Delayed Postpartum Hemorrhage — A Rare Clinical Presentation of Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome: A Case Report

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Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are rare and closely related disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Many risk factors have been reported including infection, cancer, pregnancy, a variety of drugs (e.g. anticancer drugs), and autoimmune diseases. The incidence of TTP-HUS is higher in females than in males, especially during pregnancy and the immediate postpartum period. Review of the literature reveals that delayed postpartum hemorrhage is a rare clinical presentation of TTP-HUS. We report a case of TTP-HUS with recurrent delayed postpartum hemorrhage and dismal outcome.

Key Words: delayed postpartum hemorrhage, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome
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Postpartum hemorrhage is one of the major causes of maternal death, and can be separated into early and delayed postpartum hemorrhage by the time of onset. Early postpartum hemorrhage (< 24 hours) is often the result of uterine atony or occult genital tract lacerations. Delayed postpartum hemorrhage (> 24 hours through 6 weeks postpartum) is more commonly associated with retained placental tissue, placental site subinvolution or infection [1].

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are rare disorders that share many clinical features. They are usually combined as TTP-HUS. Organ ischemia resulting from thrombotic microangiopathy is believed to be the pathogenesis of TTP-HUS. The incidence of TTP-HUS is recorded as 3.7 per million adults per year in the USA. Females are more often affected than males in a ratio of about 10:1 [2]. Pregnancy is well known as a risk factor of TTP-HUS [3]. A review of the literature reveals that women with TTP-HUS associated with pregnancy become symptomatic relatively late in pregnancy and in the immediate postpartum period. Delayed postpartum hemorrhage is a rare clinical presentation of TTP-HUS [4,5]. We report a case of TTP-HUS with recurrent delayed postpartum hemorrhage and dismal outcome.

Case Presentation

An 18-year-old woman, gravida 2, para 1, had an uncomplicated cesarean section at 38 weeks' gestation, at a local clinic under the indication of a previous cesarean section. The immediate postpartum course was uneventful.

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Her prenatal and medical histories were unremarkable. Her blood pressure was within normal limits during prenatal care and postpartum. Ten days after surgery, the first episode of delayed postpartum hemorrhage occurred. Laboratory analysis (only complete blood count) revealed a hemoglobin count of 10.4g/dL, hematocrit of 29.7%, platelet count of 368,000/mm^3, and leukocyte count of 10,700/mm^3. Two units of packed red blood cells (RBCs) were transfused and the hemorrhage subsided. The second and third episodes of postpartum hemorrhage were on the 26th and 37th days postpartum. The complete blood count for the third episode showed decreased levels of hemoglobin (8.0 g/dL) and hematocrit (23.4%). Medical treatments, including oxytocin and ergonovine maleate, and blood transfusion were administered. Fractional dilatation and curettage was also performed under the impression of retained placenta, but the pathology report revealed a picture of decidual tissue only.

The fourth episode of postpartum hemorrhage happened on the 42nd day postpartum. Laboratory analysis revealed hemoglobin 7.2 g/dL, hematocrit 20.8%, platelet count 142,000/mm^3, and leukocyte count 6,500/mm^3. No fever, diarrhea, nausea, vomiting, or right upper quadrant or epigastric pain were reported. She was referred to our hospital because of recurrent postpartum hemorrhage with unknown cause and low platelet count. At our hospital, icteric sclera was the first noted sign. Vital signs included a temperature of 37.5 °C, pulse of 82 beats per minute, respiratory rate of 20/minute, and blood pressure of 130/78 mmHg. Vaginal bleeding was not vigorous and subsided with oxytocin treatment. A few hours after admission, she developed a fever of more than 38 °C with rapidly progressive jaundice. Oligouria and a small amount of tea-colored urine were also noted. Laboratory studies showed a normal leukocyte count (5,450/mm^3), hemolytic anemia (hemoglobin 7.5 g/dL, hematocrit 21.3%, and positive fragmentation of RBCs), low platelet count (85,000/mm^3), elevated lactate dehydrogenase (2,987 u/L), elevated aspartate transaminase (198 IU/L), and acute renal failure (blood urea nitrogen 53 mg/dL, creatinine 4.3 mg/dL). Direct and indirect Coombs' test were both negative. Coagulation studies (prothrombin time and partial thromboplastin time) were within normal ranges. No mental status change was noted. Because her clinical symptoms and laboratory studies suggested postpartum TTP-HUS, she was transferred to the hematologic department on the day after admission. Initial plasma transfusion and steroid administration were followed by emergency plasma exchange and hemodialysis on the third day of admission. Further laboratory analyses revealed poor response to treatment (hemoglobin 7.5 to 3.5 g/dL, platelet count 85,000 to 104,000/mm^3). Serum creatinine concentration was persistently elevated (4.3 to 8.3 on the third day of admission) despite continued hemodialysis. Unfortunately, she died on the fourth day of admission due to severe pulmonary edema and multiple organ failure.

Discussion

TTP and HUS are entities on a spectrum of thrombotic microangiopathies. The classical features of TTP-HUS are microangiopathic hemolytic anemia, thrombocytopenia, renal failure, fever, and neurologic symptoms. Only 40% of patients will have all the classical pentad of clinical features [6]. Anuria indicates a poor prognosis. In a case series of TTP-HUS associated with pregnancy, neurologic symptoms (seizure, headache), gastrointestinal symptoms (nausea, vomiting and abdominal pain), and decreased amounts of urine are the usual initial presentations of TTP-HUS [4,5,7]. Many other diseases, including preeclampsia, eclampsia, and the HELLP syndrome (hemolysis, elevated liver enzymes, low platelet level), share the clinical symptoms and signs of TTP-HUS and it is difficult to distinguish between them. Kahra et al reported a case with probable coexistence of HELLP syndrome and HUS that was confirmed by renal biopsy [8]. According to our patient's medical record, major causes of delayed postpartum hemorrhage, including retained placental tissue and infection, can be excluded. In this case, recurrent delayed postpartum hemorrhage was the initial presentation, and limited laboratory studies provided the clinicians with little information about her first three episodes of postpartum hemorrhage. When she was transferred to our university hospital, she developed an acute illness, including hemolytic anemia, thrombocytopenia, acute renal failure, and fever, which matched the features of TTP-HUS. We excluded septic or hemorrhagic shock and disseminated intravascular coagulopathy according to the initial stable vital signs and laboratory studies. HELLP syndrome typically develops in the third trimester with only a few cases developing in the postpartum period, and the manifestations resolve within the first 2 weeks postpartum. Besides, renal failure is relatively unusual in HELLP syndrome. According to her unremarkable prenatal and medical histories, HELLP syndrome was considered very unlikely.

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In case series of TTP-HUS associated with pregnancy, delayed postpartum hemorrhage is a rare clinical symptom [4,5,7]. Review of the literature from a Medline search, 1966–2005, using the key words "pregnancy, postpartum hemorrhage, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome," revealed only two previous articles [9,10]. Rosen et al reported a 25-year-old patient who developed postpartum TTP-HUS following an exploratory laparotomy for hemoperitoneum resulting from a left uterine artery laceration [9]. Wu et al reported a 32-year-old patient who developed postpartum HUS following abruptio placenta [10]. TTP-HUS developed in the immediate postpartum period in both cases and both had a complicated pregnancy or obstetric procedure. In our case, it was reported that TTP-HUS developed on the 42nd postpartum day with the initial symptom of postpartum hemorrhage. Vaginal bleeding may lead the clinician to wrongly interpret laboratory studies (low hematocrit and hemoglobin, and decreased amount of urine) and miss the possibility of hemolysis. Wu et al emphasize the importance of observation of peripheral blood smears in patients with abruptio placenta who develop thrombocytopenia after delivery [10]. In this case, TTP-HUS could have been diagnosed earlier if peripheral blood smears had been performed for the first three episodes of postpartum hemorrhage.

The definite etiology of TTP-HUS is unknown. Many factors have been implicated, including infection, cancer, pregnancy, a variety of drugs (e.g. anticancer drugs), and autoimmune diseases. Pregnancy may be a risk factor for TTP-HUS because of the association of pregnancy with increasing concentrations of procoagulant factors, decreasing fibrinolytic activity, loss of endothelial cell thrombomodulin, and decreasing activity of von Willebrand factor cleaving metalloproteinase [11]. Early diagnosis and immediate adequate treatment, including plasma exchange, plasma infusion, and corticosteroid therapy, are very important factors associated with a favorable outcome of TTP-HUS. Without treatment, the mortality rate of TTP-HUS is more than 95% [12]. Plasma exchange has been reported to produce a response rate of about 77% and a 30-day mortality rate of 10% [13].

This case gave us an unusual experience, showing that we should consider TTP-HUS in the differential diagnosis when delayed postpartum hemorrhage is combined with a disproportional decrease in hemoglobin and urine amount and thrombocytopenia.

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遲發性產後出血：血栓性血小板減少性紫斑—溶血性尿毒症候群之罕見臨床表現—病例報告

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在臨床上，血栓性血小板減少性紫斑症和溶血性尿毒症兩者的臨床表現相當的相似，常常被一起稱為血栓性血小板減少性紫斑—溶血性尿毒症候群。這個症候群的發生可能和病毒或細菌的感染、懷孕、惡性腫瘤、某些藥物 (如化學治療藥物) 和自體免疫性疾病等有關。病人臨床的特徵往往包括有溶血性貧血、血小板缺乏、腎機能異常、發燒以及神經疾患等等。女性的發生率高於男性且容易發生於懷孕中或剛生產後。回顧文獻報告，此類疾病極少以延遲性產後出血來表現。本文中，我們報告一位反覆發作延遲性產後出血的產婦，其最後診斷為血栓性血小板減少性紫斑—溶血性尿毒症候群之罕見案例。

關鍵詞：遲發性產後出血，血栓性血小板減少性紫斑，溶血性尿毒症候群

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