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Review

Pregnancy-related thrombotic microangiopathies: Clues from complement biology

Fadi Fakhouri *

Department of nephrology and immunology, ITUN, INSERM UMR, S-1064 CHU de Nantes, France

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ABSTRACT

Pregnancy is a high-risk period for various types of thrombotic microangiopathies (TMA). The improvement of our understanding of the pathophysiology of TMAs has translated into better management of pregnancy-related TMAs. The two main types of TMA, TTP (thrombotic thrombocytopenic purpura) and hemolytic uremic syndrome (HUS), can both occur during pregnancy and postpartum. TTP is related in most cases to acquired or congenital deficiency of ADAMTS13; it tends to develop mainly during the second and third trimesters of pregnancy. The treatment of pregnancy-TTP aims to restore a detectable ADAMTS13 activity through plasma therapy, and if needed, to induce or sustain remission, immunosuppressive agents. In contrast, HUS develops mainly in the postpartum period. Accumulating data indicate that pregnancy-HUS is an atypical, i.e., complement-mediated HUS, triggered by pregnancy. Its treatment therefore should include the use of the anti-C5 humanized monoclonal antibody eculizumab. In other TMA-like disorders associated with pregnancy, including HELLP (hemolysis, elevated liver enzymes, low platelets) and pre-eclampsia/eclampsia, complement involvement, and the need for specific anti-complement therapies, is an active area of investigation.

Contents

1. Introduction

Thrombotic microangiopathy (TMA) encompasses a heterogenous group of disorders that share common pathological features (endothelial cells injury and microvascular thrombosis) and clinical findings – a triad of thrombocytopenia, hemolytic anemia, and organ failure (mainly in, but not limited to, the kidney and the brain).

Pregnancy has been associated with a wide spectrum of TMAs ranging from thrombotic thrombocytopenic purpura (TTP) to hemolytic uremic syndrome (HUS) and HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count). Several recent breakthroughs in the study of the pathogenesis of the TMAs have helped dissect the mechanisms of pregnancy-associated TMAs.

The first breakthrough came with the identification of the von Willebrand factor (vWF) cleaving protease ADAMTS13 as a major actor in the pathogenesis of TTP [1,2], a form of TMA characterized by profound thrombocytopenia and more often neurological disturbances as opposed to severe renal involvement. The congenital or acquired (typically inhibitory autoantibodies) mediated ADAMTS13 deficiency pathognomonic of TTP leads to the persistence of circulating and vessel-bound ultra-large multimers of vWF, which tether platelets with ensuing thrombosis. During pregnancy, ADAMTS13 deficiency leading to TTP occurs mainly during the second and third trimesters of pregnancy [3]. It

* Department of nephrology and immunology, ITUN, INSERM UMR, S-1064 CHU de Nantes, France. Tel.: +33 240087437.
E-mail address: fadi.fakhouri@univ-nantes.fr.

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is facilitated by the increased release of vWF antigen, which occurs during a normal pregnancy [4], leading to consumption of ADAMTS13. Once the ADAMTS13 activity level has decreased below 10% of normal, TTP is recognized. Until recently, most cases of pregnancy-TTP were believed due to acquired ADAMTS13 deficiency, but a new report indicates that up to 24% of pregnancy-related TTP may be due to congenital ADAMTS13 deficiency [5], and that this large fraction of cases had been missed as physicians failed to test for ADAMTS13 inhibitors, and if not found, to sequence the ADAMTS13 gene. In either case, identification of the underlying pathogenic mechanism of pregnancy-TTP translated in the use of curative or preventive plasma therapy in order to restore a detectable ADAMTS13 activity and an uneventful pregnancy [3].

The second breakthrough derived from the identification of dysregulation of the alternative complement pathway as a major risk factor for the occurrence of atypical HUS (i.e., HUS not associated with shiga toxin or other disorders) [6–9]. In the setting of aHUS, the loss of the protection of endothelial cells against damage induced by uncontrolled production of terminal complement components C5a and C5b-9 leads to a procoagulant and proinflammatory phenotype in endothelial cells and platelets that promotes TMA. These findings have prompted some investigators to raise the hypothesis that some forms of secondary HUS (i.e., TMAs with ADAMTS13 >10% occurring in the presence of an associated condition or disease) may also result from dysregulation of the alternative complement pathway.

Pregnancy-HUS, for decades, has been considered as a prototypic secondary HUS. However, in the only published series to date [10], pregnancy-HUS had a similar presentation, the same severe outcome (76% risk of end-stage renal disease), and the same apparent pathophysiology (frequency of identifiable complement genes mutations of 86%; 48% in CFH, 14% in CFI, 9% in C3, and 5% in MCP (CD46)) as non-pregnancy-HUS and aHUS. This series involved only 21 patients; its findings remain to be confirmed in a larger international cohort. Nevertheless, it has provided valuable information regarding pregnancy-HUS. First, pregnancy-HUS is relatively frequent: one woman out of five in the French aHUS registry developed HUS in the setting of pregnancy [10]. Second, in contrast to pregnancy-TTP, HUS occurs mainly (80%) in the post-partum period. Therefore, the timing of TMA presentation, as well as the intensity of thrombocytopenia (usually profound in TTP, but much less in HUS), and the degree of acute kidney injury (severe in HUS, mild or absent in TTP), should help clinicians distinguish TTP from HUS while awaiting the results of ADAMTS13 activity and inhibitor measurements.

The frequent occurrence of HUS in the post-partum has been previously recognized and is intriguing. Indeed, pregnancy by itself triggers complement activation, particularly in the placenta [11], the interface between the mother and the fetus (a hemi-allograft). One would thus expect complement dysregulation associated HUS to develop during pregnancy in a woman congenitally susceptible to such a syndrome. One hypothesis is that complement activation in the placenta is controlled by the membrane bound protein decay accelerating factor (DAF) [12]. Of interest, this regulatory factor – a key component of the acquired hemolytic disease paroxysmal nocturnal hemoglobinuria (PNH) for which, like aHUS, eculizumab is approved – has not yet been implicated in the pathogenesis of HUS (i.e., no DAF mutations detected in aHUS patients). Second, the complement lectin pathway also appears to have a role in the control of complement activation in the placenta, but likewise it has not been linked to HUS pathogenesis [13]. However, post-partum, when bleeding, chorioamniotic infections, and the passage of fetal cells into the maternal circulation with induction of anti-HLA antibodies (particularly in a second or subsequent pregnancy) can activate the alternative complement pathway and trigger HUS in congenitally predisposed patients.

Thus, pregnancy-HUS is most probably an atypical HUS precipitated by pregnancy. This finding has important clinical implications given, in the last five years, the clinical availability of eculizumab, which has dramatically changed the management of atypical HUS [14,15]. Available data from the before-mentioned retrospective study [10], as well as case reports [16,17], indicate that pregnancy-HUS should be managed as any other atypical HUS with an early use of eculizumab. However, further studies are needed to establish a large consensus regarding the management of pregnancy-HUS.

The main difficulty in the approach to an HUS-like syndrome occurring in pregnancy is the establishment of a definite diagnosis of HUS. To date, there is no definite clinical or biological test for the diagnosis of HUS; diagnosis is based mainly on exclusion. When a TMA occurs post-partum following an uneventful pregnancy, the diagnosis should be rather simple. Measurement of ADAMTS13 activity and inhibitors permits distinction between HUS and TTP. However, several complications in pregnancy display features of TMA, and may mimic HUS.

The first condition is HELLP. HELLP is a TMA affecting the liver sinusoids [18] and, inconstantly, the kidney microvasculature [19]. The most frequent pathological findings in kidneys of patients with HELLP and acute kidney injury is acute tubular necrosis; a TMA is recognized in only one-third of the cases [19]. This may explain why acute kidney injury in the setting of HELLP usually recovers rapidly and completely, without anti-complement interventions, in sharp contrast to HUS [20].

Two studies assessed the frequency of complement gene mutations in patients with HELLP. The first [21] included eleven patients, with significant acute kidney injury in seven. Four patients had complement genes mutations (one each in CFH and MCP, 2 in CFI). Three additional patients had features of uncontrolled alternative complement pathway activation, but no detected complement-associated mutations. A second, larger study [22] included 33 patients; it reported an incidence of complement-related mutations <10%. An unpublished study from France (Fakhouri, Frémeaux-Bacchi) similarly found complement-related gene mutations in 11% of HELLP patients, and rare variants of these genes in an additional 9%. Thus, the suggestion that complement dysregulation is predominant in the pathogenesis of HELLP is less certain than initially reported, and as compared to pregnancy-HUS. HELLP may involve an imbalance between antiangiogenic (soluble Flt1 and endogline) and proangiogenic (placental growth factor [23,24]) factors. Complement dysregulation appears to be just one, rather