JMSCR Vol||11||Issue||04||Page 75-78||April 2023

http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v11i4.11

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Pregnancy Associated Atypical Hemolytic Uremic Syndrome – A Two-Case Report of a Rare Entity

Authors
Tanvi Katoch[1], Mahak Bhardwaj[2*], Aashima Arora[3]
[1]Senior Resident, Department of Obstetrics and Gynecology
[2]Senior Resident, Department of Obstetrics and Gynecology
[3]Associate Professor, Department of Obstetrics and Gynecology
Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh, India
*Corresponding Author
Mahak Bhardwaj
Senior Resident, Department of Obstetrics and Gynecology
Post Graduate Institute of Medical Education and Research, Chandigarh, India

Abstract
Atypical hemolytic uremic syndrome (aHUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. Atypical HUS is not caused by infections, rather have a genetic predisposition and pregnancy is one of the triggers. Being a rare entity and due to other masquerading events in pregnancy, it can be masked and lead to late diagnosis and increased morbidity. We present two cases of aHUS triggered by pregnancy, which were managed timely and discharged successfully, though long-term prognosis is poor. Recombinant monoclonal antibody therapy Eculizumab delays the progression of disease but is very expensive and most of the patients can't afford it, as it is a long term therapy. Plasma exchange remains the mainstay of treatment initially and later on, if eculizumab is unaffordable. The main challenges are identification of the disease and timely intervention before increase in morbidity.
Keywords: *atypical haemolytic uremic syndrome, pregnancy, plasma exchange, eculizumab.*

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare life-threatening disease which often has genetic component. It is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure[1]. The most common cause of thrombotic microangiopathy (TMA) and HUS is Shiga-toxin-producing infections. Atypical HUS is called so as it is not caused by infections producing Shiga toxin. Severe renal injury is prominent feature as it involves uncontrolled activation of alternate complement pathway leading to TMA and thereby renal ischemic injury. Due to incomplete penetrance of the genetic mutation associated with the entity, a trigger is needed to initiate the disease, and pregnancy is one of the triggers. Pregnancy associated aHUS has an incidence of 1 in 25000[2]. Early diagnosis and management of the disease are both challenging and expensive. Herein we present two cases of pregnancy associated aHUS.

Case-1

A 25-year-old P_1L_1 woman was referred on second day of caesarean section (done for non-progress of labour at term), to our centre due to anuria developed 24hours post-surgery. She had also developed thrombocytopenia and elevated liver enzymes. Her antenatal period was uncomplicated and there was no postpartum hemorrhage. On admission, she did not respond to fluid and diuretic challenge. She was promptly taken up for hemodialysis. Laboratory investigations as inumerated in Table 1, suggested a diagnosis of atypical HUS associated with pregnancy. She was managed with four sittings of plasma exchange and six sittings of hemodialysis during hospital stay. She remained afebrile. Work up was done and sepsis was ruled out. Gradually there was fall in hemoglobin, on sixth day of hospitalisation hemoglobin was 5.2g/dL. Packed cells were transfused during hemodialysis sittings. Computed tomography revealed acute cortical necrosis in bilateral kidneys. Patient responded partially to management, as her hemoglobin and platelet count improved and there was no further fall in laboratory values. But her renal function did not improve, and she was advised hemodialysis thrice a week on discharge.

Case-2

A 30-year-old P_{4012} woman was referred to our facility on ninth day following caesarean section with anuria and anasarca. Patient had undergone caesarean section for severe pre-eclampsia with oblique lie at 36weeks 6days gestation. After first 24-hours of surgery, she developed breathing difficulty, oliguria and deranged liver and renal functions. On ultrasonography, bilateral medical renal disease and collection in uterine cavity were found. Antibiotics were given and she received four sittings of hemodialysis. But she did not improve and was referred to our centre. She had no post-partum hemorrhage and was afebrile. On admission, hemodialysis was continued once every 72 hours. On ultrasound, there were retained products of conception for which evacuation was done on first day of admission. Work up for sepsis was done and sepsis was ruled out. Her laboratory investigations as charted in Table 1 indicated a diagnosis of pregnancy associated HUS. Patient was managed with five hemodialysis and two plasma exchange sittings. Multiple packed cells were transfused during hemodialysis to maintain hemoglobin above 7g/dL. Blood pressure was controlled with antihypertensives. Computed tomography revealed acute cortical necrosis of bilateral kidneys. Hemolysis improved and patient maintained hemoglobin and platelet count but remained oliguric. She still had a deficient renal function and relied on maintenance hemodialysis twice-thrice every week.

Table 1: Laboratory investigations of patients (on admission**)**

Investigations on admission	Case 1	Case 2
Serum creatinine (mg/dL)	3.75 (raised)	6.5 (raised)
Hemoglobin (g/dL)	9.3	6.7 (decreased) (Post LSCS = 9.2)
Platelet count (per mm^3)	59,000 (decreased)	1,24,000
LDH (U/L)	2626 (raised)	1107 (raised)
Total bilirubin (mg/dL)	2.62 (raised)	0.79
SGOT (U/L)	392 (raised)	39
Haptoglobin (mg/dL)	28.3 (decreased)	6.22 (decreased)
Peripheral smear	normocytic normochromic red blood cells with presence of schistocytes	normocytic normochromic red cells with presence of schistocytes
C3 levels (mg/dL)	94.6	83 (less than normal)
C4 levels (mg/dL)	12.5 (less than normal)	26.4

At present, both the patients are on thrice-a-week hemodialysis and are stable. Both the patients are unable to afford Eculizumab.

Discussion

Atypical HUS is a rare and progressive systemic disease in which alternate complement pathway is activated. It often involves genetic predisposition of individuals, but the disease requires a triggering factor to precipitate, pregnancy being one[1,2]. This is because penetrance of complement gene mutation is 40-50% only[1,2]. Due to uncontrolled activation of complement pathway, platelets are activated, endothelium is damaged and white blood cells are activated, leading to thrombotic microangiopathy and hemolysis. This leads to multi-organ damage, especially renal system due to microthrombi related ischemia.

Atypical HUS usually presents in post-partum period[3]. Presenting features of patient are acute renal failure, thrombocytopenia and microangiopathic hemolytic anemia. These features with multi-organ dysfunction are also seen in TTP, AFLP, HELLP, acute kidney injury and in some instances postpartum hemorrhage and sepsis, due to which diagnosing pregnancy associated aHUS is challenging[1].

Due to its life-threatening and progressive nature, plasma exchange is advised as soon as possible, even with a clinical impression of HUS[4]. Plasma exchange is to be done until blood parameters normalise completely and do not worsen when observed over an individualised time period[2]. Mainstay of treatment include: 1) Renal replacement therapy for hyperkalemia, acidosis, uremia and pulmonary oedema; 2) Blood transfusion to maintain hemoglobin level; 3) Prompt plasma exchange. Involvement of multi-disciplinary team of obstetricians, anaesthesiologists, hematologists, transfusion-medicine pathologists and nephrologists, is indispensable.

In more than 60% patients who have acute renal failure due to pregnancy associated aHUS, end stage renal disease occurs within a year or the patient dies of the disease[5]. Though plasma exchange helps in improving the blood parameters, the complement system remains activated and continues to damage the organs irreversibly, particularly kidneys. Use of complement inhibiting recombinant monoclonal antibody therapy Eculizumab has shown to improve overall quality of life and delay in progression of disease, if started before significant renal injury[5]. But most of the Indian patients are unable to avail its benefit because it is ultra-expensive and long-term therapy is required.

Pregnancy outcome is rarely affected by aHUS, but the long-term renal prognosis is poor. However, it remains unclear, whether pregnancy affects this prognosis or aHUS naturally has this renal prognosis irrespective of pregnancy being the trigger of disease[6].

Conclusion

Due to other mimicking conditions in pregnancy, the diagnosis of aHUS can be missed. Pregnancy is a trigger factor for aHUS and it is a progressive systemic disease which depletes the alternate complement pathway. Its early diagnosis and early intervention for treatment can reduce the maternal morbidity and mortality. Mainstay of management is plasma exchange, hemodialysis and supportive measures. Eculizumab should be offered to the patients as it delays the progression of disease; however cost is a limiting factor. Involvement of multi-disciplinary team of obstetricians, anaesthesiologists, hematologists, transfusion-medicine pathologists and nephrologists, is indispensable.

Ethical Statements

Acknowledgements: None

Funding: None

Conflict of Interest: The authors declare that they have no conflict of interest.

Statement of Ethics: The study was approved by the Ethics Committee, Department of Obstetrics and Gynecology, PGIMER.

Consent: The participants have consented to the submission of the case report to the journal. Further, the text has been sufficiently anonymized, and images have no identifying information of the patient.

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