



## Postpartum TTP-HUS Syndrome: A Rare Autopsy Case Report in a Tertiary Care Hospital

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### ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are the two main disorders included under Thrombotic Microangiopathy. 1 in 25,000 pregnancies present with these rare disorders, mostly seen after uncomplicated gestation and delivery. A diagnostic pentad for TTP was given by Amorosi & Ultmann in 1966: thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms and signs, renal functional abnormalities and fever without other explanation. HUS has features of TTP along with acute renal failure. 12%-31% of TTP patients are women during pregnancy or postpartum period. Pathological diagnosis requires hyaline thrombi in terminal arterioles and capillaries. We present a case of a 28 years old primigravida female, with 38 weeks of gestation, who was apparently alright earlier and presented with prolonged second stage of labour. However, day 2 postpartum she developed fever, breathlessness, loose motions and vomiting. She also developed pallor, icterus and petechial haemorrhages. Laboratory investigations revealed low platelet count, elevated bilirubin (direct more than indirect), elevated serum creatinine, and mildly raised hepatic transaminases. Day 5, she developed anuria and grade 3 dyspnoea and succumbed to death. Complete autopsy was performed. Histopathology on sections from kidneys revealed glomerular capillaries and arterioles showing platelet-fibrin thrombi and diffuse thickening of glomerular capillary wall with double contour of glomerular basement membrane. Lungs showed lobar pneumonia. Cause of death given was acute renal failure with lobar pneumonia with HUS-TTP in a postpartum female. TTP-HUS is a rare disorder and although some clinical features may suggest diagnosis, histopathological examination of renal specimen and applying special stains like PAS stain, silver stain and MSB (Mauritus,Scarlet,Blue) stain for fibrin, confirms the diagnosis.

**Keywords:** Postpartum, TTP-HUS, Autopsy, Platelet-fibrin Thrombi

### Introduction

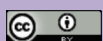
Thrombotic Microangiopathy (TMA), where the characteristic pathogenesis is occlusive micro vascular thrombosis, clinically manifests as thrombocytopenia, microangiopathic hemolytic anemia, and variable features of organ ischemia. [1] Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are the two primary syndromes under TMA. There are several distinct pathophysiologic mechanisms responsible for these syndromes. However it is difficult to distinguish between TTP and HUS. TTP was first described by Moschowitz in 1924. HUS has triad of thrombocytopenia, anemia and renal insufficiency. TTP has pentad of thrombocytopenia, anemia, neurologic deficit, renal dysfunction and fever. [2, 3]

HUS-TTP occurring postpartum is a rare entity, but if it manifests it is most commonly seen in early postpartum primiparous women with mean age of 27 years, after an uneventful uncomplicated pregnancy and delivery (no pre-eclampsia, hemorrhagic shock, DIC or sepsis). [3] It is characterized by acute onset renal failure, thrombocytopenia, and thrombotic microangiopathic hemolytic anemia, mildly elevated liver function tests, normal coagulation profile parameters of PT, aPTT and

increased serum Lactate Dehydrogenase levels. Risk factors include decrease in platelet count, fibrinolytic activity and prostaglandin (PGI-2) production. Other risk factors are deficiency of vWF-cleaving protease (ADAMTS 13), increase in fibrinogen, factor VIIa, VIII, vWF, plasma thrombomodulin levels plasminogen activator inhibitor-I and hypercoagulability. [3] Histopathological examination of renal biopsy often reveals dramatic destruction of the renal cortex. Glomerular thrombosis is characteristic, with an enlarged appearance that suggests capillary congestion rather than ischemia. Extension of thrombosis into the afferent arteriole is common. Mesangial changes appear to be uncommon. The tubules are often atrophic, may show necrosis, and frequently contain hyaline casts and red blood cells. [3,4]

### Case Report

A 28 years old primigravida with 38 weeks of gestation, apparently alright earlier, was referred to our institute in view of prolonged second stage of labour. On day 2 postpartum, she developed fever without chills, breathlessness, loose motions and 10-15 episodes of vomiting. Her general condition was poor with pallor, icterus, petechial hemorrhages and ecchymoses all over



body. Clinical examination showed mild hepatomegaly. Laboratory investigations showed low Hb (8.3gm/dl), elevated WBC count (14300/cu.mm), low platelet count (14000/cu.mm), elevated total/direct bilirubin (18.6/11.2 mg/dl), mildly elevated SGOT (144U/L) and SGPT (88U/L), raised serum creatinine (2.8 mg/dl), raised LDH (857 U/L). All viral markers were negative. On day 5, patient developed anuria and grade IV dyspnoea. Despite all resuscitative measures patient did not survive.

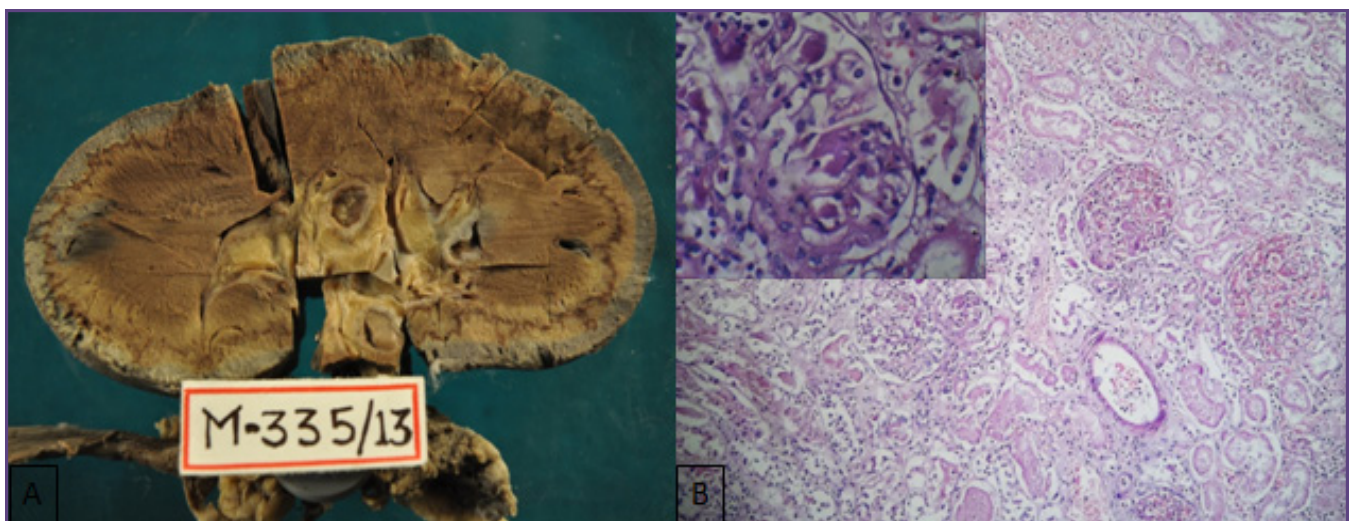
A complete autopsy was performed. On gross examination, both kidneys were mildly enlarged and cut surface showed rim of peripheral cortical necrosis (Fig 1A). Liver was enlarged and yellowish. Lungs showed features of lobar pneumonia. Other organs did not show any remarkable gross features. For histopathological examination, Hematoxylin –Eosin stain (H & E), and special stains like Periodic Acid Schiff (PAS) stain, silver stain and MSB (Mauritus, Scarlet, Blue) stain for fibrin were used. H & E stained sections from kidneys revealed glomerular capillaries and arterioles showing platelet –fibrin thrombi and fragmented RBCs without vasculitis (Fig 1B). PAS stain and MSB (Mauritus, Scarlet, Blue) stain for fibrin showed glomerular capillary thickening, fibrinoid necrosis of endothelium and fibrin thrombi in capillaries and afferent renal arterioles (Fig 2 A,B,C). Silver staining showed diffuse thickening of glomerular capillary wall with double contours of Glomerular Basement Membrane (Fig 2D).

Correlating clinical features, gross and microscopic findings, cause of death was given as acute renal failure with lobar pneumonia with HUS-TTP in a postpartum female.

## Discussion

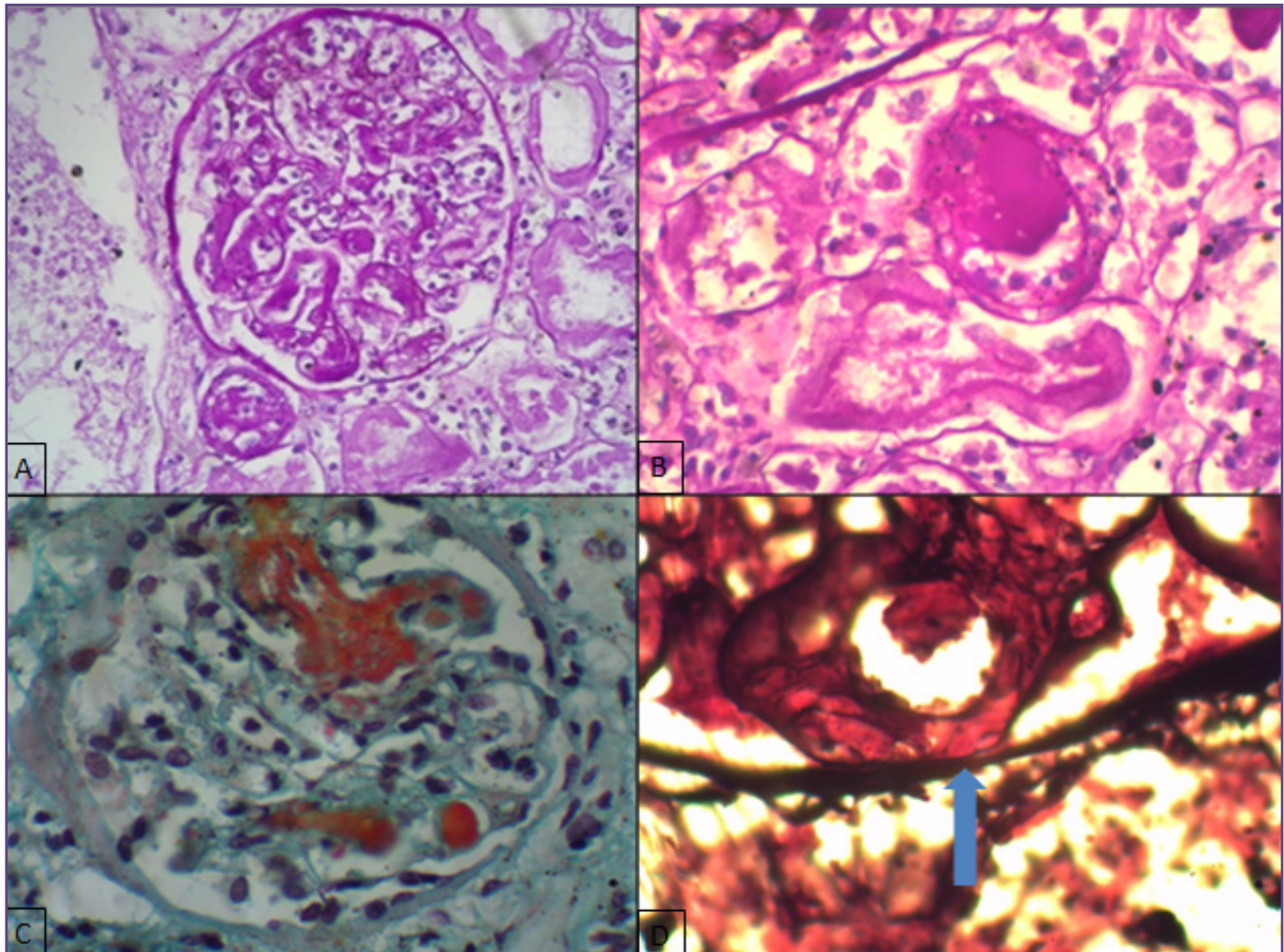
HUS-TTP occurs commonly in women, especially among pregnant ones. In pregnancy, risk period is near term and during postpartum period.<sup>[4]</sup> This period also carries profound risk for thrombotic events and other pregnancy associated syndromes like preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes and low platelets). These conditions may also present with thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, and renal insufficiency, as a result of which it is difficult in making their distinction from HUS-TTP.

ADAMTS13 enzyme, a plasma reprotin-like metalloprotease, is necessary for the proteolytic cleavage of von Willebrand Factor (vWF) under various conditions of oxidative stress.<sup>[4]</sup> Deficiency or impaired activity of this enzyme leads to TTP. The activity of ADAMTS13 progressively decreases during the course of pregnancy. During pregnancy, there is physiological increase in vWF concentrations. It has been shown that ADAMTS13 activity inversely correlates with plasma von Willebrand factor concentrations.<sup>[4]</sup> This may be the mechanism behind decreased levels of ADAMTS13 during pregnancy. The characteristic pathologic feature of both the disorders is the formation of platelet thrombi in microvasculature. Immune mediated injury or apoptosis of vascular endothelium causes endothelial damage which releases large amount of abnormal ultra large vWF multimers. This triggers formation of platelet thrombi, following which there is tissue ischemia/infarction and stress on RBCs passing through capillaries causing fragmentation.



**Fig. 1: (A)Gross:Examination of cut surface of kidney shows rim of renal cortical necrosis.(B) Glomerular capillaries and arterioles showing platelet –fibrin thrombi and fragmented RBCs without vasculitis (H & E;100X ,inset:400X).**





**Fig. 2: PAS stain (A & B) and fibrin stain (C) showed glomerular capillary thickening, fibrinoid necrosis of endothelium and fibrin thrombi in capillaries and afferent renal arterioles. Silver staining (D) showed diffuse thickening of glomerular capillary wall with double contours of Glomerular Basement Membrane.**

In this case, histopathology of the kidney showed that glomerular capillaries, glomerular infundibulum, afferent arterioles, terminal part of small interlobular arteries are involved (sparing venous circulation). There were amorphous, eosinophilic, hyaline platelet-fibrin thrombi and fragmented RBCs without vasculitis. Diffuse edematous thickening and duplication of glomerular capillary wall (double contours) were seen. Tubules showed acute necrosis, RBCs and hyaline casts with edematous and fibrous interstitium. Mild mononuclear and RBCs infiltration noted near cortical necrosis. Electron microscopy in postpartum HUS-TTP showed fluffy electron dense material in expanded sub endothelial zone. Immunofluorescence showed granular fibrinogen deposition in sub endothelial zone in glomeruli and afferent arterioles.

Acute kidney injury is severe in women with pregnancy associated HUS-TTP and 76% women progress to end stage chronic kidney disease.<sup>[5]</sup>TMA associated maternal mortality has declined in recent years to 10-20%. However, increased perinatal mortality rate (30-80%) has been reported, reasons being growth restriction and placental infarction caused by thrombosis of decidual arteries.<sup>[5]</sup>Treatment in cases of HUS-TTP includes early plasmapheresis, steroids, antiplatelet therapy and hemodialysis (80-90% survival in acute cases).<sup>[5,6]</sup>

### Conclusion

The occurrence of preeclampsia and related syndromes, the hypercoagulable state that occurs in late pregnancy and postpartum, and the progressively decreasing concentration of ADAMTS13 that occurs during late pregnancy may combine to increase the risk for the occurrence of HUS-

TTP. The prognosis in pregnancy is poor. Although clinical manifestations are highly suggestive of the diagnosis of HUS-TTP, histopathology using routine and special stains is highly confirmatory and provides new insights in the pathogenesis of HUS-TTP.

### Reference

1. Xheng XL, Sadler JE. Pathogenesis of Thrombotic Microangiopathies. *Annu Rev Pathol.* 2008; 3: 249–277.
2. Fakhouri F, Roumenina L, Provot F, Sallee M, Caillard S, Couzi L et al. Pregnancy-Associated Hemolytic Uremic Syndrome Revisited in the Era of Complement Gene Mutations. *J Am Soc Nephrol.* 2010; 21(5): 859–867.
3. George JN. The association of pregnancy with thrombotic thrombocytopenic purpura- hemolytic uremic syndrome. *Curr Opin Hematol* 2003, 10: 339–344.
4. Zheng XL. Structure-Function and regulation of ADAMTS13 protease. *J Thromb Haemost.* 2013; 11(01): 11-23.
5. Machado S, Figueiredo N, Borges A, Pais MS. Acute kidney injury in pregnancy: a clinical challenge. *J Nephrol* 2012; 25(01):19-30.
6. Furlan M, Lammle B. Hemolytic-uraemic syndrome and thrombotic thrombocytopenic purpura-new insights into underlying biochemical mechanisms. *Nephrol Dial Transplant* 2000; 15: 1112-1114.

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