CASE REPORT

Atypical haemolytic uremic syndrome (aHUS) and membranoproliferative glomerulonephritis (MPGN), different diseases or a spectrum of complement-mediated glomerular diseases?

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Accepted 27 July 2017

SUMMARY

Historically, patients with kidney diseases caused by genetic or acquired dysregulation of the complement alternative pathway have been grouped into clinical syndromes, C3 glomerulopathy (C3GN/DDD) and thrombotic microangiopathy (TMA), specifically atypical haemolytic uremic syndrome (aHUS). Recent data suggested that these diseases share a common pathophysiology and that patients can transition between glomerulopathies in this spectrum. Histopathologically, the main difference cited is the immunofluorescence (IF) findings, with C3 predominance in C3 glomerulopathy (compared with immunoglobulins and complements in immune complex-mediated membranoproliferative glomerulonephritis (MPGN)) and negative IF in TMA. We report a case in which a patient presented with hypertension, seizures, proteinuria, renal impairment and immune complex-mediated MPGN on kidney biopsy. Months later, she presented with classical TMA. She failed to respond to steroids and plasma exchange therapy but subsequently made a remarkable haematological and renal recovery after eculizumab treatment, thus supporting an underlying complement dysregulation and a diagnosis of aHUS.

BACKGROUND

Complement-mediated kidney disease has been an evolving area of nephrology. The understanding of the role of complement system dysregulation in kidney disease has led to reclassification of old disease entities like membranoproliferative glomerulonephritis (MPGN). This has also led to the discovery of effective therapies for these conditions previously described as idiopathic and not effectively treated. Patients often times present first to family physicians, general internists and emergency room physicians before they are managed by nephrologists. It is important to shed light on this old disease entity but with updated classification and treatment approaches as timely diagnosis and management improves patients' survival and renal outcomes.

CASE PRESENTATION

Our patient, a 36-year-old woman who was previously healthy, except for a history of hearing loss since childhood, presented with anasarca and was

found to have hypertension and proteinuria and subsequently developed generalised tonic-clonic seizures. She was transferred to the intensive care unit (ICU) where she was intubated and received antiseizure medications. A review of her medical condition showed that she had neither infectious or connective tissue disease symptoms nor prior evidence of deep vein thrombosis or abortions. She did not receive any medications nor did she take oral contraceptives. She had no family history of a similar illness, and her blood pressure was 200/110 mm Hg. Her blood results are shown in [table 1](#). MRI of the brain showed parenchymal changes presumably related to posterior reversible encephalopathy syndrome. An electroencephalogram (EEG) showed no epileptiform discharges, and a lumbar puncture excluded a central nervous system infection. The new onset of hypertension, active urine sediment and progressive elevation of creatinine levels from an unknown baseline were all suggestive of a glomerular pathology; hence, a kidney biopsy was performed. She was treated with three doses of intravenous methylprednisolone; subsequently, her dosage was revised to 50 mg of oral prednisone daily. Her seizures resolved, and she was discharged from the hospital. Her biopsy findings revealed eight glomeruli on light microscopy with an MPGN pattern, no evidence of global or segmental sclerosis, no crescents or necrosis, a single focus of possible fibrin thrombus and no tubular atrophy or interstitial fibrosis. Congo red staining for amyloid fibrils was negative. The immunofluorescence results showed seven glomeruli with moderate granular staining for IgG and C3 in the capillary loops, trace staining for kappa, lambda and C1q and negative IgA and fibrin staining. Electron microscopy showed one hypercellular glomerulus with subendothelial and mesangial but no subepithelial dense deposits compatible with an immune complex-mediated MPGN ([figure 1](#)). In the nephrology outpatient clinic, the patient was clinically healthy with controlled blood pressure ([table 1](#)). Her prednisone dosage was decreased to 25 mg daily. One month later, follow-up blood work showed severe haemolytic anaemia and thrombocytopenia, which prompted hospital admission and additional laboratory tests ([table 1](#)). During her hospital stay, her seizures

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To cite: Ankawi GA, Clark WF. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220974

Table 1 Laboratory investigations

	First admission	Outpatient follow-up (1 month after discharge)	Second admission (1 month after follow-up)	Most recent follow-up (7 months after starting eculizumab)
Urea (mg/dL)	26.3		42.9	22.1
Creatinine (mg/dL)	1.3	2.5	3.4	1.3
eGFR (ml/min/1.73 m ²)		21		54
Serum albumin (g/dL)	2.5		3.4	4.3
Urinalysis protein (mg/dL)	>300	>300	>300	Negative
Urine microscopy (RBC/HPF)	>100		>100	
Microalbumin/creatinine ratio (mg/g)	1649		3831 (peak)	186
24 hours urine collection for protein (mg/24 hours)	1440			
White blood cells (10 ⁹ /L)	11.2	19.4	14.1	8.7
Haemoglobin (g/dL)	12.4	9.4	6.1	11.7
Fragmented red blood cells			Positive	
Platelets (10 ⁹ /L)	265	282	88	266
Reticulocytes			High	
Lactate dehydrogenase (IU/L)			1167	173
Haptoglobin (mg/dL)			<7	
INR	1		0.9	
PTT (s)	2		21	
C3 (mg/dL)	13 (Low)		41(Low)	66
C4 (mg/dL)	4		13	19
ANA	Negative			
pANCA	Negative			
cANCA	Negative			
Anti-GBM	Negative			
Rheumatoid factor	Negative			
Hepatitis B serology	Negative			
Hepatitis C serology	Negative			
Lupus anticoagulant	Negative			
Antiphospholipid antibodies	Negative			
Cryoglobulins			Negative	
ADAMTS 13 (%)			>71	

Conversion factors for units: serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; Urea in mg/dL to mmol/L, $\times 0.357$; albumin to creatinine ratio in mg/g to mg/mmol, $\times 0.113$. ADAMTS 13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ANA, antinuclear antibody; Anti-GBM, antglomerular basement membrane antibodies; C3, complement 3; C4, complement 4; cANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; CH50, total complement activity; eGFR, estimated glomerular filtration rate; HPF, high-power field; INR, international normalised ratio; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PTT, partial thromboplastin time; RBC, red blood cell.

Figure 1 Kidney biopsy. Electron microscopy showing subendothelial dense deposits compatible with an immune complex-mediated membranoproliferative glomerulonephritis.

recurred. She appeared to have thrombotic microangiopathy (TMA) after a recent diagnosis of immune complex-mediated MPGN. Her oral prednisone dosage was increased to 70 mg daily, and plasma exchange (PLEX) was initiated, which was increased to twice a day and subsequently three times per day.¹ She received a total of 13 exchanges of 5 litres each of cryo-supernatant and fresh frozen plasma. She failed to respond to treatment and exhibited persistent lactate dehydrogenase (LDH) elevation. Her laboratory results continued to show low platelet and haemoglobin levels and elevated creatinine concentrations. The normal level of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS 13) and failure to respond to PLEX and conventional therapy for her renal impairment were consistent with a diagnosis of atypical haemolytic uremic syndrome (aHUS). She was administered a meningococcal vaccine and eculizumab at an initial dose of 900 mg intravenously weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 7 days later and then 900 mg intravenously every 14 days thereafter. While management continued, genetic analysis was performed to screen for predisposing aHUS

risk factors. Direct sequence analyses of the *CFI*, *CFH*, *CFB*, *CD46*, *CFHR5*, *C3*, *APLN* and *THBD* genes revealed a variant of unknown significance (c.3325T (p. Cys1109Ser)) in the *CFH* gene. With eculizumab treatment, all parameters dramatically improved, including LDH, haemoglobin, platelet and creatinine levels. Overall, her severe neurological manifestations required prolonged ventilatory support, tracheostomy and an extended ICU stay followed by gradual rehabilitation, but her recovery was remarkable. She was finally discharged from the hospital with a tapering dose of prednisone, eculizumab administered every 2 weeks, a tapering dose of phenytoin and four antihypertensive medications (tapered over time).

OUTCOME AND FOLLOW-UP

During follow-up, she continued to improve clinically. A repeat EEG showed normal results, and phenytoin was stopped. Her most recent follow-up blood tests are shown in table 1.

DISCUSSION

During the last 15 years, our improved understanding of complement-mediated kidney diseases has resulted in a major change in the classification of these disorders. With the development of a monoclonal antibody that acts as a terminal complement inhibitor (eculizumab), the outcome of these patients has dramatically improved, stressing the importance of accurate diagnosis. Eculizumab has proven to be effective for treating patients with aHUS.^{2,3} Fewer than 15% of patients with aHUS are refractory to eculizumab treatment.⁴ Current recommendations suggest that all patients with a diagnosis of aHUS (ADAMTS 13 > 10%, TMA without a known secondary cause) should be treated. Earlier initiation is associated with a better response. The likelihood of renal recovery in patients who commence treatment after receiving dialysis for some time is inconsistent; however, the likelihood of recovery appears to be higher in patients who are treated earlier.^{3,5} The side effects are relatively benign, and apart from meningococcal vaccine administration, no other measures are required before commencing therapy. Patients should receive vaccination against influenza, treatment against active infections and counselling regarding the increased risk of flares during infections, pregnancy and the postpartum period.⁵ The optimal duration of therapy and its discontinuation in a certain subset of patients are currently unknown. The role of eculizumab treatment is less established in patients with C3 glomerulopathies as they demonstrate variable degrees of C5 convertase dysregulation. Blockade at the C3 level may be an alternative to eculizumab.^{4,6,7} For C3 glomerulopathies, a short duration of disease and rapidly progressive or crescentic forms might favour a trial of treatment using eculizumab.⁵ However, our patient presented with an immune complex-mediated MPGN, and months later, she developed TMA with worsening kidney function. In both TMA and C3 glomerulopathies, the overactivation of the complement alternative pathway (AP) may be spontaneous or triggered by infections, vaccinations, immunosuppressive or antineoplastic agents, oral contraceptives, pregnancy, childbirth or the development of monoclonal gammopathy.⁴ In a diagnostic work-up, C3 and CFB should be considered the principal activating proteins of the AP. The key regulatory proteins of the AP are CFH, CFI, MCP and five-factor H-related proteins, CFHR1-5. CFH mutations comprise the most common genetic abnormality in aHUS with a 20% to 30% prevalence. An acquired CFH defect due to anti-CFH IgG autoantibodies accounts for 5% to 10% of adult cases.⁸ Up to 50% of patients with a diagnosis of aHUS have no identifiable mutation.

Our case highlights the challenges of diagnosing and managing this disease entity, particularly with the overlapping features of the different categories of MPGN. Our patient presented with an immune complex-mediated MPGN; however, months later, she developed TMA with progressive loss of renal function. Her TMA was associated with normal levels of ADAMTS 13, and she was resistant to PLEX therapy, making thrombotic thrombocytopenic purpura (TTP) unlikely.⁹ Prior to this report, it was thought that the immune complex negative forms of MPGN occurred in aHUS.¹⁰ Our case suggests that a diagnosis of aHUS should be considered in patients with immune complex-mediated MPGN who develop TMA with ADAMTS 13 values > 10%. The availability of effective therapy-like PLEX for TTP and some types of secondary TMA or eculizumab treatment for aHUS stress the importance of identifying which type of TMA the patient is suffering. Presently, cost and uncertainty with regard to the duration of eculizumab therapy represent ongoing challenges.

Learning points

- ▶ Complement-mediated kidney disease is an evolving area of nephrology with new emerging therapies.
- ▶ Complement-mediated kidney disease represents a disease spectrum and patients can transition between glomerulopathies in this spectrum.
- ▶ Effective therapy has been identified in the recent years, thus an accurate and timely diagnosis is important and improves patients' survival and renal outcome.
- ▶ Diagnosis of aHUS is not limited to immune complex negative forms of membranoproliferative glomerulonephritis (MPGN) and should be considered in patients with immune complex-mediated MPGN who develop thrombotic microangiopathy with a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 values > 10%.

Contributors Both authors contributed to the conception and design of the study and drafting the article. Both gave final approval of the version published. Both agreed to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

Competing interests WFC has received speaking honoraria from Octapharma.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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