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Case Report

A Case of Myeloma Kidney with Perinuclear Anti-Neutrophil Cytoplasmic Antibody and Anti-Myeloperoxidase Positivity: The Importance of Determining the True Cause of Renal Impairment

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Acute kidney injury · Glomerulonephritis · Vasculitis · Myeloma kidney · Histopathology · Kidney biopsy

Abstract
Acute kidney injury (AKI) is a common presentation which can result from a number of different underlying pathological processes. Haematological malignancies, particularly multiple myeloma (MM), are known to frequently present with AKI. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare condition which can cause crescentic glomerulonephritis (GN), resulting in AKI. We present the case of a 60-year-old man who presented with clinical features suggestive of AAV in the context of blood tests which demonstrated AKI and positive perinuclear ANCA (p-ANCA) and anti-myeloperoxidase (anti-MPO) titres. Further in-

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vestigations demonstrated an underlying diagnosis of MM. A renal biopsy was ultimately required to determine the cause of AKI, a cast nephropathy. This case is the first to our knowledge which demonstrates a rare situation in which myeloma kidney is associated with positive p-ANCA and anti-MPO titres, without any evidence of a crescentic GN. It highlights the importance of following up on all investigations sent in the context of AKI, even when a potential diagnosis seems evident. Furthermore, it demonstrates the role of renal biopsy in confirming a diagnosis in the context of AKI with multiple differential diagnoses.

Introduction

Acute kidney injury (AKI) is a common complication of many malignant processes, particularly those of haematological origin [1]. Furthermore, AKI can be a presenting feature and lead to the ultimate identification of an underlying malignant haematological condition. Multiple myeloma (MM) is one such condition and can present with AKI in up to 50% of cases [1, 2]. Myeloma screening blood tests are therefore routinely included as part of the panel of investigations requested in patients presenting with renal impairment. There are many mechanisms by which MM can cause renal impairment, including deposition of free light chain casts within tubules (cast nephropathy), proximal tubule cell injury leading to a Fanconi-like syndrome and interstitial fibrosis, hypercalcaemia, light chain deposition within glomeruli leading to glomerulonephritis (GN), amyloidosis, and cryglobulinaemia [1, 3].

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) can affect several organs, thus patients can present in a number of different ways. Renal involvement is common and many patients demonstrate AKI at the time of presentation [4]. Two types of ANCA have been identified and are routinely tested for by indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). IIF detects perinuclear ANCA (p-ANCA) and cytoplasmic ANCA (c-ANCA) staining patterns in neutrophils, and ELISA identifies the associated antibodies against the enzymes myeloperoxidase (MPO) and proteinase-3 (PR3), respectively [5]. Renal biopsy is then often used to confirm renal involvement by identifying the presence of a pauci-immune necrotising and crescentic GN [6]. AAV can result in rapidly progressive GN requiring haemodialysis at the time of presentation. Increasing numbers of patients have been reported to have concurrent malignancies, particularly haematological malignancies, associated with AAV, although this association remains rare [7].

We present the case of a 60-year-old man who presented with clinical features and serology suggestive of AAV with anti-MPO positivity and who was subsequently found to have MM with renal involvement. Several previous cases have been reported where AAV with renal involvement and a concurrent diagnosis of MM was identified [8–11]. To our knowledge, only one previous case of MM with renal involvement with positive anti-MPO and anti-PR3 serology has been identified [12], though that case did not demonstrate a positive ANCA titre.

Case Presentation

A 60-year-old man was referred by his general practitioner after presenting with a 2-month history of cramping pains in the joints of his hands and feet. He was commenced on a non-steroidal anti-inflammatory medication for presumed arthritis. Routine blood tests performed 6 weeks later revealed stage 3 AKI (Acute Kidney Injury Network classification [13]) with a serum creatinine of 550 μmol/L, from a baseline of 70 μmol/L 2 years previously, giving an estimated glomerular filtration rate of 8. His past medical history included a 10-year history of psoriasis, a previous episode of viral pericarditis with atrial fibrillation, and mild depression. He was an ex-smoker with a 60 pack-year history and was independent as to activities of daily living. His family history was significant for a brother who died following a diagnosis of renal cell carcinoma. Examination at the time of admission revealed a psoriatic rash over the extensor aspect of the elbows bilaterally, onycholysis, and mild pitting oedema to the ankles bilaterally. Most notably, there was no evidence of active arthropathy or vasculitis and no organomegaly.

Following admission an ultrasound of the kidneys and urinary tract was performed, which demonstrated unobstructed left and right kidneys with increased cortical reflectivity, measuring 11.8 and 12 cm, respectively. A few simple cysts were noted bilaterally, the largest of which measured 49 mm. Renal artery and vein duplex showed no evidence of renal artery stenosis. Urine dipstick was positive for two plus blood, protein was negative. Serum creatinine continued to rise from admission values to a peak of 650 μmol/L with urea 16 mmol/L and potassium 4.9 mmol/L. Further laboratory investigations are shown in Table 1. ANCA screen returned positive with raised anti-MPO antibodies of 157 U/ml and a p-ANCA pattern on immunofluorescence. Anti-PR3 antibodies were within normal range at 0.4 U/ml. All other immunology investigations returned within normal range (Table 1). Virology, including HIV-1 and HIV-2, HTLV-1 and HTLV-2, as well as hepatitis B and C serology were all negative.

The patient was subsequently transferred to our tertiary renal unit for ongoing care and treatment of a possible AAV. Following transfer, outstanding blood tests returned, including a myeloma screen. This revealed significantly elevated serum lambda light chains of 11,379.70 mg/L and associated kappa light chain of 56.33 mg/L. This gave an abnormal kappa:lambda serum free light chain ratio of 0.0051 (normal range 0.37–3.1 in the context of renal impairment) (Table 1). Serum electrophoresis demonstrated a monoclonal lambda chain with normal IgG, IgM, and IgA. Haematology input was sought and a bone marrow biopsy performed. Beta-2 microglobulin was elevated at 21.69 mg/L. Bone marrow biopsy demonstrated histological features consistent with plasma cell myeloma with 20–30% marrow involvement and lambda restriction. CT-PET showed no evidence of skeletal or extraskeletal myelomatous involvement, and MRI of the spine showed no evidence of diffuse or focal myeloma within the spine.

A renal biopsy was performed the following day. Two samples contained 17 normal glomeruli with no acute GN and no active lesions. The tubulointerstitium revealed eosinophilic tubular casts and associated cellular reaction; this material was periodic acid-Schiff-negative. There was a tubulointerstitial nephritis with a predominance of eosinophils and 10% fibrosis. Immunology staining showed lambda light chain restriction. Congo red stains were negative.

The patient was commenced on dexamethasone 20 mg per day on the advice of the haematology team. Serum creatinine subsequently started to fall progressively to a value of

355 μmol/L prior to discharge from hospital. He was commenced on a Velcade and thalidomide chemotherapy regimen, alongside the dexamethasone (VTD), and was discharged with a view to ongoing outpatient care. Throughout his admission he continued to pass good volumes of urine, which exceeded 1,500 mL per day, and he avoided the need to commence renal replacement therapy.

At the time of writing the patient's serum creatinine had fallen to 124 μmol/L and he remained on his second cycle of VTD chemotherapy.

Discussion

AKI is a common presenting feature of patients with MM and AAV. We present the case of a patient presenting with AKI, a new diagnosis of MM and an associated p-ANCA and anti-MPO autoantibody identified on IIF and ELISA, respectively. We are aware of only one previous case which reports the presence of AKI resulting from MM with a concurrent positive ANCA ELISA. This report, however, did not identify a p-ANCA pattern on IIF and the patient demonstrated no features of AAV [12]. The differential diagnosis for AKI in our case initially included p-ANCA/anti-MPO positive AAV with renal involvement, MM and one of the many associated causes of renal impairment (as mentioned above), and tubulointerstitial nephritis resulting from recent non-steroidal anti-inflammatory medication use. Differentiating between these potential diagnoses was difficult based purely on clinical and biochemical findings. The presenting complaint of arthropathy, alongside a positive ANCA serology and a rapidly progressive AKI, might lead a clinician to think of AAV as the most likely diagnosis. One could argue that in this case the ANCA titres were low and that arthropathy can be associated with MM; however, this simply highlights the importance of requesting, as well as following up on, all aspects of renal screening blood tests in the context of AKI. Without the results of the serum free light chain and serum protein electrophoresis, the diagnosis of myeloma might have initially been missed and resulted in a delay in commencing appropriate treatment. Furthermore, the significance of a renal biopsy is demonstrated as this was essential in ultimately confirming the presence of a cast nephropathy and ruling out a crescentic GN or aggressive drug-associated tubulointerstitial nephritis.

Following a renal biopsy the patient was commenced on high-dose steroid therapy. It is well established that the initial treatment of all the differential diagnoses discussed would have included high-dose steroid therapy [14–16]. However, distinguishing between the possible diagnoses in this case was essential in order to help guide management both in the short- and long-term setting. This includes avoiding inappropriate instigation of treatment for AAV, such as aggressive immunosuppression, which itself carries a significant risk of morbidity and mortality [17]. Furthermore, it allowed for prompt initiation of a VTD chemotherapy regimen for MM, which has been shown to help improve the likelihood of recovery of renal function [18].

The association between AAV and concurrent haematological malignant disease has been reported in several cases, and although it remains rare, it is now well established [7, 19]. The exact pathophysiological mechanism underlying this association is yet to be determined and could be the result of a number of different mechanisms, which may vary with different malignancies. In the case of MM, a study by Esnault et al. [20] identified the association between

monoclonal immunoglobulins and ANCA reactivity, by demonstrating the presence of both monoclonal and polyclonal ANCA reactivity in 12 of 125 patients' sera with concurrent monoclonal immunoglobulins. This raises the possibility that the monoclonal immunoglobulins and/or the associated light chains have direct ANCA reactivity. Further work is required in this area to help clarify the role of monoclonal immunoglobulins in ANCA reactivity and the pathophysiological role they may play.

Conclusion

We present the case of a patient presenting with a rapidly progressive AKI secondary to cast nephropathy and an associated p-ANCA and anti-MPO positivity on IIF and ELISA, respectively. Only one previous case of renal impairment secondary to cast nephropathy with a concurrent anti-MPO-positive ELISA has been reported. Our case highlights that, although rare, concurrent diagnoses of MM with cast nephropathy and ANCA positivity do exist. It demonstrates the importance of performing and following up on renal screening blood tests in the context of AKI, even when the initial clinical picture and investigations may point towards a particular diagnosis. Furthermore, it emphasises the role of a renal biopsy in making a diagnosis when multiple differential diagnoses are present. Ultimately, this allows for the timely initiation of appropriate management.

Statement of Ethics

All patient information was anonymised and written consent for publication of the case was obtained from the patient. The research was conducted ethically in accordance with the World Health Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

T. Roper reviewed the case and wrote the main body of the text. R. Elias and S. Jayawardene reviewed and amended subsequent drafts and approved the final version.

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Table 1. Laboratory results at the time of presentation

Laboratory investigations	Results		Reference range (units)	
Creatinine	550		45–120 (mol/L)	
Urea	16		3.3–6.7 (mmol/L)	
Potassium	4.9		3.5–5.0 (mmol/L)	
Bicarbonate	18		22–30 (mmol/L)	
Haemoglobin	113		130–165 (g/L)	
Mean corpuscular volume	90.5		82–98 (fL)	
Platelets	398		150–450 ($\times 10^9$/L)	
Total protein	74		60–80 (g/L)	
Albumin	42		35–50 (g/L)	
Globulin	32		25–35 (g/L)	
Corrected calcium	2.39		2.15–2.6 (mmol/L)	
ANCA				
IIF	p-ANCA positive	c-ANCA negative		
ELISA	anti-MPO 157	anti-PR3 0.4	0–3.4 (U/mL)	0–1.9 (U/mL)
Anti-GBM	<0.8		0–7 (U/mL)	
Anti-neutrophil antibody	negative			
Double-stranded DNA	1		<10 (IU/mL)	
Complement				
C3	1.34		0.7–1.65 (g/L)	
C4	0.33		0.16–0.54 (g/L)	
Rheumatoid factor	<10		0–14 (IU/mL)	
Serum free light chains				
Kappa	46.90		3.30–19.40 (mg/L)	
Lambda	9,252.0		5.71–26.30 (mg/L)	
Kappa:lambda ratio	0.0051		0.37–3.1	
Serum protein electrophoresis	monoclonal lambda chain			
IgA	0.57		0.87–4.12 (g/L)	
IgG	8.93		6.34–18.11 (g/L)	
IgM	0.14		0.53–2.23 (g/L)	
Beta-2 microglobulin	21.69		<2.40 (mg/L)	

ANCA, anti-neutrophil cytoplasmic antibody; c-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibody; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibody; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence; MPO, myeloperoxidase; PR3, proteinase-3.