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Case Report

C3 Glomerulopathy and Atypical Hemolytic Uremic Syndrome: Two Important Manifestations of Complement System Dysfunction

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C3 glomerulopathy · Atypical hemolytic uremic syndrome · Complement dysfunction

Abstract
The advances in our understanding of the alternative pathway have emphasized that uncontrolled hyperactivity of this pathway causes 2 distinct disorders that adversely impact the kidney. In the so-called atypical hemolytic uremic syndrome (aHUS), renal dysfunction occurs along with thrombocytopenia, anemia, and target organ injury to multiple organs, most commonly the kidney. On the other hand, in the so-termed C3 glomerulopathy, kidney involvement is not associated with thrombocytopenia, anemia, or other system involvement. In this report, we present 2 cases of alternative pathway dysfunction. The 60-year-old female patient had biopsy-proven C3 glomerulopathy, while the 32-year-old female patient was

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diagnosed with aHUS based on renal dysfunction, thrombocytopenia, anemia, and normal ADAMTS-13 level. The aHUS patient was successfully treated with the monoclonal antibody (eculizumab) for complement blockade. The patient with C3 glomerulopathy did not receive the monoclonal antibody. In this patient, management focused on blood pressure and proteinuria control with an angiotensin-converting enzyme inhibitor. This article focuses on the clinical differences, pathophysiology, and treatment of aHUS and C3 glomerulopathy.

Introduction

While all 3 pathways of the complement system are involved in the pathogenesis of glomerular diseases, the uncontrolled hyperactivity of the alternative pathway is gaining importance for 2 reasons [1–5]. Firstly, the advances in our understanding of the alternative pathway have clarified diagnosis of disorders related to this pathway. Secondly, the advent of therapeutic complement blockade has allowed clinicians to help their patients with alternative pathway disorders [5].

In simple terms, the unrestrained hyperactivity of the alternative pathway causes 2 related but somewhat distinct disorders that adversely impact the kidney. In the so-termed atypical hemolytic uremic syndrome (aHUS), renal dysfunction occurs along with thrombocytopenia and anemia [1–5]. This syndrome can be associated with the involvement of other systems. On the other hand, in the so-called C3 glomerulopathy, typically, kidney involvement is not associated with thrombocytopenia and anemia [1]. In addition, C3 glomerulopathy is not associated with the involvement of other organs. In this article, we present the case of a 60-year-old female patient with C3 glomerulopathy and the case of a 31-year-old female patient with aHUS and present clinical features, diagnostic elements, and pathophysiology of the 2 entities.

Case Reports

Case 1

A 60-year-old Caucasian female with a past medical history of systemic lupus erythematosus presented with the chief complaints of hematuria and fatigue for 1 month. Fatigue was accompanied by bilateral lower extremity pain. She also reported intermittent arthralgias and myalgia. She denied any spontaneous bruising, fever, chest pain, dyspnea, dysuria, and abdominal pain. Her past medical history was significant for hypertension and basal cell carcinoma (successfully treated in the past). At the time of admission, her medications included hydroxychloroquine 200 mg daily with intermittent steroids (20 mg by mouth) for systemic lupus erythematosus and amlodipine 10 mg/day for the treatment of hypertension. On physical examination, her vital signs were normal with good blood pressure control (blood pressure <140/90 mm Hg). Abdominal examination displayed no tenderness or distension. Bowel sounds were normal. Laboratory data showed normal hemoglobin and platelet count. Renal function revealed an estimated glomerular filtration rate at 54 mL/min. Uri-

nalysis demonstrated numerous dysmorphic red blood cells and proteinuria. Protein excretion was quantified at 385 mg/dL (Table 1). To investigate the possibility and class of lupus nephritis, a renal biopsy was obtained. Tissue analysis showed diffuse mesangial proliferative glomerulonephritis with dominant C3 staining, consistent with C3 glomerulopathy (Fig. 1). Hematuria resolved spontaneously. The treatment of nephropathy revolved around optimal management of blood pressure. Because of proteinuria and renoprotective capability, angiotensin-converting enzyme inhibitor was initiated. Amlodipine was discontinued. The patient was asked to have a close follow-up to watch for renal function deterioration or increment in proteinuria. Complement blockade with the monoclonal antibody (eculizumab) was not initiated.

Case 2

A 32-year-old African American female presented to the emergency department with the chief complaints of fever (103.5°F), chills, and hematuria. The patient had been experiencing 7–8 bowel movements of watery diarrhea with nausea and vomiting for the last 2–3 days. Diarrhea was accompanied by persistent pain in the right upper quadrant, 8/10 in intensity for the last 2 days, and was associated with blood at least once. Review of system revealed no chest pain, shortness of breath, spontaneous bruising, or pain with urination. Her past medical history was remarkable for HIV (diagnosed 1 year ago) and hypertension (controlled with amlodipine). The family history was also positive for hypertension, stroke, and end-stage renal disease in her cousin at the age of 39 years. On examination, she had a temperature of 99.5°F and a blood pressure of 118/57 mm Hg. Abdominal examination showed healed cholecystectomy scar with soft abdomen. There was right upper quadrant tenderness to light touch and normal bowel sounds. The rest of the examination was insignificant. In the emergency department, the patient received 1 L of normal saline, vancomycin, and gentamicin. Laboratory data revealed the constellation of anemia (7.5 g/dL) and thrombocytopenia (120 × 10^3/mL). Peripheral smear was positive for schistocytes, and Coombs test was negative. Serum haptoglobin was low at 12 mg/dL, and lactate dehydrogenase was increased to 375 U/L. Serum complement levels were normal (C3 = 85, C4 = 20). Urinalysis demonstrated proteinuria and hematuria with multiple dysmorphic red blood cells. Severe renal failure at a serum creatinine of 8.4 mg/dL necessitated hemodialysis therapy. Computed tomography of the abdomen and pelvis with contrast showed no abdominal pathology including obstruction. Blood and stool cultures were negative for Shiga toxin. ADAMTS-13 activity was normal at 70%. Based on history and clinical and laboratory result evaluation, a diagnosis of aHUS was made. After discussion with the patient, eculizumab was initiated. After a 2-week course of medication, the patient started feeling better with no hematuria, abdominal pain, and diarrhea or vomiting. Anemia and thrombocytopenia normalized; however, the patient remained dialysis dependent.

Discussion

Over the past decade, advances in our understanding of the alternative complement pathway in the pathogenesis of glomerular diseases and its blockade with the monoclonal antibody has led to a major progress in the management of these disorders. In general, 2

distinct and important forms of renal diseases are encountered with dysfunctional alternative complement pathway [6]. The 32-year-old patient demonstrated renal dysfunction in the context of anemia, thrombocytopenia, and systemic involvement with target organ injury (gastroenteritis, renal dysfunction) consistent with hemolytic uremic syndrome, while the 60-year-old patient demonstrated isolated renal involvement without the presence of anemia and thrombocytopenia, consistent with C3 glomerulopathy.

Atypical hemolytic-uremic syndrome features endothelial damage resulting in target organ injury (renal, gastrointestinal tract, liver, pancreas, and brain), consumptive thrombocytopenia, and microangiopathic hemolytic anemia [7]. Peripheral smear may or may not show schistocytes. In contrast to thrombotic thrombocytopenic purpura, patients with aHUS do not demonstrate the deficiency of the von Willebrand factor cleaving protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [8]. ADAMTS-13 activity is often greater than 5–10% in patients with aHUS [9]. In case 2, the ADAMTS-13 activity was found to be well above the 5–10% (70%). This patient also demonstrated the presence of schistocytes, low haptoglobin, and high lactate dehydrogenase. While C3 is highlighted to be low in aHUS, recent information has emphasized that many patients with aHUS demonstrate normal C3 and C4, as was the case in our patient [10]. We did not proceed to obtain a renal biopsy, as aHUS does not require tissue analysis to make the diagnosis. Renal injury (with/without other target organ injury), anemia, thrombocytopenia plus normal ADAMTS-13 constitute the diagnosis of aHUS [11]. Our case 2 demonstrated all of these features.

C3 glomerulopathy, an emerging class of glomerulonephritis that occurs at all ages, does not have a sex predilection with a majority of patients presenting with hypertension, proteinuria, hematuria, and renal dysfunction [12]. In contrast to aHUS, C3 glomerulopathy requires renal biopsy and is characterized by dominant C3 staining on immunofluorescence without any evidence of immunoglobulins. Unlike aHUS patients, these patients do not demonstrate anemia, thrombocytopenia, or multisystem involvement. Based upon the location of C3 deposits, C3 glomerulopathy is categorized into dense deposit disease or DDD (deposits of C3 are dense with intramembranous and mesangial location) and C3 glomerulonephritis or C3GN (deposits are located at subendothelial, subepithelial, intramembranous, and mesangial location) [13]. This patient did not demonstrate anemia, thrombocytopenia, or other target organ injury. Because the treatment of C3 glomerulopathy has not been conclusively established, this patient was not treated with complement blockade therapy.

Both aHUS and C3 glomerulopathy are caused by an uncontrolled activation of the alternative pathway of the complement system. However, aHUS leads to system-wide endothelial injury resulting in thrombotic microangiopathy (with anemia and thrombocytopenia) and ischemia injury to multiple organs [14]. On the other hand, C3 glomerulopathy results in renal injury due to deposition of C3 in the kidney. The diagnosis of C3 requires a renal biopsy and demonstration of C3 without immunoglobulins [15]. The diagnostic approach also focuses on genetic testing investigating the presence of mutations related to factor H, I, and membrane co-factor protein and autoantibody assessment [16]. The auto-antibodies called C3 nephritic factor and anti-CFB stabilize C3 convertase, activate the alternative pathway, and induce renal damage by depositing C3 in the mesangial, subendothelial, intramembranous, and subepithelial space [17].

Recent information emphasizes that C3 glomerulopathy may differ from aHUS in the location where the alternate pathway dysregulation occurs [18, 19]. It has been documented that the alternative pathway consists of a network of complement regulatory proteins in either the fluid phase, as soluble plasma proteins, or in the solid phase, as cell membrane proteins. The underlying defect in most instances of the C3 glomerulopathy is felt to be excessive activation of the alternative complement pathway in the fluid phase. By contrast, the endothelial damage that is a hallmark of aHUS is considered, in most cases, to result from dysregulation at the level of the cell membrane, or in the solid phase. This solid phase dysregulation makes aHUS a more homogenous syndrome than the C3 glomerulopathy, which has major implications in terms of prognosis and response to therapy (Table 2).

The prognosis of aHUS is poor as compared to C3 glomerulopathy. While the mortality rate approaches 25% during the acute phase, renal function is severely impaired in nearly half of the patients, necessitating renal replacement therapy [20]. Our case 2 had severe renal failure and required hemodialysis therapy.

A humanized monoclonal clonal antibody (eculizumab) has recently been employed for the management of patients with C3 glomerulopathy and aHUS [21–29]. Eculizumab effectively blocks the cleavage of C5 and averts the formation of membrane attack complex [5, 29]. While eculizumab is approved for the treatment of patients with aHUS by the US Food and Drug Administration, its use in C3 glomerulopathy remains controversial [5, 29]. There have been recent reports of the use of eculizumab for the treatment of C3 glomerulopathy [21–28]. The largest prospective trial of eculizumab administration for the management of C3 glomerulopathy included 6 subjects [27]. These patients were treated with eculizumab for 1 year. Following therapy, a significant reduction in serum creatinine was found in 2 patients. One patient with nephrotic syndrome demonstrated remission. Another patient demonstrated stable renal function based upon laboratory data. However, 2 out of the 6 patients continued with progressive worsening of renal function. Based upon these results, it is hard to endorse eculizumab for the treatment of C3 glomerulopathy. Clinical trials with a large sample size are needed to conclusively establish the superiority of eculizumab in the management of C3 glomerulopathy. In contrast, once the diagnosis is accurately established, eculizumab is the appropriate treatment of aHUS. Eculizumab administration results in a rapid improvement in laboratory parameters and target organ injury [5, 9, 20, 29]. In patients with aHUS, eculizumab must be initiated promptly in order to avoid significant morbidity and mortality associated with this syndrome.

Conclusion

While both entities are related to the uncontrolled activation of the alternative complement pathway, C3 glomerulopathy (isolated renal disease) is distinct from aHUS (multisystem involvement with renal predilection). Complement blockade has provided an effective way to ameliorate the damage brought on by aHUS. However, definitive treatment for C3 glomerulopathy continues to evolve. A better understanding of the complement pathway and targeted blockade of the complement system are needed to optimally treat patients with complement disorders. More studies with a larger sample size and appropriate design are

needed to conclusively establish the role of eculizumab in the treatment of C3 glomerulopathy.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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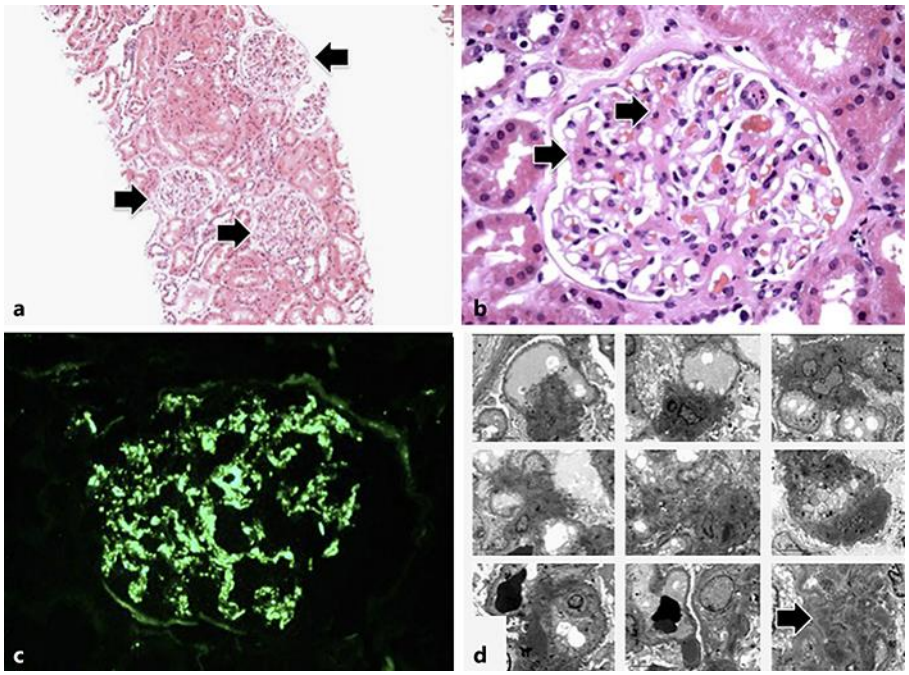

Fig. 1. Kidney biopsy is shown. Several glomeruli are noted in the cortex (arrows) (**a**). A glomerulus showing mild mesangial expansion (arrows) (**b**). Immunofluorescence microscopy demonstrating mesangial C3 deposition (green staining) (**c**). Ultrastructural examination revealing mesangial electron-dense deposits (**d**).

Table 1. Laboratory parameters of the 2 female patients

	Case 1 (C3 glomerulopathy)	Case 2 (aHUS)
Sodium, mmol/L	140	135
Potassium, mmol/L	4.4	3
Chloride, mmol/L	97	101
Calcium, mmol/L	9.4	9.8
Total protein, g/dL	6.8	
Albumin, g/dL	4.2	2.6
Blood urea nitrogen, mg/dL	15	22
Creatinine, mg/dL	1.11 (high)	5.83
eGFR, mL/min/1.73 m^2	54 (low)	16
WBC, $\times 10^9$/μL	7.2	15.2
RBC, $\times 10^6$/μL	5.26	3.66 (low)
Hemoglobin, g/dL	16	12.2
Hematocrit	47.4	36.9
MCV	90	99
MCH	30.4	30.3
MCHC	33.8	30.6
RDW	14.4	19.7 (high)
RBC morphology	normal	abnormal
Platelets	199	117
Neutrophils	54	43.1
Lymphocytes	36	36.5
Urinalysis		
Specific gravity	1.021	1.020
pH	6.5	6.0
Urine color	yellow	amber
Appearance	cloudy	cloudy
Proteins	Trace	300
Glucose	negative	negative
Ketones	negative	negative
Occult blood	3+ (abnormal)	large
Urobilinogen	0.2	0.2
Nitrites	negative	negative
WBC	0–5	3–5
RBC	11–30 (abnormal)	8–10
Epithelial cells	0–10	many
Protein/creatinine ratio	385 (high)	

aHUS, atypical hemolytic uremic syndrome; eGFR, estimated glomerular filtration rate; WBC, white blood cell count; RBC, red blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, red cell distribution width.

Table 2. Differentiating features of C3 glomerulopathy and aHUS

	C3 glomerulopathy	aHUS
Clinical features	Hematuria, proteinuria, renal failure	Hematuria, proteinuria, renal failure, thrombocytopenia and anemia
Multi-system involvement	No	Yes
Laboratory parameters	Proteinuria, hematuria, increased BUN and Cr, low GFR	Proteinuria, hematuria, increased BUN and Cr, low GFR Thrombocytopenia (relative or absolute), anemia, low haptoglobin, elevated LDH, schistocytes on peripheral smear can be observed
ADAMTS-13	At present no role in establishing the diagnosis	Important in establishing the diagnosis
Renal biopsy	Required to make the diagnosis	Not required to make the diagnosis
Pathophysiology	Alternate complement pathway dysregulation (fluid phase)	Alternate complement pathway dysregulation (solid phase)
Prognosis	Relatively better prognosis	Worse prognosis with high recurrence
Treatment	Role of complement pathway blockade is controversial	Role of complement blockade established

aHUS, atypical hemolytic uremic syndrome; BUN, blood urea nitrogen; Cr, creatinine; GFR, glomerular filtration rate; LDH, lactate dehydrogenase.