Clinical Case Report

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Acute renal failure in a patient with PR3-ANCA and monoclonal immunoglobulin deposition disease

Case report

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Abstract

Rationale: Acute renal failure developing over a short period of time with evidence of glomerular disease by urine sediment microscopy characterizes the clinical syndrome of rapidly progressive glomerulonephritis (RPGN), of which the most common causes are ANCA-associated glomerulonephritis (GN), immune-complex mediated GN and anti-GBM disease.

Patient concerns: This was a middle-aged gentleman who presented with acute renal failure and a positive PR3-ANCA.

Diagnosis: Renal biopsy showed an unusual combination of PR3-ANCA GN with focal crescents, monoclonal immunoglobulin deposition disease (MIDD) and mesangial IgA deposition on renal biopsy.

Interventions: Serum and urine protein electrophoresis (UPEP) and immunofixation showed no detectable monoclonal paraprotein; bone marrow biopsy was negative for plasma cell neoplasia. He received high dose steroids and rituximab.

Outcomes: The patient did not respond to treatment and progressed to end-stage renal failure within 2 months after presentation.

Lessons: To our knowledge, the simultaneous occurrence of MIDD, PR3-ANCA and mesangial IgA has not been reported. This case highlights not only the diagnostic but also the therapeutic challenges that such a complex case presentation poses to clinicians, where the culprit may not always be what would seem most obvious (such as ANCA in a patient with RPGN) but may, in fact, be an underlying and unsuspected disease, or possibly a combination of both.

Abbreviations: ANA = anti-nuclear antibodies, ANCA = anti-neutrophil cytoplasmic antibodies, anti-GBM - anti-glomerular basement membrane, CH1 = heavy chain constant domain 1, ESRD = end-stage renal disease, FLC = free light chain, GBM = glomerular basement membrane, GN = glomerulonephritis, IF = immunofluorescence, MIDD = monoclonal immunoglobulin deposition disease, PR3 = proteinase 3, RPGN = rapidly progressive glomerulonephritis, SPEP = serum protein electrophoreses, TBM = tubular basement membrane, UPEP = urine protein electrophoresis.

Keywords: acute renal failure, monoclonal immunoglobulin deposition disease, PR3-ANCA

1. Introduction

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome characterized by progressive loss of renal function over a short period of time and evidence of glomerular disease by urine sediment microscopy. The histological correlate is extensive crescent formation, usually involving greater than half of glomeruli present.[1] Anti-neutrophil cytoplasmic antibodies (ANCA)-associated small vessel vasculitis is the most common cause of RPGN, followed by immune-complex mediated GN and anti-glomerular basement membrane (GBM) disease.[2] Even though positive serologies to ANCA or anti-GBM antibodies provide strong clues as to what the underlying disease causing RPGN might be, a renal biopsy is essential not only to confirm the diagnosis but also to assess the extent of crescentic involvement and the degree of chronic changes. Rarely, the renal biopsy may also reveal unsuspected concomitant disease processes that might be of prognostic and therapeutic importance as exemplified by the present case report.

2. Case presentation

2.1. Patient information and clinical findings

A 53-year-old male presented to the emergency department with elevated blood pressure detected during an outpatient visit to the nephrologist office. At physical examination, blood pressure was 211/124 mmHg; there were no other significant findings. Laboratory tests revealed an elevated creatinine (4.36 mg/dL), urinalysis showed 4+ proteinuria and moderate hematuria, and urine microscopy revealed frequent red blood cell casts. His past medical history was unremarkable with no evidence of current or

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Table 1

Laboratory data.

Variable	At presentation	1st week	2nd week	3rd week	4th week	At 3 months	At 6 months	Reference Range
Blood								
ANCA IgG IFA	<1:20				<1:20			<1:20
MPO antibodies, AU/mL	15				4	<1.0		0–19
Serine Protease 3 IgG, AU/mL	102				10	<1.0		0–19
Kappa FLCs, mg/dL	8.65	6.01		5.33				0.33–1.94
Lambda FLCs, mg/dL	1.78	1.13		1.87				0.57–2.63
Kappa/lambda ratio	4.86	5.32		2.85				0.26–1.65
Creatinine, mg/dL	4.51	5.42	3.73	4.10	4.32	4.69	4.75	0.80–1.30
WBC, 10^3/uL	8.3		19.8	7.7	10.2	12	9.36	4.1–11.0
RBC, 10^3/uL	3.5		3.2	3.1	2.4	3.9	4.6	4.6–6.1
Hemoglobin, g/dL	10.8		9.5	9.5	7.5	11.3	11.1	13.5–18.0
Hematocrit, %	31.4		28.2	28.0	21.4	34.8	31.2	41.0–53.0
Platelet count, 10^3/uL	287		192	24	105	281	351	150–450

ANCA = anti-neutrophil cytoplasmic antibodies, FLC = free light chains, IFA = immunofluorescence assay, MPO = myeloperoxidase, RBC = red blood cell count, WBC = white blood cell count.

recently treated infections except for 33 years of smokeless tobacco use. The patient was admitted to hospital for blood pressure control and investigation of acute renal failure. Work-up revealed PR3-ANCA at 102 AU/mL and an equivocal anti-GBM at 25 AU/mL. Proteinuria was 2.145 g/24 h, serum and UPEP were both negative. ANA was negative, complement levels were within normal limits, and serologies for HIV, hepatitis C, and hepatitis B were all negative. Serum kappa free light chains (FLCs) were elevated at 8.65 mg/dL, lambda FLCs were normal at 1.78 mg/dL, and kappa/lambda ratio was elevated at 4.86 (laboratory data summarized in Table 1). Based on clinical and laboratory findings, the patient received a presumptive diagnosis of ANCA-associated RPGN and was started on high dose steroids and rituximab while renal biopsy was arranged.

2.2. Diagnostic assessment - renal biopsy

The biopsy contained 56 glomeruli, 2 of which were globally sclerosed. Four glomeruli had cellular crescents and the remaining 50 showed diffuse and nodular increase in mesangial matrix with no significant mesangial hypercellularity (Fig. 1). The glomerular capillaries contained a few circulating mononuclear cells and neutrophils (Fig. 1). Interstitial fibrosis and tubular atrophy were moderate (approximately 40%), with patchy mononuclear inflammatory infiltrates and mild edema. There was mild hyaline arteriolosclerosis, severe arterial sclerosis, and no arterial vasculitis. Immunofluorescence (IF) showed linear staining along glomerular and tubular basement membranes (TBM) for IgG and kappa that was stronger than albumin (Fig. 2 and Supplementary Fig. 1, http://links.lww.com/MD/C722). There was also granular mesangial IgA (1+), kappa (1+), and lambda (1+) (Fig. 2). Fibrinogen highlighted the cellular crescents and C3 showed segmental peri-hilar staining. C1q was negative. Electron microscopy revealed granular powdery electron dense deposits along the subendothelial aspect of the GBMs and the outer aspect of TBMs (Fig. 3). The mesangium contained similar powdery electron dense material (Fig. 3) and was expanded by matrix. Tubuloreticular inclusions were not observed. A few capillary loops showed subendothelial widening and cellular interpositioning. A final diagnosis of PR-3 ANCA GN superimposed on IgG-kappa monoclonal immunoglobulin deposition disease (MIDD) and incidental IgA nephropathy was provided.

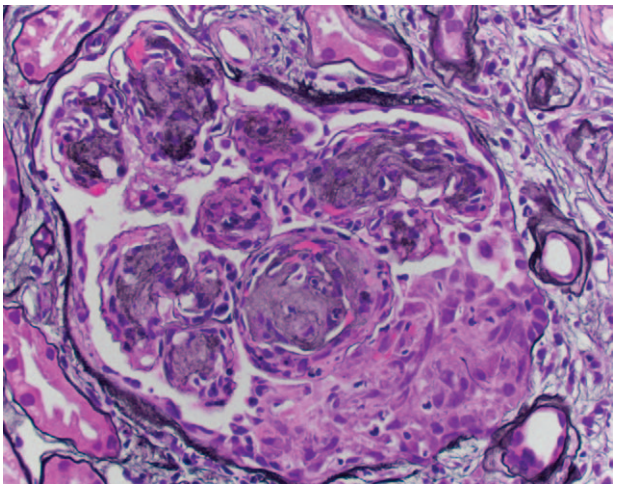

Figure 1. Glomerulus showing nodular mesangial expansion that is weekly Silver positive, one cellular crescent and rare intracapillary neutrophils. (Jones Silver stain 400×).

2.3. Diagnostic assessment, therapeutic intervention, follow-up, and outcomes

During the initial hospitalization, no lung involvement or extra-renal manifestations of ANCA-associated disease were detected. Anti-GBM IgG was repeated given the initial equivocal levels and returned at 17 AU/mL. Serum renin activity and aldosterone were within normal limits. Repeated serum and UPEP and immunofixation failed to detect a monoclonal paraprotein. Kappa FLCs remained elevated at 6.01 mg/dL, with normal lambda FLCs at 1.13 mg/dL, and an abnormal kappa/lambda ratio of 5.32. Peripheral blood showed normocytic anemia, while white blood cell and platelet counts were within normal limits. After the third dose of rituximab, the patient developed significant abrupt thrombocytopenia, mild lymphocytopenia, but no significant changes in red or white blood cell counts. Heparin-induced platelet antibodies were negative. A bone marrow biopsy and aspirate were performed and showed normocellular marrow with normal trilineage hematopoiesis. Specifically, there was no increase of plasma cells (1.3%) and kappa to lambda positive plasma cells ratio was approximately 2:1 by in-situ hybridization. Serum kappa FLCs were still elevated at 5.33 mg/dL, lambda FLCs were normal at 1.87, and kappa/lambda FLCs ratio was

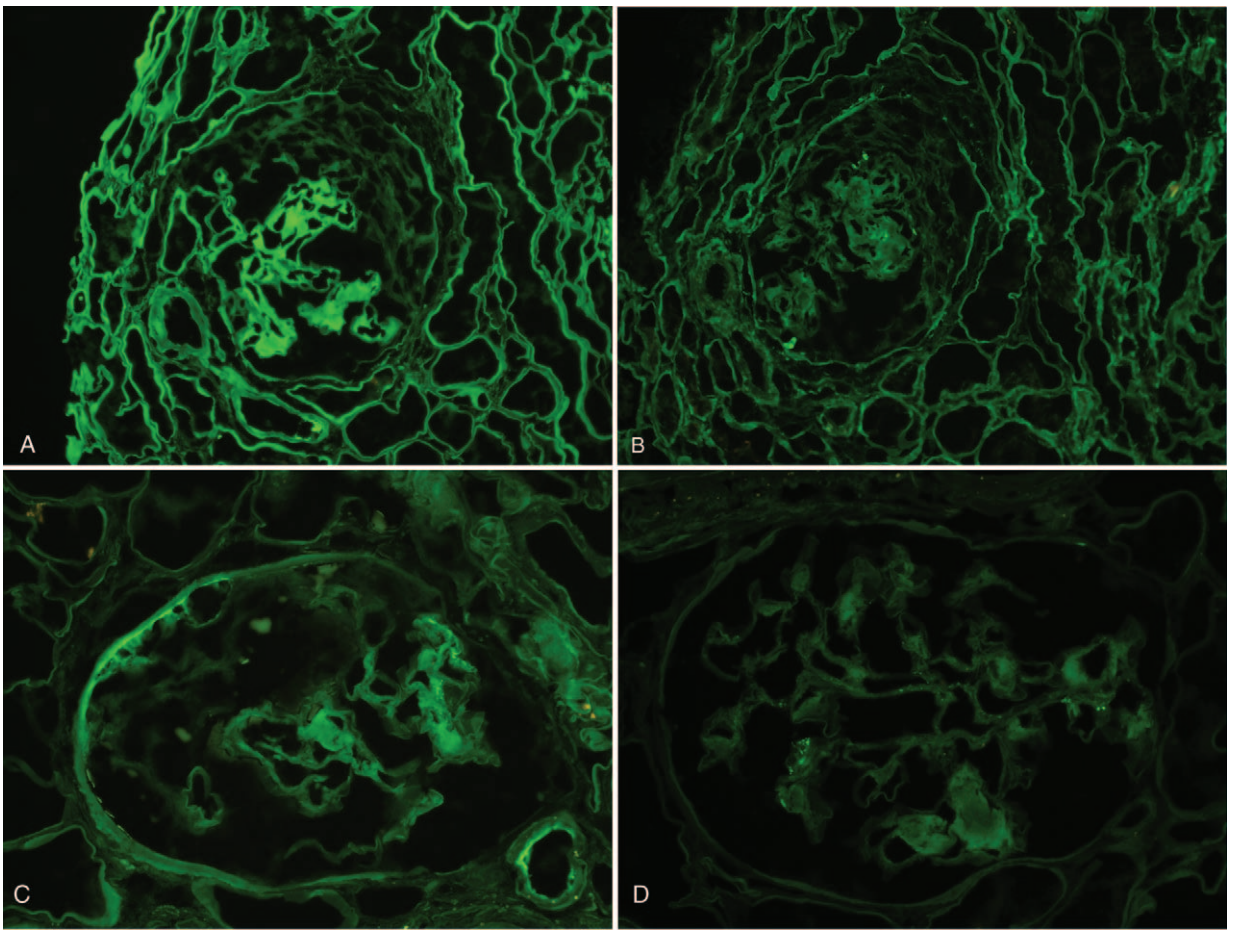

Figure 2. Linear staining along glomerular and TBMs for IgG (A) that was stronger than albumin (B) and kappa (C), with negative lambda (D). Also present was mild granular mesangial staining for kappa and lambda, in a similar distribution to IgA. IF = immunofluorescence, TBM = tubular basement membrane.

2.85. Thrombocytopenia was transient and attributed to a possible viral illness, slowly returning to normal values within 2 weeks. The patient received 4 weekly doses of rituximab and steroids treatment with no improvement in renal function. Dialysis had to be initiated on an urgent basis due to volume overload 45 days after the diagnosis. Four months after the initial presentation, he has remained dialysis-dependent and was referred for transplant assessment.

The patient has consented for his case to be reported in an anonymized form for publication.

3. Discussion

We present the case of a middle-aged male with no significant past medical history who presented with hypertensive urgency and presumed acute renal failure after not having seen his primary care practitioner for 5 years. An active renal sediment, nephrotic-range proteinuria, and positive PR3-ANCA prompted renal biopsy, which revealed a unique combination of diseases that included IgG-kappa MIDD, PR3-ANCA GN, and IgA nephropathy. Anti-GBM levels were initially borderline but became normal upon retesting ruling out a double positive anti-GBM and PR3-ANCA GN.

Given the importance of early treatment in patients with RPGN, the patient was promptly admitted with a presumptive clinical diagnosis of ANCA-associated RPGN and started on high dose steroids and rituximab.[3] However, there was no response to treatment and the patient eventually progressed to end-stage renal failure probably as a consequence of treatment targeting ANCA-associated GN but not the underlying MIDD.

MIDD is a systemic disease of monoclonal immunoglobulin deposition along basement membranes that can involve glomerular and TBMs as well as the mesangium.[4] It is characterized by linear GBM and TBM staining on IF and finely granular deposits on electron microscopy.[5] The coexistence of MIDD with other glomerular or tubulointerstitial diseases is not rare but when that happens, it usually involves lesions that are also associated with the paraproteinemic neoplastic process, such as myeloma cast nephropathy or focal interstitial infiltration by neoplastic plasma cells.[5,6] A few cases with overlapping features of diabetic nephropathy and 1 case with concomitant oxalate nephropathy have been previously described.[5–7]

We are unaware of previous case reports demonstrating the combination of MIDD and PR3-ANCA GN. To our knowledge, a single case of so-called IgG3 MIDD with membranous features and MPO-ANCA has been reported.[8] However, detailed review of that report describes discrete deposits that were subepithelial rather than having the typical granular powdery appearance and subendothelial GBM location that defines MIDD. That suggests that the diagnosis was, in fact, monoclonal membranous nephropathy rather than true MIDD.[5]

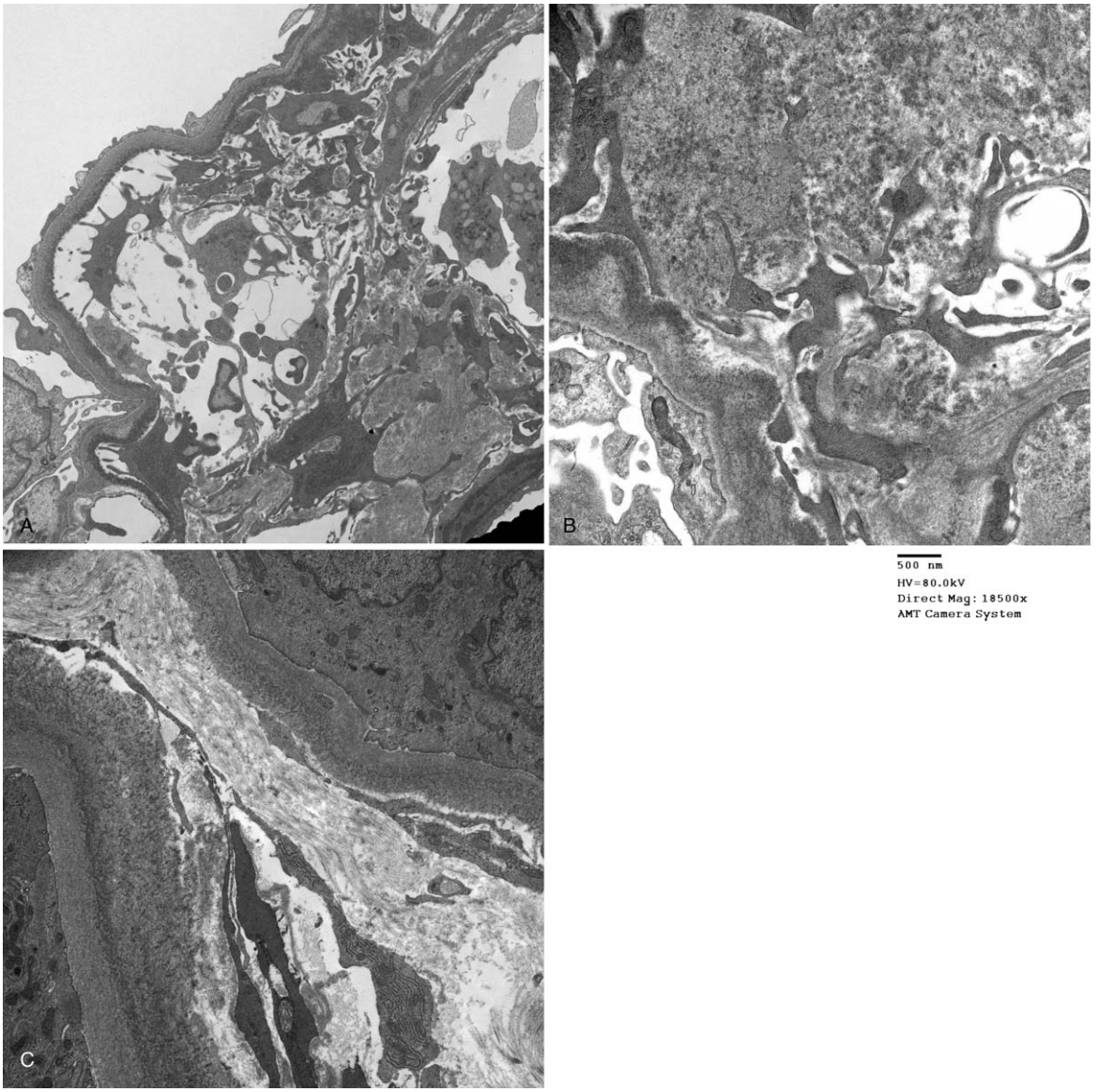

Figure 3. Granular powdery electron dense deposits along the subendothelial aspect of the GBM (A), mesangium (B) and outer aspect of TBMs (C). Electron microscopy 6800× (A), 18500× (B) and 9300× (C). GBM = glomerular basement membrane, TBM = tubular basement membrane.

MIDD can occasionally present with focal cellular crescents; most commonly in cases of alfa heavy chain deposition disease,[9,10] but given the PR3-ANCA positivity in our patient, we cannot rule out completely a contribution of ANCA to crescent formation.

In one of the largest series of isolated MIDD reported to date, patients were predominantly male and generally younger than those with myeloma cast nephropathy and light chain amyloidosis.[5] In that series, the most important factor associated with the development of end-stage renal disease (ESRD) was elevated serum creatinine at the time of biopsy. Overall, more than half of patients with MIDD progressed to ESRD.[5] Conversely, the prognosis of ANCA-associated GN alone with focal involvement of glomeruli by crescents and no significant glomerulosclerosis is usually good with renal survival above 90% at 5 years.[11,12] It is important to emphasize, however, that the ANCA-associated GN classification was developed for pure ANCA-GN cases, in which the definition of "focal" implies 50% or more of normal glomeruli.[11] In our case, even though less than 10% of glomeruli were involved by crescents and only two were globally sclerosed, the remaining fifty glomeruli could not be considered "normal" as they had diffuse nodular glomerulosclerosis due to MIDD. The widespread glomerular involvement likely explains why the patient outcome was poor even though only a small percentage of glomeruli were involved by crescents or globally sclerosed.

ANCA-associated GN has occasionally been reported to occur superimposed to other glomerular diseases. In those cases, outcomes appear to be worse than in patients with ANCA-associated GN alone.[13–18] Similar to our observation, the occurrence of ESRD in those cases did not correlate with the percentage of glomeruli involved by cellular crescents but rather with high serum creatinine at presentation.[16,17]

While Nasr has suggested that the simultaneous occurrence of membranous nephropathy and ANCA-associated GN is probably coincidental based on the frequencies of both diseases and their different pathogenetic mechanisms,[17] Haas has proposed

that immune-complexes may act synergistically with ANCA to produce more severe GN than would be seen with either process alone.[16]

The simultaneous occurrence of ANCA-associated GN and underlying mesangial IgA deposition is not a new observation.[13] One potential explanation for this concurrent finding is the recently described association of both diseases with *Staphylococcus* infection.[19] Our patient, however, did not have any evidence of current or recently treated infection. Therefore, in the absence of mesangial or endocapillary hypercellularity and overall low level of staining, we considered the presence of mesangial IgA an incidental finding which has been described in up to 3% of the population in autopsy series.[20]

The pathological diagnosis of MIDD not infrequently precedes clinical evidence of dysproteinemia.[5,6] Up to one-third of patients with MIDD have no identifiable M-spike on SPEP or UPEP at presentation.[5] In up to 8% of patients, a monoclonal paraprotein is only detected 4 to 36 months after a tissue MIDD diagnosis. Bone marrow biopsy is positive in only 35% of cases.[6] Nevertheless, there is invariable evidence of dysproteinemia in the form of an abnormal FLC ratio as was the case with our patient.[5]

Despite considerable renal tissue involvement that likely contributed to development of ESRD in our patient, subsequent investigations have failed to demonstrate a monoclonal paraprotein in serum or and urine up to this date almost nine months after presentation. This phenomenon has been well described and the reasons might include a rapid tissue deposition rate or paraprotein levels below detection limits of standard techniques.

Specifically, with regards to gamma heavy chain deposition disease, all cases reported to date have shown a deletion of the CH1 domain which may impair their detection by standard serum protein electrophoresis and immunofixation studies.[10,21,22] A similar CH1 deletion has also been reported in a case of light and heavy chain deposition disease.[23] Since our patient had concomitant gamma heavy chain deposition, it is possible he also had a truncated gamma heavy chain lacking the CH1 domain which would be preventing detection by standard techniques. That hypothesis could have been proven by CH1 IF (if a deletion was present, there would be no staining), however, the tissue in the frozen block had been exhausted, so staining for CH1 and IgG subclasses could not be performed in our case.

Renal transplantation is generally considered safe in patients with monoclonal gammopathies of undetermined significance;[24–26] however, in patients with MIDD, recurrence in the allograft is almost universal even in the absence of detectable paraprotein in the serum or urine.[27,28] Therapy with either autologous stem cell transplantation or proteasome inhibitor aiming to achieve deep hematologic response is considered a prerequisite to achieve renal responses.[7]

This case highlights the importance of renal biopsy, even in cases in which a diagnosis may seem clinically straightforward based on clinical and laboratorial data, such as in a patient with RPGN and positive ANCA. Biopsy may not only provide prognostic information with regards to disease activity and chronic changes but also reveal otherwise unsuspected disease processes that may have a bearing on the patients' ultimate outcome (Table 2).

Table 2

Teaching points.

Renal biopsy in patients with RPGN and ANCA may not only inform on extent of crescentic involvement and degree of chronic changes but also reveal unsuspected underlying disease processes
Prognosis tends to be poorer when ANCA co-exists with other diseases, does not always correlate with the extent of crescentic involvement but rather with serum Creatinine at presentation
MIDD may coexist with ANCA and the underlying nodular glomerulosclerosis may have a bearing in response to treatment and prognosis
Patients with MIDD not infrequently have undetectable paraprotein in the serum and/or urine but will invariably show evidence of dysproteinemia in the form of an abnormal serum FLC ratio

ANCA = anti-neutrophil cytoplasmic antibodies, FLC = free light chain, MIDD = monoclonal immunoglobulin deposition disease, RPGN = rapidly progressive glomerulonephritis

Author contributions

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References

[1] Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. Am J Kidney Dis 1988;11:449–64.
[2] Jennette JC. Rapidly progressive crescentic glomerulonephritis. Kidney Int 2003;63:1164–77.
[3] Moroni G, Ponticelli C. Rapidly progressive crescentic glomerulonephritis: early treatment is a must. Autoimmun Rev 2014;13:723–9.
[4] Randall RE, Williamson WCJr, Mullinax F, et al. Manifestations of systemic light chain deposition. Am J Med 1976;60:293–9.
[5] Nasr SH, Valeri AM, Cornell LD, et al. Renal monoclonal immunoglobulin deposition disease: a report of 64 patients from a single institution. Clin J Am Soc Nephrol 2012;7:231–9.
[6] Lin J, Markowitz GS, Valeri AM, et al. Renal monoclonal immunoglobulin deposition disease: the disease spectrum. J Am Soc Nephrol 2001;12:1482–92.
[7] Kourelis TV, Nasr SH, Dispenzieri A, et al. Outcomes of patients with renal monoclonal immunoglobulin deposition disease. Am J Hematol 2016;91:1123–8.
[8] Ito A, Miura N, Kimura Y, et al. Myeloperoxidase anti-cytoplasmic antibody related crescentic glomerulonephritis in a patient with IgG3λ monoclonal immunoglobulin deposition disease with membranous features. Intern Med 2012;51:2393–7.
[9] Alexander MP, Nasr SH, Watson DC, et al. Renal crescentic alpha heavy chain deposition disease: a report of 3 cases and review of the literature. Am J Kidney Dis 2011;58:621–5.
[10] Bridoux F, Javaugue V, Bender S, et al. Unravelling the immunopathological mechanisms of heavy chain deposition disease with implications for clinical management. Kidney Int 2017;91:423–34.
[11] Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010;21:1628–36.
[12] Bjørneklett R, Sriskandarajah S, Bostad L. Prognostic value of histologic classification of ANCA-associated glomerulonephritis. Clin J Am Soc Nephrol 2016;11:2159–67.
[13] Neumann I, Regele H, Kain R, et al. Glomerular immune deposits are associated with increased proteinuria in patients with ANCA-associated crescentic nephritis. Nephrol Dial Transplant 2003;18:524–31.
[14] Haas M, Eustace JA. Immune complex deposits in ANCA-associated crescentic glomerulonephritis: a study of 126 cases. Kidney Int 2004;65:2145–52.
[15] Nasr SH, D'Agati VD, Said SM, et al. Pauci-immune crescentic glomerulonephritis superimposed on diabetic glomerulosclerosis. Clin J Am Soc Nephrol 2008;3:1282–8. Erratum in: Clin J Am Soc Nephrol. *2009;4:516*.
[16] Nasr SH, D'Agati VD, Park HR, et al. Necrotizing and crescentic lupus nephritis with antineutrophil cytoplasmic antibody seropositivity. Clin J Am Soc Nephrol 2008;3:682–90.
[17] Nasr SH, Said SM, Valeri AM, et al. Membranous glomerulonephritis with ANCA-associated necrotizing and crescentic glomerulonephritis. Clin J Am Soc Nephrol 2009;4:299–308.

[18] Chen SF, Wang H, Huang YM, et al. Clinicopathologic characteristics and outcomes of renal thrombotic microangiopathy in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis. Clin J Am Soc Nephrol 2015;10:750–8.
[19] Satoskar AA, Suleiman S, Ayoub I, et al. Staphylococcus infection–associated GN–spectrum of IgA staining and prevalence of ANCA in a single-center Cohort. Clin J Am Soc Nephrol 2017;12:39–49.
[20] Sinniah R. Occurrence of mesangial IgA and IgM deposits in a control necropsy population. J Clin Pathol 1983;36:276–9.
[21] Aucouturier P, Khamlichi AA, Touchard G, et al. Heavy-chain deposition disease. N Engl J Med 1993;329:1389–93.
[22] Moulin B, Deret S, Mariette X, et al. Nodular glomerulosclerosis with deposition of monoclonal immunoglobulin heavy chains lacking CH1. J Am Soc Nephrol 1999;10:519–28.
[23] Cohen C, El-Karoui K, Alyanakian MA, et al. Light and heavy chain deposition disease associated with CH1 deletion. Clin Kidney J 2015;8:237–9.
[24] Bancu I, Cañas L, Juega FJ, et al. Outcomes of monoclonal gammopathy of undetermined significance in patients who underwent kidney transplantation. Transplant Proc 2015;47:2344–5.
[25] Naina HV, Harris S, Dispenzieri A, et al. Long-term follow-up of patients with monoclonal gammopathy of undetermined significance after kidney transplantation. Am J Nephrol 2012;35:365–71.
[26] Jimenez-Zepeda VH, Heilman RL, Engel RA, et al. Monoclonal gammopathy of undetermined significance does not affect outcomes in patients undergoing solid organ transplants. Transplantation 2011;92: 570–4.
[27] Bansal T, Garg A, Snowden JA, et al. Defining the role of renal transplantation in the modern management of multiple myeloma and other plasma cell dyscrasias. Nephron Clin Pract 2012;120: c228–35.
[28] Leung N, Lager DJ, Gertz MA, et al. Long-term outcome of renal transplantation in light-chain deposition disease. Am J Kidney Dis 2004;43:147–53.