Role of pregnancy in the pathogenicity of risk mutations for thrombotic microangiopathy

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NefroPlus 2022;14(1):71-74

ABSTRACT

Thrombotic microangiopathy (TMA) is a clinicopathologic diagnosis characterized by thrombocytopenia, microangiopathic hemolytic anemia, and microthrombi. Several pathogenetic mechanisms have been proposed, we focus on the potential contribution of genetic mutation in Complement-Mediated TMA (CM-TMA).
A 21-year-old female presented at our hospital in the context of an unsupervised pregnancy and a presumptive diagnosis of pre-eclampsia was given. Laboratory studies revealed microangiopathic hemolytic anemia and kidney insufficiency that continue to worse after delivery. Plasmapheresis and eculizumab were provided with initial analytic stabilization followed by progressive improvement. She was dialysis dependent for one month. The genetic study revealed a new mutation, previously undescribed likely pathogenic variant, associated to CM-TMA. She continues eculizumab treatment and the investigation of TMA. This is an interesting case since new mutations are not that difficult to find, but there pathogenetic role is challenging to establish.

Keywords: Complement-Mediated Thrombotic Microangiopathy. Eculizumab. Pathogenic Mutation.

INTRODUCTION

Thrombotic microangiopathy (TMA) is a clinicopathologic diagnosis characterized by thrombocytopenia, microangiopathic hemolytic anemia, and microthrombi leading to ischemic tissue injury[1,2]. Diagnosis and management are especially complex, the first approach must focus on distinguishing primary syndromes, namely hereditary or immune thrombotic thrombocytopenic purpura (TTP), drug-induced TMA syndromes, complement-mediated TMA, Shiga toxin-mediated hemolytic uremic syndrome and hereditary disorders of vitamin B_{12}, from other systemic disorders that can present with TMA such as autoimmune disorders (systemic lupus erythematosus) severe preeclampsia, HELLP (*h*emolysis, elevated *l*iver enzymes, and *l*ow *p*latelets) syndrome, systemic infections and malignancies, or severe hypertension[3,4].

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Revisión por expertos bajo la responsabilidad de la Sociedad Española de Nefrología.

The complement-mediated TMA/complement-mediated hemolytic uremic syndrome (CM-HUS), previously known as atypical hemolytic uremic syndrome, is a clinical condition that presents with microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury.

Complement system activation in patients with TMA implicates complement dysregulation as a key pathway in the pathogenesis of TMA and its disease phenotype. The endothelial dysfunction is an important factor in the sequence of events leading to microvascular thrombosis often conditioning kidney injury[4,5].

In these situations, there is no severe deficit of ADAMTS13, neither Shiga toxin[2-5].

Complement dysregulation can be due to autoantibodies or caused by hereditary deficiency of regulatory proteins or a hereditary abnormality of proteins[4,5].

A hereditary condition can manifest during pregnancy or postpartum which requires excluding systemic disorders like HELLP syndrome, that occur only during pregnancy and the *postpartum* period and resolve after delivery, or TTP[6].

This case represents a challenge in the diagnosis and management of CM-HUS.

DESCRIPTION OF CASE

We present the case of a 21-year-old Caucasian woman with a personal history of arterial hypertension, pre-eclampsia in 2019, recurrent urinary infections, obesity, chronic lymphedema of the lower limbs and atrophic left kidney, initially admitted with the provisional diagnosis of pre-eclampsia in the context of an unsupervised pregnancy. The patient had family history of a father and a paternal uncle with unknown etiology chronic kidney disease on hemodialysis, she was not taking any medication and had no vascular devices. At admission she was hypertensive (221/128 mmHg) and presented the following lab test results: Hb 10.8 g/dL, platelets 153 000/µL, serum creatinine (SCr) 1.88 mg/dL, LDH 275 IU/L, normal hepatic function, and a urine dipstick test positive for protein (not quantified at the time). With the use of antihypertensive drugs, it was possible to control blood pressure within 24 hours. An emergency caesarean section was performed and in the postpartum period the situation progressed to microangiopathic anemia (Hb 7.1 g/dL), thrombocytopenia (84 000/µL), haptoglobin < 8 mg/dL, LDH 722 IU/L, direct Coombs test negative, normal peripheral blood smear and progressive decline in renal function (SCr 3.54 mg/dL). The urine dipstick test was repeated and detected hematuria.

Ophthalmoscopy, performed 5 days after delivery, excluded malignant hypertensive retinopathy. ADAMTS13 activity was 57%; C3 and C4 levels were normal. Anti-factor H antibody test was negative. Antinuclear antibodies (ANA), extractable nuclear antigens (ENA's), anti-ds-DNA antibodies, hepatitis C antibodies, hepatitis B antigen, human immunodeficiency virus antibodies and syphilis total antibodies were negative. IgG antibodies to Epstein Barr virus, Parvovirus, and cytomegalovirus were positive, with IgM antibodies negative. Vitamin B_{12} levels were normal (206 pg/mL). On the 4th day after delivery, she continued to worse and complement-mediated TMA was assumed as a probable diagnostic hypothesis, and plasmapheresis (PLEX) was initiated. The peripheral blood smear did not show any schistocytes presumably due to an effective reticuloendothelial system. After four plasmapheresis sessions, she presented hematological and renal worsening (SCr 4.95 mg/dL, Hb 7.58 g/dL, platelets 51 000/µL), which led to treatment with eculizumab being initiated, starting dose 900 mg/week (four weeks) and maintenance dose 1200 mg every 15 days. Prophylactic medication was delivery: vaccine to prevent meningococcal disease and flu and antibiotic (amoxicillin/clavulanate) during the first 15 days. Nine days after delivery, she began hemodialysis with SCr 7.22 mg/dL.

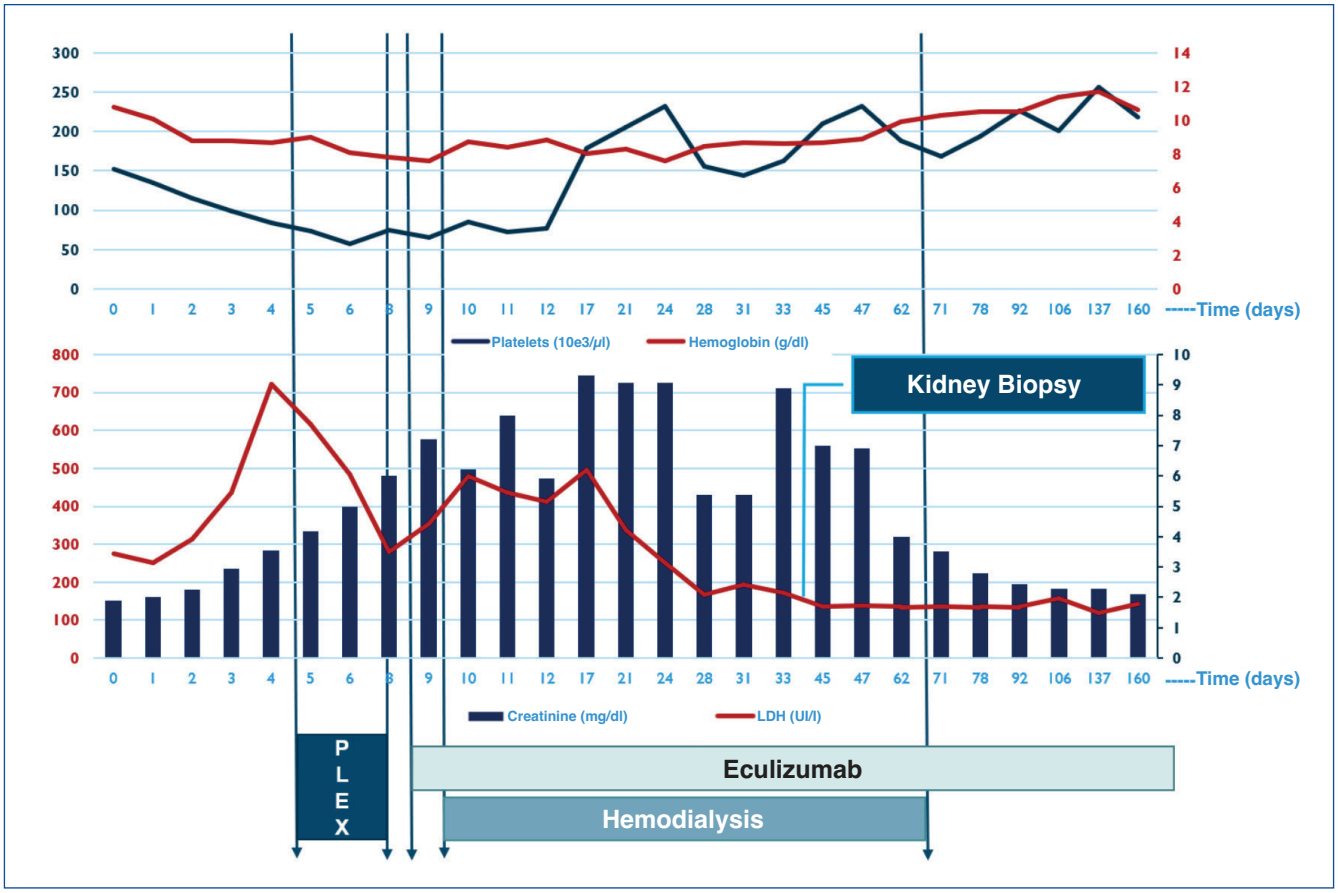

Figure 1. Analytical evolution over time (days), were zero represents delivery day.
PLEX: plasmapheresis; LDH: Lactate Dehydrogenase.

About 72 h after starting treatment with eculizumab serum LDH, platelets and hemoglobin levels were stabilized, and on the 9th (platelets levels) and 24th (LDH levels) day the values count normalized (fig. 1). Schizocytes were observed only once after delivery, and eculizumab treatment had already been started one month before. The genetic study, the results of which were subsequently available, revealed a mutation on exon 22 of the *ADAMTS13* gene, c.2854C>T, p.Pro952Ser in heterozygosity, corresponding to a previously undescribed likely pathogenic variant, in addition to *CFHR3-1* deletion in heterozygosity.

A genetic study of the father was also performed and showed no changes.

After 34 days of eculizumab treatment a kidney biopsy was performed, when patient's hemoglobin levels were stabilized. The kidney fragment sampled contained three glomeruli: one was sclerosed, the others all had signs of ischemia; one had segmental sclerosis and some double contours of the glomerular basement membrane were observed focally. The interstitium presented diffuse fibrosis in about 40% of the sample, with tubular atrophy in the areas of fibrosis and acute tubular necrosis in the non-atrophic tubes. The arterioles showed exuberant endotheliosis and one of them had a thrombus (fig. 2). Six weeks after starting hemodialysis, this treatment was stopped, due to recovery of kidney function.

Currently, the patient remains under treatment with eculizumab at a dose of 1200 mg every 15 days. The CH50 assay was 15 U/mL (normal level 45 to 95U/mL, which represents a CH50 activity between 30% to 16%), remaining above the expected value for a patient treated with eculizumab (< 10%). For this reason, treatment is expected to continue at a dose of 1200 mg every two weeks until suppression of CH50 activity is achieved.

A genetic consultation was also requested to continue the investigation of the case.

DISCUSSION AND CONCLUSION

The diagnosis of CM-HUS continues to be a diagnosis of exclusion that implies the investigation of all possible etiological factors that may be involved in the etiopathogenesis of the disease. Another important fact is the understanding of the evolution of the disease over time. In this case, the absence of improvement despite supportive therapy, suggest CM-HUS over other systemic disorders and high level of suspicion must be maintained.

Kidney biopsy is not helpful for determining the etiology of a primary TMA syndrome but confirms the diagnosis. Genetic study although not being essential for diagnosis, can support it and it can give relevant information about the management and prognosis of the disease.

Severe *ADAMTS13* deficiency (< 10%) is associated with homozygosity or compound heterozygosity in the *ADAMTS13* gene. However, several studies report that partial *ADAMTS13* deficiency in patients with complement-mediated TMA may be a predisposing factor for TMA[7-9]. The haplotype CFH-H3 in homozygosity is associated with a 2- to 4- fold increased risk of CM-HUS[10-12]. It is however controversial whether the presence of heterozygous CFHR3-1 deletion, in the absence of anti-factor H antibody, concomitant with other genetic or acquired risk factors, may be a risk factor for CM-TMA, although some reports have suggested that this may be the case[16]. We therefore consider, knowing that penetrance of CM-TMA in mutation carriers is approximately 50%, that although these two variants do not individually have a marked pathogenic effect per se, they may have a cumulative effect in the presence of a trigger (which in this patient may have been pregnancy) for an TMA phenotype[13-15].

Plasma exchange is the first line treatment in TMA, and it should be started within the first 24 to 48 hours with exclusive volume replacement with fresh frozen plasma[3,5]. The response

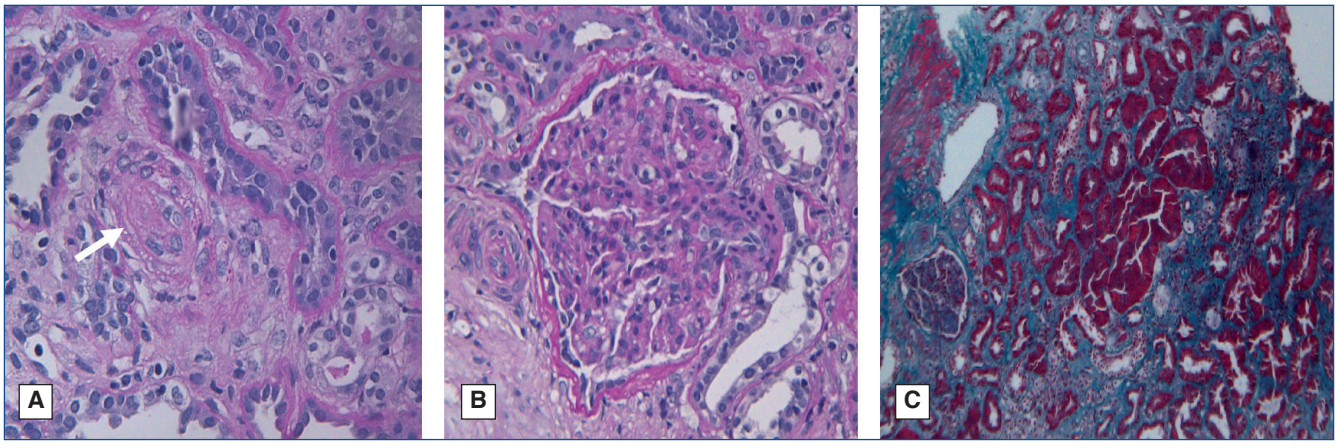

Figure 2. Kidney biopsy with fragment sampled containing three glomeruli presented on light microscopy.
A) Haematoxylin & Eosin stain showing arteriole with exuberant endotheliosis and a thrombus inside (arrow).
B) Haematoxylin & Eosin stain showing ischemic glomerulus. **C)** Masson trichrome stain showing interstitium presenting diffuse fibrosis, with tubular atrophy in the areas of fibrosis and acute tubular necrosis in the non-atrophic tubes.

to this treatment varies depending on the mutation found[12]. Eculizumab should be started as soon as possible, and meningococcal vaccination, flu vaccination and prophylactic antibiotic should be taken for 15 days. Timing to discontinue eculizumab is uncertain[17]. The decision to stop this therapy should consider the disease activity (hematologic and biochemical analyses should be performed and CH50 should be measured – normal activity is expected under 10%) and the risk of relapse when pathogenic variants are identified. In this case we do not know if the identified mutation corresponds to a pathogenic variant.

The authors also recall the importance of early recognition and treatment of the disease, which in this case may have been decisive in the recovery of renal function.

Financial support

None to declare.

Conflict of interest

The authors have no conflicts of interest to declare.

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