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Case Report

"Pregnancy-Related Acquired Hemophilia-A", The Nightmare of Non-Hematologists. A New Case Report

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Abstract

Acquired Hemophilia-A (AHA) is a rare bleeding condition, secondary to the sudden development of autoantibodies against FVIII. Affected individuals are predisposed to spontaneous as well as posttraumatic hemorrhage. Pregnancy-related AHA (P-AHA) accounts for 7-21% of all AHA cases, usually emerging in the postpartum period, but can exceptionally be seen during pregnancy. We hereby, describe the clinical course of a 29-year-old, healthy multiparous woman who presented with isolated postpartum hemorrhage 5 days after an uneventful vaginal delivery. She developed intermittent episodes of heavy vaginal bleeding necessitating the performance of several surgical interventions, prolonged ICU stay, and multiple blood transfusions before diagnosis 25 days later. One of the obvious particularities of P-AHA is the substantial proportion receiving initial care by obstetricians/gynecologists. The treatment of postpartum P-AHA is fundamentally similar to that of AHA of other etiologies, nonetheless, treatment during pregnancy remains enigmatic due to the lack of guidelines and the rarity of the condition. Early accurate diagnosis is critical in P-AHA particularly those presenting with isolated postpartum hemorrhage, as this can reduce mortality and abate the frequently performed hysterectomies among young women of low parity. Unexplained massive postpartum hemorrhage should instigate the coagulation profile assessment and the utilization of bypassing hemostatic agents, after consultation with the hematologist, or the referral of the patient to a specialized hematology center. Enhancing familiarity, particularly among obstetricians, and the coordinated management with experienced hematologists, can substantially improve the outcome of this rare yet potentially precarious bleeding condition.

Keywords*: Isolated postpartum hemorrhage, massive postpartum hemorrhage, postpartum AHA, Pregnancy-related-AHA, FVIII-inhibitors.*

Introduction

Acquired Hemophilia A (AHA) is a rare disorder that develops when the immune system suddenly produces autoantibodies that inhibit the functions of FVIII. Bleeding can vary from major life-threatening hemorrhages to minor clinically insignificant bleeds. This condition has been reported to exist concomitantly with certain medical conditions in about 50% of cases including certain malignancies, respiratory, dermatologic, autoimmune conditions, pregnancy, and drug/allergic reactions, with an ever-expanding list that included recently COVID-19 infection and post COVID-vaccination [1-KNOBLE-2012] In the remaining 50%, FVIII inhibitors can appear spontaneously without any concomitant clinical conditions. AHA is an extremely rare bleeding condition with an incidence of 0.2-1 per million individuals/year. [2-FRANCHINI-2006] This figure, however, might not accurately reflect the true incidence, owing to the lack of population-based screening studies, unawareness of the condition, and the existence of asymptomatic cases. Moreover, it is mostly underreported, and any related mortality has been attributed to concomitant conditions as seen with malignancies or early postpartum hemorrhage. It usually affects the elderly population (80%) with equal gender prevalence or less commonly it might affect younger age groups, mostly females, in association with pregnancy, ruptured corpus luteum cyst, and OHSS. [3-BAUDO-2003, 4-MATSUOKA-2017, 5-MELO-2021, 6-TANAKA-2003] According to the largest registry database from Europe, AHA was present in 8.4% during the postpartum period and is estimated to affect 1 in 350,000 births. [7-TENGBORN-2012] We hereby describe the clinical course of a multigravid woman who presented with heavy vaginal bleeding 5 days postpartum. Similar to most women presenting with isolated postpartum hemorrhage, she was subjected to a series of invasive surgical procedures and received multiple transfusions before reaching the diagnosis 25 days later. She showed a dramatic improvement after the initiation of I.V. Methylprednisolone and was discharged less than a week later on oral Prednisone. Complete eradication of the inhibitor was documented 3 days after discharge. Given the rarity of P-AHA, we opted to describe the clinical course and discuss the management caveats encountered in this “near-miss case”, particularly to fellow obstetricians who are the principal front-line providers when AHA presents as isolated postpartum hemorrhage.

Case Description

A 29-year-old woman, G4P4A0, was discharged home one day after a normal uneventful vaginal delivery at a different health facility. She presented to our hospital four days later with heavy vaginal bleeding of several hours’ duration. At admission, (21/11/2021) the patient looked pale, tachypneic, and dizzy. Pulse:123 BPM, BP:100/70 mmHg, afebrile, spO2: 91 %. Hb: 9.2gm/dl, Hct: 28.1%, Plts: 372 X 109/L, WBC: 13,250, INR:1.14, PT:13.4s, aPTT: 58.9s. She gave no history of easy bruising, personal or familial bleeding

tendencies. The Pelvic examination revealed an intact birth canal with blood seen pouring from the uterine cervix. Large multiple blood clots were removed from the uterine cavity and upper vagina. The abdomen was soft while the uterine fundus was well-contracted and non-tender. Emergent D&C was done for a presumed RPOC suspected on the interpretation of a bedside ultrasound examination. Minimal tissues were retrieved. Heavy bleeding resumed so an intrauterine 3-way Foley was introduced and kept in situ for tamponading. Following this, and after giving 2 units of PRBCs, the patient became stable with minimal bleeding. Tests of malignancy or autoimmune disorders were negative. The abnormal aPTT was misinterpreted as a probable consequence of heavy bleeding (early DIC). Bleeding became intermittent and fluctuated between mild and heavy without notice. D&C was repeated two more times over the following few days, then a hysterectomy was done along with bilateral hypogastric artery ligation. Heavy bleeding recurred several days later, which mandated two exploratory laparotomies and pelvic packing to secure hemostasis, without major success, despite receiving countless units of PRBCs and FFPs. CT-Scan showed retroperitoneal and iliopsoas hematomas. Bleeding was finally curbed with the use of rFVIIa on 4 consecutive days. Concomitantly, prolonged aPTT was empirically treated with I.V. Methylprednisolone for the suspicion of an autoimmune process, as recommended by the hematologist pending the results of FVIII-inhibitor and coagulation factors sent to an outside laboratory. Two days later Laboratory results disclosed an FVIII:c of 22%, and an FVIII-inhibitor of 1.5 BU confirming the diagnosis of P-AHA. Steroids continued following which she showed a dramatic clinical improvement with normalization of aPTT within 5 days and was discharged one week later on a tapered Prednisone regimen that was withdrawn at the disposal of the hematologist a few weeks later. Three days after discharge, no inhibitor was detected and FVIII activity was 100%. She was followed regularly by the hematologist and serial laboratory exams revealed sustained complete remission of the condition. Six weeks later, she was admitted for removal of a Double-J-catheter. Six months after discharge she underwent uneventful herniorrhaphy. In both instances, the coagulation profile was normal. Upon contact, one month later (7 months after initial discharge) by her obstetrician, she disclosed leading a healthy life with her infant. She was counseled about the risk of recurrence of AHA in future pregnancy and the need to practice reliable contraception for at least one year of stable complete remission.

Discussion

De-Novo autoantibodies development against coagulation factors is a rare condition, and the majority of cases develop against FVIII. [8-FRANCHINI-2011] Clinically, there is an emergence of bleeding among individuals without a personal or a family history of bleeding diathesis, and without receiving anticoagulant medication. Its manifestations vary widely between minor clinically insignificant to severe life-threatening bleeding. Furthermore, AHA might also be asymptomatic, as FVIII inhibitors were identified incidentally at routine

preoperative assessment of the coagulation profile among 20% of healthy individuals. [9-IGIMAN-1992] AHA can exceptionally in 8.5% be related to pregnancy. [[7-TENGBORN-2012]. The management caveats in this case were also described by other case reports. The foremost important one was the management by obstetricians at presentation. P-AHA is usually underdiagnosed for several reasons, principally due to unawareness of this condition among non-hematologists. Because of the extreme rarity of this condition, it is believed that many obstetricians/gynecologists worldwide may be unfamiliar with the specialized laboratory assessments necessary to confirm the diagnosis. [1-KNOEBL-2012] Patients with AHA may present initially to physicians in different specialties, who may not have experience with this rare disorder. [10-JAMES-2017]. In this case, the diagnosis and initiation of appropriate treatment were unduly delayed. None of our entire obstetric staff had a previous encounter with a similar case. This permitted a series of emergent hemostatic surgical interventions with all related complications, together with the exposure to successive massive transfusions, all of which could have been abated if only the possibility of AHA was entertained and the cause of isolated prolonged aPTT had been judiciously elucidated. A similar management approach and sequence of complications have been observed in several cases presenting with isolated early or late postpartum hemorrhage and managed by obstetricians. [11-Seethala-2013, 12-Paidas-2013, 13-El Demerdash-2022] Another serious event, that might have delayed diagnosis and compounded the bleeding tendency, was the series of emergent hemostatic surgical procedures performed despite prolonged aPTT, assuming that surgery would promptly arrest the hemorrhage. Performing surgery in the absence of appropriate hemostatic and immunosuppressive treatment can result in catastrophic consequences. [5-MELO-2022] It seems that evading surgery if possible is safer, but when surgery is inevitable, the perioperative administration of a BPA becomes mandatory.

A BPA in the form of rFVIIa, as ordered by the hematologist, was used for 4 consecutive days, 7 days before the confirmed diagnosis, following which bleeding became minimal. These agents have been used effectively as a second-line treatment to arrest massive postpartum hemorrhage and other bleeding incidences irrespective of the specific defect in coagulation. [14-HOSSAIN-2007] These agents are not expected to restore the normal pathway or to correct a prolonged aPTT, as their main action is on extrinsic and common cascade pathways but can gap the defect in the process of activating Factor X crucial for the proper coagulation. BPA are monitored clinically with the assessment of bleeding severity. In a similar case, Bin Waqar et al described the use of these hemostatic agents to arrest epidural and retroperitoneal bleeding before the confirmed diagnosis of P-AHA. [15-WAQAR-2021] It would be safer if BPA were administered to arrest massive bleeding, even before confirmation of AHA, and particularly before emergent invasive hemostatic procedures. IST in the form of Methylprednisolone was also tried two days before diagnosis (day 23) as recommended by the hematologist, and this has resulted in a dramatic correction of aPTT. We found this approach beneficial

after failing all classical medical and surgical interventions to arrest postpartum hemorrhage even before reaching a definite diagnosis.

A delayed diagnosis seems to be common among postpartum P-AHA cases, particularly those presenting with isolated PPH, prompting obstetricians to provide conventional hemostatic procedures and medications commonly used in the management of PPH. These women were consequently exposed to multiple invasive procedures and surgery-related complications such as hematomas, hemoperitoneum, vaginal vault hematomas, and wound hematomas. In a few unfortunate cases, catastrophic complications such as hemorrhagic, septic shock, ARDS, liver dysfunction, AKI, MOF, and even death followed these hasty interventions. [11, 12] All these shortcomings could have been averted if AHA had been excluded before doing any hemostatic surgical interventions.

On the other hand, bleeding at other sites such as skin, mucosa, hematomas, serosa, GI, or involving multiple sites, usually oriented care providers to suspect a bleeding diathesis and seek early hematologist advice. The coagulation profile is routinely assessed before cesarean delivery and the odds of identifying AHA or other bleeding disorders are high. Early postpartum hemorrhage following vaginal delivery, however, usually does not prompt the assessment of the coagulation profile and the usual response is to search for common causes of PPH such as uterine atony, birth canal lacerations, and RPOC. The contribution of congenital or acquired bleeding diathesis, including AHA, as the etiology of early PPH, is estimated to be in <1%. Consequently, and given it is a rare cause, it is currently recommended that AHA should be suspected only after the failure of routine classical hemostatic measures to arrest bleeding. We believe that in cases with persistent or massive hemorrhage, as suggested by Davey et al, it might be prudent to suspect promptly the existence of AHA. [16-DAVEY-2018].

Conclusion

This case highlights the need to improve awareness of AHA, particularly among obstetricians, and demonstrates the important role of experienced hematologists in the diagnosis and management of rare bleeding disorders. The clinical course improved dramatically only following the late consultation of the hematologist.

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Consent for Publication

Written informed consent was obtained from the patient for publication of this case report.

Conflict of interests

The authors individually declared no competing interests.

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