A Case of Anemia with Schistocytosis, Thrombocytopenia, and Acute Renal Failure Caused by Adenomyosis

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Abstract

A 51-year-old woman with adenomyosis was admitted because of anemia with schistocytosis, thrombocytopenia, and acute renal failure (ARF). Thrombotic microangiopathy (TMA) was considered. Plasma exchange and steroid therapies improved laboratory results. However, renal biopsy specimen revealed acute tubular necrosis (ATN), but not TMA, and thrombocytopenia, diagnosed it as disseminated intravascular coagulation (DIC) but not TMA. Few cases of DIC associated with benign tumors of the uterus and, especially, adenomyosis have been reported. In adenomyosis patients, ARF is usually caused by obstructive uropathy. However, the rare case suggests that hemolytic anemia, DIC, and ARF due to ATN can occur in adenomyosis patients.

Key words: hemolytic anemia, disseminated intravascular coagulation, acute tubular necrosis, thrombotic microangiopathy, adenomyosis

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Introduction

Adenomyosis is a benign gynecological condition characterized by the presence of endometrial glands and stroma within the myometrium (1). Disseminated intravascular coagulation (DIC) is an acquired coagulopathy induced by a variety of clinical conditions. Few cases of DIC associated with benign tumors of the uterus have been reported. Adenomyosis is frequently associated with other uterine conditions, such as leiomyoma (35-55%) and pelvic endometriosis (5-20%). Acute renal failure (ARF) in such cases is usually caused by obstructive uropathy from adenomyosis or by coexisting conditions, such as bulky leiomyoma and ureteral endometriosis. Only 2 cases of DIC in adenomyosis patients have been reported, and the patients exhibited renal damage due to DIC, which was not confirmed by renal biopsy (2, 3). We report a rare case of hemolytic anemia, DIC, and ARF due to acute tubular necrosis (ATN) in an adenomyosis patient; renal biopsy examination confirmed these findings.

Case Report

A 51-year-old woman suffering from adenomyosis was treated with leuprolein acetate (gonadotropin-releasing hormone agonist) from November 2006 to April 2007. She was not consistent in consulting a doctor. Thereafter, laboratory test abnormalities were not detected by routine physical examination.

In late September 2010, her menstruation started, and sudden nausea and vomiting occurred. Therefore, she was referred and admitted to our hospital on the following day. She had no medical history except for 2 cesarean operations. Vital signs, including body temperature (36.3°C), were stable. Physical examination revealed slight conjunctival anemia. An extremely enlarged uterus was palpable at the level of the umbilicus, and slight tenderness was noted on her lower abdomen. The results of a peripheral blood cell analysis were as follows: white blood cell count, 21,000 cells/μL; hemoglobin level, 10.8 g/dL; hematocrit, 32.1%; and platelet count, 49,000 cells/μL. A peripheral blood smear revealed numerous schistocytes (5.7%). Blood chemistry results were as follows: total bilirubin, 2.0 mg/dL; direct bilirubin, 0.3...
mg/dL; aspartate aminotransferase (AST), 78 U/L; alanine aminotransferase (ALT), 20 U/L; lactate dehydrogenase (LDH), 2,317 U/L; creatine phosphokinase (CPK), 181 U/L; C-reactive protein (CRP), 27.3 mg/dL; serum urea nitrogen, 55 mg/dL; and creatinine, 3.92 mg/dL. Coagulation test results were as follows: prothrombin time (PT), 16.2 s; activated partial thromboplastin time (aPTT), 30.1 s; fibrinogen, 410 mg/dL; and fibrinogen/fibrin degradation product (FDP) D-dimer, >300 μg/mL. Urine test results were as follows: protein, 1+; daily urinary protein excretion, 0.33 g; occult blood, 2+; urinary α1-microglobulin, 108 mg/L, urinary N-acetylglucosaminidase, 10.3 U/mL; and urinary β2-microglobulin, 46.100 μg/L. Serologies for antinuclear antibodies (ANA), anticytoplasmic antibodies (ANCA), and anti-glomerular basement membrane antibody (anti-GBM) were all negative. Complement levels were within the normal range. A full-body computed tomography scan did not yield any remarkable finding except for an enlarged uterus. Magnetic resonance imaging (MRI) revealed that the enlargement was caused by adenomyosis with microhemorrhage. Based on the laboratory findings of microangiopathic hemolytic anemia, thrombocytopenia, and progressive renal dysfunction, a diagnosis of thrombotic microangiopathy (TMA) was considered.

Treatment with glucocorticoid (1,000 mg daily of methylprednisolone pulse therapy for 3 consecutive days followed by 60 mg daily of prednisolone) and plasma exchange (plasma volume of 2,400 mL daily for 3 consecutive days) was initiated in mid-September 2010. Moreover, hemodialysis was initiated due to deterioration of renal function and dyspnea for volume overload two days later. In late September 2010, her menstruation ended. From around that time, hemoglobin and platelet count levels increased, inflammation subsided, and hemodialysis could be withdrawn (Fig. 1A).

Thereafter, it was shown that the LDH isozyme pattern was as follows: LDH-1, 19.4%; LDH-2, 22.5%; LDH-3, 19.9%; LDH-4, 16.4%; and LDH-5, 21.8%. These data indicated that LDH-4 and LDH-5 were dominant. ADAMTS13 activity was 68.3% (normally 70-120 %), and ADAMTS13 inhibitor level was <0.5 BU/mL. These data were not consistent with TMA. In addition, high levels of FDP-D dimer and remarkable tubulointerstitial damage compared with glomerular damage (e.g., the levels of urinary protein excretion and occult blood) were not consistent with TMA.

Based on these data inconsistencies, a renal biopsy was performed on the end of September 2010. On light microscopy, a slight thickening of the glomerular capillary walls was found. However, increased mesangial matrix and occlusion of glomerular capillaries due to thickened walls or endothelial cell swelling were not noted in the examination of the specimens (Fig. 2A). Flattened proximal tubular cells, enlarged proximal tubular lumen, and detachment of proximal tubular cells from the tubular basement membrane were observed (Fig. 2B). These findings were consistent with acute tubular necrosis (ATN), not TMA. Immunofluorescence examination did not demonstrate any particular deposits characteristic of immunoglobulins or complements (data not shown).

During the good clinical course, the patient suddenly developed lower abdominal pain and fever (38°C) in early October 2010. CRP levels increased remarkably and platelet count decreased dramatically on the following day. Therefore, ovariohysterectomy was performed on the same day. The resected uterus consisted of diffusely hypertrophied myometrium stippled with foci of ectopic endometrium in the macro findings. Endometrial glands and stroma were surrounded by hypertrophied myometrium in the micro findings. Neither macro nor micro hemorrhage was found in the resected uterus. Clinical findings and laboratory data subsequently improved, and she was discharged uneventfully two weeks later (Fig. 1B).

**Figure 1.** Clinical course. The solid line with squares indicates changes in serum creatinine levels, the dotted line with diamonds indicates changes in hemoglobin levels, the dotted-and-dashed line with circles indicates changes in C-reactive protein levels, and the dotted line with triangles indicates changes in platelet count. Abbreviations: PSL: prednisolone, PE: plasma exchange, HD: hemodialysis, Cr: creatinine, Hgb: hemoglobin, CRP: C-reactive protein, Plt: platelet.
A pathway, which evokes systemic thrombin generation and to the tissue factor activates the tissue factor coagulation necrotic degradation of the myometrium. Exposure of blood to the tissue factor is produced through the above hypothesis. We speculate that neither macro nor micro activation of the LDH-5 isozyme in this case study support the bocytopenia with high levels of the FDP-D dimer, and elevation of proximal tubular lumen, and detachment of proximal tubular cells from the tubular basement membrane were seen.

**Discussion**

TMA is characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, neurological deficits, and renal abnormalities, whereas DIC is an acquired coagulopathy. Because of similarities in clinical manifestations and laboratory findings, distinguishing between TMA and DIC is difficult. However, in TMA, thrombus formation appears to be attributed primarily to platelet aggregation with a lesser contribution by fibrin, whereas in DIC, fibrin is the main component (4). Therefore, the remarkably high levels of FDP-D dimer in this case study are consistent with DIC, not TMA. DIC is induced by many clinical conditions such as malignant tumors or infections. However, DIC cases associated with benign tumors are relatively rare. In the gynecological field, limited reports on DIC associated with leiomyoma have been published. Harris et al (5) and Caputo and Kanbour-Shakir (6) reported chronic DIC development in nonpregnant patients with leiomyoma. Only 2 cases of DIC in adenomyosis patients have been reported (2, 3). We believe that the following is the mechanism of occurrence of DIC. Intramural hemorrhage in the adenomyosis region, especially for menstruation, causes blood stagnation, which leads to the formation of thrombin and subsequent microthrombosis. Microthrombosis causes ischemic damage to the myometrium, and tissue factor is produced through the necrotic degradation of the myometrium. Exposure of blood to the tissue factor activates the tissue factor coagulation pathway, which evokes systemic thrombin generation and leads to DIC. Hemolytic anemia with schistocytosis, thrombocytopenia with high levels of the FDP-D dimer, and elevation of the LDH-5 isozyme in this case study support the above hypothesis. We speculate that neither macro nor micro hemorrhage was found in the resected uterus, because the early resection was performed in the next day when the lower abdominal pain occurred.

Although the treatment of DIC is generally the supression of hypercoagulability using anticoagulants and/or plasma infusion of coagulation factors, because a diagnosis of thrombotic microangiopathy was considered, plasma exchange was performed in this case. Because plasma exchange replaces coagulation factors, there is the possibility that plasma exchange improved DIC to some extent. However, intramural hemorrhage due to menstruation is closely associated with DIC, as our hypothesis suggests. Therefore, the termination of menstruation might contribute more than the treatment with plasma exchange to the quick improvement of DIC.

ARF is typically caused by obstructive uropathy in adenomyosis patients. Thus far, only 2 cases of renal damage from other causes have been reported. These cases were presumed to be caused by DIC but were not confirmed by renal biopsy (2, 3). The present study represents the first finding of ATN revealed by renal biopsy. Miyashima et al reported that DIC is primarily initiated by injury to the capillary endothelium and that changes on the endothelial surface contribute to the development of DIC (7). When the endothelium is injured, there is a marked increase in F-actin aggregates in the basal and basolateral aspect of renal microvascular endothelial cells in the corticomedullary junction, and alterations in the integrity of the adherence junctions of the renal microvasculature are observed. These changes correlate with the greatest extent of the permeability defect in the renal microvasculature (8). In addition, Wu et al noted that cecal ligation and puncture in a murine model of sepsis resulted in dramatic reduction in capillary perfusion by damage to the endothelial cells and that morphologic changes including loss of brush border, tubular cell sloughing, tubular dilation, and tubular vacuolization in-

**Figure 2.** Findings of renal biopsy. Light microscopic analysis of the renal biopsy specimen (Periodic acid-Schiff stain, ×200). (A) Slight thickening of the glomerular capillary walls was observed. However, increased mesangial matrix and occlusion of glomerular capillaries due to the thickened walls or endothelial cell swelling were not found. (B) Flattened proximal tubular cells, enlargement of proximal tubular lumen, and detachment of proximal tubular cells from the tubular basement membrane were seen.
creased in terms of severity with a fall in capillary perfusion (9). We speculate that ATN occurred in this case because of the renal peritubular capillary dysfunction caused by endothelial injury from DIC, as mentioned above. Therefore, the rapid amelioration of DIC due to the termination of menstruation and therapy with plasma exchange might contribute to the quick improvement of ATN. In conclusion, we observed a rare case of hemolytic anemia, DIC, and ARF by ATN in an adenomyosis patient and renal biopsy examination confirmed these findings.

The authors state that they have no Conflict of Interest (COI).

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References