Am J Transl Res 2021;13(6):6182-6190
www.ajtr.org /ISSN:1943-8141/AJTR0125699

Original Article

Acute kidney injuries induced by thrombotic microangiopathy following severe hemorrhage in puerperants: a case series and literature review

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Received November 5, 2020; Accepted February 8, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Background: Acute kidney injury in puerperants is generally caused by acute tubular necrosis and occasionally by thrombotic microangiopathy (TMA) following post-partum hemorrhage. However, TMA leads to worse clinical outcomes and is rarely reported in the literature. Therefore, this study aimed to evaluate the pathological mechanism behind the development of TMA in puerperants to improve the diagnosis and treatment of this condition. Methods: Three patients diagnosed with severe postpartum hemorrhage and TMA from 2014 to 2017 at a nephrology center were retrospectively investigated. Results: All patients had severe hemorrhage during delivery with a mean blood loss, 4.0 L (range, 2.7-5.0 L). AKI developed rapidly in these patients and was treated with hemodialysis. Following treatment, the mean volume of packed red blood cells was 2.3 L (range, 1.2-3.6 L), and the mean volume of resuscitation fluid was 3.7 L (range, 3.5-4.0 L). All patients had renal biopsy specimens with typical TMA and ATN changes on light microscopy. Two patients required a hysterectomy while another two patients received respiratory support. Only one patient received plasma exchange. None of the patients had recovered normal kidney function by the final follow-up (26-61 months), with two patients having stage 3 chronic kidney disease, and one patient having an end-stage renal disease requiring maintenance hemodialysis. Conclusion: Severe postpartum hemorrhage could lead to TMA, in addition to the common finding of ATN. Renal histology revealed that poor renal outcomes could be attributed to TMA coexisting with ATN. The potential mechanism was ischemia-reperfusion, which was followed by endothelial cell injury and activation of the alternative complement pathway.

Keywords: Severe postpartum hemorrhage, thrombotic microangiopathy (TMA), pregnancy, acute tubular necrosis (ATN)

Introduction

Thrombotic microangiopathy (TMA) describes a pathological process in which platelet aggregation and thrombus formation in small blood vessels cause luminal narrowing or occlusion, eventually leading to end-organ ischemia and infarction [1, 2]. The clinical consequences of TMA are thrombocytopenia, mechanical hemolytic anemia, and ischemic injuries to different organs, especially in the kidneys. TMAs are rare, severe conditions associated with serious morbidity and up to 90% mortality rate, if left untreated [3]. Pregnancy is a high-risk period for women to develop various types of TMA. However, TMA induced by severe postpartum hemorrhage is rarely reported.

Acute kidney injury (AKI) is a severe complication induced by postpartum hemorrhage as a result of acute tubular necrosis (ATN). The condition generally has a favorable renal outcome [4]. However, thrombotic microangiopathy (TMA) could also be found in severe postpartum hemorrhage, especially when abnormality of renal function persists. The pathogenesis of TMA induced by severe postpartum hemorrhage is unclear. Herein, we present a case series of TMA induced following severe postpartum hemorrhage at our center. In this case series, we will evaluate the possible pathogenesis behind TMA leading to prolonged AKI following severe postpartum hemorrhage to facilitate the diagnosis of the disease and hence provide a more effective treatment.

Materials and methods

Patients selection

Three patients with severe postpartum hemorrhage induced TMA, diagnosed in the Renal Department of China-Japan Friendship Hospital between January 2014 to December 2017, were recruited in this study. Inclusion criteria were defined as follows: (1) patients suffered from acute kidney injury following severe postpartum hemorrhage; (2) a diagnosis of TMA confirmed by laboratory features; (3) pathologically confirmed TMA. Exclusion criteria were defined as follows: (1) patients with chronic kidney disease (CKD), or with comorbid other renal diseases, for instance, anti-glomerular basement membrane disease, IgA nephropathy or diabetic nephropathy; (2) patients with systemic diseases, such as scleroderma and systemic lupus erythematosus.

Diagnostic criteria

TMA was diagnosed by (1) thrombocytopenia (platelets $<150\times10^9$/L or >25% fall from baseline); (2) microangiopathic hemolytic anemia (MAHA) [hemoglobin <100 g/L with red cell fragments (schistocytes)]; (3) the clinical and laboratory abnormalities attributable to organ-specific dysfunction [Lactate dehydrogenase elevated, Haptoglobin low, Bilirubin elevated, Direct antiglobulin (Coombs') test negative, Coagulation screening tests (APTT, INR, fibrinogen) normal (except in DIC, lupus anticoagulant, therapeutic anticoagulation), etc.] [1]; and (4) renal pathology were as per TMA changes. Severe postpartum hemorrhage was defined as a blood loss of ≥1500 mL at the time of delivery [5].

Acute renal injury was diagnosed creatinine ≥1.5 times baseline or increase of ≥0·3 mg/dL within any 48 h period, or urine volume [6]. The possible occurrence of kidney hypoperfusion was considered when mean arterial pressure was lower than 60 mmHg on two separate occasions between delivery and the fourth day after. Patients receiving vasoactive support (norepinephrine) after severe postpartum haemorrhage were considered hypotensive [7, 8].

Clinical data collection and follow-up

Clinical data were collected for all patients, including the clinical features (age, gestational age, pregnancy disorders, blood loss, kidney hypoperfusion/hypotensive, first 24-h urinary volume, etc.), laboratory data (creatinine, hemoglobin, platelet count, ALT, AST, LDH, ADAMTS13, etc.), severe postpartum hemorrhage treatment and other treatment, kidney disease outcome. All the clinical and laboratory data was collected from electronic medical records of our hospital. The estimated glomerular filtration rate (eGFR) were calculated by the CKD-EPI (Epidemiology Collaboration) formula, as previously described [9].

The biopsy specimens were divided into three portions and were processed and evaluated according to a previous standardized protocol as follows. One portion was fixed in buffered formalin, processed into paraffin blocks for light microscopy, and stained with hematoxylin and eosin, periodic acid-Schiff (PAS), silver methenamine, and Masson trichrome. The second portion was frozen for direct immunofluorescence studies by using fluorescein isothiocyanate conjugated antibodies detecting IgG, IgA, IgM, C3, C4, C1q, and fibrinogen. The third portion was fixed in Trump's EM fixative and processed into resin blocks which were then sectioned into ultrathin slices and stained with uranyl acetate and lead citrate and subjected to transmission electron microscopy [10].

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 for Windows (IBM SPSS Statistics, Armonk, NY, USA). Data are expressed as means (range; for data that were not normally distributed) for age, blood count, blood loss and serum creatinine, et al.

Results

Patient characteristics

The patients were numerically coded and their clinical characteristics are summarized in **Table 1**. The mean age of the patients in this study was 32.7 (range, 29-38) years at diagnosis. Among the three patients with severe postpartum hemorrhage and TMA, one was primiparous (No. 3). None of the patients were known to have nephropathy or other significant diseases, except for No. 2, who had controllable gestational hypertension and diabetes without proteinuria.

Table 1. Characteristics of patients with postpartum hemorrhage and TMA

	No. 1	No. 2	No. 3
Clinical features			
Age (y)	29	38	31
Childbearing history	Second-born	Second-born	First-born
Gestational age (w)	40	39	39
Gestational hypertension	-	+	-
Gestational diabetes	-	+	-
Peripartum data			
Mode of delivery	Cesarean section	Vaginal delivery	Cesarean section
Pregnancy disorders			
Blood loss (L)	4.2	2.7	5
Duration of hemorrhage (h)	4.0	7.5	5.5
Hypotensive	+	+	+
First 24-h urinary volume (L)	0	0	0
Laboratory data			
Creatinine (μmol/L)	826	944	1155
Hemoglobin (g/L)	57	49	67
Platelet count ($\times 10^9$/L)	23	38	40
ALT (IU/L)	257	168	94
AST (IU/L)	369	345	412
LDH (IU/L)	3001	3706	2020
DIC	+	-	-
Coombs' test	-	-	-
ADAMTS13 activity (%)	65	77	71
CFH (μg/ml)	379	342	350
Renal pathology	TMA+ATN	TMA+ATN	TMA+ATN
Treatment			
Red blood cells (L)	2.1	1.2	3.6
Crystalloid/Colloid (L)	4.0	3.5	3.5
Respiratory support	+	-	+
Hysterectomy	-	+	+
Hemodialysis	+	+	+
Plasma exchange	+	-	-
Kidney disease outcome			
Follow-up (m)	26	27	61
eGFR at 6 m postpartum	23.5	16.0	13.4
eGFR at 12 m postpartum	35.6	11.4	17.3
eGFR at 24 m postpartum	36.5	Dialysis dependence	25.2
eGFR at last report	37.0	ESRD	30.9

Note: eGRFs expressed in mL/min/1.73 m^2. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATN, acute tubular necrosis; CFH, complement factor H; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

The mean pregnancy term was 39.3 (range, 39-40) weeks. A cesarean section was performed an all patients except No. 2 who had a vaginal delivery. All deliveries were complicated by severe postpartum hemorrhage (blood loss >1,500 ml), and average blood loss was 4.0 L (range, 2.7-5.0 L). At admission to the intensive care unit (ICU), all the patients had hypotension, elevated liver enzymes, and AKI. The direct antiglobulin (Coombs') test was negative

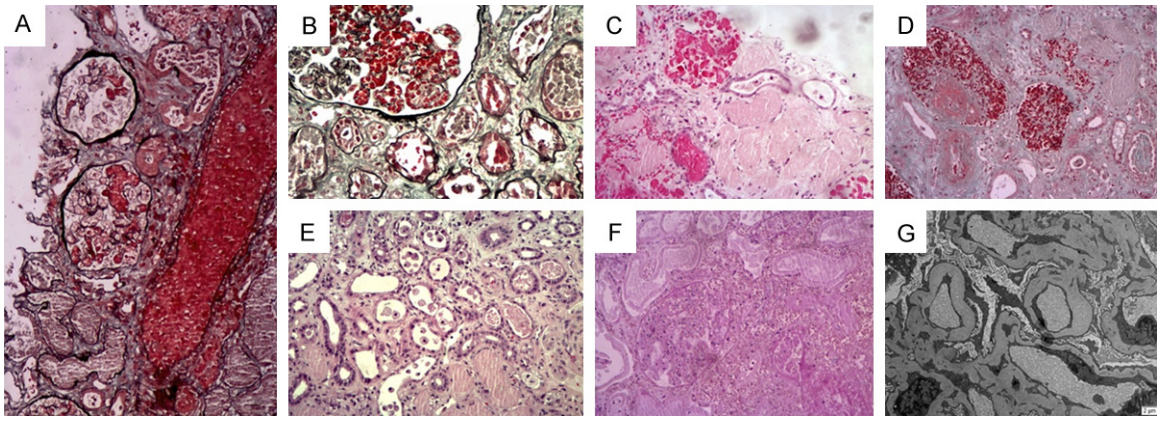

Figure 1. Typical renal histopathological findings. (A) The biopsy sample (No. 3) revealed endothelial swelling and glomerular intracapillary thrombosis. Venous injury may be seen with widespread thrombosis. (PASM, 40×). (B and C) Kidney biopsy specimen (No. 3) showed glomerular intracapillary thrombosis with accumulation of fragmented erythrocytes within capillary lumens. (B. PASM, 200×; C. HE, 200×). (D) Kidney biopsy specimen (No. 2) showed severe arteriolar injury may be seen with thrombosis. (MASSON, 200×). (E and F) The biopsy samples (No. 1 and No. 2) revealed significant proximal tubule cell damage with intraluminal accumulation of apical membrane fragments and detached cell, thinning of proximal tubular cells to maintain monolayer tubule integrity, and dividing cells and accumulation of white cells within the microvascular space in the peritubular area. (E. HE, 200×; F. PAS, 200×). (G) Kidney biopsy specimen (No. 2) showed loose layer in basement membrane thickening and basement membrane shrinking on electron microscopy (5000×).

in all patients. ADAMTS13 activity and complement factor H level were also normal in all patients.

Renal features

All patients were admitted to the ICU with AKI and blood tests were performed. Anuria was reported in all of them, and the mean serum creatinine level was 975 (range, 826-1155) μmol/L. Kidney biopsies were performed in all the patients. The immunofluorescence micrograph showed sparse, nonspecific glomerular complement C3 and immunoglobulin M (IgM). Fibrin deposition was present not only within the glomerular capillaries, but also in the lumen, subintima, and media of arterial vessels. Renal histological features on light microscopy included arteriolar and glomerular intracapillary thrombosis with an accumulation of fragmented erythrocytes within capillary lumens and focally ischemic or congested glomerular tufts. Severe arterial and arteriolar injury was seen with widespread thrombosis (**Figure 1A-D**). In addition to TMA features, these patients also have the classical hallmark signs of acute tubular necrosis (ATN), such as the loss of the apical brush border of the proximal tubular cells, patchy detachment, and subsequent loss of tubular cells exposing areas of denuded tubular basement and focal areas of proximal tubular dilatation along with the presence of distal tubular casts. The sloughed tubule cells, brush border vesicle remnants, and cellular debris in combination with Tamm-Horsfall glycoprotein form the classical muddy-brown granular casts (**Figure 1E**, **1F**). The electron microscopy revealed endothelial swelling, loose layer in basement membrane thickening, and basement membrane shrinking (**Figure 1G**).

Treatment

All patients received hemodialysis. A mean volume of packed red blood cells of 2.3 (range, 1.2-3.6) L, and a mean volume of resuscitation fluid and colloid solution and/or crystalloid solution of 3.7 (range, 3.5-4.0) L were transfused. Two patients (No. 2 and No. 3) were forced to undergo hysterectomies after all other hemostatic treatments failed. All patients received hemodialysis therapy due to persistent anuria with one patient (No. 1) receiving additional plasmapheresis and the other two patients received respiratory support.

Kidney disease outcome

None of the patients had recovered normal kidney function at the last follow-up (26-61

months); 2 were at CKD stage 3, and 1 had ESRD with maintenance hemodialysis. Patient 2 had the worst renal prognosis. Compared with the other two patients, Patient 2 was older and had underlying diseases (gestational hypertension and diabetes). Blood loss volume, hemodynamic parameters, hemoglobin level, hemolysis features, serum creatinine level, and the type of renal pathology were similar among the three patients.

Discussion

ATN is the most common finding for persistent AKI in peurpepant patients with severe hemorrhage [11]. However, TMA is rarely described in renal pathological investigations. The pathogenesis of TMA is not very clear, which might result from endothelial injury in the microcirculation, with activation of the complement and coagulation systems. However, TMAs could also be triggered by non-pregnancy related conditions such as thrombotic thrombocytopenic purpura (TTP), as well as pregnancy-related conditions, such as preeclampsia with severe features or eclampsia with HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome [12-14]. TMA is associated with adverse maternal and fetal outcomes due to the development of ESRD and ultimately leading to increased maternal mortality [15, 16]. Three puerperant patients were recruited in this study with severe hemorrhage and AKI, and following renal histopathology, TMA was found to coexist with ATN. Preeclampsia/eclampsia or HELLP syndrome were ruled out in these three postpartum women with TMA, which was rarely reported in the past. We speculated that the occurrence of TMA may have be related to severe postpartum hemorrhage, and thus we summarized the cases in our center and reviewed the literature.

It is generally considered that ATN should be the pathogenesis of AKI in severe hemorrhage puerperant women, especially when the impairment in renal perfusion is either severe or prolonged in duration. The clinical course was the typical oliguria/anuria stage and followed by polyuria stage, and generally had a good renal outcome. This implies that when the renal function has not improved, other factors should be considered [17]. Although TMA induced by severe postpartum hemorrhage is rarely reported, once it happens, it indicates that the condition is critical and the prognosis is poor. As poor outcome was also demonstrated in our study as none of the patients had recovered normal kidney function at the last follow-up, with two-thirds of the patients requiring a hysterectomy. The mechanism of TMA caused by severe postpartum hemorrhage is still not fully understood. However, based on the three cases evaluated at our hospital, we deduce that the following pathological mechanism is involved: Initially, uterine contraction dysfunction leads to severe postpartum hemorrhage [18, 19]. This is followed by insufficient circulating blood volume which in turn leads to renal hypoperfusion and epithelial cell injury [7, 20-22] as was demonstrated by the intimal mucoid swelling and thickening of the vascular wall in interlobular arteries identified during renal pathology. As a result of the severe postpartum hemorrhage, the patients required the transfusion of a large amount of red blood cells, plasma, and resuscitation fluid. This could potentially have caused an ischemia-reperfusion injury in renal epithelial cells [23, 24], further promoting the alternative complement pathway activation, and the amplification of the complement-mediated injury [25, 26]. The dysregulation of the alternative complement pathway may induce TMA [27]. Ischemia-reperfusion injury is also one of the known causes of TMA after kidney transplantation [25, 28]. The intravascular stenosis caused by TMA reduced the glomerular perfusion and filtration rate eventually leading to downstream tubular ischemia, ATN, and ultimately lead to renal failure. Hypoperfusion, epithelial cell injury, and complement activation might lead to a vicious circle, which leads to TMA in severe postpartum hemorrhage.

TMAs include several conditions, like TTP and hemolytic uremic syndrome (HUS), which are characterized by the formation of fibrin and platelet microthrombi in small vessels in multiple organ systems leading to organ damage. Although these syndromes have very similar pathological and clinical features, they have distinct etiologies and pathogenesis. TTP is a rare, life-threatening TMA characterized by a severe deficiency in ADAMTS-13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 domain 13) [29]. Pregnancy is a known trigger of TTP [1-3, 30-32]. However, TTP was excluded by normal ADAMTS13 in these three

patients [33], and complement-mediated thrombotic microangiopathy (C-TMA) also known as atypical hemolytic-uremic syndrome was considered. Pregnancy-associated aHUS has been considered as a prototypic secondary HUS [34]. aHUS is characterized by excessive unregulated activation of the alternative complement pathway (ACP) likely due to genetic mutations in complement regulatory proteins [13], the most common being complement factors H (CFH), and complement factors I (CFI). Other factors include C3, membrane cofactor protein (MCP), a combination of the above, as well as novel and rare variants [13, 35, 36]. Plasma exchange (PE) can be only temporarily or partially effective in the majority of cases of aHUS, with no recovery of renal function in up to 80% of cases [13]. Definitive treatment, instead, is with the administration of eculizumab, an anti-C5 antibody that inhibits C5 cleavage and prevents the generation of the membrane attack complex [37-40].

AKI in late pregnancy and postpartum may be associated with preeclampsia with or without HELLP syndrome, TTP, or HUS. It is difficult to distinguish these syndromes based on clinical features alone. The differential diagnosis between HELLP and pregnancy-associated atypical hemolytic uremic syndrome (p-ahus) is difficult due to the similar biochemical characteristics [41, 42]. The diagnostic criteria for aHUS were proposed in 2011, and the incidence is increased in pregnancy and postpartum [43]. Renal biopsy is rarely required to identify ATN due to postpartum hemorrhage, as the renal outcome for AKI with ATN is generally good, and also since chronic renal dysfunction was developed with aHUS [44-46]. At present, there are few studies on renal pathology of AKI complicated with postpartum hemorrhage. If AKI persists for a long time, renal biopsy may be required to confirm the diagnosis and determine the prognosis. In this study, a renal biopsy was performed in all three patients at the appropriate time, confirming the diagnosis of TMA which has important implications on providing the appropriate treatment and ultimately prognosis.

Renal biopsy was essential for identifying the etiology of AKI and to distinguish it from other pathological types of TMAs. Severe postpartum hemorrhage could induce a first shot phenomenon of tubular ischemia; since the renal tubular epithelium is very sensitive to hypoxia and procoagulant factors leading to ATN [38]. Patients with ATN alone exhibited complete recovery of renal function in general [44, 47]. The main lesion of AKI is ischemic acute tubular necrosis, which can explain the reversibility of acute renal injury in most patients. However, renal histological features on electron microscopy in the patients in our study revealed endothelial swelling, and typical TMA and ATN changes. Endothelium injury-induced thrombotic microangiopathy also induced tubular ischemia, sequentially aggravated by postpartum hemorrhage and ischemia-reperfusion. It is worth noting that some studies have shown that the occurrence of TMA with ATN might increase the severity of CKD [48, 49] as also demonstrated by the development CKD in our study. Since the renal prognosis of TMA combined with ATN induced by severe postpartum hemorrhage is relatively poor we recommend the use of early renal biopsy to confirm the disease and thus limit disease progression.

The mechanism of AKI induced by TMA caused by severe postpartum hemorrhage is very complicated, involving numerous factors. A better understanding of the potential key role for the complement system in the mechanism of TMA might offer opportunities for early diagnosis, monitoring, and therapy. Apart from supportive care, other therapies including plasma exchange and eculizumab may also be used to treat this disease. The long-term renal outcomes of AKI and TMA caused by severe postpartum hemorrhage are still not clear.

Conclusion

In this case series, we evaluated the potential mechanism behind the development of TMA induced by severe postpartum hemorrhage. Our findings suggest that severe postpartum hemorrhage leads to renal hypoperfusion and endothelial cell injury, followed by activation of the alternative complement pathway, which eventually lead to the occurrence of TMA in our study, and the clinical manifestation of AKI. The renal histological features of these patients on light microscopy revealed typical TMA and ATN changes indicating a poor disease prognosis. Furthermore, the role of anti-complement treatment in reducing the risk for developing ESRD

warrants further investigation. However, our study was conducted in only one center with a limited number of cases and therefore this mechanism needs to be further investigated in a larger cohort. Successful pregnancy-related TMA management requires a multidisciplinary approach with close collaboration with nephrologists, obstetricians, intensivists, and other team members.

Acknowledgements

The research was conducted in compliance with the Declaration of Helsinki and was approved by the Human Ethics Review Committee of the China-Japan Friendship Hospital. All patients provided written informed consent including consent to publish and report individual patient data.

Disclosure of conflict of interest

None.

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