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Complement-mediated thrombotic microangiopathy associated with lupus nephritis

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Key Points

- CM-TMA is a unique subset of patient with LN.
- CM-TMA in LN is responsive to complement inhibition with eculizumab.

Complement-mediated thrombotic microangiopathy (CM-TMA) is a clinical disorder driven by the generation of excess complement. It is characterized by thrombocytopenia and microangiopathic hemolytic anemia (MAHA) with microvascular thrombosis resulting in systemic organ damage (TMA). One form of CM-TMA, atypical hemolytic uremic syndrome (aHUS), is characterized by pathologic complement activation due to the loss of the natural regulators of the complement system, which results in systemic endothelial and organ damage. Lupus erythematosus is a multisystem immune complex disorder associated with activation of complement, as well as renal failure termed lupus nephritis (LN). A subset of these patients also develop TMA, with progressive life-threatening thrombocytopenia, MAHA, and progressive renal failure similar to aHUS. This subset of patients is poorly responsive to corticosteroids, cyclophosphamide, immunomodulation, and plasma exchange. In this article, we report 11 cases of LN associated with TMA progressing through these therapies, 10 of which were successfully treated with complement inhibition. Complement-regulatory protein mutations, including complement factor H (CFH), factor I, factor B, membrane cofactor/(CD46) and thrombomodulin, and CFH-related 1-3, were identified in 6 of 10 patients tested. One patient had a loss of a renal allograft. Three patients had concurrent antiphospholipid syndrome. Two of the 3 patients had normal D-dimers at this presentation. We believe that this subset of lupus patients, with clinical and pathologic manifestations of aHUS, define a separate entity that we believe should be termed CM-TMA associated with LN.

Introduction

Complement-mediated thrombotic microangiopathy (CM-TMA) is a clinical disorder driven by the generation of excess complement. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA) with microvascular thrombosis resulting in systemic organ damage (TMA). One form of CM-TMA, atypical hemolytic uremic syndrome (aHUS), is characterized by pathologic complement activation due to the loss of the natural regulators of the complement system, resulting in systemic endothelial and organ damage.[1] This pathogenic complement activation may result from a loss of inhibition by the natural regulators of the complement system and/or the generation of excess complement activation due to infection, pregnancy, malignancy, medication, or autoimmunity.[1-4] CM-TMA is distinguished from other causes of TMA by normal ADAMTS13 activity and the absence of infection with Shiga toxin–producing bacteria.[1]

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Lupus erythematosus is a multisystem immunopathic disorder associated with immune complex activation of complement. These immune complexes can be associated with renal injury, termed lupus nephritis (LN). LN is characterized by progressive renal failure due to focal or diffuse membranous glomerulonephritis.[5-8] A subset of these patients, 17.5%, develop TMA with progressive, life-threatening thrombocytopenia, MAHA, and progressive renal failure despite treatment with high-dose corticosteroids, aggressive immune-modulatory therapy (cyclophosphamide, calcineuric inhibitors, azathioprine, rituximab, mycophenolate mofetil), and plasma exchange.[5,6] Because the clinical and laboratory presentation of CM-TMA associated with LN is indistinguishable from aHUS, the use of complement inhibition is appropriate. Complement inhibition has been successfully used in aHUS, refractory Shiga toxin–producing *Escherichia coli*–hemolytic uremic syndrome, in refractory systemic lupus erythematosus (SLE), and in renal allograft rejection associated with TMA.[9-11]

We present 11 cases of TMA-associated LN, refractory to plasma exchange, glucocorticoids, and immune-modulatory therapies, who were treated with complement inhibition using eculizumab. Upon molecular screening for mutations in the complement-regulatory proteins, 60% of these patients had complement-regulatory protein mutations associated with aHUS.

Patients and methods

This was a retrospective review of 11 patients seen between 2009 and 2018 with LN and TMA. Ten patients were diagnosed while hospitalized at 2 large urban teaching hospitals in Los Angeles. One patient was seen and diagnosed at the START Cancer Center. The study was approved by the institutional review board of the University of Southern California and done in accordance with the Declaration of Helsinki.

All patients fulfilled criteria for lupus erythematosus with LN as defined by the American College of Rheumatology.[5-8]

Testing for ADAMTS13 activity was performed by a chromogenic, enzyme-linked immunosorbent assay (ELISA) method at Quest Diagnostics. Mutation analysis for complement-regulatory protein abnormalities was done by Machaon Diagnostics. Genomic DNA was extracted from patient whole blood samples. The genomic DNA was used as a template for a highly multiplexed polymerase chain reaction scheme designed to specifically amplify the exons, splice sites, and untranslated regions, in addition to several deep intronic and promoter sites, of the 12 genes of interest (*CFH*, *CFI*, *CFB*, *CFHR1*, *CFHR3*, *CFHR4*, *CFHR5*, *CD46/MCP*, *C3*, *THBD*, *PLG*, and *DGKE*). These polymerase chain reaction amplicons were further processed into libraries for sequencing on a next-generation sequencer. Sequence data were aligned to the human reference genome (Hg19) to identify nucleotide variants. The variants were checked against private and public databases (1000 Genomes and www.fh-hus.org, for example) to help with interpretation. Patients were also screened for inhibitory antibodies against complement factor H (CFH).

All patients were treated with eculizumab per the US Food and Drug Administration–approved aHUS dosing schedule; 4 weekly doses of 900 mg followed by 1200 mg on week 5, repeated every 2 weeks. Patients received meningococcal vaccinations (quadrivalent and type B) as well as penicillin prophylaxis at initiation of therapy.[9]

Results

Eleven patients with LN and TMA were reviewed. The patients ranged from 22 to 59 years of age. (Table 1) The majority of patients were women (9 of 11). Seven of the 11 patients had an antecedent history of SLE. The remaining 4 were diagnosed at the time of presentation of the TMA. In all patients, there was evidence of progressive renal insufficiency, with elevated serum creatinine (sCr), MAHA (elevated lactate dehydrogenase [LDH]: average, 718 U/L; median, 456 U/L; range, 247-2013; normal value, $<$200 U/L), low haptoglobin, fragmented red blood cells on peripheral smear, and thrombocytopenia. The mean sCr was 3.2 mg/dL (median, 3.2 mg/dL; range, 1.3-5.7); mean hemoglobin was 8.7 g/dL (median, 8.4 g/dL; range, 5.4-12.6). The mean platelet count was 68.3×10^9/L (median, 60×10^9/L; range, 8-160) (Table 1). Renal biopsies were obtained in 8 of 10 living patients and there was autopsy pathology in the 1 patient who died. The pathology was consistent with LN and TMA in 7 of 8 patients (Table 1). Autopsy material on the 1 patient who died was consistent with extensive TMA as well as fungemia. Infection was the most common precipitating factor (bacteria, viral, fungal) for the onset of CM-TMA in our patients. The ADAMTS13 activity was $>$5% in all patients tested. Complement 3 and complement 4 levels varied in our patients (Table 1) and did not change or correlate with treatment response to eculizumab.

Three patients had laboratory findings consistent with APLS (lupus anticoagulant, anti-cardiolipin antibodies, and/or B2-glycoprotein 1 antibodies); all 3 patients had clinical criteria for diagnosis having a history of thrombosis. They were on anticoagulation at the time of their diagnosis of LN with TMA; 2 of 3 had normal plasma D-dimers. Of the patients with a history of APLS, 2 of 3 had underlying complement mutations (1 with normal dimers, 1 with high dimers). One patient, without antiphospholipid antibodies, was anticoagulated due to a deep vein thrombosis prior to presentation, believed to be due to LN-associated nephrotic syndrome.

Of the 11 patients treated with eculizumab, 1 patient died with progressive TMA within 24 hours of receiving eculizumab. Autopsy showed extensive TMA and disseminated fungal infection, most likely due to prolonged high-dose corticosteroid treatment of her LN.

The 10 surviving patients responded with a reduction in LDH, an increase in platelet count to $>100 \times 10^9$/L, improvement in renal function, and anemia (Table 1). The mean duration of eculizumab treatment was 82.2 weeks, with a median of 63.5 weeks (range, 7-190 weeks). During hospitalization, 7 of 10 living patients (70%) were on dialysis. Of the 7 patients on dialysis, 4 were able to discontinue during the hospitalization. One patient stopped hemodialysis on day 1 of eculizumab treatment, a second within 2 weeks of starting eculizumab, a third patient within 3 weeks of starting eculizumab, and a fourth patient stopped on day 60 of eculizumab treatment. Of the 3 patients who remained on dialysis after discharge, 1 patient was able to discontinue peritoneal dialysis 36 weeks after starting eculizumab. Another patient who had a previous history of an allogeneic renal transplant with loss of the graft due to TMA, combined with biopsy evidence of rejection, remains on dialysis. The initial cause of the renal failure necessitating kidney transplant was attributed to LN. Although graft rejection has been associated with TMA, a deleterious thrombomodulin mutation was identified in that patient, suggesting that underlying

Table 1. Demographic, renal, and hematologic findings at presentation in patients with LN and aHUS

Patient	Age, y/sex	Renal biopsy	Status pre-eculizumab	Cr on admission, mg/dL	LDH, U/L	Platelets on admission, $\times 10^9$/L	C3, mg/dL	C4, mg/dL	ADAMTS13, % activity
1	39/F	FSGLN, membranous LN, antibody-mediated rejection, TMA	ESRD due to LN Renal allograft rejection	3.64	2013	91	Not obtained	Not obtained	Not obtained
2	25/F	Diffuse proliferative glomerulonephritis class IV, TMA	ESRD due to LN	1.30	368	48	13	3	67
3	22/F	Diffuse proliferative LN class IV, TMA	ESRD due to LN	3.87	461	82	14	<2	98
4	37/F	Not obtained	ESRD due to LN	5.58	325	57	80	26	Not obtained
5	31/F	LN class III, TMA	ESRD due to LN fungemia	2.46	672	90	21	2	89
6	42/F	Chronic interstitial nephritis and diffuse mesangial hypercellularity, TMA	LN never on dialysis APLS	2.00	247	78	96	11	123
7	59/F	Not obtained	LN never on dialysis	1.98	456	8	54	8	99
8	22/F	Membranous lupus glomerulonephritis, mixed class III, V, clinical TMA	LN never on dialysis; nephrotic syndrome	3.17	254	160	18	<2	Not obtained
9	31/M	Diffuse LN class IV-G, TMA	ESRD due to LN	3.64	335	49	Not obtained	Not obtained	89
10	34/F	Interstitial fibrosis, TMA	ESRD LN myocarditis APLS	2.86	806	60	119	21	151
11	57/M	Not obtained	ESRD LN APLS	4.13	1955	28	128	28	Not obtained

All patients met criteria for systemic lupus erythematosus.
APLS, antiphospholipid antibody syndrome; C3, complement 3; C4, complement 4; Cr, creatinine; ESRD, end-stage renal disease; F, female; FSGLN, focal segmental glomerulonephritis; M, male.

complement dysregulation may have played a role in the TMA and graft loss.[10]

With the exception of the 1 patient who died of disseminated fungal infection, there were no infectious complications related to the eculizumab treatment in the 10 surviving patients treated, or the 8 who have continued on eculizumab. One patient elected to discontinue treatment after 1 year. She did not have any identified mutations. Her sCR remains stable at 1.54 mg/dL, 12 months after discontinuation. She has anemia without evidence of MAHA, normal LDH, a platelet count of >150 000 but persistent hypertension controlled with medication. A second patient discontinued eculizumab after 26 weeks. She presented 8 weeks after discontinuing eculizumab with evidence of recurrent TMA, with progressing renal failure requiring dialysis as well as altered mental status that has not improved with dialysis. She is a heterozygote for thrombomodulin, plasminogen mutation as well as polymoprhisms in CFH. Since submission, 1 patient has died of intractable heart failure due to her underlying cardiomyopathy without clinical evidence of TMA. She did not have any underlying complement-regulatory mutations.

All 10 patients surviving the initial TMA event were evaluated for mutations of complement-regulatory proteins. In 6 of 10 patients, abnormalities in complement-regulatory genes were identified (see Table 2). No CFH antibodies were identified.

Discussion

LN is a complex antigen-antibody disorder associated with complement activation.[5-8] The presence of glomerular C4d deposits and decreased serum levels of the complement-regulatory protein, factor H, are associated with poor renal outcomes in patients with LN.[12-15] Both complement C3 and C4 levels are often low in LN, suggesting that activation of both the classical and alterative pathways of complement are involved in the development of TMA in these patients.[5,12,13,16,17] Levels of Bb, C3a, C5a, and soluble C5b-9 are significantly elevated in patients with active LN compared with those in remission, the patients with active SLE without renal involvement group, and normal controls, supporting a unique role of the alternative pathway, as well as terminal complement activation, in LN.[16] In a recent analysis of renal biopsies in LN, terminal complement deposition, as noted by C9 staining, is a marker of poor prognosis.[13] However, the authors did not specifically comment on the presence of TMA in the biopsies reviewed. In addition, increased terminal complement deposition, lower levels of CFH, and impaired function of CFH has been demonstrated in LN compared with normal control.[14,15,18,19] Although the presence of a mutation alone may not cause TMA, the presence of a complement-amplifying condition increasing complement activation may be enough to allow the patient to manifest the disease.[20] Jodele et al found an enrichment in CFHR1-3 associated with hematopoietic stem cell transplantation (HSCT)-associated TMA.[21,22] In addition, the presence of multiple complement "variants" predicts a worse outcome in HSCT-associated TMA. The resultant dysregulation of the complement system is indistinguishable from that seen with aHUS.

The presence of TMA on renal biopsy is predictive of a poor renal outcome when associated with LN.[5-7] It has been reported to be an independent risk factor for poor long-term renal outcomes in patients with LN.[14,15,18,19] In patients with LN and TMA, <23 years of age, 80% develop end-stage renal disease (ESRD) within 5 years

Table 2. Patient mutation status and acute event survival outcomes with eculizumab

Patient	Mutation status	Acute response to eculizumab	Platelets post-eculizumab, $\times 10^9$/L	Survival outcome
1	Thrombomodulin (heterozygous) c.127G>A, pAla43Thr; CFH heterozygote chr1: 196642980, G>A	Ongoing dialysis	291	Living, remains on eculizumab 190 wk
2	CFH polymorphisms (homozygous) p.val62Ile; p.hist402Tyr	Off dialysis	320	Living, remains on eculizumab 139 wk
3	No mutation identified	Off dialysis	153	Living, remains on eculizumab 124 wk
4	No mutation identified	Ongoing dialysis	194	Living, remains on eculizumab 170 wk
5	Not obtained	Expired	Expired	Expired, due to disseminated fungemia and TMA
6	CFB C.724A>C, pIle242Lue(homozygous); CFHR5 c.384G>T, p.ser128Ser (heterozygote) polymorphism; CD46 IVS9-78 G>A polymorphism; CFH p.Val62Ile, p.his402Tyr	Non-HD, improvement in renal function	155	Living, remains on eculizumab 75 wk
7	No mutation identified	Non-HD, improvement in renal function	165	Living, discontinued eculizumab after 52 wk no evidence of recurrence
8	Thrombomodulin (heterozygous) C1456G>T p.Asp 488 Tyr; PLG (heterozygote) c.1567C>T p.arg523TRP polymorphism; CFH (heterozygous) p.val62Ile(homozygous) p.His402Tyr	Non-HD improvement in renal function	205	Living, discontinuation of eculizumab at 26 wk; recurrent TMA + HD
9	CFHR1-CFHR3 (homozygous); PLG (heterozygous) c.1335G>C, p.Arg445Ser; MCP/CD46 (heterozygous) IVS9-78G>A	Peritoneal dialysis	96	Living, remains on eculizumab 36 wk; discontinued dialysis 36 wk after starting eculizumab
10	No mutations identified	Off dialysis	175	On eculizumab 30 wk, died of heart failure due to cardiomyopathy
11	Factor I (homozygous) missense c.1217G>A, p.Arg406His; CFHChr1:196620917 C>T exon 18 c2808G>T, p.GLN672GLN exon 13 2016A>Gp.GLN672GLN	Off dialysis	100	Living, remains on eculizumab 7 wk

CFB, complement factor B; CFHR1-3, complement factor H–related 1-3; CFI, complement factor I; HD, hemodialysis; MCP, membrane cofactor; PLG, plasminogen; THMB, thrombomodulin.

of diagnosis.[8] In our patients, the C3 and C4 levels varied widely and did not correlate with the need for long-term hemodialysis or hematologic response to complement inhibition. In a recently published article, only 4 of 22 patients with aHUS had low C3 levels in contrast to patients with C3 nephritic factor or C3 glomerulonephritis patients in whom the C3 levels were low.[23] In addition, C3 levels in the aHUS patients did not change with eculizumab therapy.[23,24] C3 levels in the C3 nephropathy patients remain low reflecting on going alternative pathway activation in the setting of C5 blockade.[23,24] One would not expect any change in C3 levels with eculizumab therapy as it exclusively blocks C5 convertase and does not affect C3 convertase.[9,24]

In our cohort, treatment of the acute LN-associated TMA with plasma exchange, corticosteroid, and immune modulation did not have a significant impact on recovery of the platelet count or renal function. Given the evidence of complement dysregulation in LN, and the clinical similarities with aHUS, it was logical to consider complement inhibition in these patients. Two previous reported cases of LN successfully treated with eculizumab have been reported, 1 with diffuse proliferative glomerulonephritis and 1 with TMA.[10,25-28] Our cohort represents the largest series of LN patients with TMA treated with complement inhibition reported to date. All of the 10 patients living after the initial presentation had complete recovery of the hematologic parameters, and 8 of 10 had recovery of renal function. Six of 10 patients had underlying complement-regulatory mutations/variants consistent with aHUS. This is consistent with the data from the eculizumab aHUS trials, as well as the HSCT data, which found complement-regulatory mutations in only 50% to 60% of the patients treated.[9,22] When compared with responses to plasma exchange and other standard treatments, anticomplement therapy with eculizumab was associated with a significant improvement in thrombocytopenia, renal function, anemia, and a reduction in LDH with minimal toxicity. CM-TMA–associated LN represents a unique subset of LN patients with a progressive and dismal outcome. Complement inhibition represents a paradigm shift in the treatment of this subset of patients with LN and TMA.

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Authorship

Contribution: M.H.P. and I.C.W. collected data, and wrote drafts of the manuscript; and N.C. and S.U. collected patient data.

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