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Case Report
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Postpartum Atypical Hemolytic Uremic Syndrome. Diagnostic Importance of Flow Cytometry

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Abstract

Background: Thrombotic Microangiopathies (TMA) are not very common diseases characterized by forming small clots in the microvasculature. Atypical Hemolytic Uremic Syndrome (aHUS) is a relatively rare form of primary TMA that is progressive and can lead to end-stage renal involvement.

Case: We describe the case of an otherwise healthy 35-year-old woman who developed acute anuric kidney injury with laboratory attributes of TMA after elective induction of labor. Flowcytometry examination demonstrating decreased CD46 fluorescence was used to confirm the diagnosis of aHUS.

Conclusion: Flowcytometric CD46 testing represents a new available test capable of shortening the time to aHUS diagnosis and initiation of eculizumab therapy, which may favorably contribute to improving the outcome of patients with this variant of primary TMA.

Keywords: aHUS; Thrombotic microangiopathy; CD46 Flow Cytometry

Introduction

Thrombotic Microangiopathies (TMAs) are a variety of conditions marked by the development of tiny clots in the microvasculature. Clinically, TMAs are usually manifested by a combination of several facts - non-immune hemolytic anemia with the presence of schistocytes in the blood smear, thrombocytopenia and organ involvement caused by microvascular occlusion. TMAs include a variety of subgroups. Primary TMAs include Thrombotic Thrombocytopenic Purpura (TTP) caused by an ADAMTS13 enzyme deficiency, Shiga Toxin related Hemolytic Uremic Syndrome (ST-HUS) and atypical HUS (aHUS), recently recommended for naming as Complement-mediated HUS (C-HUS) [1]. Secondary TMAs include a heterogeneous group of diseases. Very often, there can overlap between primary and secondary TMAs (a triggering condition leading to an episode of one of the primary forms).

Atypical HUS is caused by deregulation and excessive activation of the alternative complement pathway. It is a relatively rare form of TMA (approximately 1% of all TMAs) that can lead to rapidly progressive and end-stage renal involvement. Activation occurs either due to genetic deficiency of regulatory proteins that generally prevent activation of the alternative complement pathway [2] or acquired factor H and I deficiency caused by the presence of antibodies. In approximately 50% of cases, the trigger for aHUS is an infection. In a smaller number of cases, it is surgery; the classic trigger is pregnancy. The definitive treatment is eculizumab, a monoclonal antibody fragment that inhibits C5 convertase, thereby blocking the terminal complement pathway.

In this report, we describe the case of a young woman who developed atypical hemolytic uremic syndrome after childbirth. The disease was manifested by acute kidney disease, gastrointestinal bleeding, cardiomyopathy and respiratory failure with pleural effusions.

Case Presentation

A 35-year-old woman without comorbidities or chronic medication was admitted for elective labor induction (4th pregnancy, second delivery). She delivered a healthy baby vaginally with epidural analgesia at term (40w+2). Postpartum was complicated by obstetric hemorrhage requiring

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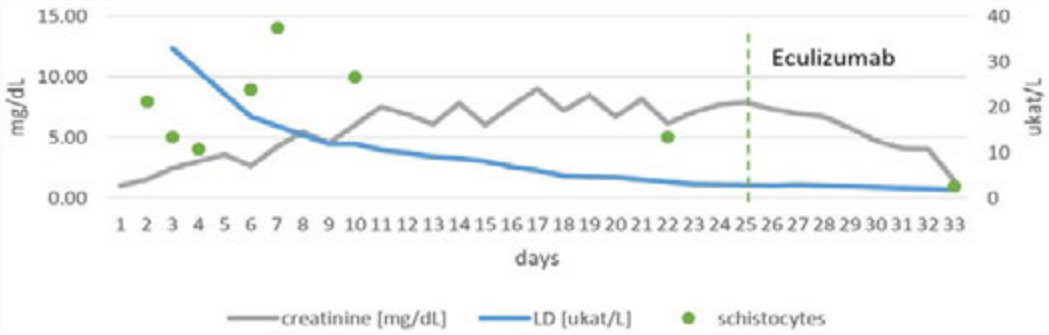

Figure 1: Laboratory findings.

surgical revision of the uterus; total estimated blood loss was 1200 mL. She developed an anuric acute kidney injury on postpartum day 3, and her laboratory results in the anesthesiology department were remarkable. She developed thrombocytopenia 83 × 10^9/L, and a significant number of schistocytes was detected in her blood (14/1000). Hemodynamically, she tended to hypertension after the initial bleeding.

In the following days, she developed respiratory insufficiency with pleural effusions (biochemically transudate) and need for drainage, the elevation of inflammatory parameters and melena without a gastroscopically detectable source of bleeding. Echocardiography detected a decreased LV ejection fraction with diffuse hypocontractility (LV EF 30%). Hemodialysis with ultrafiltration was initiated with improvement in respiratory parameters. Given the suspected TMA with normal ADAMTS13 level (61%) and absence of antiphospholipid antibodies, the diagnosis of atypical HUS was considered. Flowcytometry was added with a decrease in cMFI CD46 (16.68), a compatible finding with the diagnosis of aHUS. Treatment with eculizumab 900 mg weekly was initiated with the rapid repair of renal catabolites without requiring further dialysis procedures. Laboratory findings were a decrease in schistocytes, no signs of coagulopathy, and platelets in the normal range. Follow-up TTE with normalized LV EF without any focal kinetic abnormalities. Twenty days after delivery, she was discharged to outpatient dispensary care with normal diuresis and improved renal parameters. After three months of treatment, mild renal insufficiency persisted (GFR by CKD 0.73 mL/s/1.73 m^2) and continues with a maintenance dose of eculizumab 1200 mg every two weeks. The infant was born without clinical or laboratory remarkable throughout. The diagnosis of aHUS was subsequently confirmed by genetic testing (risk homozygous mutation CD46, heterozygous mutation CFH-H3, heterozygous mutation MBL2) (Figure 1).

Discussion/Conclusion

Several forms of TMAs threaten women during and immediately after pregnancy. Preeclampsia, eclampsia, and HELLP syndrome can be severe complications. HELLP syndrome is a TMA affecting the liver predominantly and rarely the kidneys. TTP, the most common form of TMA, occurs mainly during the second and third trimesters, with little occurrence in the postpartum period. Similar to our patient's case, aHUS are most common in the postpartum period. Catastrophic antiphospholipid antibody syndrome cannot be excluded from the differential diagnosis due to similar clinical findings but is differentiated by detecting specific antiphospholipid antibodies. Although the temporal aspect is an essential clue in diagnosing TMA in the postpartum period, the specific differentiation of TMA remains a challenge. HELLP syndrome's clinical symptoms are strictly related to pregnancy; persistence or non-resolution of renal impairment or another organ dysfunction suggests a different clinical subunit of TMA. The diagnosis of TTP is based on confirmation of reduced ADAMTS13 levels. Confirmation of the diagnosis of aHUS is more constraining. Currently, the diagnosis is based on the laboratory attributes of MAHA and thrombocytopenia, along with the exclusion of other forms of TMA, i.e., it is primarily made by per exclusion. Most hospitals currently cannot diagnose aHUS in short time frames. Determination of C3, C4, and CH50 levels that can be determined very quickly does not have sufficient sensitivity or specificity, and more sophisticated assays (e.g., soluble C5b-9 levels) might be helpful, but these are not widely available. Genetic testing for aHUS usually takes weeks.

Rapid diagnosis is crucial in aHUS. aHUS have a poor outcome with a high mortality rate; approximately 50% of patients develop end-stage renal failure. The possibility of recurrence is also high, described in approximately 70% of cases [3].

Flowcytometric testing of cMFI CD46 may represent an available assay capable of detecting a significant number of patients with aHUS. Membrane Cofactor Protein (MCP; CD46) plays a major role in regulating glomerular C3 activation. It is a widely expressed transmembrane regulator of complement that is present in most cells (except erythrocytes in humans). It is highly expressed in the kidney, which plays a lead role in regulating glomerular C3 activation [4].

Low surface expression of MCP on peripheral blood mononuclear cells by FACS (Fluorescence-Activated Cell Sorting) was seen in 75% of reported cases with mutations. This may provide a method to screen for MCP mutations, although it will not detect the 25% of mutants with regular expression but decreased function. To definitively exclude MCP mutations, FACS should be combined with gene mutation screening [5].

Based on new findings, TTP and aHUS have been separated as different entities with distinct etiologies and treatments. Eculizumab, a cornerstone of treatment for patients with aHUS, is a human monoclonal antibody that inhibits the cleavage of C5 into C5a and C5b, thereby preventing the formation of the C5b-9 complex. Its early administration can dramatically change patients' prognoses and help repair renal functions in advanced renal damage that has already developed.

In our case, the diagnosis of postpartum aHUS was accelerated and determined by CD46 flowcytometry, a new available diagnostic

method that can also be used as a screening test.

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