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Postpartum Acquired Haemophilia A and Post-partum Life-Threatening Haemorrhage Following COVID-19 Infection: A Case Report

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Abstract

Objectives: Although there is a significant number of reports regarding acquired haemophilia A (AHA) following COVID-19 infection in non-pregnant females, and especially in elderly males, there is a lack of data on similar cases among pregnant or postpartum women. Here, we present a case of confirmed COVID-19-induced life-threating postpartum haemorrhage (PPH) and share some diagnostic challenges leading to severe maternal morbidities.

Case Presentation: A 32-year-old woman came to the emergency department with massive vaginal bleeding on 13th day of post-elective cesarean section (CS). Her hemodynamic condition got rapidly deteriorated and haemorrhagic shock occurred. She had no comorbidities in her two gestations and obstetrical and systemic physical examinations were unremarkable except for ongoing massive vaginal bleeding and the findings were compatible with haemorrhagic shock.

The Primary Diagnoses, Interventions, and Outcomes: Emergent hysterectomy was performed after first line PPH medical treatment failure, and clinical status got worse. Additionally, as the patient had close contact with a confirmed COVID-19 infected case and a low-grade fever was detected, nasopharyngeal swab and chest CT-scan were taken. The results were in favour of infection. Partial thromboplastin time (PTT) was also prolonged, which was initially assumed due to excessive bleeding. Returning PTT to normal values after blood products transfusion enhanced our diagnosis as well. Since endometritis and subinvolution of placental sites were the two most suspicious diagnoses, the standard treatment protocol was applied. Additionally, due to COVID-19 pulmonary involvement, antiviral therapy was also initiated. Finally, the patient was discharged in good condition. Again, on 28th day of post-CS, she referred with abdominal distension and malaise and a second laparotomy was considered due to a retractable large intraperitoneal haematoma and skin site bleeding. PTT was again prolonged, which was not corrected after blood products transfusion. Hence, recombinant factor seven was also transfused. At last, since bleeding recurred and coagulation profile deteriorated in second postoperative period, she was transferred to a tertiary centre. A third laparotomy was done as another life-threating resistant intraperitoneal bleeding re-occurred. Next, due to persistent prolonged PTT, hematologic consultation was done. AHA was suspected due to recent viral infection by COVID-19. Activated PTT (aPTT) mixing test and competitive inhibitory antibodies assay confirmed the diagnosis of COVID-19-induced postpartum acquired haemophilia A (PPAHA). Subsequently, full-dose immunosuppressive therapy was initiated and PTT reached normal values after 8 days.

Conclusions: We highly recommend close monitoring of coagulopathy by doing complete blood cell count, aPTT, and prothrombin time in postpartum period of COVID-19 infected women even in women without abnormal bleeding in immediate postpartum period. Patient follow-ups and awareness of possible COVID-19-induced AHA in peri-partum population can reduce maternal morbidity and mortality.

Keywords: Hemophilia A, COVID-19, Postpartum haemorrhage, Case reports, Blood coagulation disorders, Pregnancy

Introduction

Late post-partum haemorrhage (PPH) is an obstetric condition which can lead to significant maternal morbidity and mortality (1). Coagulation disorders are responsible for approximately 0.5% of all puerperium haemorrhage. As an immune-mediated disorder with an incidence of one per 1-2 million, acquired haemophilia A (AHA) is one of these disorders. In this disease, inhibitory antibodies formation leads to a decrease in factor VIII or IX levels and subsequent bleeding tendency (2,3). Despite its rare prevalence, the mortality rate could reach to 30% among affected patients (4). Predisposing factors such as autoimmune diseases and malignancies are seen in approximately 50% of the affected cases (4). According to the European Acquired Haemophilia Registry (EACH2) definition, if there are no prior personal or family history of bleeding disorders in a peripartum woman, an unexplained isolated prolongation of activated Partial thromboplastin time (aPTT) should be considered AHA until proven otherwise (5). In literature, there are some evidence in favour of the association between SARA-CoV-2 (COVID-19) infection or vaccination and AHA incidence (6). Following COVID-19 vaccination, some serious adverse events have been reported such as

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myocarditis, thromboembolic events, and AHA incidence (7-14). In COVID-19-induced AHA reported cases, patient age widely varies (39 to 95 years old) (15).

According to the last update of AHA treatment guideline, immunosuppressive treatment should be initiated as soon as diagnosis is confirmed (16,17); however spontaneous disappearance of inhibitory antibodies has also been reported (15). Extending our knowledge on COVID-19-induced AHA in pregnant or postpartum women can help obstetricians to keep this diagnosis in their minds. This consequently would lead to on-time diagnosis and subsequent proper management. To the best of our knowledge, there are no reports on COVID-19-induced postpartum AHA among peri-partum population. Hence, we aim to report a case of retractable life-threatening PPH associated with confirmed COVID-19 lower respiratory tract infection. We share our management strategy and the outcomes in an attempt to help obstetricians in dealing with similar cases.

Case Presentation

First Admission

Presentation

A 32-year-old gravida 3 live birth 2 pregnant woman underwent term scheduled repeated caesarean (CS) section in May 2021 at Shahid Beheshti Hospital, Kashan, Iran. The whole current pregnancy course was uneventful. She had no history of previous PPH or personal or familial history of coagulation disorders. She had been discharged home on second day postpartum. Sutures were also removed on day 6 and surgical site was unremarkable.

The patient came to the emergency department complaining of massive vaginal bleeding on 13th day postpartum. She was lethargic and her vital signs were as follow: blood pressure (BP) of 83/55 mm Hg, pulse rate (PR) of 118 beats/minute, respiratory rate (RR) of 14/minute, oral body temperature (T) of 38 °C, and O2 saturation of 98% at room temperature.

Interventions

Immediately, stepwise resuscitation was initiated, and a blood sample was sent for complete blood cell count (CBC), coagulation profile, liver and kidney function tests, electrolytes, erythrocyte sedimentation rate, C-reactive protein, blood culture, and cross-matching. A urine sample was also sent for bacterial culture. The uterus was contracted, and genital tract had no abnormalities. She had no costovertebral tenderness, and her upper respiratory tract exam was normal. Whole abdominopelvic sonographic scan demonstrated no abnormalities and lower extremities colour Doppler study showed no thrombus formation. As the patient was febrile, Ampicillin 2 g QID, gentamycin 80 mg TDS, and clindamycin 900 mg TDS were given intravenously to treat suspected endometritis. A single 1-gram dose of Tranexamic acid was also infused. As the patient declared close contact with a confirmed COVID-19 infected caregiver, a nasopharyngeal swab and a chest CT scan were done (results are shown in Table 1). Due to hemodynamic instability, the patient was transferred to operating room. During surgery, two units of packed red blood cell (PC) were transfused. Initially, both uterine arteries were ligated but as sever haemorrhage was ongoing, subtotal emergent hysterectomy was undertaken.

Outcomes

The patient was transferred to the intensive care unit (ICU). Also, because there were scattered patchy ground glass opacities in the left lower lobe of the lung, antibiotic regimen changed to broader spectrum coverage with intravenous Meropenem 1 g QID and vancomycin 1 g BID. Additionally, as nasopharyngeal swab was positive for COVID-19, oral rifampicin 300 mg TDS and hydroxychloroquine 200 PO BID were also initiated as some favourable effects on COVID-19 treatment have been reported. Finally, she got afebrile on 4th day post-operation. Trends in CBC and coagulation tests are also illustrated in Table 1. After afebrile period of 7 days, the patient was discharged with oral antibiotic regimen of levofloxacin 750 mg daily, Rifampin and clindamycin 300 mg TDS for additional seven days.

Table 1. The patient's Initial Laboratory Tests and Their Trends During Her Three Admissions

	Hb	aPTT	PT	INR	Transfused Blood products			
					Packed Cell	FFP	Platelet	Factor 7
On CS admission	11.3	32	11	1.1	-	-	-	-
Post CS	10	31	12	1.11	-	-	-	-
14th Day post CS (time of hysterectomy)	7.1	59	11.4	1.0	2	-	-	-
After hysterectomy	8.8	31	12	1.08	-	-	-	-
28th post CS (time of second laparotomy)	6.4	68	11	1.09	3	3	3	1
Postoperative care	7.2	85	13	1.3	2	2	2	-
33th Day post CS (time of third laparotomy)	4.8	74	12	1.2	2	2	-	-
The first postoperative day after the third surgery	6.2	98	12	1.4	8	8	6	1
8th Postoperative care of the third surgery	9.8	31	12	1.01	0	0	0	0

Second Admission

Presentation

Nine days later, the patient referred with complaints of gradually worsening abdominal pain and distension and malaise. Her vital signs were as follows: BP of 110/75 mm Hg, PR of 125 beats/minute, RR of 24/minute, oral temperature of 37.4 centigrade, and peripheral O2 saturation of 96%. The patient was generally ill, her abdomen was mildly distended and tender. Speculum vaginal exam revealed no leukorrhea, but a large tender mass was palpated on digital bimanual examination.

Diagnostic Approach and Interventions

Laboratory findings revealed anaemia and mildly impaired aPTT (Table 1). Abdominopelvic CT scan also revealed a large heterogeneous mass suspicious for hematoma formation. Consequently, 3 units of PC, 3 units of fresh frozen plasma (FFP), and recombinant factor VIIa 90 mcg/kg were transfused. An explorative laparotomy was considered due to persistent internal bleeding, superimposition of skin site bleeding, a haemoglobin drop to 5 g/dL, and prolonged aPTT of 62 seconds despite blood products transfusion.

Intraoperative Findings

A supra-umbilical midline incision was performed under general anaesthesia. Several points of active bleeding and a massive intraperitoneal hematoma were evident. There was also a 5-centimeter haemorrhagic right ovarian cyst which oophorectomy was anticipated due to patient's hemodynamic instability. Two peritoneal hemovac drains were inserted. Blood products and an additional dose of recombinant factor VIIa were also transfused during surgery.

Postoperative Period

The patient was under close observation at the ICU and received an extra of 2 units of packed cell, 2 units of FFP, and 2 units of platelet. Shortly, after ICU admission, bleeding re-occurred through skin sutures and both drains. Bedsides ultrasound scan revealed significant free fluid collection in abdominopelvic cavity. We consulted with the tertiary centre of Ayatollah Taleghani hospital, Tehran, Iran, which had a multidisciplinary team.

Clinical Course at the Last Center

Finally, the patient was transferred to Ayatollah Taleghani hospital on 33th day post-CS. Due to persistent prolonged aPTT despite blood products transfusion, haematology consultation was done. Due to recent COVID-19 infection and persistent prolonged aPTT, AHA was highly suspicious. So, aPTT mixing test was performed, which was suggestive of slow reactive inhibitory antibodies presence. Hence, a sample was sent for a coagulation factors assay. Concurrently, intravenously systemic glucocorticoid therapy was initiated by methylprednisolone 1 mg/kg daily. Unfortunately, despite transfusion of 2 units of packed cell and 2 units of FFP, haemoglobin level dropped to 4.8 g/dL, 800 cc fresh red blood was observed in her drains in few hours, and the patient's condition deteriorated. So, third laparotomy was planned. A large hematoma in subcutaneous space and active bleeding from ruptured pulsatile inferior epigastric artery was detected, which was ligated. Additionally, multiple sites of active bleeding from cervical stump incision and previous oophorectomy site were seen. Finally, an iatrogenic laceration on spleen was found, and splenectomy was done due to retractable oozing (Figures 1 and 2). The patient received extra blood products of 6 units of packed cell, 6 units of FFP, 6 units of platelet, a prothrombin complex concentrate 75 IU/kg, and a dose of recombinant factor VIIa 90 µg/kg.

In post-operation period, aPTT was still high (Table 1), and 4 hours after operation, she had a severe episode of haemorrhage from midline skin incision while drains output were unremarkable. Local compression was applied, and bleeding was controlled.

On 5th day after the last surgery, factor VIII inhibitor

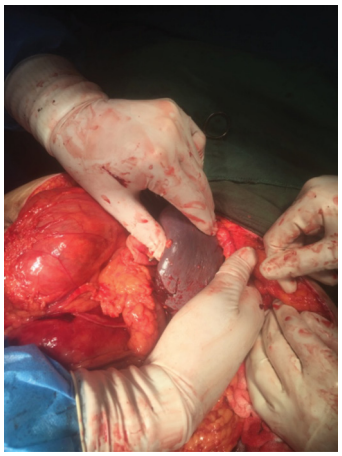

Figure 1. Laceration of the patient's Spleen found out intra-operatively.

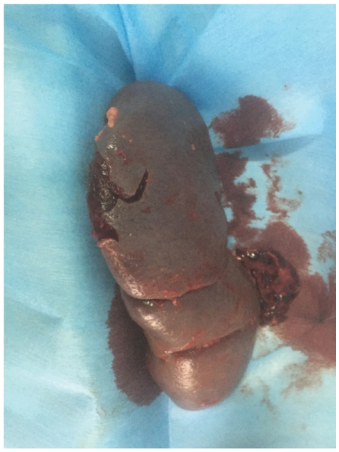

Figure 2. The patient's Spleen appearance after Splenectomy.

level of 190 Bethesda units was reported while factor VIII level was 2%. Hence, diagnosis of AHA was confirmed. So, full-dose immunosuppressive treatment was considered by adding cyclophosphamide 1-2 mg/kg/d. Finally, gradual decrease in aPTT and inhibitor antibodies and subsequent rise in factor VIII level were observed and tests reached normal value on 8th day post third surgery. The patient was under close observation for an additional 5 days and was discharged later in good clinical condition.

Discussion

Sever late PPH could be an emergent life-threatening complication which can lead to maternal mortality. In postpartum patients who present with severe PPH while the uterus is contracted, genital tract is unremarkable and endometritis or placental subinvolution has been ruled out, coagulation disorders should be kept in mind. Pregnancy-associated AHA consists 7%-11% of the disease burden, with majority of cases presenting within one to four months after delivery and varying amount of bleeding (18,19). As observed in the current case, after COVID-19 pandemic and its widespread vaccination programme, COVID-19-induced AHA should be considered as a cause of retracted bleeding among bleeding postpartum patients. In fact, AHA occurs as a result of inhibitory antibodies production against factor VIII. Massive haemorrhage is of particular concern, especially when it is refractory to standard haemostatic interventions.

Plasma level of inhibitory antibodies could be predictable of bleeding episodes. Studies have shown that higher titres of inhibitor antibodies levels do not easily disappear and are resistant to immunosuppressive therapy (20). Diagnosis of post-partum AHA (PPAHA) is triggered when abnormal bleeding is unresponsive to common first line treatments or there are abnormal lab tests in favour of the diagnosis. The symptoms may vary from mild subcutaneous and mucosal bleeding to severe bleeding episodes. Also, as seen in our case, mild bleeding could turn to a severe massive haemorrhage as a result of delayed diagnosis.

It is not known whether PPAHA was present at the time of delivery in our case, but it seems unlikely, because no bleeding was observed at CS time or the early postpartum period. Moreover, it is not exactly understood why bleeding tendency appeared late in postpartum; however, she had close contact with confirmed COVID-19 after discharge which might be considered as a trigger for COVID-19-induced inhibitory antibodies formation and AHA clinical manifestation. In fact, abnormal aPTT test was noted at hysterectomy time, which was assumed due to excessive blood loss. It should also be noted that aPTT returned to normal values in post-hysterectomy period. A single isolated abnormal aPTT might have triggered investigation for possible PPAHA, as our patient did not respond to the first line treatment.

In recent studies, about 20%-55% of COVID-19 patients had laboratory evidence of coagulopathy including prolongation of aPTT (21). In COVID-19 patients with bleeding tendency, higher levels of D-dimmer, fibrin degrading products, prolonged prothrombin time (PT), and PTT have been reported and 71% of non-survivors fulfilled disseminated intravascular coagulopathy criteria (22,23). The induction of autoantibodies formation has been proved in previous studies; for example, in a cohort of 3 814 479 COVID-19 cases, the patients had higher chance of new onset systemic lupus erythematous and vasculitis (24). In a systematic review assessing potential association between SARS infection and influenza vaccines and AHA, the authors concluded that although antibody formation risk is very low but if happens, serious adverse events may be observed. Although there were more affected men than women, gender effect remains unknown due to low overall and relative prevalence (25). Sharathkumar et al designed a 1:3 propensity score-matched retrospective cohort study to assess if hemophilia could protect against disease severity or lower thromboembolic events occurrence. They declared that after adjusting for demographic features, the presence of hemophilia increased bleeding chance but it could not affect the COVID-19 severity (26). This is in association with COVID-19-induced immune dysregulation and the close interaction between the virus and haemostatic system, as reported in the literature (27).

In any post-partum woman with abnormal bleeding, aPTT, PT, and platelet count should be assessed. If aPTT is prolonged and the two other parameters are within normal limits, PPAHA should be suspected and consultation with a haematologist should be considered. Treatment of PPAHA includes bleeding control, elimination of causative factor that has induced antibodies production, and reduction of plasma levels of inhibitory antibodies through immunosuppressive therapy (16,17).

Our patient's immunosuppressive regimen consisted of intravenous systemic glucocorticoids plus cyclophosphamide. It is not well-understood whether immunosuppressive therapy of COVID-19-induced AHA could lead to aggravation of signs and symptoms of viral infection. However, in the presented case, no deterioration was observed clinically.

There is a report of relapsing AHA induced by COVID-19 infection in a 86 year-old man after one year of complete remission (28). In a study by Collins et al (2), the median of 7.5 months was reported for AHA relapse; so, close follow-up of the patients seems essential and Japanese guideline recommends monthly follow-ups during first 6 months and every 2 months for the next 6 months (16).

Most recently, cases of AHA following COVID-19 infection have been reported (29-31). COVID-19 spike proteins have also been shown to activate complement via lectin pathway and may produce immunoglobulin G antibodies against factor VIII and Von Willebrand complexes leading to AHA (32,33). In affected

patients, clinical presentations vary from asymptomatic to moderate to severe haemorrhage in deep tissues (34). Januszewski et al performed a propensity matched cohort study to compare the estimated blood loss and obstetric haemorrhage frequency among COVID-19-infected and non-infected labouring women. They observed that infected patients were more prone to higher blood loss, PPH and need for peritoneal cavity drain insertion and PC transfusion (35). Some other studies also showed similar results (36,37).

Kalsar et al reported a case of PPH who had positive rapid antigen test for COVID-19. She suffered PPH immediately after CS and underwent a second laparotomy; both uterine arteries and ovarian arteries were ligated and B-lynched sutures were done (38). Their patient had uterine atonia that was resistant to first-line drug treatment and PTT was not abnormal. However, they did not specifically declare this. In comparison to them, our case had no uterine atonia and lab tests were in favour of AHA.

To the best of our knowledge, this case is the first postpartum woman with confirmed diagnosis of PPAHA following COVID-19 infection. However, due to initial pitfall in diagnostic approach, the presence of a causative relation could not be proven strongly.

Conclusions

All obstetricians should consider COVID-19-induced AHA as an underlying cause of refractory cases of postpartum bleeding when other most common etiologies have been ruled out and concomitantly the woman has signs and symptoms of COVID-19 infection in her clinical or para-clinical findings. Hence, in this situation, confirmatory inhibitory antibodies detecting tests should be performed. Finally, we recommend screening of coagulopathy in postpartum period of COVID-19-infected women to prevent delay in diagnosis. It would be reasonable to do PT and PTT tests, as well as CBC to screen at-risk patients on labour admission and closely follow asymptomatic patients with abnormal findings.

Authors' Contribution

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Writing–review & editing: Seyedeh Mojgan Ghalandarpoor-Attar

Conflict of Interests

Authors have no conflict of interest.

Data Availability Statement

Any additional data about the patient is available from the corresponding author if requested.

Ethical Issues

Informed consent was obtained from the patient for publication of this report.

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