

# Thrombotic microangiopathies and acute kidney injury induced by artificial termination of pregnancy

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## Abstract

Thrombotic microangiopathy (TMA) is a rare, but potentially lethal condition requiring rapid recognition, diagnosis and initiation of therapy. Here, we present two cases of women with hemolytic anemia, thrombocytopenia and acute kidney injury shortly after surgical termination of pregnancy. Histological examination of their kidneys revealed endothelial cell swelling and luminal stenosis or fibrin-containing thrombi in the glomeruli and arterioles, which support the diagnosis of TMA. The patients were treated with hemodialysis, plasma infusion and corticosteroids with or without immunosuppressive agents. Three weeks after treatment, one patient was cured and symptoms of the other patient markedly improved. Reporting of more cases of TMA associated with surgical termination of pregnancy will provide further insights into this rare disease, possibly aiding in identifying risk factors and improving time to clinical diagnosis, treatment and prognosis.

**Key words:** Acute renal failure, case studies, induced abortion, pregnancy, thrombotic microangiopathy

**Date of Acceptance:** 29-Jul-2013

## Introduction

Thrombotic microangiopathy (TMA), a rare and life-threatening syndrome, is characterized by hemolytic anemia (HA) with schistocytes and thrombocytopenia associated with variable signs of organ injury due to platelet thrombi in the microcirculation.<sup>[1,2]</sup> Several potential causes, including autoimmune disorders, infections, transplantation, malignancy, medications, anti-phospholipid syndrome and pregnancy, have been identified.<sup>[3]</sup>

TMA occurs with increased frequency during or in relation to pregnancy. It has been reported to occur in 1 in 25,000 pregnancies.<sup>[4,5]</sup> Pregnancy-associated TMA typically occurs during late pregnancy, especially the second and early third trimesters.<sup>[6,7]</sup> Cases of TMA associated with induced abortion in the first trimester of pregnancy are rarely reported and are poorly understood.<sup>[3,8]</sup> There has only been one case report from Japan describing a Russian woman with systemic lupus erythematosus, anti-phospholipid syndrome and renal failure at 14 weeks of pregnancy, who developed TMA shortly after surgical abortion.<sup>[8]</sup> However, cases of

TMA associated solely with induced abortions have not been reported. Here, we present two unusual cases of women with TMA diagnosed in close relation to termination of pregnancy in the first trimester. These patients were treated with hemodialysis, infusion of plasma and high-dose corticosteroids with or without immunosuppressive agents. After treatment, one patient was cured and the symptoms associated with the other patient were markedly attenuated.

## Case Reports

### Case 1

A 41-year-old woman was admitted to our hospital with a 3-h history of vaginal bleeding due to taking mifepristone orally after a 12-week pregnancy. At the beginning of pregnancy, she had taken ethinylestradiol and cyproterone acetate tablets orally for 21 days to promote contraception. There was no history of chronic diseases. Obstetric history included six abortions and two live births. Suction dilation

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and curettage were performed after admission because of the quantity of vaginal bleeding due to expulsion of the embryo and placental tissue. The quantity of decidua tissue and crur was measured to 300 ml.

On the first post-operative day, patient had fatigue, headache and oliguria and was confused and disoriented. The hemoglobin level declined from 107 g/L pre-operatively to 73 g/L post-operatively. The laboratory findings [Table 1] indicated that patient had anemia, thrombocytopenia, renal failure, proteinuria, microscopic hematuria, urinary siderosis, elevated reticulocyte and serum L-lactate dehydrogenase (LDH) levels and more importantly, schistocytosis; all these findings supported the TMA diagnosis. Meanwhile, her anti-cardiolipin antibodies, anti-nuclear antibodies, anti-double stranded deoxyribonucleic acid (DNA) antibodies, myeloperoxidase anti-neutrophil cytoplasmic autoantibodies, (MPO-ANCA) proteinase-3 anti-neutrophil cytoplasmic autoantibodies, (PR3-ANCA) anti-glomerular basement membrane (GBM) antibody, Coombs test and Ham test were all negative.

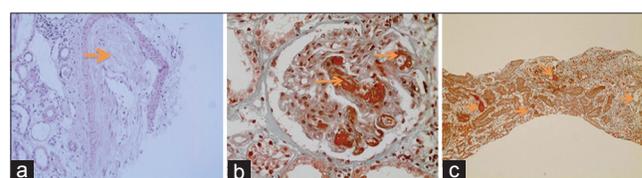
Renal biopsy on the 12 day of hospitalization revealed segmental proliferation of mesangial cells and matrix in the glomeruli, diffuse vacuolar degeneration of cells in the tubules and intima mucoid edematous thickening and endothelial cell swelling with luminal stenosis in the arterioles [Figure 1a]. Fibrin thrombi were not found in the glomeruli or arterioles. No immune deposits were

shown by electron microscopy or by immunofluorescence microscopy.

Patient was diagnosed with TMA and acute renal failure. Hemodialysis and plasma infusion were initiated while she was given pulse hexadecadrol (10 mg/day, three doses) and oral prednisolone (1 mg/kg). Three weeks after corticosteroid treatment, laboratory investigations showed renal function, platelet count, red blood cell number, hemoglobin level and LDH level recovered to normal levels and there were no schistocytes in the peripheral blood smear.

## Case 2

A 38-year-old woman was admitted to our hospital with a 3-year history of edema and anuria. Medical history



**Figure 1:** Histological findings of renal biopsy specimens (a) Light micrograph of the renal biopsy from the patient in Case 1, showing endothelial cell swelling and luminal stenosis in the arterioles (arrow) H and E,  $\times 400$ . (b) Light micrograph of the renal biopsy from the patient in Case 2, showing fibrin thrombi in the glomeruli (arrows) Masson trichrome stain,  $\times 400$ . (c) Light micrograph of the renal biopsy from the patient in Case 2, showing fibrin thrombi in the glomeruli and arterioles (arrows) Masson trichrome stain,  $\times 400$ .

**Table 1: Laboratory data from the two patients in the study**

Laboratory tests	Case 1		Case 2		Normal value
	At admission	Post-treatment	At admission	Post-treatment	
RBC, $10^{12}/L$	3.03	3.77	2.97	2.54	3.50-5.00
Hb, g/L					
Pre-operative	107	114	126	71	110-150
Post-operative	73		67		
WBC, $10^9/L$	7.3	9.3	10.7	9.8	4-10
PLT, $10^9/L$	58	147	83	200	100-300
Hematocrit, L/L	0.217	0.35	0.215	0.23	0.370-0.480
Reticulocytes, $10^{12}/L$	0.11	0.09	0.13	0.04	0.0224-0.0829
Creatinine, $\mu mol/L$	359.6	72.1	717.1	291.9	44.0-115.0
BUN, mmol/L	13.02	7.58	27.15	9.61	3.20-7.00
LDH, U/L	421	190	2147	291	135-226
Indirect bilirubin, $\mu mol/L$	26.4	9.1	12.5	5	5.1-21.4
Serum total protein, g/L	47.7	60.3	45.4	53.4	60.0-83.0
Serum albumin, g/L	23.6	35.7	25.1	29.9	35.0-55.0
Urinary proteinuria	+	-	3+	+	-
Urinary occult blood	3+	-	3+	3+	-
Urinary sediments RBC per high-power field	0.5	0.5	608.2	6.7	0.0-5.0
Urinary protein excretion, g/day	0.09	0.10	No data	No data	<0.20
Urinary siderosis	+	+	+	+	-
Serum C3, g/L	0.748	0.10	0.80	0.12	0.90-1.80
Serum C4, g/L	0.17	0.30	0.14	0.40	0.10-1.40
Peripheral blood smear	Schistocytes	-	Schistocytes	-	-

BUN=Blood urea nitrogen; C=Complement; Hb=Hemoglobin; LDH=L-lactate dehydrogenase; PLT=Platelet; RBC=Red blood cell; WBC=White blood cell

review revealed that patient had had suction dilation and curettage 9 days ago for an induced abortion after an 8-week pregnancy. The day after the operation, hemoglobin declined from 126 g/L pre-operatively to 77 g/L post-operatively and platelets declined from  $220 \times 10^9/L$  pre-operatively to  $47 \times 10^9/L$  post-operatively. There was no remarkable history of chronic diseases. Obstetric history included one live birth. At admission, the patient suffered from abdominal pain, nasal hemorrhage and edema and her urinary volume was only 40 ml/day. Physical examination revealed a body temperature of 38°C, severe anemia and edema.

The laboratory findings [Table 1] indicated that the patient had anemia, thrombocytopenia, renal failure, proteinuria, microscopic hematuria, urinary siderosis, elevated reticulocyte and serum LDH levels and more importantly, schistocytosis. Meanwhile, her anti-cardiolipin antibodies, anti-nuclear antibodies, anti-double stranded DNA antibodies, MPO-ANCA, PR3-ANCA, anti-GBM antibody, Coombs tests and Ham test were all negative. Renal biopsy on the 2<sup>nd</sup> day of hospitalization revealed fibrin thrombi in the glomeruli [Figure 1b] and arterioles [Figure 1c] in the absence of immune deposits, which is characteristic of TMA. Electron microscopy showed no electron-dense deposit.

She was diagnosed with TMA and acute kidney injury. Hemodialysis and plasma infusion were initially performed. Meanwhile, she was given a bolus of methylprednisolone (500 mg/day, three doses) and cyclophosphamide (0.6 g/day, 1 dose/month). Patient then continued on oral prednisolone (1 mg/kg/day). Three weeks after corticosteroid treatment, edema and anuria were corrected. Laboratory investigations showed renal function, platelet count, red blood cell count and hemoglobin levels improved. LDH recovered to normal levels and there were no schistocytes in the peripheral blood smear.

## Discussion

TMA is a rare, but serious disorder that is associated with anemia and significant organ failure due to the deposition of fibrin and platelet thrombi in the microcirculation.<sup>[9]</sup> Pregnancy is one of the common precipitating events for TMA. This is thought to be due to the association of pregnancy with increasing concentrations of procoagulant factors, decreasing fibrinolytic activity, loss of endothelial cell thrombomodulin and changes of hormones.<sup>[4,5]</sup> Interestingly, anemia and even thrombocytopenia emerged in both cases shortly after surgical termination of pregnancy. TMA is believed to manifest from endothelial dysfunction, but the mechanistic relationship between TMA and termination of pregnancy in the present cases is unknown. It is unlikely that the operation by itself triggered the onset of TMA. Rather, decreasing human chorionic gonadotropin (HCG) levels after termination of pregnancy, possibly in synergy with

endothelial and hemostasis dysfunction, may have caused a predisposition for development of TMA.

It was challenging to make a correct diagnosis for TMA in the present cases. The following set of five signs and symptoms has been associated with TMA: thrombocytopenia, microangiopathic HA, neurological abnormalities, renal failure and fever.<sup>[6,7]</sup> The diagnostic laboratory features of TMA in pregnancy are identical to those in the non-pregnant state, which include anemia and thrombocytopenia. Evidence of red cell fragmentation (schistocytes and polychromasia) should be sought on the peripheral blood smear; elevated LDH and indirect hyperbilirubinemia are also commonly seen. A negative direct Coomb's test is necessary to exclude autoimmune HA.<sup>[10]</sup>

The diagnosis of TMA was confirmed by renal biopsy. In TMA, glomerular endothelial damage leads to the formation of microthrombi within the glomerular capillaries and subsequent endothelial cell proliferation, thickening of the basement membrane and formation of double contours.<sup>[11]</sup> In the first case, we did not have prior experience with the diagnosis of TMA and there was a delay of 12 days for the renal biopsy. The second case, in contrast, featured an immediate renal biopsy due to prior experience in the diagnosis. In the first case, although fibrin thrombi and double contours were not found in the glomeruli or arterioles, intima mucoid edematous thickening, endothelial cell swelling in the arterioles, and luminal stenosis of arterioles were observed, which were consistent with TMA. In the second case, renal biopsy revealed fibrin thrombi in the glomeruli and arterioles in the absence of immune deposits, which is characteristic of TMA.

At present, the most effective therapeutic regimen for acute TMA is plasma exchange or infusion due to complement dysregulation.<sup>[12]</sup> Although plasma exchange had not been carried out in our patients, hemodialysis and plasma infusion were shown to be effective. Meanwhile, several trials suggested that the administration of high-dose steroids improves clinical outcomes.<sup>[12-14]</sup> Hence, corticosteroids were given in the present cases. Other trials have suggested that cyclophosphamide provides comparably high remission rates in severe TMA with acceptable side-effects and should be considered in the more severe patients.<sup>[15]</sup> Patient in Case 2 was given cyclophosphamide because of the severity of symptoms and kidney injury. After 3 weeks of treatment, one patient was cured and the other patient's symptoms were markedly improved.

## Conclusion

The present cases show that TMA may be associated with termination of pregnancy. An accurate diagnosis of TMA is challenging when symptoms occur in women after

termination of pregnancy. More reports of TMA in patients with pregnancy will likely provide further insights into the pathogenesis of this rare disease, possibly uncovering underlying mechanisms to aid in early diagnosis and development of effective therapies.

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**How to cite this article:** ???

**Source of Support:** Supported by Jilin province Science and Technology Development Project, project number 201201036,

**Conflict of Interest:** None declared.

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