Atypical hemolytic uremic syndrome secondary to lupus nephritis, responsive to eculizumab

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Abstract

Among the spectrum of disease manifestations associated with systemic lupus erythematosus, lupus nephritis is particularly concerning due to the potential for renal failure. This autoimmune attack may not, however, be limited to the kidney and is increasingly being recognized as a trigger for atypical Hemolytic Uremic Syndrome (aHUS). Atypical HUS falls under the spectrum of the thrombotic microangiopathies (TMAs) – a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end organ damage. Although plasma exchange is considered first-line therapy for thrombotic thrombocytopenic purpura – a TMA classically associated with autoimmune depletion of ADAMTS-13 – aHUS demonstrates less reliable responsiveness to this modality. Instead, use of the late complement inhibitor Eculizumab has emerged as an effective modality for the management of such patients. Diagnosis of aHUS, however, is largely clinically based, relying heavily upon a multidisciplinary approach. Herein we present the case of a patient with atypical HUS successfully treated with Eculizumab in the setting of Class IV-G (A) lupus nephritis and hypocomplementemia.

Introduction

Complement mediated TMA (also referred to as atypical Hemolytic Uremic Syndrome) is a rare (annual incidence 1:500,000)1 entity belonging to the family of disorders collectively called thrombotic microangiopathies (TMAs).3 The pathophysiology of complement-mediated TMA involves unchecked activation of the alternative pathway leading to excessive deposition and deleterious action of complement on the endothelium, often with a predilection for the renal vasculature.4 Failure to control complement activation is due predominantly to inherited or acquired deficiencies of complement regulatory proteins – described in over 50% of individuals with complement mediated TMA.5,6 Known mutations leading to sporadic and recurrent complement mediated TMA include those that affect regulatory proteins that are both soluble (Factor I, which, in cooperation with Factor H, MCP and other proteins cleaves C4b and C3b; Factor H, which binds C3b and disrupts the alternative pathway C3 convertase) and membrane bound (Membrane Cofactor Protein, CD46); a number of other defects have also been described.7 Patients with complement mediated TMA, even those in whom a clear genetic or antibody-mediated predilection is absent, may experience recurrences that may also damage renal allografts following kidney transplantation.5

Typically, complement mediated TMA will present as a microangiopathic hemolytic anemia, with thrombocytopenia, evidence of mechanical hemolysis (presence of schistocytes on peripheral blood smear, increased LDH, decreased haptoglobin), and varying degrees of end-organ dysfunction.2 Other manifestations include severe hypertension, central nervous system features (such as altered mental status, diplopia, or motor deficits), acute coronary syndrome due to cardiac microangiopathy, distal ischemic gangrene, and acute multi-organ failure.2

Responses to plasma-based therapeutics (either plasma infusion or plasma exchange) in complement-mediated TMA appears highest among those with MCP mutations (97%) and lowest among those with CFI mutations (25%) with 3 year outcomes of ESRD or death as high as 77% among those with CFH and lowest among those with CFI mutations (25%).5 Despite treatment responses to individual bouts of TMA, therefore, plasma based therapeutics are not uniformly effective.

Eculizumab, an inhibitor of human C5 complement protein, has emerged as an important therapeutic agent in the treatment of complement mediated TMA. This agent was studied by Legendre and colleagues in 37 patients with complement mediated TMA with or without thrombocytopenia.3 Eculizumab was dosed intravenously within 1-6 hours of most recent plasma therapy at a dose of 900 mg per week for 4 weeks, then 1200 mg on week 5, then 1200 mg every 2 weeks beginning week 6. Patients continuing plasma based therapeutics during eculizumab treatment received 600 mg eculizumab booster before plasma infusion or within 1 hour following completion of each plasma exchange. In the group with thrombocytopenia, median platelet-count improvements of 73×109/L from baseline occurred by week 26 of therapy; 45 patients discontinued dialysis. In the group without thrombocytopenia, 80% achieved TMA-free status.

Here we present a unique case of aHUS which developed in a patient with newly diagnosed systemic lupus erythematosus (SLE), failed a course of therapeutic plasma exchange, but that subsequently responded to eculizumab.

Case Report

A 25 year-old Vietnamese female presented with a one month history of arthralgias, daily symmetric arthritis of the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and metatarsophalangeal (MTP) joints accompanied by two hours of morning stiffness. In addition, she reported myalgias, facial swelling, intermittent nausea, vomiting, diarrhea, and generalized headaches associated with photo/phonosensitivity but no visual or focal neurologic deficits. Ten days prior to admission, she developed a mild, productive cough but no fever or chills. She also had dyspnea on exertion, one-pillow orthopnea, and intermittent pleuritic chest discomfort – most pronounced on deep inspiration. On exam she was noted to have a subtle malar rash and diffuse tenderness on abdominal exam.

Pertinent laboratory results include a positive antinuclear antibody (ANA; in an atypical speckled pattern suggestive of SSA/Ro) with a titer to >320; anti-double stranded DNA with a titer to >5120; positive ANCA but negative MPO and PR3 antibodies. Anti-Smith IgG was elevated at 31 U (0-19), SSA (RO) was elevated at 31 U (0-19), SSA (RO) was elevated at 31 U (0-19), SSA (RO) was elevated at 31 U (0-19), SSA (RO) was elevated at 31 U (0-19), SSA (RO) was elevated at 31 U (0-19).
at 120 U (0-19) but SSB (LA) was normal range at
15 U (0-19). Hypocomplementemia was noted with reduced levels of C3 and C4 – 3
mg/dL (16-47) and 13.9 mg/dL (88-201) respectively.

Admission blood urea nitrogen (BUN) and
creatinine (Cr) were both elevated at 20 mg/dL
(7-25) and 1.3 mg/dL (0.6-1.2). Urinalysis was
positive for protein at >500 mg/dL, hemoglob-
inuria (LARGE), red blood cells 58/hpf, white
blood cells 1/hpf. Renal ultrasound demonstrated
ormal sized kidneys with increased echogenicity. A renal biopsy (Figure 1) per-
formed on hospital day #4 showed diffuse pro-
liferative lupus nephritis, Class IV-G (Active)9
with wire loop deposits, hyaline thrombi, dif-
fuse endocapillary proliferation, and extravasated red cells suggestive for thrombot-
ic microangiopathy. Activity levels for
ADAMTS-13 (A Disintegrin And Metalloproteinase with a Thrombospondin
Type 1 Motif, Member 13), however, were nor-
mal at 99% (normal ≥67%). Admission urine
spot Protein:Creatinine ratio was 3.52 – con-
sistent with nephritic range proteinuria.

Complete blood count showed white blood
cell count (WBC) of 4.1 K/mcL (4.0-10.5),
hemoglobin (Hb) of 8.7 g/dL (11.5-15.0),
hematocrit (Hct) of 25.2% (34.0-44.0), and
platelet count (Plt) of 50 K/mcL (150-400).
Lactate dehydrogenase was elevated at 341 U/L
(140-271), haptoglobin suppressed at <30
mg/dL (44-215), and Total bilirubin was normal
at 0.5 mg/dL (0.3-1.0). Direct Antiglobulin Test
(DAT) was weakly positive using both IgG and
C3d specific antihuman globulin (AHG); the
eluate was negative. Schistocytes at approxi-
mately 2-3 per high power field were noted on
the peripheral smear. Coagulation tests
showed normal results for Prothrombin Time
(PT), International Normalized Ratio (INR),
Partial Thromboplastin Time (PTT), and
Fibrinogen (Fib). D-Dimer was non-elevated.
Studies for lupus anticoagulant, anticro-
tilolin IgG and IgM, Beta 2 Glycoprotein 1 IgG
and IgM were negative.

Given her history of cough, dyspnea, and
abdominal discomfort with tenderness to pal-
pation, computed tomography scanning of the
chest, abdomen, and pelvis was obtained.
Trace pericardial and bilateral pleural effu-
sions were noted. Prominent axillary and
mediastinal lymph nodes were felt to be hyper-
plastic in nature and consistent with active
SLE. Minimal interstitial pulmonary edema
was noted as well as subtle, peripherally dis-
btributed ground glass micronodules suggestive
for an infectious process, prompting empiric
antibiotic therapy. A ventilation perfusion scan
was low-probability for pulmonary embolus.
Echocardiogram was unremarkable with nor-
mal systolic function and no significant valvu-
lar vegetations.

There was no improvement during initial
treatment with empiric antibiotics, high-dose
corticosteroids, and mycophenolic acid with
progression of renal failure to a peak Cr of 2.5
mg/dL by day 16 and proteinuria (by spot urine
PrCr ratio) to a peak of 11.55 mg/mg by day 19
(Figure 1). In addition, a significant progress-
ion in her microangiopathic hemolytic pic-
ture occurred, with development of red cell
transfusion dependence and hemolysis to a
nadir hemoglobin of 6.4 g/dL by hospital day 10
and nadir platelet count of 21 K/mcL by day 13.
This was accompanied by a rise in the LDH to
peak of 1689 U/L on day 12. Concern existed for
intercurrent mycophenolic acid-mediated
cytopenias, so this drug was stopped. To
address the lupus nephritis, cyclophosphamide
was administered on Day 14.

Plasma-based therapy was initially withheld
given absence of microthrombi on preliminary
(but not final; Figure 2) renal biopsy report.
This was felt to be justified with return of
ADAMTS-13 activity level at 99%. However,
after further multi-disciplinary discussion, it
was decided that a therapeutic trial of plasma
exchange would proceed following first dose of
rituximab (with appropriate window to prevent
premature apheresis removal of rituximab,
which was added as a salvage agent for lupus
nephritis)10 with plan to convert to ecu-

Figure 1. Renal biopsy images demonstrating the presence of Class IV G (active) lupus nephritis. A) Jones Silver stain demonstrating fibrin thrombus (arrow) within a hilar arte-
riole; B) Hematoxylin & Eosin stain demonstrating diffuse endocapillary hypercellularity
(white arrows) and wire loops (black arrow).
renal recovery occurred during Eculizumab therapy with improvement in BUN, Cr and urine Pr:Cr to 25 mg/dL, 1.1 mg/dL, and 1.64 g/day also by day 83. Her proteinuria continued to improve with spot urine Pr:Cr ratio of 0.65 mg/mg by day 160. At last follow up, day 226 eculizumab maintenance had continued to repress hemolytic activity with Hb 11.9 g/dL, platelet count 306 K/mcL, Cr 0.9 mg/dL, and spot urine Pr:Cr 0.46 mg/mg.

**Discussion**

We describe a case of complement mediated TMA with lupus nephritis as the apparent driver in a patient with negative aHUS gene panel and partial (platelets only) response to therapeutic plasma exchange. Important aspects of this case include the continued hemolysis and transfusion requirement in the face of daily plasma exchange as well as the requirement for at least 5 weekly doses of eculizumab prior to complete cessation of hemolysis.

Our patient demonstrated a significant degree of hemolytic involvement with resolution of haptoglobinemia only after multiple (in our case 5) doses of eculizumab. Coppo et al.,

reiterate this experience in their case report of a child with diffuse proliferative lupus nephritis also associated with significant proteinuria (with spot urine Pr:Cr as high as 10 mg/mg) and atypical HUS whose haptoglobinemia did not improve until after 3 doses of eculizumab. As with our case, theirs demonstrated exquisite platelet responsiveness to eculizumab, a negative aHUS genetic screening panel, and significant improvement in renal function and proteinuria.

We noted a selective response to plasma exchange in our patient – platelet counts, and possibly creatinine improved, but hemolysis was unresponsive. A very similar patient, also with diffuse proliferative lupus nephritis, Class IV G with nephrotic-range proteinuria (4 g/day) and detectable ADAMTS-13 (33%) activity did respond to treatment with therapeutic plasma exchange.

Interestingly, eculizumab may also bear value in the setting of recallitrant, non-TMA lupus nephritis. Pickering and colleagues report a patient in whom Class IV-G (A/C) lupus nephritis involving hypocomplementemia and nephrotic range proteinuria refractory to multiple rounds of cyclophosphamide, rituximab, mycophenolate mofetil, and tacrolimus responded to eculizumab therapy. Notably, renal function and proteinuria responded dramatically following initiation of eculizumab therapy (4 weekly doses of 1200 mg followed by two 1200 mg doses every 2 weeks).

The connection between complement activation and thrombotic processes involved during microangiopathy has recently been explored. Binding of C3a and C5a to their respective receptors leads to activation of endothelial membranes and enhanced expression of adhesion molecules and secretion of von Willebrand Factor and P-selectin with subsequent platelet binding and activation. Concomitantly, downregulation of surface thrombomodulin expression further enhances the prothrombotic phenotype by impairing the Protein C pathway. Receptors for C3a and C5a also appear on platelets leading to platelet activation upon complement binding.

An aHUS panel, performed in our patient by an outside laboratory specializing in aHUS diagnostics, was negative. The presence of either a known-but-untested or an as-yet undescribed genetic complement abnormality remains possible. In two large series of patients with both familial and sporadic aHUS, the absence of detectable genetic abnormalities was reported in ~25% to 48% of individuals.
The tendency toward unchecked complement activation following sometimes innocuous triggers, such as upper respiratory tract infection, gastroenteritis, or pregnancy, may initiate a potentially fatal microangiopathic process that ultimately leads to end-stage renal disease in over 50% and death in over 30% of affected individuals. While an alternative driver — such as infection — was certainly possible in our patient, there was not an appreciable response with empiric antibiotics and the overall clinical presentation appeared most consistent with systemic lupus erythematosus disease activity.

We therefore conclude that the primary driver for complement activation — as evidenced by hypocomplementemia persisting even in the face of daily receipt of donor plasma (a source of donor complement) during therapeutic apheresis — was a renally focused (lupus nephritis) nidus of intense immunologic activity. Unfortunately, the immunofluorescence samples in our case were corrupted thus no immunofixation results exist. Initiation of eculizumab to halt what was a secondary consequence of primary lupus nephritis proved effective.

Once on eculizumab, it is difficult to know when the medication can be discontinued. In many instances, maintenance treatment is continued indefinitely; an important factor given estimated annual drug costs of $350,000 to $645,000. Early reports suggest that maintenance dosing may be modified, and in some cases even suspended, provided complement activity remains suppressed and patients are carefully surveilled (using home urine dipstick for hemoglobinuria and periodic laboratory testing for markers of hemolysis and schistocytosis) to detect relapse, which would require immediate reinstitution of eculizumab. Gatault et al., studied the use of eculizumab trough levels finding that elimination half-life varied significantly based upon weight with an increase from 7.8 days in a 100 kg patient to 19.5 days in a 40 kg patient. Preliminary data, therefore, suggested that 1200 mg maintenance doses could be spaced to every 4 weeks in patients <90 kg and every 6 weeks in patients <70 kg but that additional studies involving individualized dosing were necessary.

In conclusion, our case emphasizes the need for a high degree of clinical awareness surrounding complement-mediated TMA, as well as lupus nephritis as a primary driver. Results for ADAMTS-13 activity and aHUS gene panels may be non-diagnostic, but hypocomplementemia is an important clue. Renal outcomes in the setting of complement-mediated TMA, even in the setting of intercurrent hematologic responses, are typically poor. Eculizumab, although expensive, is highly effective at inducing both hematologic and renal responses. Although plasma-based therapeutics can be initiated, clinicians should have a low threshold to move on to late-complement inhibition in the face of non-response — particularly if the ADAMTS-13 activity level is detectable. Although experience is growing in terms of recognition of complement-mediated TMA, additional studies are required to more clearly identify optimal eculizumab dosing, treatment schedules, monitoring, and endpoints for therapy.

References
1. Constantinescu AR, Bitzan M, Weiss LS, et al. Non-enteropathic hemolytic uremic syndrome: causes and short-term course. Am J Kidney Dis 2004;43:976-82.
2. Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis 2011;6:60.
3. George JN, Nester CM. Syndromes of thrombotic microangiopathy. New Engl J Med 2014;371:654-66.
4. Davin, JC, van de Kar NCAJ. Advances and challenges in the management of complement-mediated thrombotic microangiopathies. Ther Adv Hematol 2015;6:171-85.
5. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol 2010;5:1844-59.
6. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol 2007;18:2392-408.
7. Nester CM, Barbour T, Rodriguez de Cordoba S, et al. Atypical HUS: state of the art. Mol Immunol 2015;67:31-42.
8. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 2013;368:2169-81.
9. Weening JJ, D’Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15:241-50.
10. Gunnarsson I, Jonsdottir T. Rituximab treatment in lupus nephritis – where do we stand? Lupus 2013;22:381-9.
11. Coppo R, Peruzzi L, Amore A, et al. Dramatic effects of eculizumab in a child with diffuse proliferative lupus nephritis resistant to conventional therapy. Pediatr Nephrol 2015;30:167-72.
12. Samson M, Audia S, Leguy V, et al. Haemolytic-uraemic syndrome during severe lupus nephritis: efficacy of plasma exchange. Int Med J 2012;42:95-8.
13. Schwartz J, Winters JL, Padmanabhan A, et al. Guidelines on the use of therapeutic apheresis in clinical practice. Evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apheresis 2013;28:145-284.
14. El-Husseini A, Hanaan S, Awad A, et al. Thrombotic microangiopathy in systemic lupus erythematosus: efficacy of eculizumab. Am J Kidney Dis 2015;65:127-30.
15. Pickering MC, Ismaili M, Condon MB, et al. Eculizumab as rescue therapy in severe resistant lupus nephritis. Rheumatology (Oxford) 2015;54:2286-8.
16. Morigi M, Galbusera M, Gastoldi S, et al. Alternative pathway activation of complement by shiga toxin promotes exuberant c3a formation that triggers microvascular thrombosis. J Immunol 2011;187:172-80.
17. Conway EM. HUS and the case for complement. Blood 2015;126:2085-90.
18. Cugno M, Gualtierotti R, Possenti I, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome. J Thromb Haemost 2014;12:1440-8.
19. Ardissino G, Testa S, Possenti I, et al. Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. Am J Kidney Dis 2014;64:633-7.
20. Gatault P, Brachet G, Ternant D, et al. Therapeutic drug monitoring of eculizumab: rationale for an individualized dosing schedule. MAbs 2015;7:1205-11.