Ampicillin, TMP/SMX, Clopidogrel, and Phenytoin [14]. We present a case of life-threatening bleeding caused by acquired factor VIII deficiency, occurring 24 days post-op, and complicated by multiple venous thrombi. While only a handful of cases have associated surgery with AHA, our case directly implicates trauma and/or surgery as a primary culprit, and was successfully treated with Rituximab. Furthermore, as most reports cite AHA developing peri-operatively, this case may be novel as it presented 24 days following trauma and reparative surgery.

Case Report

A 21-year-old African-American man with no significant medical history presented with multiple abdominal organ injuries secondary to multiple gunshot wounds (GSWs). The coagulation panel was within normal limits upon admission. He immediately underwent an exploratory laparotomy with repair of the abdominal wall, colonic resection, splenectomy, and gastric repair.

At 14 days post-op, the patient developed right femoral vein and bilateral cephalic vein thrombi despite being on prophylactic doses of enoxaparin to prevent such thrombi. A therapeutic dose of enoxaparin was started, bridging him to warfarin until a therapeutic INR was achieved. At 24 days post-surgery, the patient started bleeding from multiple mucosal sites, including the GI tract, and internally, resulting in an abdominal hematoma (Figure 1A, 1B). Continued massive bleeding caused hemodynamic instability, and warfarin was stopped, while multiple units of erythrocytes, fresh frozen plasma, and vitamin K were transfused.

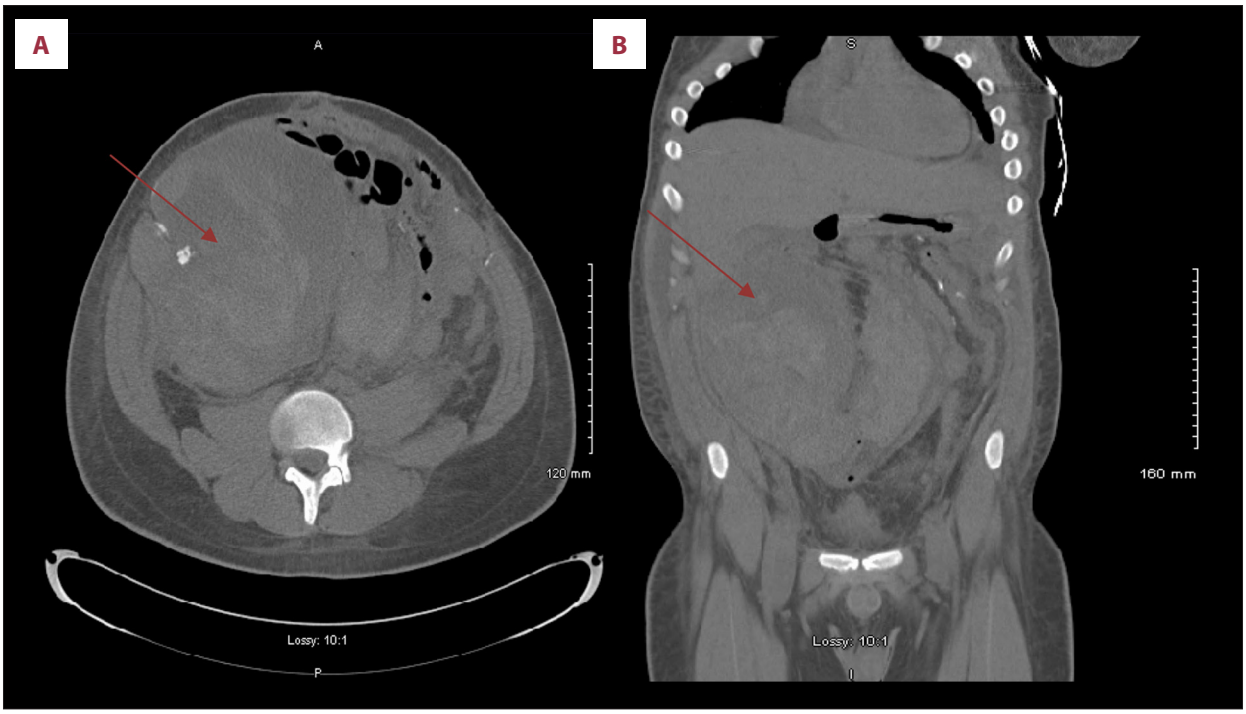

Figure 1. (**A**) Showing transverse section and (**B**) showing coronal section of the abdomen with red arrows indicating a large abdominal wall hematoma displacing the intra-abdominal structures.

The bleeding failed to improve, requiring routine infusions of blood products. Coagulation studies showed an elevated partial thromboplastin time (PTT) >100, with near-normal PT (16). Further hematological workup revealed the absence of lupus anticoagulant, ruling out SLE. A mixing study showed minimal correction of PTT, indicating the presence of a coagulation factor inhibitor. Follow-up tests found factor VIII to be less than 1% (normal range: 80–150% of expected). A Bethesda Assay quantified the strength of the Factor VIII inhibitor to be 12 Bethesda units (BUs), normal range: 0–0.4.

The patient was started on methylprednisolone 40 mg IV q 8 h and recombinant factor VIIa, thereby bypassing any factor deficiencies, activating the clotting cascade, and leading to immediate improvement. Once stable, Rituximab infusions were started. Infusions were calculated from a dose of 375 mg/m^2, resulting in an 825 mg infusion with normal saline, beginning at 50 mg/h and titrating up to a maximum rate of 400 mg/h until complete. Infusions were continued once weekly for 4 weeks with a plan to continue until levels normalized. A repeat Bethesda assay done 3 weeks later showed factor inhibitor strength of 5.2 BUs (down from 12), indicating successful treatment response.

Discussion

Clinical presentation

In terms of clinical presentation, hemarthrosis is the hallmark of congenital hemophilia, but it is rare in the acquired form. Patients with acquired hemophilia present more commonly with purpura, GI bleeds, and soft tissue and sub-cutaneous bleeding, with large hematomas and hematuria [2]. While many patients live with congenital hemophilia A, acquired factor VIII deficiency often results in severe, life-threatening bleeding, with mortality rates as high as 8–22% [13,15].

Diagnosis

While many conditions can elevate both PT and PTT, the hallmark of acquired factor VIII deficiency is a prolonged PTT. The differential diagnosis for prolonged PTT includes both congenital and acquired factor deficiencies, specifically factor VIII (hemophilia A), IX (hemophilia B), and von Willebrand disease, as well as the development of lupus anticoagulant, medication side-effects, and heparin contamination.

The initial work-up for prolonged PTT is to re-draw the coagulation panel, eliminating heparin contamination as a possible contaminant. Once eliminated, a medication history should be taken to rule-out iatrogenic causes. The next step is to order a mixing study, allowing the physician to differentiate between the presence of an inhibitor such as the lupus anticoagulant, versus a factor deficiency such as congenital hemophilia or von Willebrand disease. If the coagulopathy was caused by a deficiency, the addition of normal blood will correct the PTT. If the PTT remains prolonged, the coagulopathy is being caused by an inhibitor, which will persist when mixed with the normal blood [16]. Follow-up testing can then be done to determine presence/absence of lupus anticoagulants, which factor is defective, and the strength of an inhibitor/autoantibody using a Bethesda assay.

Treatment

The following treatment recommendations are derived from literature searches and divided into management based on the presence or absence of active bleeding.

In the presence of active bleeding

In the setting of hemodynamic instability with active uncontrolled bleeds, the first-line treatment is to bypass the deficiency altogether, and activate the clotting cascade [17–19]. Activated prothrombin complex concentrates (aPCCs), such as recombinant factor VIIa (used here) or FEIBA (factor VIII inhibitor bypass agent), have been shown effective in controlling over 80% of acute bleeds [20].

Active bleeding in hemodynamically stable patients may be treated with desmopressin (DDAVP) at a dose of 0.3 mcg/kg/day subcutaneously for up to 5 days [1,21,22] as a means to activate the remaining quantities of factor VIII. Note that DDAVP is contraindicated in hemodynamically unstable patients because it is thought to hyperactivate autoantibodies. Alternative treatments include concentrated or porcine factor VIII administered as a bolus until the desired response is achieved [1,23,24]. IVIG has also shown limited, but potential, efficacy as an alternative for treatment refractory bleeding [16,25]. If available, plasmapheresis with immunoabsorption is a fast-acting alternative [26].

In the absence of active bleeding

Once bleeding has stopped, the deranged cell line originating antibodies to factor VIII must be suppressed. The mainstay of this treatment is prednisone 1 mg/kg/day for 3 weeks [10,27,28]. For second-line treatments, either cyclophosphamide 1 mg/kg/day or a combination of cyclophosphamide and prednisone for another 3 weeks has shown a 50% success rate in refractory cases [27]. New alternative second-line treatments include rituximab, which was used with this case. Rituximab, when administered once per week at a dose of 375 mg/m^2 has shown tremendous efficacy in early trials, successfully treating 80% of cases [29,30].

It should be noted that while the above treatments are common, there is a paucity of research comparing the efficacy of different immunosuppressive regimens. Current guidelines are based upon literature reviews and clinical judgement, and not on large randomized trials [31].

Post-operative/traumatic etiology of acquired factor VIII deficiency

There has been substantial research documenting the dangers of surgery in patients with undiagnosed, pre-existing acquired hemophilia [32]. Analyzing 15 case studies, Brack et al. (2009) [32] emphasized the importance of following up irregular coagulation panels and asking patients, even for minor surgeries, about any histories of abnormal bleeding.

However, documentation of trauma or surgery as etiologies themselves is rare. Alumkal et al. (1999) [33] and Theodossaides et al. (2001) [34] both published cases of patients with no previous histories developing acquired hemophilia immediately following surgery. Green and Lechner (1981) [35] also found an association with trauma and/or surgery after reviewing 215 patients.

While both surgery and trauma have been sparingly documented as potential etiologies for acquired hemophilia [33–36], the burden and incidence of this severe complication remains unclear. Furthermore, as our patient suffered multiple abdominal organ injuries from GSWs, and as his surgery was equally involved, it seems evident that the trauma, the surgery, or both could have caused his AHA.

Of note, while previous cases have shown acquired hemophilia developing immediately following surgery [33,34], our patient did not develop AHA until 24 days post-op. This lag seems to indicate the development of IgG autoantibodies. While IgM is produced rapidly after antigen exposure, substantial levels of IgG are not found in serum until 10–14 days later [37] and does not peak until 3–4 weeks later [38]. This late peak and presentation loosely corresponds with our case's timetable, and therefore extends the window period for life-threatening complications from days to weeks.

Conclusions

Because of its extreme rarity and a varied presentation, acquired hemophilia remains a diagnostic menace for post-operative bleeding, resulting in high mortality rates. While an isolated peak in PTT may be classic, a relative increase in PTT must also raise suspicion. Regardless of medical history, acquired hemophilia must be considered in cases of post-operative bleeding. The link between trauma/surgery and acquired hemophilia must be illuminated if the mortality rate is to be controlled. This case adds to the small but growing body of work indicating trauma and/or surgery as etiologies, implicates IgG as a culprit, and highlights the need to expand the window of risk to 3–4 weeks post-op.

In the absence of treatment guidelines, current recommendations are based mostly on literature reviews and clinical judgment. Acutely, restoring the coagulation pathway through aPCCs is paramount. Long-term treatment must suppress the cell lines producing the auto-antibodies. There is growing evidence for the use of rituximab, although further research is needed to determine its indications and contraindications. Increased research and awareness are needed to address AHA as a predictable and late complication of surgery/trauma, as it persists as an often fatal diagnostic dilemma.

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