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Case Report

Pregnancy-Associated Haemolytic Uraemic Syndrome

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I N F O

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A B S T R A C T

Haemolytic Uraemic Syndrome (HUS) is a rare and severe form of thrombotic microangiopathy associated with a poor renal prognosis. Approximately 10-20% of the diagnoses of atypical Haemolytic Uremic Syndrome (aHUS) are related to pregnancy. Pregnancy acts as a trigger for aHUS, especially in the setting of preeclampsia and haemorrhage. It should be differentiated from other similar conditions such as severe preeclampsia, HELLP syndrome, and severe postpartum haemorrhage.

Keywords: Atypical-HUS, Pregnancy-Induced aHUS, Renal Failure

Introduction

Pregnancy-associated HUS is defined as HUS occurring during pregnancy or in the postpartum period. Pregnancy acts as a complement-amplifying state. Preeclampsia and haemorrhage trigger the development of pregnancy-associated HUS. Its diagnosis requires a typical blood picture, complement measurement or kidney biopsy. Its treatment includes plasma exchange, corticosteroid or eculizumab. Severe outcomes such as persistent renal failure requiring dialysis, renal transplant and death are seen more in adult patients as compared to children.

Case History

A 25-year-old female presented with complaints of pedal oedema, decreased urine output, and vomiting for 14 days. There was no history of fever, cough, sore throat, or shortness of breath. There was also no associated history of diarrhoea, burning micturition, or haematuria. There was no significant medical or family history. The patient had a history of caesarean section 6 weeks back and a history of raised blood pressure during the last trimester of pregnancy.

Initial evaluation revealed raised blood pressure and pedal oedema. All other systemic examinations were normal. Initial laboratory investigation and investigations done during the course of the hospital stay are shown in Table 1. Urine routine and microscopic examinations were normal and there was no proteinuria on the dipstick. Renal ultrasonography showed a bilateral kidney size of 9.4 x 6.4 cm, maintained corticomedullary junction with mildly raised cortical echogenicity. Electrocardiography showed mild mitral regurgitation with an ejection fraction of 60% and chest radiography revealed a clear lung field with normal cardiac size. On the peripheral smear, there were few schistocytes. Blood gas analysis showed metabolic acidosis.

The patient was started on conservative management. Due to a rising trend of creatinine, oliguria and metabolic

acidosis, the patient was dialysed frequently, but there was no improvement in renal function, and in view of unexplained renal failure and normal renal structure on USG, investigations were sent to rule out other aetiology of acute renal failure (Table 2). Urine for active sediments was also negative. Blood, urine and stool culture, and workup for secondary causes of hypertension were also normal (Table 2). Bilateral renal artery doppler also didn't reveal any abnormality. With no aetiology of renal failure and raised BP, a renal biopsy was done. On renal biopsy, light microscopy revealed myointimal hyperplasia of small and medium-sized vessels, medial mucoid oedema, and fibrinoid deposit in lumen with entrapped fragmented RBCs (Figures 1-3). Immunofluorescence revealed deposits of C3 and fibrinogen in the wall of medium-sized blood vessels. Electron microscopy revealed diffuse effacement of the foot process of podocyte and tubulovillous degeneration. These findings were consistent with features of haemolytic uraemic syndrome with features of severe hypertension.

The patient was started on pulse steroid and was frequently dialysed, but there was no improvement in renal function. Plasmapheresis and eculizumab were deferred due to non-availability. Despite treatment, the patient's condition continued to worsen and she developed refractory pulmonary oedema and ultimately succumbed to her illness.

Table 1.Laboratory Parameters

Parameters	Day 1	Day 7	Day 14
Haemoglobin (gm/dl)	10.0	9.8	10.0
Total leucocyte count (cells/µl)	13600	12000	12500
Differential leucocyte count	70/25/4/1	80/15/3/2	79/14/5/2
Platelet count (cells/µl)	1.1 lakhs	90000	98000
Serum creatinine (mg/dl)	11.6	8.8	9.1
Blood urea (mg/dl)	152	131	125
Serum sodium	135	133	140
Serum potassium	5	4.6	4.8
Serum calcium (mg/dl)	6.4	7.6	7.5
Serum phosphate (mg/dl)	7.6	5.5	5.3
Total bilirubin (mg/dl)	1.1	0.9	1.0
SGOT (U/L)	40	39	37
SGPT (U/L)	20	28	25
Prothrombin time (seconds)	12.5	13.6	12.7
APTT (seconds)	34.6	34.2	33.6
D-dimer	125	330	258

Table 2.Workup for Secondary Causes of Hypertension

Parameters	Report
ANA (immunoflourescence)	Negative
P-ANCA	Negative (1.2 U/L)
C-ANCA	Negative (2.7 U/L)
Complement (C3)	74 mg/dl (75-175)
Complement (C4)	28 mg/dl (22-45)
HIV	Non-reactive
HBsAg	Non-reactive
Anti-HCV antibody	Non-reactive
TSH (mU/l)	3.2
T3 (nmol/l)	80

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T4 (nmol/l)	1.4
Serum cortisol (mcg/dl)	20

Table 3.Causes of Haemolytic Uraemic Syndrome

1. Typical HUS - Shiga toxin-secreting strain of E coli (O157:H7) or Shigella dysenteriae.
2. Atypical HUS - Congenital or acquired defect in complement regulation (Factor H, I, CD46, C3).
3. Pneumococcal HUS - Infection with neuraminidase-producing Streptococcus pneumoniae.
4. Cobalamin deficiency - associated HUS.
5. Secondary HUS – Drugs (quinine, antiviral, anti-VEGF), autoimmune disease (SLE, scleroderma, antiphospholipid syndrome), malignancy etc.

Table 4.Differentating Features among TTP, HUS, HELLP and Preeclempsia

Clinical features	Preeclampsia	HELLP Syndrome	TTP	HUS
Fever	Absent	Absent	Present	Present
Haemolysis	Absent	Present	Present	Present
Hypertension (%)	100	85	20-75	80-90
Renal failure	Absent	Present	Present	Present
Neurological dysfunction	Absent	Present	Present	Less common
Platelet count (cells/mm^3)	> 100000	> 20000	< 20000	> 20000
Liver enzyme	Mild elevation	Severe elevation	Mild elevation	Mild elevation
Proteinuria	++	+	+ or haematuria	+
Jaundice	Absent	Present	Rare	Rare

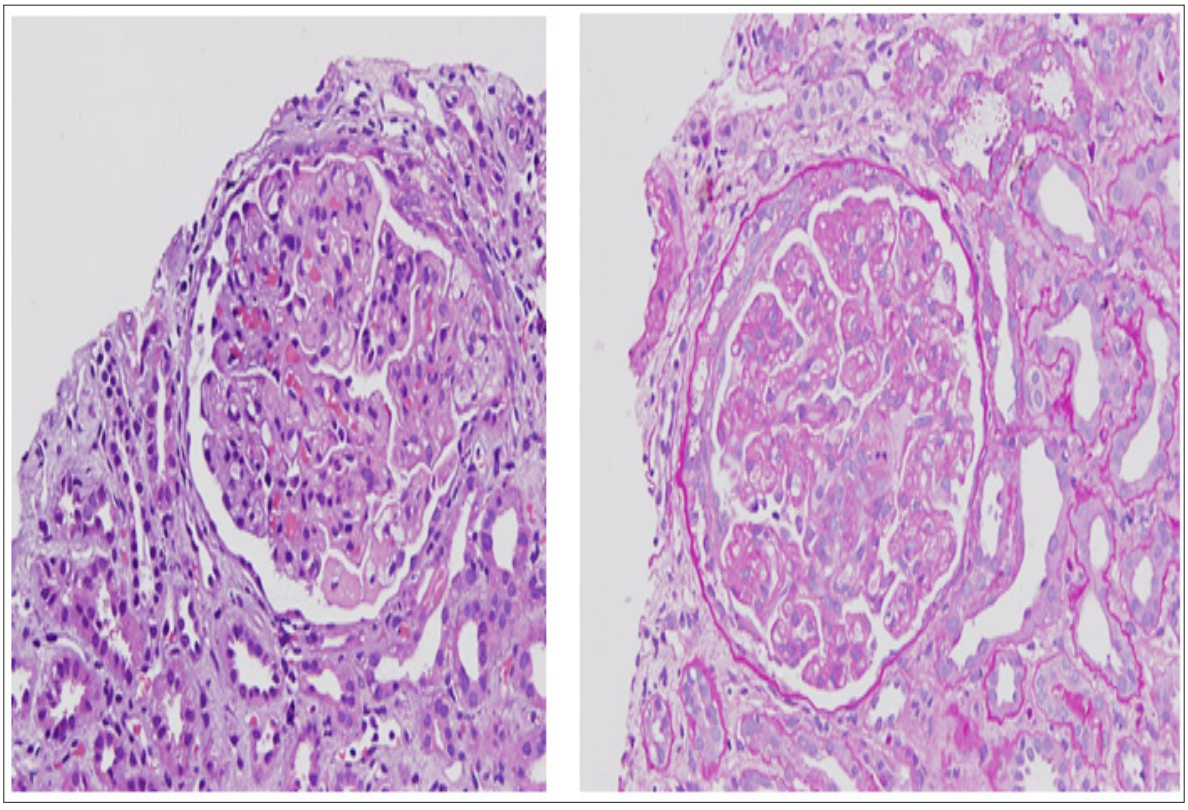

Figure 1(a,b).Glomeruli Showing Mesangiolysis with Prominent Subendothelial Oedema

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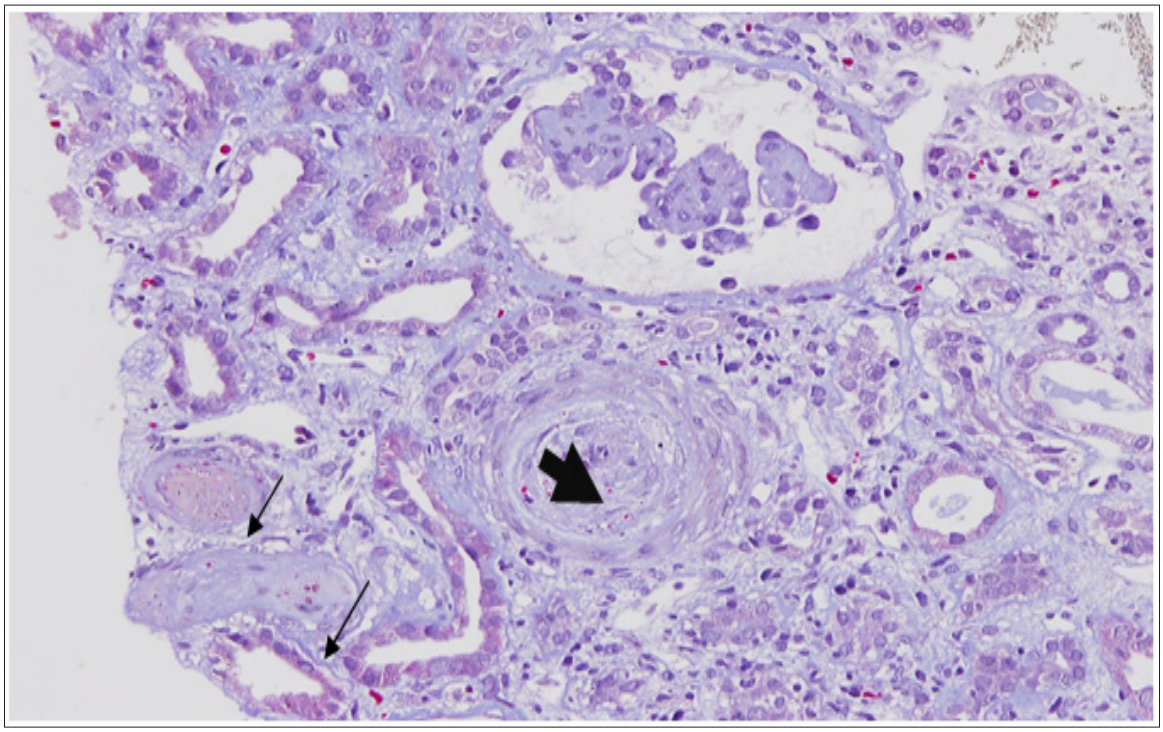

Figure 2.Prominent Vessel Changes. The Small-sized Vessels Show Myointimal Hyperplasia (Thick Arrow) with Schistocytes in the Vessel Wall. The other 2 Blood Vessels (Thin Arrows) Show Fibrinoid Deposits with Entrapped Schistocytes Occluding the Lumen. The Tubules Show Acute Tubular Injury

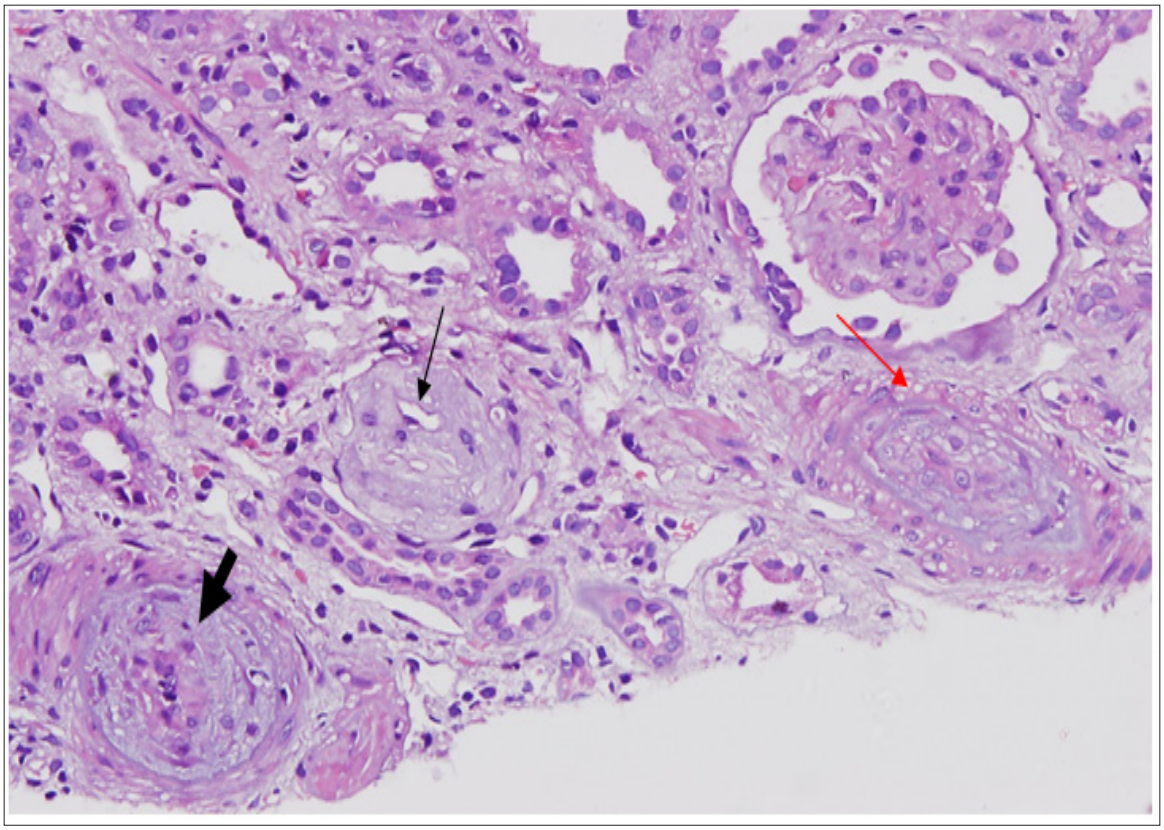

Figure 3.Two Glomeruli. One Glomerulus is Sclerosed (Thin Black Arrow) and the other Shows Mesangiolysis (Red Arrow). The Small Arteries Show Medial Mucoid Oedema (Thick Black Arrows)

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Discussion

Haemolytic Uraemic Syndrome (HUS) is a rare and severe form of thrombotic microangiopathy characterised by haemolysis, thrombocytopenia and renal failure. Typical HUS is associated with haemorrhagic diarrhoea and is caused by a strain of E coli (STEC O157:H7). Atypical HUS is caused due to congenital or acquired defects in complement regulation. Other causes of HUS are shown in Table 3. HUS mostly occurs in children where approximately 95% of children survive and severe sequelae are present in 5 to 10% only,[1] but in adults mortality is high and many (about 25%) are left with chronic renal failure.[2]

Pregnancy-associated HUS was defined as HUS occurring during pregnancy, or in the postpartum period (up to 12 weeks after delivery). Approximately 10% to 20% of aHUS diagnoses are related to pregnancy, where it is referred to as pregnancy-associated atypical haemolytic uraemic syndrome.[3] Maternal exposure to semi-allogenic foetal material increases during the course of pregnancy, peaking at birth.[4,5] Pregnancy is a complement-amplifying state[6] and regulators of the alternative complement pathway that are soluble and membrane-bound, typically reduce excessive complement activation.[7,8] However, hereditary mutations in complement regulators, which are frequent in pregnancy-associated aHUS, predispose to greater complement activation.[1,9] In complement-deficient patients, preeclampsia and haemorrhage trigger the development of pregnancy-associated HUS. Most of the patients with pregnancy-associated HUS go into disease remission but adverse outcomes such as persistent renal failure, dialysis requirement or death are seen in up to 24% of the cases.[10]

Diagnosis of pregnancy-induced HUS can be difficult and should be differentiated from other similar conditions such as severe preeclampsia (hypertension, proteinuria), HELLP Syndrome (haemolysis, elevated liver enzyme, low platelet count), thrombotic thrombocytopenic purpura, and severe postpartum haemorrhage (Table 4). HUS may be suspected by the presence of microangiopathic haemolytic anaemia, thrombocytopenia, hypertension and renal impairment or typical features of thrombotic microangiopathy in a kidney biopsy (fibrin/ platelet thrombi, endothelial cell swelling and detachment from the basement membrane). ADAMTS 13 should be done to exclude thrombotic thrombocytopenic purpura. Complement levels should be done such as C3, C4, and complement factors I and H to establish the diagnosis of atypical HUS.

In our case, C3 was in the low normal range, C4 was normal and assays for complement factors I and H were not done due to non-availability. Diagnosis of HUS was established by kidney biopsy which showed features of thrombotic microangiopathy with C3 deposits. Treatment of atypical HUS includes plasma exchange, corticosteroid or eculizumab, a complement protein C5 inhibitor.[3] In our case, we treated the patient with pulse steroid and frequent dialysis but there was no improvement in renal failure and patient condition. In a case report by Anacleto et al., a 17-year-old female was diagnosed with pregnancy-induced HUS in the postpartum period on the basis of renal biopsy treated with steroid and haemodialysis but the patient had persistent renal failure as the final outcome.[11] In a systematic review by Gupta et al., eculizumab was associated with a higher remission rate (88% vs 57%, p = 0.02).[10] Long-term outcomes include disease remission, hypertension, and persistent renal failure leading to end-stage renal disease, which ultimately requires dialysis or renal transplant, and may lead to death.

Conclusion

Pregnancy-associated HUS is a rare disease entity and should be suspected in patients presenting with haemolysis, thrombocytopenia, and nephropathy. It should be differentiated from other diseases with similar conditions such as severe preeclampsia, HELLP syndrome, and severe postpartum haemorrhage. Its treatment consists of corticosteroids, plasma exchange, haemodialysis or eculizumab, but the latter is associated with a higher remission rate.

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Conflict of Interest: None

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