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Clinical Report

Membranous glomerulopathy with superimposed pauci-immune necrotizing crescentic glomerulonephritis

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Abstract
We describe a 61-year-old woman with acute kidney injury, nephrotic range proteinuria and hematuria. Kidney biopsy showed membranous glomerulopathy (MG) with superimposed pauci-immune necrotizing crescentic glomerulonephritis (PNCGN). Coexistent MG and PNCGN is a rare occurrence. The diagnosis of such an exceptionally rare combination relies on the combination of renal biopsy findings and serologic testing. We also review previous reported cases and discuss possible pathogenesis of this rare dual glomerulopathy.

Keywords: anti-glomerular basement membrane disease; antineutrophil cytoplasmic antibodies; membranous glomerulopathy; pauci-immune necrotizing crescentic glomerulonephritis

Background

Common precipitants of acute kidney injury (AKI) include prerenal causes, intrinsic renal disease of various types, including both glomerular and nonglomerular diseases and postrenal causes such as urinary tract obstruction. Prerenal etiologies and acute tubular injury (ATI) are among the most common causes of AKI. In these cases, the diagnosis is often clinically evident, and renal biopsy is not required. However, when the cause of an AKI remains unknown after clinical and radiologic evaluation, renal biopsy may allow differentiation of, for example, acute interstitial nephritis, acute glomerulonephritis, thrombotic microangiopathy, or ATI, each with different implications for treatment. We discuss a patient with AKI with nephrotic range proteinuria and hematuria. A renal biopsy was performed to establish a definitive morphologic diagnosis, plan for management, and to obtain prognostic information.

Case report

Clinical history and initial laboratory data

A 61-year-old woman with history of Type 2 diabetes, hypertension and gout developed worsening hypertension and new-onset hematuria. Evaluation by her cardiologist showed hypochromic and microcytic anemia with hemoglobin 9.4 mmol/L (normal range 8.4–10.9 mmol/L) and AKI with serum creatinine 710.0 μmol/L (baseline <133 μmol/L). The patient was transferred to a tertiary referral hospital for further evaluation of AKI.

On physical examination, she appeared acutely ill. Temperature was 37.4°C, blood pressure 176/89 mm Hg, pulse 63 and res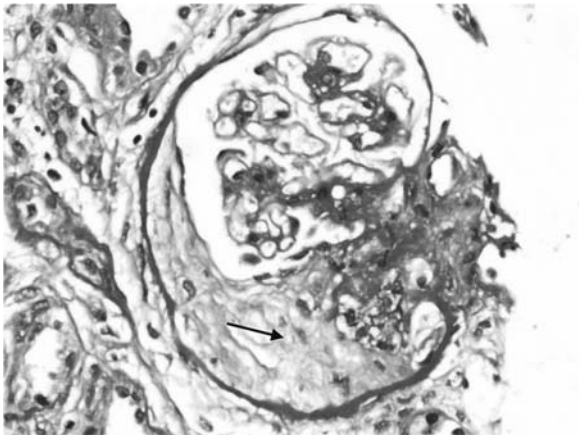pirations 21/min. Physical examination demonstrated normal heart sounds with no murmur, clear lungs, a soft, nontender, obese abdomen with no organomegaly and 2+ pitting edema of the lower extremities bilaterally. There was no skin rash. Laboratory data demonstrated sodium 138 mmol/L, potassium 4.7 mmol/L, chloride 106 mmol/L, bicarbonate 18 mmol/L, calcium 2.2 mmol/L, phosphorus 1.1 mmol/L, BUN 8.8 mmol/L, creatinine 790 μmol/L, glucose 12.5 mmol/L, total serum protein 61.0 g/L and albumin 31.0 g/L. Serum titers of antinuclear antibody, antidouble-stranded DNA, c-antineutrophil cytoplasmic antibody and antiglomerular basement membrane (GBM) antibodies were negative. Complement levels (C3 1.5 g/L, C4 0.4 g/L) were within normal limits. Serum and urine protein electrophoresis revealed no monoclonal spike. However, p-ANCA was >100 kU/L (normal <2.8 kU/L) and antimyeloperoxidase was >1:640 (normal <6 kU/L). Urinalysis showed proteinuria and microscopic hematuria with dysmorphic red blood cells. Proteinuria was 15.0 g/24 h. Renal ultrasonography showed the right kidney 10.4 cm and the left 11.2 cm in length. There was no history of alcohol abuse or smoking. She had poorly controlled Type 2 diabetes and hypertension for 10 years, complicated by neuropathy. She had no familial history of kidney disease. A percutaneous renal biopsy was performed to assess the cause of her rapidly progressive glomerulonephritis.

Renal biopsy findings

The renal biopsy specimen included two pieces of cortex containing nine glomeruli, four of which were globally sclerosed. There was mild increase in mesangial matrix and cellularity but no endocapillary proliferation. The GBM showed very rare spikes and rare holes (Figure 1), segmental corrugation and split appearance. Two
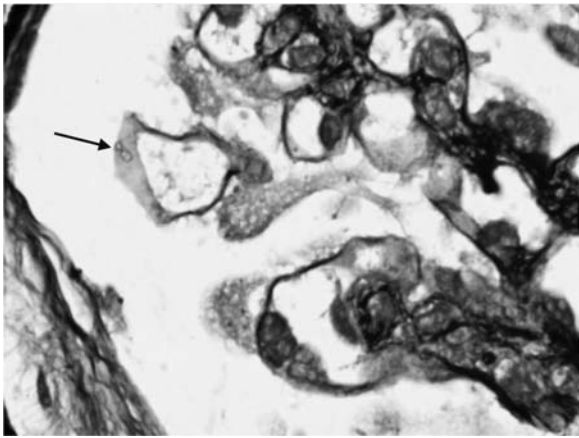
Fig. 1. A glomerulus with segmental 'holes' that represents the absence of staining of the deposits when cut tangentially on silver stain (arrow) (Jones' silver stain, original magnification ×400).

Fig. 3. Segmental finely granular 1+ staining of glomerular capillary wall for IgG (anti-IgG immunofluorescence, original magnification ×400).
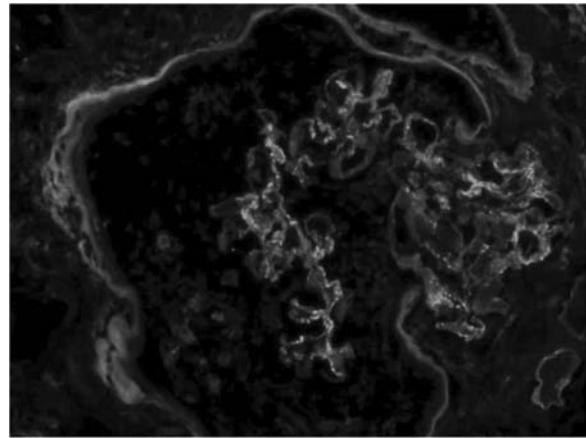

Fig. 2. A glomerulus with fibrocellular crescent (arrow) and segmental sclerosis with adhesion (Periodic acid-Shiff (PAS) stain, original magnification ×400).

Fig. 4. Subepithelial immune complex deposits (arrow) with extensive foot process effacement (transmission electron microscopy, original magnification ×5600).
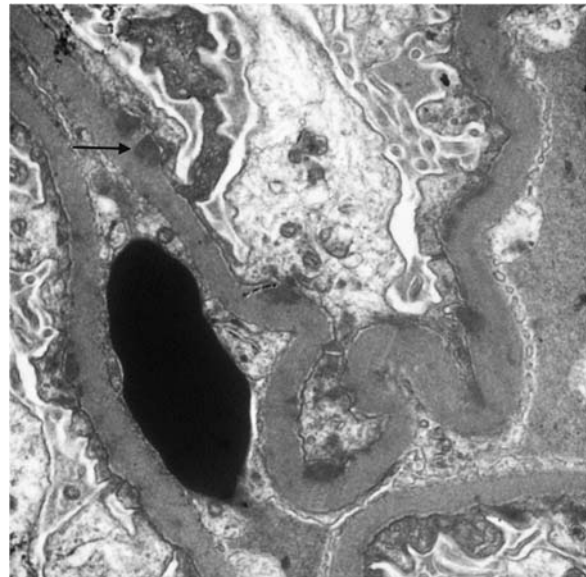
glomeruli had fibrinoid necrosis with fibrocellular crescents and segmental sclerosis with adhesions (Figure 2). There was ~40% interstitial fibrosis with proportional tubular atrophy and mild lymphoplasmacytic infiltrate. There was ATI involving ~20% of tubular profiles with sloughing off of tubular epithelial cells. There were rare proteinaceous casts. There were no crystals or polarizable material. Arterioles were unremarkable. Interlobular arteries showed mild tortuosity without fibrinoid necrosis or inflammation.

Five glomeruli were present in frozen sections processed for immunofluorescence microscopy. There was 1 + (0 to 3+ scale) segmental granular capillary loop and mesangial staining for immunoglobulin G (IgG) (Figure 3) and 1+ C3 and equal 1+ kappa and lambda light chain staining in a similar pattern as IgG. There was no glomerular staining for IgA, IgM and C1q. There was no tubular basement membrane staining for any antisera. Immunofluorescence studies for subclasses of IgG, namely IgG1, IgG2, IgG3 and IgG4 were performed. There was dominant IgG4 segmental granular capillary loop and mesangial staining. IgG1, IgG2 and IgG3 were negative.

On electron microscopy, GBM showed normal thickness of lamina densa with occasional to scattered small to medium subepithelial deposits (Figure 4), very rare small subendothelial deposits and rare mesangial deposits. There was ~60% podocyte foot process effacement. There were no fibrin tactoids, tubuloreticular arrays and no increase in mesangial matrix or cellularity. There were no tubular basement membrane deposits.

Diagnosis

Early membranous glomerulopathy (MG), with superimposed pauci-immune necrotizing crescentic glomerulonephritis (PNCGN) and focal ATI.

Treatment and follow-up

The patient was treated with hemodialysis and plasmapheresis × 5, and begun on immunosuppression with intravenous cyclophosphamide and prednisone.

Her renal function did not recover and she remained on dialysis 6 months after the renal biopsy. Currently, she is being evaluated for renal transplantation.

Discussion

The biopsy showed the unusual combination of MG and crescents. There were very rare small mesangial immune complex deposits, insufficient to specifically raise the possibility of secondary MG. Idiopathic/primary MG rarely presents with superimposed crescentic injury [1]. The possibility of a mixed ISN/RPS Class V membranous lupus nephritis with superimposed focal or diffuse Class III or Class IV lupus nephritis is raised when crescents or fibrinoid necrosis are present. Typically, such a mixed pattern of lupus nephritis lesions would also have associated endocapillary proliferation and concomitant subendothelial immune complex deposits. Most cases of lupus nephritis also have tubuloreticular arrays and so-called 'full-house' staining by immunofluorescence, with all three immunoglobulin classes (IgG, IgA and IgM) and both classic and alternate complement staining (C3 and C1q). Of note, some cases of lupus nephritis, such as lupus nephritis Class IV-S with segmental lesions, may have more extensive fibrinoid necrosis with less prominent subendothelial deposits and endocapillary proliferation and may behave more aggressively [2]. However, there were no tubuloreticular arrays, staining by immunofluorescence was limited to IgG and C3, and the patient did not have systemic lupus erythematosus clinically.

Anti-GBM antibody glomerulonephritis can also cause crescents. The combination of anti-GBM antibody glomerulonephritis and MG, albeit rare, is well recognized [1, 3]. Detection of linear staining along the GBM in a case of anti-GBM disease combined with MG is often difficult due to obscurement by the intense granular staining of the subepithelial immune complex deposits. On high power examination, glomerular capillary wall immunofluorescence staining for IgG can be resolved as inner layer of linear positivity and an outer layer of finely granular staining [4]. In MG, the granular staining of kappa and lambda is usually weaker than IgG; thus, it may be helpful to examine staining of kappa and lambda to detect underlying linear staining. This dual pattern of positivity was not present in our patient, and serum anti-GBM antibody was absent. Therefore, there was no evidence of anti-GBM disease superimposed on MG.

MG is the most common cause of nephrotic syndrome in Caucasian adults, accounting for more than one third of cases [5]. At time of presentation, most patients with MG have preserved renal function [5]. Pathologically, MG is characterized by the formation of subepithelial immune complex deposits with resultant changes to the GBM, most notably spike and apparent 'hole' formation on silver stains. The spikes represent a matrix reaction to the deposits cut in cross section and stained with silver stain. The holes represent the absence of silver staining of the deposits when cut tangentially. Approximately 25% of cases of MG are thought to result from secondary causes [6], most commonly systemic lupus erythematosus, infection (e.g. hepatitis B or C virus), malignancy, or drugs, whereas the remaining 75% of cases represent primary disease [6]. The etiology of secondary MG is due to circulating immune complexes deposited in a subepithelial distribution, whereas primary MG is due to

antibodies reacting to planted, endogenous podocyte-related antigens, recently demonstrated to be the trans-membrane glycoprotein M-type phospholipase A2 receptor in most such cases [7]. The natural history of MG is variable, with about one-third of patients progressing to end stage renal disease within 10 years [6].

PNCGN is characterized by glomerular fibrinoid necrosis and crescent formation in the absence of significant endocapillary proliferation and in the presence of no more than a 'paucity' of glomerular immune complex deposits. Most patients with PNCGN with or without associated systemic vasculitis have circulating ANCAs which have been directly implicated in the pathogenesis of this pattern of glomerular injury [6]. In contrast to patients with MG, those with PNCGN typically present clinically with RPGN and active urine sediment with red blood cell casts, as seen in our patient [8].

PNCGN superimposed on MG is very rare [6]. The diagnosis of such an exceptionally rare combination relies on the combination of renal biopsy findings and serologic testing. The presence of p-ANCA and anti-myeloperoxidase in the serum supported the diagnosis of PNCGN in addition to MG as a cause of this patient's crescents. There was no pulmonary involvement in this patient.

Table 1. Clinical data, treatment and outcome in previously reported cases and current case of MG and Pauci-immune necrotizing crescentic glomerulonephritis[a]

Pt	Age/sex	Initial SCr (μmol/L)	Protein (g/24 h)	Treatment	Outcome
1	57/F	221.7	2+ on UA	i.v. PC/MMF	ESRD, died
2	65/M	195.1	5.8	p.o. PC	Stable renal function
3	37/F	310.3	5.5	i.v. PC	Stable renal function
4	39/F	115.3	6.8	p.o. PC	Stable renal function
5	47/M	762.5	14	i.v. PC	ESRD, died
6	71/M	266.0	6.6	p.o. PC	Stable renal function
7	50/M	79.8	0.8	PA/p.o. PC	Stable renal function
8	62/F	363.5	16	p.o. P, i.v. CY	Stable renal function
9	78/M	354.6	Anuria	P, i.v. CY	Stable renal function
10	79/F	789.1	3+ on UA	None	Died
11	59/M	532.0	3.5	P, i.v. C	ESRD, dialysis
12	69/M	478.8	1.9	P, p.o. CY, PLX	Died
13	51/M	771.3	5.8	NA	ESR, died
14	58/F	274.8	5.0	PC	Stable renal function
15	30/M	106.4	1.5	PC	Stable renal function
16	39/M	150.7	Oliguria	PC	Recovery
17	41/M	124.1	20.6	PC	Stable renal function
18	58/F	53.2	3.5	PA/PC	ESRD, dialysis
19	63/M	487.6	Oliguria	PA	Died
20	64/M	133.0	2.4	None	ESRD, dialysis
21	65/M	212.8	0.4	PC	Recovery
22	65/M	239.4	0.4	PC	Died
23	68/M	283.7	22	PC	Died
24	70/M	106.4	Oliguria	PC/PLX	Recovery
25	61/F	700.4	15.0	PC/PLX	ESRD, dialysis

[a]Patients 1–14 are from Nasr et al. [6], patients 15–24 are from Tse et al. [13] and patient 25 is the current case.
SCR, serum creatinine; i.v., intravenous; PC, prednisolone and cyclophosphamide; MMF, mycophenolate mofetil; ESRD, end stage renal disease; p.o., oral; PC, prednisolone and azathioprine; CY, cyclophosphamide; P, prednisolone; UA, urinalysis; PLX, plasmapheresis; NA, not applicable; A, azathioprine.

Coexistent MG and PNCGN is a rare occurrence, with only 24 reported cases in the English literature in which clinical and pathologic findings are detailed [6, 9–14]. The reported cases of coexistent MG and PNCGN include 15 men and 9 women, with a mean age of 59.7 years (Table 1). Hill *et al.* [15] reported an unusual variant of MG with abundant crescent formation and suggested that there is a form of MG with crescent formation unrelated to anti-GBM antibodies, which has capacity to recur after renal transplantation. Our case is similar to the other cases reported, in that MG and PNCGN were diagnosed simultaneously at presentation. This is different from the situation of anti-GBM disease superimposed on MG, in which MG preceded the development of anti-GBM antibody glomerulonephritis in nearly 50% of reported cases [4]. In the case of anti-GBM disease superimposed on MG, immune complex deposition along the GBM may cause release of damaged GBM antigen into the circulation, or unmask cryptic epitopes, which lead to the formation of nephritogenic anti-GBM antibodies.3

Data from Nasr *et al.* [6] suggest that the coexistence of PNCGN and MG likely represents a chance occurrence of two unrelated disease processes. Their patients with MG and PNCGN were likely to have heavier proteinuria and worse prognosis than patients with PNCGN alone [6]. The presence of immune deposits has also been shown to augment glomerular injury induced by ANCA in mice [16]. Treatment data were available for 13 of the 14 patients reported by Nasr *et al.* (Table 1), 12 of 13 were treated with prednisone and cyclophosphamide (i.v. in six, oral in five, i.v. followed by oral in one). In addition, three patients also received pulse methylprednisolone, one received mycophenolate mofetil and one was treated with plasmapheresis. One of 13 patients with available treatment data died before the treatment started. Four of the remaining 13 patients were on dialysis and of these, 3 died later. Renal function did not return to normal in the remaining eight patients.

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