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Proliferative glomerulonephritis with monoclonal immunoglobulin deposits masquerading as renal-specific thrombotic microangiopathy

Hayley J Duxbury [1], Vincent W Lee [2,3], Fiona Kwok,[4] Seethalakshmi Viswanathan [1,3]

[1]Tissue Pathology and Diagnostic Oncology, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales, Australia
[2]Westmead Applied Research Centre, The University of Sydney, Sydney, New South Wales, Australia
[3]Westmead Clinical School, The University of Sydney, Sydney, New South Wales, Australia
[4]Department of Haematology, Westmead Hospital, Westmead, New South Wales, Australia

Correspondence to
Dr Seethalakshmi Viswanathan; seethalakshmi.viswanathan@sydney.edu.au

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SUMMARY

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits is a form of monoclonal gammopathy of renal significance that can rarely co-occur with thrombotic microangiopathy (TMA). We report a rare case in a patient who presented with nephrotic syndrome, in whom the renal biopsy showed TMA and underlying granular electron-dense deposits predominantly along the subendothelial aspect of the glomerular basement membrane and mesangium. Immunofluorescence performed on proteinase-digested formalin-fixed, paraffin-embedded sections showed IgG3 kappa light chain restriction. Further clinical, radiologic and haematologic investigations showed no evidence of any underlying neoplastic B-cell or plasma cell clone. Following multidisciplinary team input, the patient was treated with bortezomib and plasma exchange, allowing long-term clinical stabilisation.

BACKGROUND

Monoclonal gammopathy of renal significance (MGRS) can show various renal manifestations with unclear treatment implications. Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is usually a disease of older adulthood, with a mean age of onset of 55 years.[1 2] Monoclonal gammopathy is seen in approximately 20% of patients with renal thrombotic microangiopathy (TMA) over 50 years of age, predominantly without but uncommonly with monoclonal immunoglobulin deposits.[3–5] Both PGNMID and TMA often present with proteinuria, haematuria and impaired renal function with reduced estimated glomerular filtration rate (eGFR) with nephrotic syndrome and oedema.[1 2 4 6 7] TMA may also provoke systemic manifestations of intravascular haemolysis; however, such as in this case, these may not be present.[3–5 8] Early diagnosis, treatment and long-term follow-up are essential due to the risk of end-stage renal failure (ESRF) and recurrence in future allografts. We report a case of PGNMID with concurrent TMA in which diagnosis and treatment were driven by the initial pathologic identification of nephrotoxic monoclonal immunoglobulin.

CASE PRESENTATION

A woman in her 60s presented with several months of pedal oedema with leg cramps, weight gain and worsening hypertension. On examination, she was noted to have bilateral lower limb oedema and blood pressure of 160/80 mmHg. She had a medical history of hypertension, hypercholesterolaemia, thyroidectomy and previous renal angiomyolipoma. Her usual medications included antihypertensives (telmisartan, amlodipine), antilipidemics (ezetimibe, atorvastatin) and thyroxine. A long-term health professional, she had no known personal or family history of renal disease and was a non-smoker with no alcohol intake. Subsequent investigations were undertaken with multidisciplinary team input.

INVESTIGATIONS

On investigation (table 1), a 24-hour urine analysis showed significant proteinuria (17.58 g/day, reference range normal <150 mg/24 hours) with raised albumin/creatinine ratio (818.3 mg/mmol, reference range <3.5 mg/mmol creatinine), consistent with nephrotic syndrome. The creatinine was 192 µmol/L (reference range 45–90 µmol/L) with an eGFR of 24 mL/min/1.73 m^2 (reference range normal ≥90). There was associated hypoalbuminaemia (17 g/L, reference range 35–50 g/L) and impaired glucose tolerance. Haemoglobin showed anaemia (107 g/L, reference range 115–165), which fluctuated with darbepoetin alfa treatment. On further investigation for TMA, no evidence of thrombocytopaenia (platelet count 454×10^9/L; reference range 150–400), disseminated intravascular coagulopathy, hepatitis B and C or HIV was identified. No schistocytes were seen initially on the blood film. Haptoglobin was not performed due to its poor predictive value in the setting of hypoalbuminaemia. Complement studies were not pursued following subsequent diagnosis (see later). Serum protein electrophoresis and immunofixation did not show any paraprotein. The serum free kappa light chain level was 28.90 mg/L (reference 3.3–19.4), and the lambda free light chain level was 21.52 mg/L (reference 5.71–26.30) with a normal kappa:lambda ratio of 1.34 (Freelite assay). Urine electrophoresis and immunofixation did not show any Bence Jones protein.

A renal biopsy was performed. Light microscopy (LM) showed a membranoproliferative pattern of glomerulonephritis with increased mesangial matrix and cellularity with nodular sclerosis pattern (periodic acid-Schiff positive, Congo red negative) (figure 1). Many capillary loops showed double contours, with loop obliteration, and an occasional

glomerular capillary showed platelet/fibrin thrombi. No arteriolar thrombi, fragmented red cells or arteriolar intimal oedema were noted. Moderate chronic interstitial inflammation, tubular atrophy and interstitial fibrosis (approximately 30% interstitial fibrosis and tubular atrophy [IFTA]) as well as mild vascular changes were present in the background.

Immunofluorescence (IF) showed 'a full house staining pattern' with interrupted granular capillary loop positivity for IgG (++), IgM, IgA and prominent C3 and C1q staining deposition (figure 2). There was a predominance of kappa (2–3+) over lambda light chains (faint staining) on IF. Furthermore, IF evaluation with IgG subclasses following proteinase antigen retrieval on formalin-fixed, paraffin-embedded sections was performed. This showed restriction for IgG3 (3–4+) with negative staining for IgG1, IgG2 and IgG4. The overall impression was of monoclonal immunoglobulin deposition along the capillary loops with IgG3 kappa restriction.

Electron microscopy (EM) showed capillary loops markedly distorted by poorly defined non-organised granular subendothelial, intramembranous and occasional subepithelial electron-dense deposits (figure 3). The subendothelial space showed marked expansion by electron-lucent material with cellular debris, mesangial and cellular interposition, irregular thickening and double contour formation of the glomerular basement membranes. Several capillaries showed aggregates of cross-linked fibrin and endothelial swelling with loss of fenestrations. There was extensive and diffuse fusion and effacement of foot processes. The mesangium was expanded with increased matrix and cellularity. No interstitial or tubular basement membrane deposits or vascular deposits were seen. The tubules showed nonspecific degenerative changes and the arterioles, hyaline change.

Without evidence of systemic manifestations, a diagnosis of PGNMID with renal-limited TMA was made. The biopsy prompted haematological investigations for the evaluation of an underlying lymphoproliferative disorder or plasma cell dyscrasia. A bone marrow examination was within normal limits without increased lymphoid cells (14%) and with mildly increased polyclonal plasma cells (1%). Cytogenetics with standard karyotyping showed no abnormalities. A CT scan showed no lymphadenopathy, splenomegaly or lytic lesions. Serum cryoglobulin was not detected.

OUTCOME AND FOLLOW-UP

Following a multidisciplinary team meeting with a local drug committee discussion, the patient completed a total of six cycles of bortezomib, cyclophosphamide and dexamethasone. Despite remission with a reduction in proteinuria from 17.58 to 4 g/day 6 months post bortezomib therapy, the patient had fluctuating renal function (creatinine 292–549 µmol/L, eGFR 14–7 mL/min/1.73 m^2; see figure 4) and five cycles of plasma exchange (PLEX) were performed 8 months post completion of bortezomib therapy to assess whether the progression was secondary to active circulating paraprotein or progression to ESRF. PLEX was ceased due to lack of response, and by 2 months later, the patient progressed to ESRF requiring peritoneal dialysis, 14 months post initial presentation. This was possibly due to the initial chronic renal damage, which was moderate, in conjunction with concurrent TMA. Clinically stable after 8 years of follow-up, the patient remains on peritoneal dialysis without evidence of a monoclonal gammopathy, lymphoproliferative disorder or plasma cell dyscrasia. Renal transplantation has been considered; however, due to her clinical stability, high risk of PGNMID recurrence in the allograft, in addition to the patient's preference to avoid renal transplantation, this has not proceeded.

DISCUSSION

The term monoclonal gammopathy refers to the secretion of partial or complete monoclonal immunoglobulins ('paraproteins') by a monoclonal B-cell or plasma cell population.[1 9] When this involves the kidney alone, without fulfilment of haematologic malignancy disease-specific criteria, this is referred to as MGRS.[1 6 10] MGRS causes damage either directly through immunoglobulin deposition as in PGNMID or indirectly through complement activation without renal immunoglobulin deposition as seen in TMA, and this is the initial feature used to divide forms of MGRS.[1 9–11]

MGRS with renal monoclonal immunoglobulin deposits is then further divided by the deposits being organised or non-organised.[10] Organised forms include fibrillar, microtubular or crystalline/inclusions.[10] Immunoglobulin-related amyloidosis, the most common form of MGRS lesion accounting for 64% of cases, is characterised by Congo red positive, solid fibrils 7–12 nm in diameter.[10 12] Fibrillar forms also include monoclonal fibrillar glomerulonephritis (GN), accounting for <1% of MGRS, with haphazardly arranged Congo red negative or weakly positive 10–30 nm fibrils; and microtubular forms, including cryoglobulinaemic GN types I and II comprising 6% of MGRS; as well as the glomerular-limited immunotactoid GN, comprising 1% of MGRS lesions and characterised by 17–52 nm hollow tubules.[10–12] The crystalline/inclusion forms include light chain proximal tubulopathy, which accounts for 3% of MGRS lesions; crystal storing histiocytosis, which shows light chain crystals within renal histiocytes and proximal tubule cells; and cryocrystalglobulinaemic GN with extracellular crystals within the glomerular capillaries and arterioles.[10 12] The latter two each account for <1% of all MGRS cases.[12]

MGRS with non-organised deposits includes monoclonal immunoglobulin deposition disease (MIDD), which accounts for 11% of MGRS-related lesions, and PGNMID.[10 12] MIDD involves linear, punctate glomerular and tubular basement membrane deposits, usually composed of IgG1 lacking the first constant domain; it is then divided into light or heavy chain only or both.[1 10] In contrast, PGNMID, accounting for 6% of MGRS-related lesions, results from paraprotein deposition solely in the glomerulus.[1 12] The most commonly deposited subclass of gamma heavy chain is IgG3, which can self-aggregate and become entrapped within the glomeruli with subsequent activation of complement through fixation of C1q.[1 2 6] This provokes glomerular inflammation.[6 9] These conditions may be associated with prominent complement deposition on the biopsy, as noted in this case.[1 10] Additionally, PGNMID must lack evidence of cryoglobulinaemia, as seen here.[2]

MGRS without renal deposits includes C3 glomerulopathy (C3 GN) with monoclonal gammopathy (further divided into C3 GN and dense deposit disease) and TMA. C3 GN shows characteristic C3 deposits within the glomerulus; both account for 3% of MGRS lesions.[10 11] TMA is caused by endothelial injury resulting in the occlusion of small blood vessels and end-organ damage.[3 4 7] It can occur in the setting of monoclonal gammopathy predominantly without but rarely with paraprotein deposition, where the immunoglobulin triggers complement activation.[3 5 7–9 11]

In this case, the TMA was accompanied by tissue deposition of paraprotein, causing MGRS alongside TMA. In such cases, apart from temporality, the pathogenetic relationship between

Table 1 Relevant investigations

Site	Parameter	Value	
Serum	Creatinine (µmol/L) (reference range 45–90)*	At presentation: 192 3 months: 230 6 months†: 280 12 months: 292 14 months‡: 549	
	eGFR (mL/min/1.73 m^2; reference range ≥90 µmol/L)*	At presentation: 24 3 months: 19 6 months†: 15 12 months: 14 14 months‡: 7	
	Albumin (g/L; reference range 35–40)*	At presentation: 17 3 months: 22 6 months†: 31 12 months: 25 18 months: 26 Current§: 33	
	Haemoglobin (g/L; reference range 115–165)*¶	At presentation: 107 3 months : 87 6 months†: 81 12 months: 87 18 months: 73 Current§: 94	
	Platelets (×10^9/L; reference range 150–400)*	At presentation: 454 3 months: 441 6 months†: 305 12 months: 264 18 months: 389 Current§: 298	
	Serum protein electrophoresis and immunofixation	No paraprotein detected	
		Alpha1 globulin (g/L; reference range 1.9–4.6)	1.7
		Alpha2 globulin (g/L; reference range 2.8–7.7)	9.6
		Beta globulin (g/L; reference range 5.1–14.0)	8.2
		Gamma globulin (g/L; reference range 5.1–14.0)	2.3
	Serum free light chains	Kappa light chains (mg/L; reference range 3.30–19.40)	28.9
		Lambda light chains (mg/L; reference range 5.71–26.30)	21.52
		Kappa:lambda ratio (reference range 0.26–1.65)	1.34
	Lactate dehydrogenase (U/L; reference range 120–250; critical high >1000)	373	
	Total bilirubin (µmol/L; reference range 10–20)	3	
	Cryoglobulins	Not detected	
	Antiglomerular basement membrane antibodies	Not detected	
	Peripheral blood film	At presentation: no evidence of schistocytes 3 months post initiation of bortezomib therapy: very occasional schistocytes 5 months post completion of bortezomib therapy: maximum 1–2 schistocytes per 10 high-power fields**	
Urine (24-hour collection)	Albumin:creatinine ratio (mg/mmol, reference range <3.5 mg/mmol creatinine)	At presentation: 818.3 Current§: 2000	
	Protein (g/day, reference range <150 mg/24 hours)	At presentation: 17.58 6 months†: 4 Current§: 9	
	Urine electrophoresis and immunofixation	No evidence of Bence Jones protein. Presence of albumin and other serum proteins suggestive of glomerular protein loss	
Bone marrow	Aspirate, trephine	Normocellular, with no increase in plasma cell numbers	
Imaging	Skeletal survey	No lytic lesions	
	CT of the chest/abdomen/pelvis	No lymphadenopathy or splenomegaly seen	

*Time post presentation.
†1 month post bortezomib course completion.
‡Peritoneal dialysis was commenced at 14 months post initial presentation.
§8 years post initial presentation.
¶Darbepoetin alfa intermittently given during this time.
**Considered subclinical due to mildly increased lactate dehydrogenase, mild anaemia consistent with anaemia of chronic disease, consistently normal bilirubin and platelet count.
eGFR, estimated glomerular filtration rate.

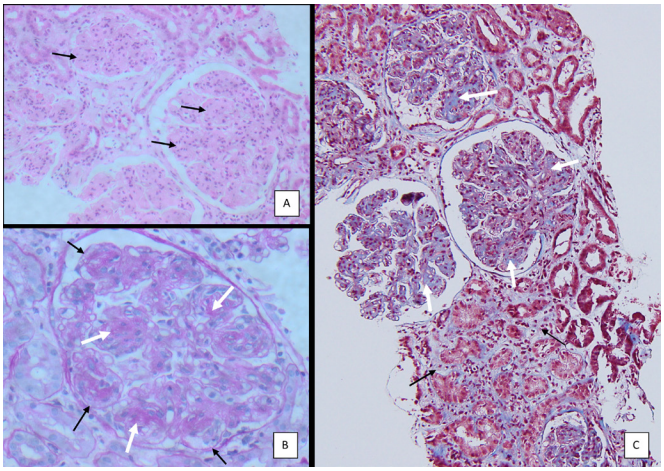

Figure 1 (A–C) Renal core biopsy of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) with thrombotic microangiopathy (TMA), light microscopy. (A) Glomeruli show chronic membranoproliferative pattern with increased mesangial matrix and cellularity (black arrow), (H&E ×200). (B) Glomerulus showing double contours (black arrow) with scarring in the mesangium (white solid arrow) (periodic acid-Schiff stain ×400). (C) Chronic moderate interstitial fibrosis (black arrow) with scarring in the mesangium (white arrow) (Masson's trichrome ×100). Link text: PGNMID with TMA light microscopy.

the TMA and the paraprotein can be unclear.[8] This requires multidisciplinary discussion and interpretation to allow appropriate management.[8]

Investigation of MGRS requires screening for monoclonal immunoglobulin proteins (with serum and urine electrophoresis with immunofixation as well as serum free light chains)

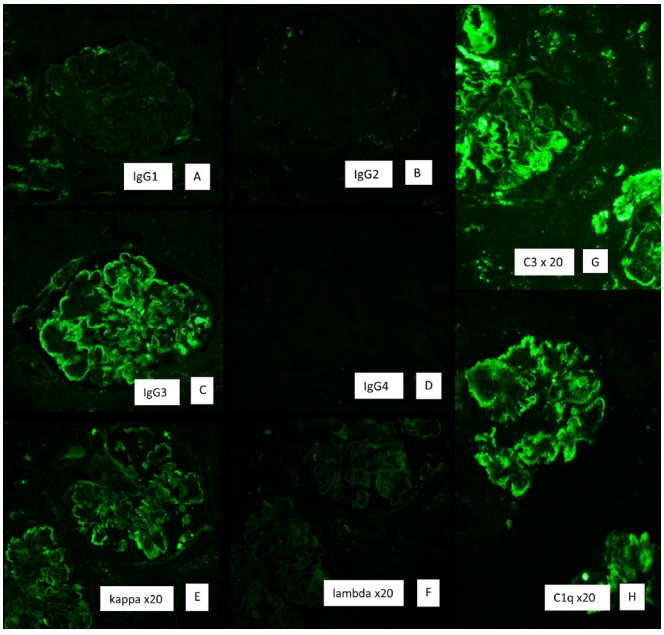

Figure 2 (A–H) Immunofluorescence (IF) findings. (A–F) Glomeruli showing IgG3 kappa restriction along with strong staining for complement components C3 and C1q (G–H). Please note the absence of staining in the tubules. Permission has been obtained from the referral laboratory for IF images obtained after proteinase digestion of formalin-fixed, paraffin-embedded tissue.

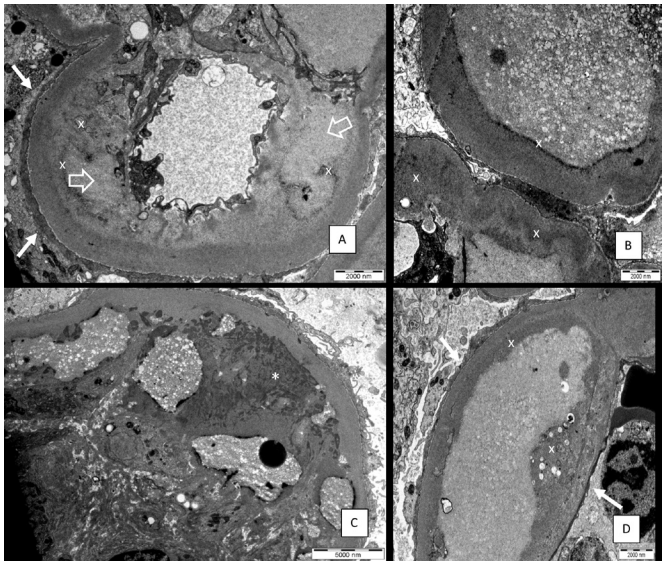

Figure 3 (A–D) Electron microscopy (EM) findings. Podocyte foot process effacement (solid white arrow), occasional electron-dense deposits (x), granular powdery non-organised deposits in the subendothelial location of the capillary basement membrane with subendothelial expansion with electron-lucent material (hollow white arrow) and fibrin tactoids (white asterisk) consistent with thrombotic microangiopathy (TMA). Link text: proliferative glomerulonephritis with monoclonal immunoglobulin deposits with TMA EM.

and investigation for clonal B-cell and plasma cell population on bone marrow (histopathology, flow cytometry and genetics) and with imaging.[2 4 6 7 10 13] However, these tests do not correspond to the severity of renal injury and are often not sufficiently sensitive to identify the underlying clone as seen here; the clone is only identified in approximately 20–30% of PGNMID cases.[2 10 13] Hence, using the most sensitive tests available to interrogate for haematologic clones (such as flow cytometry with a lower limit of detection of 0.001%) is required. At the time of diagnosis of this case, using such sensitive tests was not local practice and/or unavailable for MGRS; however, this has since changed. Renal biopsy is essential for diagnosis and may be the first modality to reveal an underlying monoclonal gammopathy as observed here.[10]

On renal biopsy, PGNMID shows characteristic features as seen here, including monoclonal immunoglobulin deposition limited to the glomeruli, without involvement of the tubular basement membrane, interstitium or blood vessels.[1 6] The LM findings, IF findings of IgG3 kappa restriction and EM findings were characteristic of those described in the literature.[1 2 10 13]

TMA may be indicated by thrombocytopaenia and microangiopathic haemolysis (red cell fragments on blood film, raised lactate dehydrogenase, reduced haptoglobin and so forth).[3 4] In addition to endothelial cell swelling, classical subendothelial electron-lucent material and double contours (as seen in this case) and pathognomonic fibrin thrombi, renal biopsy LM may also show more chronic changes, such as mesangiolysis or arterial intimal proliferation with mucoid material and luminal narrowing.[3 4] The thrombi must be distinguished from pseudothrombi of immunoglobulin aggregates.[8]

The ideal treatment for many MGRS lesions is unknown.[3 11] Identification of a pathogenic plasma cell or B-cell clone allows for targeted treatment, which provides a better response over empirical chemotherapy.[1 2 6 13] A management dilemma arises

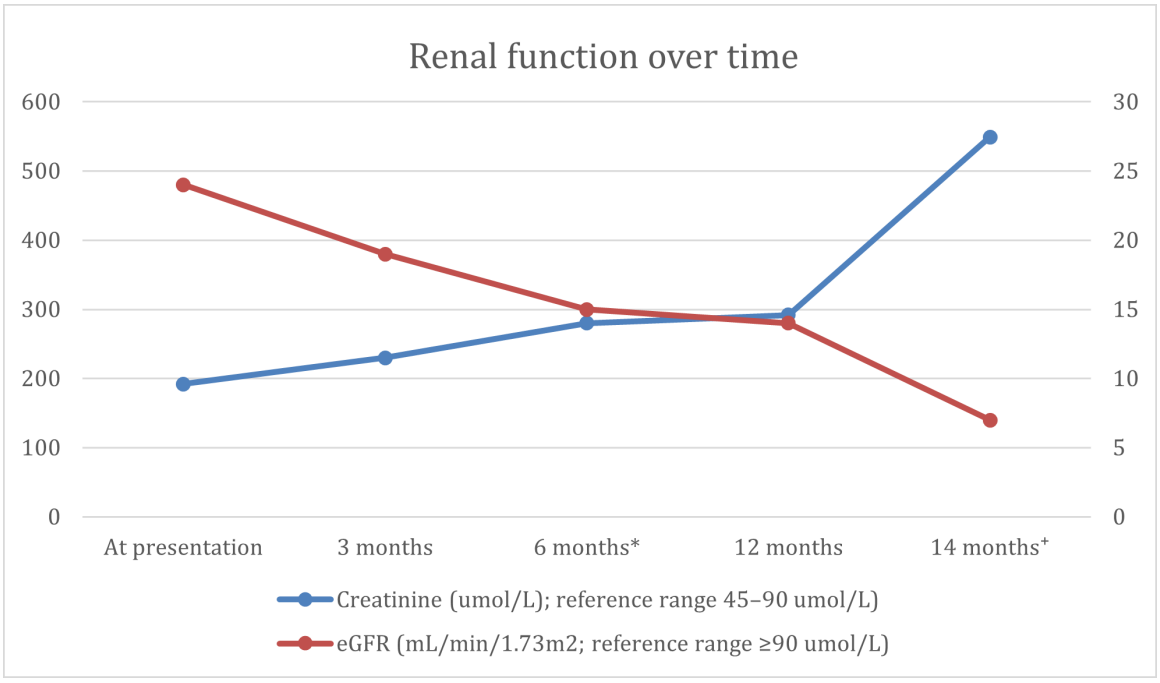

Figure 4 Graph to show renal function parameters (creatinine and eGFR) over time. *1 month post bortezomib course completion. +Peritoneal dialysis was commenced at 14 months post initial presentation. eGFR, estimated glomerular filtration rate.

if the haematologic clone cannot be identified.[3 4] Bortezomib was chosen here as it has efficacy against both B-cell and plasma cell clones. Anticlonal treatment of both PGNMID and TMA with monoclonal gammopathy may halt progression to ESRF.[1 3 6] However, sometimes, the damage may already be done, and pretreatment eGFR of <30 mL/min/1.73 m^2, global glomerulosclerosis, tubular atrophy, interstitial fibrosis or arteriosclerosis predict worse renal response to chemotherapy.[1] Paraprotein removal alone by plasmapheresis or PLEX provides only a temporary management option.[1 5 7]

More than 20% of PGNMID cases and approximately one third of TMA with monoclonal gammopathy cases result in ESRF.[1 2 4 6 13] Recurrence of both entities in native and renal allografts is common, with associated poor prognosis.[1–3 6 13] Long-term follow-up is required due to the ~1% per year risk of development of lymphoproliferative or plasma cell neoplasia.[2 6 13]

This is a rare case of combined TMA and PGNMID without an identified pathogenic clone. To our knowledge, this combined diagnosis has been described only once previously by De La Flor *et al*, who described a case of TMA with PGNMID in which a pathogenic plasma cell clone was identified.[11] In our case, the initial diagnosis of TMA was identified by biopsy only, without systemic manifestations (renal-specific TMA), emphasising the utility of the proteinase digestion technique in the diagnosis and characterisation of MGRS. This case highlights the intricacies and importance of pathological and multidisciplinary input, allowing disease recognition and significantly altering management. Early histopathological consideration of the possible presence of an MGRS lesion is key to accurate diagnosis and shifts the diagnostic workup and management towards identifying and treating the underlying clone.

Learning points

- Thrombotic microangiopathy, proliferative glomerulonephritis with monoclonal immunoglobulin deposits and other monoclonal gammopathy of renal significance (MGRS) lesions may present with non-specific renal manifestations and without monoclonal gammopathy. Renal biopsy is essential for accurate diagnosis.
- The combined use of IgG subclasses along with light chain restriction is key to establishing a conclusive diagnosis of MGRS. Immunofluorescence on formalin-fixed, paraffin-embedded tissue after proteinase digestion is a helpful technique to facilitate this.
- Investigation and management of any identifiable pathogenic plasma cell or B-cell clone requires multidisciplinary team input. A management dilemma arises when no clone can be identified. All available and sensitive tests should be used in an effort to identify the small B-cell or plasma cell clone driving MGRS lesions.

X Vincent W Lee @vwslee

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ORCID iDs
Hayley J Duxbury http://orcid.org/0009-0005-9909-8531
Vincent W Lee http://orcid.org/0000-0002-9400-3696
Seethalakshmi Viswanathan http://orcid.org/0000-0003-4571-6996

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