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Clinical Report

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Recovery of renal function succeeding stem cell transplant: a case of C3 Glomerulonephiritis secondary to monoclonal gammopathy

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Abstract
Membranoproliferative glomerulonephritis (MPGN) and C3 glomerulonephritis (C3 GN) can be secondary to monoclonal gammopathy and multiple myeloma. MPGN Type 1 is caused by activation of the classical pathway by immune complex formation, and C3 GN results from abnormalities in the alternative pathway of complement. In previously reported cases of MPGN and C3 GN secondary to monoclonal gammopathy/multiple myeloma, renal outcome has been poor. Here, we present the first patient, to our knowledge, who showed full renal recovery and normalization of the complement system after chemotherapy and stem cell transplantation.

Keywords: C3 glomerulonephritis; membranoproliferative glomerulonephritis; monoclonal gammopathy

Background

Renal involvement in monoclonal gammopathy and multiple myeloma is well described and the most common is tubular damage by light chain cast nephropathy (myeloma kidney) and glomerular damage through amyloidosis or light chain deposition disease (LCDD).

Membranoproliferative glomerulonephritis (MPGN) associated with monoclonal gammopathy has also been described, and Sethi *et al.* [1] introduced the term monoclonal-associated MPGN (MG-MPGN) to characterize a type of MPGN with monoclonal immunoglobulin (Ig) deposits (whole molecule or subunits), which mimics immune complex MPGN and differs from LCDD by the absence of Ig deposition on tubular and vascular basement membranes, and by the non-linear, granular appearance of glomerular deposits.

Monoclonal gammopathy has also been linked to C3 glomerulonephritis (C3 GN) [2, 3]. C3 GN is an uncommon, recently described, condition characterized by bright complement C3 staining and the absence of Ig on immunofluorescence. It can be with or without MPGN morphology with mesangial and/or subendothelial electron dense deposits on electron microscopy [4–6]. It typically results from abnormalities in the alternative pathway of complement (CAP), which can be both genetic and acquired. Recently, Bridoux *et al.* [7] described six patients with C3 GN secondary to monoclonal gammopathy.

In previously reported cases of monoclonal gammopathy and C3 GN, renal outcome has been poor [3, 7]. Although chemotherapy has been reported to improve renal function [7, 8] and to normalize C3 nephritis factor (C3NeF) activity [8], no previous reports on renal outcome succeeding stem cell transplant have been found.

Here, we present a patient with a combination of MG-MPGN and C3 GN secondary to monoclonal gammopathy, which show full recovery after chemotherapy and stem cell transplantation.

Case report

A 64-year-old woman was referred to the hospital with continuous proteinuria and microscopic haematuria in the past 3 years. She had noted foaming urine several times and slight peripheral oedema during urinary tract infections. Apart from this, she has had no prior significant illness and her well-being was unaffected at the time of admission.

There was no family history of kidney disease.

At the time of admission, the physical examination was normal. Urine analysis revealed significant proteinuria and kappa light chains were found in the urine together with a urine IgG(K) M-component. Urine microscopy showed over 100 erythrocytes per high power field, no leucocytes or erythrocyte casts. Kidney function was normal. A positive plasma M-component was found with elevated free kappa light chains. Remaining blood samples were in the normal range. No erythrocyte sedimentation or complement factors were measured at this point. Selected laboratory findings are specified in Table 1.

A normal renal ultrasound was found prior to a renal biopsy. The biopsy showed a light microscopic picture of MPGN (Figure 1). Electron microscopy revealed subendothelial

Table 1. Laboratory findings

	Reference	November 2009	November 2010	August 2011	December 2011	March 2012	September 2012	May 2013
Serum creatinine	45–80 µmol/L	77	83	88	85	100	70	62
eGFR	mL/min per 1.73 m^2		60	56	59	49	73	84
Proteinuria	g/24 h	3.22		3.2			0.4	
Urine M-component			Positive	Positive	Positive	Positive	Negative	
Urine kappa light chain	<10		51	43		214	10	
Serum haemoglobin	7.1–9.3 mmol/L	7.2	7.2	6.6	6.1	6.7	7	8
Serum albumin	37–48 g/L		28	27	27	29	31	
Erythrocyte sedimentations rate	<20					104	25	
Serum M-component	g/L	8	11		29	37	<2	Negative
P-IgA	0.7–3.7 g/L	1.3				0.36	1.11	
P-IgG	6.1–14.9 g/L	14.1				40.4	11.7	8.3
P-IgM	0.4–2.1 g/L	1.2				0.58	0.82	
P-free kappa light chain	3.3–19.4 mg/L	98.4	80.1		425.1	720.3	22.8	10.8
P-free lambda light chain	5.7–26.3 mg/L	10.2	10.8		7.9	7.2	16	9
P-kappa/lambda ratio	0.62–1.70	9.65	7.45		54.1	99.7	1.4	1.2
Plasma complement C3	0.9–1.8 g/L				0.24		1.02	1.09
Plasma complement C4	0.1–0.4 g/L				<0.04		0.25	0.22
Complement factor B	54–154%					9	92	
Complement C3NeF cleavage	Positive >10%					40	3	
Complement C3NeF haemolytic assay	Negative ≤15%					3.5	3	
Complement factor I	60–152%					260	117	
Complement factor H	69–154%					155	115	

November 2009: admission, stage of MGUS; December 2011: stage of light chain myeloma; March 2012: treatment with chemotherapy is started; September 2012: 3 months after stem cell transplant; May 2013: 1 year after stem cell transplant.

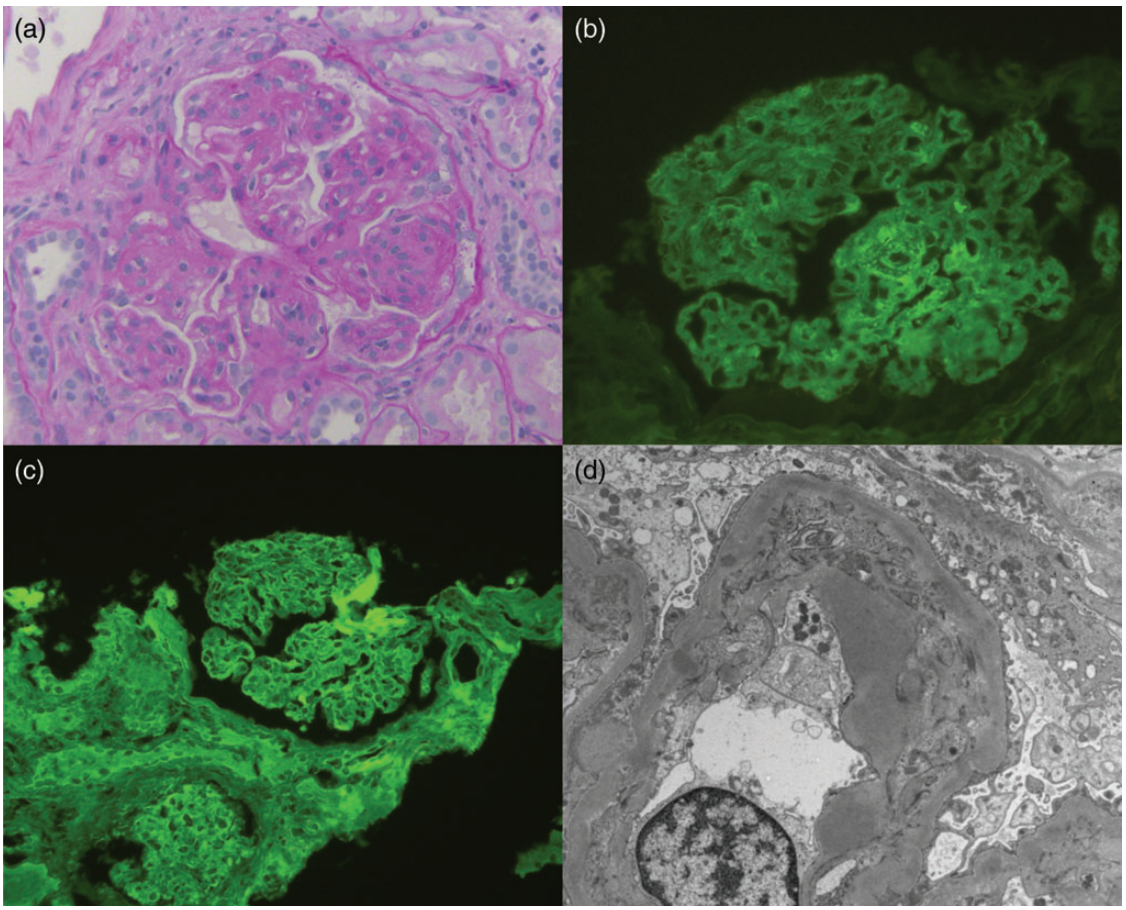

Fig. 1. Renal biopsy. (**a**) Membranoproliferative glomerulonephritis, Periodic Acid Schiff ×200; (**b**) immunofluorescence for C3, ×200; (**c**) immunofluorescence for kappa light chain, ×200; (**d**) electron microscopy demonstrating splitting of the glomerular basement membrane and deposits.

deposits in the peripheral glomerular basement membrane, which also showed a sign of splitting. Deposits were, moreover, present in the mesangium. Immunofluorescence revealed strong reaction to C3 corresponding to the deposits, but no Ig. Kappa light chains were present all over the tissue. A bone marrow biopsy was performed showing a normal haematopoietic marrow with all cells represented. There was no myeloma infiltrates, but there was a small amount of single multiple myeloma oncogene 1 (MUM1)-positive plasma cells. Both kappa and lambda colouring were strong and inconclusive. No atypical plasma cells were seen in the smear. The findings were interpreted as a state of monoclonal gammopathy of undetermined significance (MGUS).

The patient started treatment with an angiotensin-converting enzyme inhibitor to improve renal dynamics, to decrease proteinuria, to control blood pressure and to limit glomerular leucocyte infiltration.

In the succeeding 18 months, the patient's condition was stable. There was sustained proteinuria and increased kappa light chain in blood samples (Table 1). Twenty-five months after admission, the patient had increasing plasma light chains and plasma M-component with an even more distinct kappa–lambda ratio. Plasma IgG had also increased. The proteinuria and kidney function were, however, unchanged.

At this time, the patient was discussed, as the significant amount of peripheral C3 deposition in the kidney biopsy arouse the question of a possible C3 GN and serum complement was measured. Both plasma C3, C4 and factor B were reduced. A C3NeF was found estimated by a positive fluid phase C3NeF cleavage, although negative C3NeF haemolytic assay [9, 10]. Complement factor I (CFI) and H (CFH) were affected. Erythrocyte sedimentation was highly elevated and the patient had become anaemic (Table 1). Therefore, a new bone marrow biopsy was performed showing increased amounts of atypical plasma cells, 10–15% with a positive reaction to MUM1, and kappa monoclonal chains were also found in the smear and imprint. Thus, the patient had progressed to a state of light chain myeloma and treatment was started with three series of bortezomib and dexamethason followed by cyclophosphamide priming and autologous stem cell transplant.

Three months after a successful transplant, proteinuria had decreased. The patient's blood samples, including Igs and complement factors, were in the normal range. One year after stem cell transplantation, the proteinuria had disappeared, kidney function was normal and complement factors, haematological parameters and Igs were all normal (Table 1).

Discussion

Here, we present a patient, who has a light- and electromicroscopic picture of MPGN with subendothelial and intramembranous deposits of C3 and the absence of Ig. Thus, C3 GN seems straightforward, but there are also substantial amounts of kappa light chains in the tissue, especially surrounding the C3 deposits, suggesting that the deposition of light chains might cause the secondary C3 deposition, as the monoclonal Ig in the case of MG-MGPN described by Sethi *et al.* [1] Sethi *et al.* hypothesized that the deposition of monoclonal Ig activates the complement system to cause acute injury to the glomerular capillary walls and mesangium causing proliferative and reparative changes. This hypothesis was supported by the frequent co-localization of C3 with the monoclonal Ig in the mesangium and along capillary walls. Reduced C3 and C4 levels were described together with isolated C3 staining in three biopsies, but it is not clear if co-localization of C3 and light chains was found. Whether examinations for C3NeF were made is also unknown.

Hypocomplementemia is common in monoclonal gammopathy [7]. Abnormalities in both classical (CCP) and the alternative complement pathway (CAP) are also common [11]. CCP is activated by immune complexes as well as monoclonal light chain deposition and is typically manifested by normal/mildly decreased serum C3 and low serum C4. The CAP does not require an antibody or microbiological agent to be activated. Instead, a small amount of C3 is constantly autoactivated and can be amplified by the alternative amplification loop. CAP activation is usually marked by low C3 and normal C4 and by low factor B and CD50.

This patient shows activity in both CCP and CAP, with decreased levels of early components of each pathway namely C4 and factor B. Since multiple components are decreased through consumption in both the classic and alternative complement pathways, an acquired disorder rather than genetic seems likely and genetic testing for an inherited disorder was not performed.

The monoclonal kappa light chains causes the complement activation, either directly through activity in CCP or indirectly by uncontrolled activity in CAP as described. The mechanism is not clear. Light chains have previously been reported as the cause of MPGN through the complement activity [12, 13], but the presence of C3NeF and enhanced activity of complement factor I points to uncontrolled activity in the CAP. This is in line with the findings of Bridoux *et al.* [7]. They suggested that C3 deposition due to CAP activation was caused by autoantibody activity of the monoclonal Ig. Recently, Zand *et al.* [3] also reported a case series of C3 GN and monoclonal gammopathy in 32 patients with CAP activation, but they only found circulating C3NeF in two patients. The elevated activity of CAP could explain the elevated activity of complement factor I as well. Otherwise, transcriptional activity of CFI is enhanced in the presence of some cytokines, e.g. IL-6 [14], and IL-6 is elevated in multiple myeloma [15]. Enhanced activity of CFI could also be implicated in the pathogenesis. In mouse, administration of CFI to $CFI^{-/-}$ knockout mice cause enhanced cleavage of C3b and appearance of C3 along the basal membrane of the glomerulus [16].

Following institution of chemotherapy and stem cell transplant, serum paraprotein decreased and the renal function improved. C3NeF activity became negligible and serum complement levels were restored to normal. This strongly indicates that the complement activity in both CCP and CAP, including the C3NeF, is related directly to the monoclonal kappa light chain secreted by clonal plasma cells.

The kidney biopsy was performed 2.5 years prior to the institution of therapy. It is possible that the kidney involvement had evolved to be the result of other myeloma-associated kidney lesions, e.g. 'myeloma-kidney' at that point. However, the proteinuria and kidney function did not change significantly during the course of the haematological disease. It is possible that the improvement in proteinuria following treatment is attributable to switching off the production of kappa light chains, thus preventing their overflow into the urine, but overall we considered

the possibility of another lesion minimal and another biopsy was not performed.

The urinary light chains were not measured when proteinuria was first detected. One and 2 years later, when proteinuria was continuously high, they were detected and low. Hereafter, they increased as the myeloma evolved (Table 1).

Monoclonal gammopathy is a continuum and it seems, in this case, that the renal disease precedes the diagnostic set criteria for multiple myeloma. It also seems that the renal damage is reversible, although we have no post-treatment biopsy.

Conflict of interest statement. None declared.

References

1. Sethi S, Zand L, Leung N *et al*. Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. *Clin J Am Soc Nephrol* 2010; 5: 770–782 doi:10.2215/CJN.06760909.
2. Barbour TD, Pickering MC, Cook HT. Recent insights into C3 glomerulopathy. *Nephrol Dial Transplant* 2013; 28: 1685–1693
3. Zand L, Kattah A, Fervenza FC *et al*. C3 glomerulonephritis associated with monoclonal gammopathy: a case series. *Am J Kidney Dis* 2013; 62: 506–514
4. Fakhouri F, Frémeaux-Bacchi V, Noël LH *et al*. C3 glomerulopathy: a new classification. *Nat Rev Nephrol* 2010; 6: 494–499
5. Servais A, Noël LH, Frémeaux-Bacchi V *et al*. C3 glomerolopathy. *Contrib Nephrol* 2013; 181: 185–193
6. Sethi S, Nester CM, Smith RJ. Membranoproliferative glomerulonephritis and C3 glomerulopathy: resolving the confusion. *Kidney Int* 2012; 81: 434–441
7. Bridoux F, Desport E, Frémeaux-Bacchi V *et al*. Glomerulonephritis with isolated C3 deposits and monoclonal gammopathy: a fortuitous association? *Clin J Am Soc Nephrol* 2011; 6: 2165–2174
8. Bourke E, Champbell WG Jr, Piper M *et al*. Hypocomplementemic proliferative glomerulonephritis with C3 nephritic-factor-like activity in mutiple myeloma. *Nephron* 1989; 52: 231–237
9. Paixão-Cavalcante D, López-Trascasa M, Skattum L *et al*. *Kidney Int* 2012; 82: 1084–1092
10. Skattum L, Mårtensson U, Sjöholm AG. *J Int Med* 1997; 242: 455–464
11. Zurlo JJ, Schechter GP, Fries LF. Complement abnormalities in multiple myeloma. *Am J Med* 1989; 87: 411–420
12. Komatsuda A, Nara M, Ohtani H *et al*. Proliferative glomerulonephritis with monoclonal immunoglobulin light chain deposits: a rare entity mimicking immune-complex glomerulonephritis. *Intern Med* 2012; 51: 3273–3276
13. Meri S, Koistinen V, Miettinen A *et al*. Activation of the alternative pathway of complement by monoclonal lambda light chains in membranoproliferative glomerulonephritis. *J Exp Med* 1992; 175: 939–950
14. Minta JO, Fung M, Paramaswara B. Transcriptional and post-transcriptional regulation of complement factor I (CFI) gene expression in Hep G2 cells by interleukin-6. *Biochim Biophys Acta* 1998; 1442: 286–295
15. Lauta VM. A review of the cytokine network in multiple myeloma: diagnostic, prognostic, and therapeutic implications. *Cancer* 2003; 97: 2440–2452
16. Rose KL, Paixao-Cavalcante D, Fish J *et al*. Factor I is required for the development of membranoproliferative glomerulonephritis in factor H-deficient mice. *J Clin Invest* 2008; 118: 608–618

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