

Postpartum Acquired Hemophilia (PAH) – A Rare Entity

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Abstract: Objective: Acquired Hemophilia A (AHA) is a rare autoimmune disease that can result in life threatening bleeding. Formation of auto-antibodies (inhibitors) against coagulation factor VIII develops the hemorrhagic syndrome that may appear at any age; however, prevalence of AHA is chiefly observed in post-partum and elderly persons. Idiopathic acquired hemophilia is commonest type of acquired hemophilia whereas it is also associated with autoimmune disease, malignant neoplasm, medication and vaccinations. Post-partum acquired hemophilia (PAH) may develop due to development of antibodies against fetal FVIII. In this case report, 36-year-old Asian woman presented with complain of bruises from 2 months. There was history of cesarean section four months ago. Family history, past medical and drug history were not significant. As there was no active bleeding, patient was started an oral prednisolone along with azathioprine and was counseled regarding disease and precautions. Patient presented after 2 weeks with severe PV bleed, anemia secondary to self-induced medicine abortion. For this she receives pack cells and cryoprecipitate. Steroids and azathioprine were continued and patient was discharged in stable condition. Her ultrasound pelvis however showed small fibroids. Patient went back to her village where she again develops severe PV bleed and for that she underwent hysterectomy. Patient presented in our hospital with severe operative site bleeding, pain and anemia. She was managed with Packed Red Blood (PRBCs), Fresh Frozen Plasma (FFP), Recombinant Activated Clotting Factor VII (rFVIIa), prednisolone IV and azathioprine PO. Her Activated Partial Thromboplastin, Hemoglobin were continuously monitored. After a week bleeding was stopped but Activated Partial Thromboplastin Time (APTT) was still prolonged so we tapered rFVIIa dose and advice two sessions of plasmapheresis. APTT, hemoglobin levels, inhibitor titer, High-Sensitivity C - reactive protein (hs-CRP) levels were improved. Patient was discharged in a stable condition and was advised to continue medication at home with supportive care and wound dressing.

Keywords: Post-partum acquired hemophilia, Plasmapheresis, Autoimmune disorder, Anti FVIII antibody, By-passing agents, Factor VIII inhibitors.

INTRODUCTION

Acquired Hemophilia A (AHA) is a rare but potentially life threatening autoimmune disease resulting from the presence of auto-antibodies (inhibitors) directed against coagulation factor VIII and characterized by spontaneous hemorrhage or by bleeding induced by surgery, trauma or other invasive procedures in patients with no previous family or personal history of bleeding [1]. This hemorrhagic syndrome may appear at any age, two peak factors in AHA prevalence are predominantly observed; one associated with pregnancy, and another with older age [1, 2]. It is also existed with autoimmune diseases and malignancies [3]. This autoimmune disorder is very rare that results in bleeding diathesis with overall incidence 1.5 cases per one million population year [4, 5].

Estimated chances of easy bruising is significant i.e. 12%-55% in healthy adults. Several reasons are responsible for autoimmunity that is physical trauma, skin aging, coagulation disorders and systemic conditions [6]. Other causes that lead to autoimmunity are vaccines, infection and dietary supplements. Vaccines including influenza vaccine, Haemophilus influenza type b (Hib) and covid-19 vaccine

have association with development of autoimmunity. Dietary supplements are also reported to inhibit platelets function and develop acquired thrombocytopenia by the antibody production. SARCOV-2 and other viral infections are triggering the autoantibody production that give rise to coagulopathy. Underlying mechanism of vaccine and *Helicobacter pylori* induced autoimmunity are molecular mimicry in which the immune cross reactivity occur between foreign particle and self-protein [7].

Researchers from all over the world are studying the disease causing antibodies but very limited data is available to contribute the management. Acquired hemophilia is often under-diagnosed or misdiagnosed, clinical experience could be supportive for guiding its diagnosis and management [4]. In this case report we will briefly talk over about the pathophysiology, diagnosis, treatment and management of inhibitors against coagulation factor VIII.

CASE PRESENTATION

In February 2022, 36-year-old Asian woman presented to hematology clinic with complain of bruises for 2 months. She had a history of Cesarean section four months back. However there was no active bleeding or menorrhagia. Patient denied

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any family History of blood disorder, any drug history or significant medical history. She was vitally stable. Her Hb was 11.2 g/dl WBC: $8.1 \times 10^9/L$, PLT: $329 \times 10^9/L$, renal and liver profiles were also normal. Her PT was normal 13.5 (normal 12.5-15.5) while Activated Partial Thromboplastin time (APTT) was prolonged 72 sec (normal 26-33sec). Patient vWF Antigen was normal (93%) while FVIII was <1%. Patient inhibitor screening was advised that came out to be positive on which Bethesda assay was done that was 29.2 BU/ml as shown in Fig. (1) (normal: negative). ANA and viral profile along with *H. pylori* screening were negative. Moreover she didn't receive any vaccination Keeping in view the patient's history of post-partum bruising and lab findings diagnosis of acquired hemophilia A was made and patient was started on oral prednisolone (1mg/kg/day) with azathioprine (1mg/kg/day).

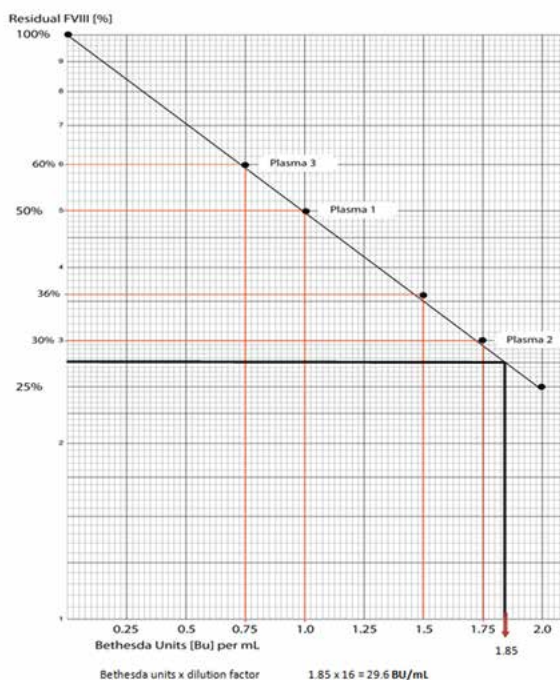


Fig. (1). The inhibitor concentration is calculated from graph of residual factor VIII activity versus inhibitor units. The derived inhibitor titer from the graph is multiplied by the chosen dilution for the final titer.

On March 3rd, 2022, she presented in ER with severe vaginal bleeding from 1 day. Upon inquiry, she told about her self-induced abortion. At the time of initial evaluation, her blood parameters reflected anemia with Hb 7.5gm/dl. Laboratory evaluation shows bleeding and clotting time of 03 mins (normal 2-7 minutes) and greater than 15 mins (normal 8-15 minutes) respectively. Continuous vaginal bleeding was managed by Tranexamic acid intravenous 1000mg stat and prednisolone was continued on same dose. Pelvic ultrasounds revealed fibroids that became the basis of continuous vaginal

bleeding which was not stopped by Norethisterone 20 mg / day. She was advised admission but refused. In subsequent visit after 2 days her Complete blood count showed Hb 6.2 gm/dl. She was managed with 6 units of cryoprecipitate and 3 pint packed red blood cells. The patient became asymptomatic and CBC became normal. However, after a few days, she developed menorrhagia again, for which she took a gynecologist consultation in her home town who advised her to for an urgent hysterectomy. The patient developed severe post-operative bleeding from operative site that was not controlled by local measures, so the patient was referred to our center.

Patient presented again in our emergency with continuous surgical wound site bleeding. She was admitted in ICU where her vitals were B.P 100/70, Temp: 98°F, pulse 135 bpm, respiratory rate 32 bpm, and oxygen saturation 92%. Lab investigation revealed Hemoglobin : 7gm/dl, white blood cells : $19.62 \times 10^9/L$, platelets : $198 \times 10^9/L$ C reactive protein-HS : 128.11 mg/L, Prothrombin time : 20 sec, Activated Partial Thromboplastin time 48 sec, International normalized ratio, 1.4, fibrinogen levels 4.84g/L (Normal 2.0 to 4.0 g/L), D-dimer : 0.7 (Normal < 0.50), Random blood sugar : 273mg/dl (steroid induced hyperglycemia?). Renal and liver functions were normal. She was urgently transfused with 4 units FFP and 2 Pint PRBCs. Gynecologist was taken on board who advised for good pressure dressing. We started recombinant factor VIIa 4mg/IV/6 Hourly. Along with IV Tranexamic acid 1gm IV 8 hourly for 07 days, Intravenous immunosuppressive therapy (prednisolone 2mg/kg/day) with oral azathioprine was continued with good glycemic control. Keeping in view the deteriorating condition of patient injection meropenem (1 gm 8H) and vancomycin (15-20mg/kg) were started empirically and high risk consent was taken from the family they were counseled about the grave condition of patient. Table 1 shows laboratory parameters of subsequent days of admission along with the management performed. The rFVIIa was initially given 6 hourly for 7 days then as the patient bleeding stopped it was slowly tapered to 8 hourly for 2 days then twice a day for 2 days and then stopped. At the 8th day of admission bleeding was reduced but Activated Partial Thromboplastin was still prolonged so 2 sessions of plasmapheresis were performed to remove the inhibitors.

After plasmapheresis her hemoglobin improved. Patient was shifted to ward. Bethesda assay and CRP.HS levels were reverted back to normal. The wound was managed with local pressure dressing with $MgSO_4$ and eusol (sodium hypochlorite). The patient was discharged on day 12th and advised to continue azathioprine, prednisolone and supportive care. The patient has regular follow-up in an outpatient clinic for dressing, assessment and monitoring.

Table 1. Monitoring and Management during Admission.

Day of Admission	Hb (g/dl)	PT (sec)	APTT (sec)	Management
Day 1 ^B	7	20	48	Transfused 4 units FFP
Day 2 ^B	6.2	18	47	Advised recombinant factor (rFVIIa) VII 4mg/IV/ 6 hourly
Day 3 ^B	8.5			3 pint PRBCs, 8 units FFP (rFVIIa)4mg/IV/ 6 hourly , 1 unit FFP
Day 4 ^B	8		50	(rFVIIa)4mg/IV/ 6 hourly ,6 units CP , 1 pint PRBCs
Day 5 ^B	8.7			(rFVIIa)4mg/IV/ 6 hourly, 2 pint PRBCs , 8 units FFP
Day 6 ^B	6.2			(rFVIIa)4mg/IV/ 6 hourly, 1 pint PRBCs , 5 units PLTs
Day 7 ^B	8.7			(rFVIIa)4mg/IV/ 6 hourly, 2 pints PRBCs , 4 units FFP
Day 8	10.8	16		(rFVIIa)4mg/IV/ 8 hourly, 4 Units FFP
Day 9	12.4	16	48	(rFVIIa)4mg/IV/ 8 hourly , 6 units FFP, 2 units CS, 2 units CP 1st session of plasmapheresis
Day 10	13	12.5	45.2	(rFVIIa)4mg/IV/ 12 hourly , 6 units FFP, 2 units CP 2nd session of plasmapheresis
Day 11		20	50	(rFVIIa)4mg/IV/ 12 hourly
Day 12	13.5			Transfused 2 units FFP (rFVIIa)4mg/IV/ 24 hourly Then stopped

FFP: Fresh frozen plasma, CP: Cryoprecipitate, PRBCs: Packed red blood cells, (rFVIIa): Recombinant activated clotting factor VII. B: Severe bleeding from operative site.

DISCUSSION

Acquired Hemophilia A (AHA) is a rare, autoimmune disorder caused by the formation of neutralizing auto antibodies against FVIII. It can leads to life-threatening hemorrhage early diagnosis of AHA limits its complication and better management of bleeding and inhibitor eradication [1, 4]. Overall incidence is 1.5 million / year but more common in adults. Occurrence remains the same in males and females, but females have greater chances to develop this between 20-40 years [8]. Association of acquired hemophilia seen in pregnancy and post-partum cases. Other risk factors include autoimmune disease, drug intoxication, severe infectious disease and malignancies [5]. High mortality rates and a challenging diagnosis without a personal and family history of disease is a clinical challenge.

On the basis of a clinical picture, AHA varies from congenital hemophilia A. Both types of hemophilia have a tendency to produce antibodies, but depending upon the type of antibodies, both are differentiated. In congenital hemophilia A, Alloantibodies are produced, whereas in AHA autoantibodies are formed. These inhibitors interfere with different kinetics to inactivate the FVIII levels. Alloantibodies follow type I kinetics and completely inactivates FVIII whereas autoantibodies incompletely inactivates FVIII by following type II kinetics. Inhibitor antibodies interferes with the interaction of FVIII and other factors (FIXa, FXI, VWF, Phospholipids and thrombin) [8].

Clinical manifestation varies from only bruises to life threatening bleeding in the gastrointestinal tract, skin, muscle, soft tissues, skin and mucous membrane. Patient can present with epistaxis, melenA, and retroperitoneal hematoma per vaginal and urologic bleeding [8]. Worsening symptoms of AHA includes bleeding secondary to trauma, surgery or spontaneous cerebral hemorrhage outcome of post-surgical bleeding is mostly grave [1].

Diagnosis is based on history and lab results. CBC is usually normal. Prolong Activated Partial Thromboplastin with normal PT, vWF Antigen levels, reduce FVIII levels and the presence of FVIII inhibitors in blood confirm the diagnosis of AHA. It may also be suspected without a preceding history of bleeding. Patients have acute onset of bleeding, prolongation of Activated Partial Thromboplastin needs further investigation to rule out coagulation factor deficiencies, lupus anticoagulant and ongoing heparin therapy [9]. Inhibitor titer should be quantified by Bethesda assay. Moreover, mixing studies help in differentiating between presence of inhibitor and congenital deficiency of factor VIII. An uncorrected APTT levels shows presence of inhibitors or lupus anticoagulant. Lupus anticoagulant has the ability to decrease factor VIII levels due to inhibition of phospholipids. While presence of alloantibodies and autoantibodies in congenital hemophilia A and acquired hemophilia A can be confirmed by Bethesda assay that quantifies the FVIII antibodies [5, 9].

Therapeutic approaches for acquired hemophilia depend upon symptoms, drugs and underlying disease. In some cases, post-partum and drug induce hemophilia A can be self-resolving after a few months or when the drug is discontinued without any treatment, only close monitoring is sufficient. However, when symptoms don't resolve or acquired hemophilia is caused by any other reason, as mentioned previously, it requires treatment and management. A treatment goal of AHA includes cessation or control of bleeding, eradication of inhibitors, treatment of underlying cause or disease for prevention of re-bleeding or trauma. Site and severity of bleeding and patient characteristics also have major roles in choosing therapy, like intracranial bleeding, intraperitoneal bleeding and muscle bleeding urgently require hemostatic therapy [9,10].

AHA has a 31 % chance of developing fatal bleeding and 9% risk of acute bleeding. During selection of treatment strategy, patient clinical presentation and history of any underlying diseases have greater significance [1,4].

Indications of anti-hemorrhage therapy are muscle bleeds, retroperitoneal hematoma, post-operative bleeding, severe hematuria and bleeding from multiple sides, regardless of inhibitor titer. Anti-hemorrhagic therapy has a role in cessation of bleeding, but if autoantibodies are present in the body, chances of fatal bleeding remain constant. So here the need for inhibitor eradication is mandatory. Bethesda assays predict the response of immunosuppressive therapy only it doesn't predict the risk of bleeding [1,4].

Post-partum acquired hemophilia is rare but serious complication of pregnancy with the unidentified etiology. It is suggested that after delivery or during the labor mother may sensitize by fetal FVIII and develop antibodies. Antibodies develop during labor have poor prognosis with unfavorable outcome that lead to severe bleeding whereas postpartum acquire hemophilia that occurs at 3 months of delivery have good prognosis and encouraging outcome [4,11]. Its symptoms may vary and disappear from few months to years. Success rate of treatment rely on the qualitative and quantitative attribute of inhibitors [4].

Anti-hemorrhagic therapy options include by-passing agents that are recombinant factor VII (rFVIIa) and activated Prothrombin complex concentrates (aPCC); FVIII concentrates, desmopressin, porcine FVII, whereas inhibitor eradication therapy includes corticosteroids, cyclophosphamide as first line agent, rituximab as second line agent and alternate treatment options consists of cytotoxic drugs that are azathioprine, vincristine, cyclosporine and mycophenolate [4, 9, 10].

Bypassing agents have a greater role as a first line therapy than salvage therapy in moderate and severe bleeding. They work by unblocking the factors that were blocked by inhibitors rather than replacing the factors. Recombinant forms are

more efficacious in post-partum cases because they don't contain human protein and have an insignificant risk of viral transmission. With low thrombogenicity, it achieves localized hemostasis [12]. Response from by-passing agents seen by clinical assessment and laboratory parameters (hemoglobin and hematocrit) are more reliable for accessing bleeding. Data on aPCC usage in AHA is limited. It has good tolerance with limited adverse drug reaction. But it has tendency to develop DIC at higher doses, so it is contraindicated in DIC and has avoid its usage within 12 hours of anti-fibrinolytic agents. It also shows trend to produce anamnestic response in a patients with acquired inhibitors to FVIII [13].

According to International recommendations, Factor VIII concentrates and desmopressin (DDAVP) are not the first line agents in the treatment of AHA. It is used in acute bleeding, low inhibitor titer and when bypassing agents are not available. It works by neutralizing the inhibitors. No research is available to validate its use in clinical practice for treatment because of its limitation, which is unpredictable and variable levels of FVIII in patients [10]. Vasopressin analog, DDAVP works by shortening the Activated Partial Thromboplastin and bleeding time. It has a prominent effect on V2 receptors and CAMP signaling pathway, which increase the FVIII: C and VWB Levels, and thus have a role in pathways. While it's cellular mechanism remains undefined. Role in clinical practice is insignificant because of greater risk of adverse drug reactions, which are water retention, convulsions, consecutive hyponatremia and increased dose frequency [9]. When human FVIII doesn't reach the desired factors levels, porcine FVIII achieve hemostasis levels but major limitation of its use is unavailability. These recombinant forms have been in phase 2 trials in congenital hemophilia A patients [9, 10].

The importance of inhibitor eradication therapy is not taken for granted because development of inhibitor related complications can leads to death [4]. So it has the greatest role in the maintenance of normal hemostasis [10,14,15]. Another approach for inhibitor eradication is plasmapheresis that remove the inhibitors from body [10]. It is indicated in interictal or complicated diseases. It works by replacing the inhibitor containing plasma with cell-rich plasma [16]. Plasmapheresis and immunoadsorption are options for the management of refractory bleeding and surgical intervention for reducing and eradicating the inhibitors and facilitating hemostasis [10].

Immunosuppressive therapy may be used alone or in combination with cyclophosphamide for decreasing the production of autoantibodies. If patient remains unresponsive with first line therapy then switch to rituximab, as it has promising results in eradication of inhibitors but current studies done in lymphoma and autoimmune disease then only option remaining are cytotoxic drugs. Immunosuppressive therapy may develop infection and sepsis [17].

In this present case, the patient came with no personal history or family history of bleeding. She developed bruises after 02 months of cesarean section. CBC was normal with elevated levels of Activated Partial Thromboplastin and normal PT that show any defect in the intrinsic coagulation pathway. For further investigation, a Bethesda assay was done that showed a rise in inhibitor titer. Overall findings were suggestive of acquired hemophilia A. She was managed accordingly with available treatment options stated in updated review of Kruse-Jarres, Rebecca, *et al.* for inhibitor eradication, which are immunosuppressant (methylprednisolone) and cytotoxic drug (azathioprine).

After one month, she returned to hospital with severe vaginal bleeding secondary to a self-induced abortion. Laboratory findings show prolonged clotting time and Activated Partial Thromboplastin. We managed her with an antifibrinolytic agent, which is Tranexamic acid 1000 mg intravenous stat dose. Due to profound anemia, patient is advised to start oral hematinics and continue inhibitor eradication therapy at the same dose. She continuously complained of vaginal bleeding and ultrasound findings were suggestive of fibroids and 3 organized hematomas in the lower abdominal wall. Bleeding was not stopped by Norethisterone. She complained of palpitations, shortness of breath, fatigue and menorrhagia. Multiple transfusions were done for management over 3 days. Afterwards she became normal and returned home with a supportive care. After 2 weeks, she again developed menorrhagia, so her gynecologist did a hysterectomy that initiated severe bleeding from the operative site and that was not managed by local measures and other supportive care, so the gynecologist referred her to our hospital. Her continuous bleeding requires hospital admission for anti-hemorrhage therapy and inhibitor eradication by first line therapy, so in light of Janie charlebois (2018) review, we started rFVIIa that was slowly tapered when bleeding was stopped. As mentioned previously, it has good efficacy and safety in severe bleeding and post-partum cases respectively. It works as the thrombin generator in the absence of factor VIII. Antifibrinolytics agent was continued with azathioprine and oral prednisolone switch to IV route with same standard dose. Considering sepsis and high risk condition meropenem and vancomycin were started. At 8th day of admission bleeding was stopped and rFVIIa dose was slowly lessened at 8th, 10th, and 12th day of admission to thrice, twice and once daily dosing respectively. Due to still high levels of Activated Partial Thromboplastin chances of re-bleeding remains same so plasmapheresis was planned. It was done for inhibitor eradication to decrease the chances of re-bleeding. From previous reports, it also shows remarkable effects on the cessation of severe bleeding as the second approach. Parameter of bleeding (hemoglobin, APTT, PT), Bethesda assay and CRP.HS were continuously monitored and reverted back to normal. The patient was discharged and advised to take oral prednisolone and azathioprine. She was

advised to repeat Activated Partial Thromboplastin and PT on 3 months for assessment.

CONCLUSION

Post-partum acquired hemophilia develops by the production of auto antibodies. Sometimes symptoms of post-partum acquired hemophilia are self-resolving and does not require any treatment; if symptoms persists or exaggerated it require anti-hemorrhage and inhibitors eradication therapy that also varies according to symptoms. Immunosuppressive treatment include corticosteroids, IVIG and cytotoxic drugs that remains the recommended treatment for acquired hemophilia A, while life threatening hemorrhage also treated by plasmapheresis [1, 9, 10]. In this case report PAH treated with first line therapy including prednisolone, azathioprine with anti fibrinolytic agent i.e. Tranexamic acid. Haemostatic control was done with rFVIIa. For diminishing the chances of re-bleeding plasmapheresis were taken in consideration also it promotes hemostasis.

CONFLICT OF INTEREST

Declared none.

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