IgA Nephropathy with Thrombotic microangiopathy: Is this secondary thrombotic microangiopathy or IgA nephropathy-triggered atypical Hemolytic Uremic Syndrome?

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ABSTRACT

IgA Nephropathy (IgAN) is the most prevalent biopsy-proven primary glomerular disease worldwide. Historically, thrombotic microangiopathy (TMA) was associated with IgAN in cases of severe hypertension or advanced chronic kidney disease, but recent data suggest that complement activation plays a crucial role in the development of TMA in IgAN. We report a case of Crescentic IgAN with complement-mediated TMA (C-TMA) in a 27-year old male patient with a pathological missense mutation in heterozygosity in the CFH gene and a rare variant in the C3 gene, treated with steroids, cyclophosphamide and plasmapheresis without recovery of kidney function. We also discuss other treatment possibilities and kidney transplant options. Additionally, we will review the latest advances that are enhancing our understanding of the association between IgAN and TMA.

Keywords: Complement; Genetics; Hemolytic Uremic Syndrome; IgA Nephropathy; Thrombotic Microangiopathies.

INTRODUCTION

IgA Nephropathy (IgAN) is a glomerular disease characterized by diffuse deposits of IgA in the mesangial areas of the glomerulus and is the most common biopsy-proven primary glomerular disease worldwide¹. Thrombotic microangiopathy (TMA) is a heterogeneous disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury caused by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall². Historically, TMA has been associated with IgAN in cases of severe hypertension or advanced chronic kidney disease (CKD)³,⁴, but emerging data is challenging this hypothesis⁵-⁷. Still, the prevalence and the pathophysiology of this association are poorly understood.

We report a case of an acute presentation of IgAN that was associated with TMA at the time of diagnosis. Additionally, we will discuss the latest advances that are enhancing our understanding of the association between IgAN and TMA.

CASE REPORT

A 27-year old male patient, with no relevant past medical history, was admitted to the emergency department due to pallor and asthenia. The patient had been in his usual state of health until approximately three weeks before admission, when he developed abdominal pain, nausea, vomiting, and diarrhea, treated with non-steroidal anti-inflammatory drugs. These symptoms lasted for five days. He reported long-term intake of protein supplement consumption, as well as other supplements, to increase his muscle mass until six months previously. He denied having a fever, rash or purpura, epistaxis, red-eye, dyspnea, cough, or lumbar pain. He had no familiar history of kidney disease.

In the emergency department, his laboratory exams revealed severe anemia (Hb 5.7 g/dl), with increased reticulocyte count to 3.5% (0.5–2.5 %), discrete thrombocytopenia (139.000 x10^9/uL), and some schizocytes (1-2/high-power field). They also revealed severe azotemia (serum urea 233 mg/dl; serum creatinine 11.62 mg/dl), increased LDH (962 U/L), and normal c-reactive protein (3.9 mg/dl). Blood gases revealed a metabolic acidosis (pH 7.33 HCO₃ 15.3 mmol/L). The Coombs direct test was negative, cloting study unremarkable, and D-dimers were normal (3.47 g/ml). Urinalysis revealed proteinuria (1.5 g/L), leucocyturia, and erythrocyturia. Renal ultrasound showed normally dimensioned kidneys.

The patient was admitted to the ward to start hemodialysis, after receiving two units of packed red blood cells. A kidney biopsy was...
performed on the next day. The anatomopathological analysis revealed 25 glomeruli, 14 of which had cellular crescents and 7 were sclerosed. There were signs of thrombotic microangiopathy, tubular necrosis, hematuria, and moderate interstitial lymphocytic infiltrate (Figure 1). Immunofluorescence showed mesangial deposits of IgA (++) . Further workup showed proteinuria 2.05 g/24 h, decreased haptoglobin (8 mg/dl) and increased serum IgA (341 mg/dl). The virologic and immunological study was negative.

A diagnosis of crescentic IgAN with TMA was assumed, and the patient started on steroids (3 pulses of intravenous methylprednisolone 500 mg and then prednisolone 1 mg/kg per os), and pulsed intravenous cyclophosphamide 1000 mg.

Due to the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and TMA in the kidney biopsy, further work-up was undertaken, and plasmapheresis with fresh plasma was
started. ADAMTS13 enzyme activity was normal (89%), and ADAMTS13 inhibitor and anti-factor H antibodies were negative. The ultrastructural study showed a diffuse expansion of the lamina rara interna, with flocculent appearance, revealing the dimension of the TMA involvement (Figure 2).

The molecular study of the complement genes revealed a missense pathological mutation in heterozygosity in the complement factor-H (CFH) gene (c.3611G>A, p.Gly1204Glu) for complement-mediated TMA (C-TMA) and a rare missense variant in heterozygosity in the C3 gene (c.463A>C, p.Lys155Gln), usually benign but associated with atypical Hemolytic Uremic Syndrome (aHUS) when co-inherited with pathogenic variants.

After ten sessions of plasmapheresis, there was no evidence of microangiopathic hemolytic anemia, and the patient was discharged on regular hemodialysis through a central tunneled catheter. There was no improvement in kidney function, despite four intravenous pulses of cyclophosphamide and daily prednisone. After the results of the molecular study of the complement genes, it was decided to stop the cyclophosphamide pulses, and the steroids were quickly tapered. A final diagnosis of crescentic IgA Nephropathy with complement-mediated thrombotic microangiopathy was considered. The patient is in a continuous ambulatory peritoneal dialysis program and is being followed in the pre-transplant clinic.

**DISCUSSION**

Crescentic IgAN is an uncommon presentation of IgAN, representing approximately 5% of all IgAN cases and is associated with poor renal prognosis8. On the other hand, crescentic IgAN with C-TMA has rarely been reported in the literature9,10.

The CFH mutation identified in our patient is highly pathogenic, with a score of 5/5 **in silico**, and affects the short consensus repeat 20 (SCR20) of the carboxyterminal region of factor H (FH), causing a substitution of a glycine residue that reduces the capacity of FH to bind to heparin11. This region is critical for the attachment of FH to the surface of host cells and consequently for the regulation of the complement alternative pathway activation12. Upon an inflammatory insult, the defective cell recognition of factor H reduces its regulatory activities of the alternative pathway and the C3b amplification loop at the surface of endothelial cells, which results in cell damage and exposure of the subendothelial matrix, causing C-TMA (Figure 3)13. Patients with CFH mutations have the worst outcome of all the patients with C-TMA, usually progressing to end-stage renal disease (ESRD) or death within one year of presentation14. The C3 variant is usually benign but can have a cumulative effect on the patient’s phenotype when co-inherited with pathologic mutations15.

In the presented case, the rapidly progressive renal insufficiency was preceded by acute gastrointestinal symptoms three weeks before.
Both IgA vasculitis and aHUS can be associated with gastrointestinal manifestations, but acute gastroenteritis, in a patient with genetic susceptibility, could have been the trigger of both the crescentic transformation of IgAN and C-TMA.

Infection is a known precipitant of C-TMA\textsuperscript{16}. Dysregulated intestinal mucosal activation due to infection also increases serum IgA and its deposition in the mesangium\textsuperscript{1,17,18}. This acute change in IgA leads to direct or indirect activation of the complement system\textsuperscript{7,19}, endothelial dysfunction, and kidney damage. This link could explain the overlap of aHUS and IgAN in the setting of infection reported in the literature\textsuperscript{10}.

In the past, it was thought that IgAN was only associated with TMA in cases of severe hypertension or advanced CKD\textsuperscript{4}. Karoui et al.\textsuperscript{5} reported for the first time that TMA is a common histopathological feature of IgAN (53\% of patients) and that TMA can occur in normotensive patients, or with near-normal renal histology. They also found that TMA is associated with worse renal prognosis, even after adjusting for the hypertension severity. Recent Chinese and Dutch retrospective studies have reported similar findings. In the Chinese cohort, histological microangiopathic lesions were present in 20.6\% of IgAN biopsies, and 23.2\% of the patients with microangiopathic lesions were normotensive\textsuperscript{7}. In the Dutch cohort, histological microangiopathic lesions were present in 23\% of IgAN biopsies, and 25\% of the patients with microangiopathic lesions were normotensive\textsuperscript{6}. In both studies, histological microangiopathic lesions were associated with worse renal outcomes\textsuperscript{6,7}. This data suggest that histological microangiopathic lesions are frequent in IgAN when both acute and chronic lesions are considered.

In the Dutch study, the kidney fragments were also restained for complement proteins using immunohistochemistry, including C4d and C5b-9\textsuperscript{6}. Microangiopathy was associated with C4d and C5b-9 deposits, a higher number of chronic lesions, and hypertension. This data suggests that local complement activation is involved in the development of microangiopathy in patients with IgAN, and hypertension does not seem to be the primary cause of TMA in IgAN. Interestingly, a strong association between mutations in complement genes and hypertension-associated TMA was also reported in another study\textsuperscript{20}. This could mean that hypertension-associated TMA in IgAN is mediated by complement dysregulation as well.

Complement activation is also involved in the pathophysiology of IgAN. Mesangial IgA, mainly polymeric IgA\textsubscript{1}, drives the activation of the mesangial cells, which is amplified by the ability of IgA to activate the complement system through the lectin and alternative pathways (Figure 3)\textsuperscript{19,21}. Genome-wide association studies (GWAS) in IgAN also hint to the role of deletions of CFH receptor (CHFR) 1, CFH\textsubscript{3} and CHFRS variants for IgAN susceptibility\textsuperscript{18,22}. In another study, five IgAN patients with low serum factor H were found to carry CFH\textsubscript{r} or complement factor I (CFI)\textsubscript{r} pathogenic variants, which suggests a decreased factor H activity in IgAN\textsuperscript{23}. Whether or not there is a relationship between complement alterations in IgAN and the development of TMA remains to be proven, but there are several anecdotal reports of this association\textsuperscript{24,25}. Ongoing trials are exploring the therapeutic effects of blocking the complement pathway in IgAN, for example, with avacopan, a C5a receptor blocker, and may also increase our understanding of the pathophysiology of IgAN\textsuperscript{26}.

The final diagnosis of crescentic IgAN with C-TMA still leaves the question: is this a secondary TMA associated with crescentic IgAN, or is this an IgAN-triggered aHUS? The association of crescentic IgAN with histological TMA is a consequence of the intense endothelial lesion associated with the glomerulonephritis pathophysiology, similarly to what happens with other glomerulopathies like Lupus Nephritis. Despite occurring a local complement activation, this usually does not cause MAHA. Our patient developed a systemic involvement with MAHA, which makes us consider that it was the Crescentic IgAN that triggered the aHUS, as a consequence of a mutated FH.

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend the use of steroids and ciclophosphamide for the treatment of Crescentic IgAN\textsuperscript{27}. Given the extent of the TMA lesions on the kidney biopsy and the mutations in the CFH and C3 genes, eculizumab, an anti-C5 antibody, could have been an effective therapy. In fact, there are case reports of crescentic IgAN\textsuperscript{28,29} and IgAN with C-TMA treated with eculizumab with different results\textsuperscript{30,31}. Genetic testing is a slow procedure, and our institution only approves eculizumab use if there is proof of pathogenic mutations associated with C-TMA or aHUS. Genetic testing results were reported approximately two months after we started taking care of this patient. At the time, there were no signs of kidney recovery despite treatment with steroids and ciclophosphamide, and we considered that starting eculizumab late in the course of the disease would be unfruitful.

Our patient’s genetic panel will also influence his future kidney transplant opportunities and prognosis. Most transplant centers would advise against related living-donation for a patient with C-TMA attributed to a genetic mutation. Although genetic analysis can be performed in donors, some patients may have more than one genetic variation, and approximately one-third of patients with C-TMA have yet-to-be-identified mutations\textsuperscript{32}. Besides, nephrectomy may trigger C-TMA in a genetically susceptible donor\textsuperscript{33}. Due to the risk of C-TMA recurrence after kidney transplantation, prophylactic therapy with eculizumab is recommended in patients with CFH or CFI mutations\textsuperscript{34,35}. Unfortunately, the optimal regimen and duration of eculizumab therapy after transplantation is not known.

The absence of Shiga-toxin testing in a patient with MAHA and gastrointestinal symptoms can be pointed out as a limitation of our diagnostic work-up. This test was not ordered on admission because the patient had no dysentery, and diarrhea had resolved two weeks before his hospital admission. On the other hand, gastrointestinal symptoms have been observed in about one-quarter of the patients with C-TMA\textsuperscript{36}.

In summary, we report a case of Crescentic IgAN with complement-mediated TMA in a 27-year-old male patient with a pathological missense mutation in the CFH gene and a rare variant in the C3 gene, treated with steroids, ciclophosphamide and plasmapheresis without recovery of kidney function. Laboratory signs of MAHA in a young patient should prompt complement genetic testing even when accompanied by another clinical entity that can be associated with TMA.

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References