A Rare Case of Post-Partum Hemorrhage with Refractory Thrombotic Microangiopathy, and Hepatic Infarction: A Diagnostic Dilemma with High Mortality

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ABSTRACT
We are presenting a very rare and unique case of postpartum hemorrhage with excessive blood loss requiring 6 units of packed red cells, 2 units of single donor platelet transfusions, 4 fresh frozen plasmas, and 4 cryoprecipitates. The patient developed a life-threatening spectrum of thrombotic microangiopathy which is known to result in pregnancy from eclampsia, pre-eclampsia, thrombotic thrombocytopenic purpura, typical and atypical hemolytic uremic syndrome, and hemolysis, elevated liver enzymes, low platelets syndrome and in non-pregnant patients with a wide differential diagnosis. The patient required 7 sessions of plasma exchange along with systemic steroids. During her illness, she developed rising liver enzymes and bilirubin, diffuse intravascular coagulation, renal failure, alveolar hemorrhage, and acute fulminant hepatic failure. A contrast-enhanced computed tomography scan revealed multiple areas of liver infarction with patent hepato-portal vessels. The patient required continuous renal replacement therapy and high supportive care. She stayed in the intensive care unit for 9 days, developed multi-organ failure, and finally expired. It is highly imperative to be aware of the complications of post-partum hemorrhage, as it should be treated promptly to minimize the possible cascade of multi-organ failure with high maternal and fetal mortality. Liver transplantation is the only possible radical therapy in cases with fulminant hepatic failure, worth considering, if clinically possible and applicable.

Keywords: Liver infarction, Mortality, Plasma exchange, Postpartum hemorrhage, Thrombotic thrombocytopenic purpura

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Introduction
Thrombotic microangiopathy (TMA) is potentially a life-threatening and extremely rare entity, well known in pregnant and non-pregnant patients. It includes red blood cell fragmentation with microangiopathic hemolytic anemia (MAHA), low platelet counts, and a variety of clinical syndromes, leading to end-organ damage (1). It is a challenge to differentiate between these entities by clinical and laboratory methods and their treatment can vary (2).

Case Report
A 24-year-old female is not known to have any medical illness. Gravida is four and Para is three. They were full-term with spontaneous vaginal delivery. No history of any previous complications.

She recently had a spontaneous vaginal delivery at a local hospital, five days ago. It was complicated by postpartum hemorrhage, managed by six units of packed red cells, two units of single donor platelet transfusions, four fresh frozen plasmas, and four cryoprecipitates, followed by dilatation and curettage, and intrauterine packing. They transferred her to our hospital after stabilization for further management.

In our hospital, she developed a complicated course that required several interventions over 9 days as mentioned in timeline figure 1.
On day 1, we admitted her to the intensive care unit (ICU), as a suspected case of thrombotic thrombocytopenic purpura (TTP), having anemia, high lactate dehydrogenase (LDH), renal impairment, fragmented red blood cells (RBCs) on a peripheral blood film, and low haptoglobin consistent with microangiopathic hemolytic anemia, and fulminant hepatic failure with very high ammonia level. We sent all the other laboratory investigations, as shown in table I. We did an abdominal and pelvic ultrasound, which was within normal limits.

On day 2, we started the 1st session of plasma exchange (PEX).

On days 3-4, the patient developed respiratory distress requiring a high-flow nasal cannula (HFNC). However, she continued to get worse and we electively intubated her. Because of the high PaO2/FiO2 ratio, we started the acute respiratory distress syndrome (ARDS) protocol. We suspected her respiratory failure to be secondary to alveolar hemorrhage. Her Chest X-ray shows bilateral air space disease consistent with ARDS with normal cardiac size and endotracheal tube in place (Figure 2). We started her on pulse steroid therapy. She re-

Table I: Laboratory shows a picture of microangiopathic hemolytic anemia and hepatic failure

<table>
<thead>
<tr>
<th>Routine Blood test</th>
<th>Units</th>
<th>Day 1</th>
<th>Day 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>gm/dL</td>
<td>7.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Platelets</td>
<td>109/L</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>WBC</td>
<td>109/L</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Schistocytes</td>
<td>%</td>
<td>9</td>
<td>4.4</td>
</tr>
<tr>
<td>INR</td>
<td>1.33</td>
<td>43</td>
<td>82</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dL</td>
<td>3.60</td>
<td>3.03</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>g/L</td>
<td>&lt; 6</td>
<td>0.14</td>
</tr>
<tr>
<td>Ammonia</td>
<td>micromol/L</td>
<td>-</td>
<td>2180</td>
</tr>
<tr>
<td>D dimer</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>LDH</td>
<td>U/L</td>
<td>2051</td>
<td>611</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serology</th>
<th>Units</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAMTS-13 antibodies</td>
<td>U/mL</td>
<td>6.8</td>
</tr>
<tr>
<td>ADAMTS-13 activity</td>
<td>IU/mL</td>
<td>0.52</td>
</tr>
<tr>
<td>ADAMTS-13 antigen</td>
<td>IU/mL</td>
<td>0.30</td>
</tr>
<tr>
<td>Anti-Nuclear Antibodies</td>
<td>Index</td>
<td>0.3</td>
</tr>
<tr>
<td>Anti-dsDNA Abs</td>
<td>IU/mL</td>
<td>6.61</td>
</tr>
<tr>
<td>Lupus Anti-Coagulant</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis Screen</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>HIV Test</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>C3</td>
<td>mg/dL</td>
<td>84.5</td>
</tr>
<tr>
<td>C4</td>
<td>mg/dL</td>
<td>14.2</td>
</tr>
<tr>
<td>ANCA (c ANCA and p ANCA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-PR3</td>
<td></td>
<td>&lt;20</td>
</tr>
<tr>
<td>Anti-MPO</td>
<td></td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

mained hemodynamically stable. Sometimes, we gave intravenous boluses of labetalol 20-40 mg, for episodes of hypertension reaching 220/110 mmHg. We continued the PEX treatment without significant improvement in her platelet count, which mostly remained in the 40s.

On days 5-6, we continued her steroid maintenance. The condition remained static. All septic workup was negative. Antibiotics were meropenem and vancomycin after ID consultation, because of persistent leukocytosis. Her liver enzymes started becoming elevated.

On days 7-8, the patient became hemodynamically unstable, requiring high-dose vasopressors. We also started continuous renal replacement therapy (CRRT) because of worsening renal function. PEX sessions were continued.

Her liver enzymes continued to rise and serum ammonia reached very high levels of 2810.

The rise of bilirubin and alanine transaminase (ALT) is shown in figure 3.

She was in acute fulminant hepatic failure. We did a computed tomography (CT) scan of the abdomen and pelvis. The CT revealed multiple hypo-dense areas which were highly consistent with hepatic infarctions, as shown in figure 4.

We planned to refer the patient to a liver transplant center. She reached maximum inotropic support with lactic acidosis and persistent hyperkalemia. We continued CRRT along with lactulose and antibiotics. We also added an antifungal agent.

On day 9, the patient expired because of refractory shock and multi-organ failure.

Discussion

The case described above shows a challenging, rare case of TMA triggered by postpartum hemorrhage (PPH), as there was no evidence of preeclampsia or eclampsia before or at the time of delivery. It is highly important to differentiate among them, as treatments may be contradictory. The most important of these entities during pregnancy are TTP, atypical hemolytic uremic syndrome (aHUS), and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome (3). The diagnosis often remains unclear despite recommendations. Liver infarc-
tation is a very rare catastrophic condition. It is very difficult to diagnose early because its early presentation is nonspecific. It carries a high mortality and morbidity because of fulminant hepatic failure. It has been rarely described in TMA, reportedly more often in HELLP syndrome and antiphospholipid syndrome (4).

Our patient had a potential risk factor of PPH requiring major transfusions. We performed a variety of clinical tests. We did the ADAMTS-13 test before starting PEX, but after multiple blood transfusions, was negative, suggesting many possibilities. ADAMTS-13 negative test usually means TTP is unlikely, but it does not rule it out as after transfusing a large number of blood products, the validity of the test is reduced. This narrows down the diagnosis to aHUS either typical or atypical and other TMA-associated conditions. Typical hemolytic uremic syndrome (HUS) has a positive Shiga toxin, which was negative in our patient. So we are left with atypical HUS, which is a complement-mediated syndrome and a diagnosis of exclusion. HELLP syndrome is a severe spectrum of pre-eclampsia/eclampsia which has not been documented throughout her pregnancy, so it was also unlikely.

Other TMA-associated conditions include antiphospholipid syndrome, systemic lupus erythematosus (SLE), drugs, vasculitis, human immunodeficiency virus (HIV), etc. All the laboratory tests done ruled out those entities (5).

Treatment with PEX was continued. Anti-C5 medication was not available. The mortality rate has been high in TMA cases during pregnancy.

Figure 5 shows a simplified approach that helps in the differential diagnosis of TMA.

The most important initial approach in the differential diagnosis is the clinical history regarding pregnancy, recurrent miscarriages, and family history of TMA. A drug history would lead to the diagnosis of drug-induced TMA. Gemcitabine, bevacizumab, mitomycin C, interferon, cyclosporine A, or tacrolimus are the drugs described. However, the exact mechanism causing TTP is unclear except for gem-

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**Figure 5: A simplified algorithm for thrombotic microangiopathy in pregnancy**

**TMA pregnancy**

**With Hypertension**

Pre-eclampsia/Eclampsia

+/- HELLP

Induction or Termination of pregnancy and supportive care

**Without Hypertension**

Postpartum hemorrhage

ADAMTS 13

Positive < 20

- TTP

PEX

+/- Rituximab

**HUS, aHUS, Others (APS, SLE, HIV)**

**Stool PCR**

Shiga toxin +

- Typical HUS

Shiga toxin –

- Atypical HUS

- Others

Start Anti-C5 therapy with Eculizumab/Ravulizumab

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**Legend:**

- TMA: Thrombotic microangiopathy
- Hb: Hemoglobin
- LDH: Lactate dehydrogenase
- HELLP: Hemolysis, elevated liver enzymes, low platelets
- ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs
- TTP: Thrombotic thrombocytopenic purpura
- HUS: Hemolytic uremic syndrome
- aHUS: Atypical hemolytic uremic syndrome
- APS: Antiphospholipid syndrome
- SLE: Systemic lupus erythematosus
- HIV: Human immunodeficiency virus
- PEX: Plasma exchange
- PCR: Polymerase chain reaction
citabine. Patients who undergo stem cell transplants are also at risk. The presence of pre-eclampsia/eclampsia is most important in the differential diagnosis of pregnant patients. PPH is also an important clinical indicator of risk. Acute fatty liver of pregnancy is also in the differential diagnosis of pregnancy.

After confirming the MAHA by peripheral blood smear, ADAMTS-13 is the most important initial laboratory test to differentiate between TTP and Non-TTP conditions. Among the non TTP, conditions are HUS (typical and atypical) which can be differentiated by performing a Stool Shiga toxin assay. Atypical HUS has a positive Shiga toxin. All other conditions have negative Shiga toxin. If ADAMTS-13 and Stool Shiga toxin are negative, then we should consider other conditions like catastrophic antiphospholipid syndrome, which is often suggested by a prolonged activated partial thromboplastin time (aPTT) and confirmed by lupus anticoagulant, anti-cardiolipin antibody, and aP2GPI-Ab tests. Certain infections can be associated with TMA including HIV, Hepatitis B/C, brucellosis, babesiosis, malaria, hemorrhagic fever, viral infection, etc. A septic shock with disseminated intravascular coagulation (DIC) can also have features of TMA and should be considered and confirmed by blood cultures and procalcitonin levels. If a patient has renal involvement and polyserositis, SLE should be considered in the differential diagnosis.

A severe Cobalamin deficiency (Vitamin B12), gives Pseudo TTP features. Low reticulocyte counts, very high LDH, and a high methylmalonic acid level differentiate it from TTP.

The treatment depends on the specific diagnosis. Plasma exchange is the initial treatment of choice for all patients with TTP (6). It reduces mortality to 10-20%. It is also beneficial in a few Shiga toxin-negative HUS cases. Rituximab is the anti-CD20 monoclonal antibody that has shown benefits in PEX and steroid-refractory cases, and relapsing immune-mediated TTP. These refractory cases have also been treated with other forms of immunosuppressive therapy like vincristine, cyclophosphamide, and splenectomy.

Eculizumab is a terminal complement inhibitory drug. It is the drug of choice for atypical HUS (7). Currently, it is also being tested in secondary HUS because of drugs and solid organ/stem cell transplants.

In catastrophic antiphospholipid syndrome, plasma exchange is also an important treatment modality, besides steroids, intravenous immunoglobulin, and anticoagulation.

**Conclusion**

The differential diagnosis of thrombocytopenia and hemolysis in pregnancy is wide. An early workup and treatment are essential to reduce mortality. Despite early diagnosis and treatment, morbidity and poor outcome remains significant, which is often related to the uncertainty which exists in the management of patients, with TMA in pregnancy. The medical staff needs to have a high index of suspicion in these cases. Doctors should become more familiar with different treatment options in these patients including termination of pregnancy, PEX, rituximab, and anti-C5 medications based on the specific diagnosis (6,7). Hepatic infarction has emerged as a serious complication leading to fulminant hepatic failure, for which the only modality of treatment may be a liver transplant.

**Authors’ contributions:** Established the diagnosis, managed the patient, wrote the manuscript, searched the literature, and designed the article for submission.

**Conflicts of interest:** Authors declare the absence of any conflicts of interest and their financial interests that might be construed to influence the results or interpretation of their manuscript.

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**References**


