

Multiple intra-renal pathological injury patterns in resistant myeloma

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CASE STUDY

Please cite this paper as: Rangaswamy D, Madken M, Vankalakunti M, Attur RP, Nagaraju SP. Multiple intra-renal pathological injury patterns in resistant myeloma. AMJ 2016;9(9):308-312.

<http://doi.org/10.21767/AMJ.2016.2660>

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ABSTRACT

Renal dysfunction in patients with multiple myeloma has a heterogeneous aetiology ranging from pre-renal, intra-renal to post-renal causes. Common pathological forms of paraproteinemic disease include cast nephropathy, amyloidosis and Immunoglobulin chain deposition disease. Infrequently cryoglobulinemic glomerulonephritis and light chain proximal tubulopathy have also been described. The presence of multiple intra-renal pathological injury patterns has been described only once previously with immunoglobulin light chains. We report a patient with long standing treatment resistant multiple myeloma and new onset progressive renal failure with heavy and light-chain amyloidosis, cast nephropathy and proximal tubulopathy on renal biopsy.

Key Words

AHL amyloidosis, chemotherapy, multiple myeloma, proximal tubulopathy

Implications for Practice:

1. What is known about this subject?

Renal lesions associated with monoclonal gammopathy depend on the physiochemical properties of the immunoglobulin produced and are usually present pathologically as solitary injury pattern.

2. What new information is offered in this case study?

The presence of multiple intra-renal pathological injury patterns is seen in patients exposed to several chemotherapeutic agents, secondary to mutated plasma clones.

3. What are the implications for research, policy, or practice?

Though physiologic properties of abnormal light chains are thought to determine the pattern of renal injury in multiple myeloma, the pathophysiology appears to be more complex.

Background

Kidney disease is a common manifestation of multiple myeloma (MM) in approximately 50 per cent of patients having renal dysfunction at presentation.¹ The spectrum of renal lesions associated with monoclonal gammopathy is extensive and depends on the physiochemical properties of the immunoglobulin produced. Solitary pattern, mainly cast nephropathy is the most common pattern of renal injury in patients who undergo a biopsy. Therapy with multiple chemo-therapeutic drugs especially alkylating drugs could influence the para-proteins secreted resulting in multiple injury patterns on renal histology.

Case details

A 45-year-old female was diagnosed to have MM during an evaluation for severe lower backache with multiple lytic lesions on skeletal survey. She had 19 per cent atypical plasma cells on bone marrow, a monoclonal spike showing restriction for IgG heavy chain and lambda (λ) light chain with a normal renal function. In the last seven years she was

treated with steroids, thalidomide, lenalidomide, bortezomib, melphalan and cyclophosphamide as part of various treatment regimens. On therapy, she had an episode of acute kidney injury secondary to hypercalcemia and recurrent vomiting. Her serum creatinine increased from 0.7mg/dL to a peak of 4.5mg/dL (N: 0.6-1.2mg/dL), which recovered only partially to a new nadir of 2.2mg/dL over next 4 weeks. She also became hypertensive and was started on calcium channel blockers. Few months later her serum creatinine again showed an increasing trend from a stable value, for which she underwent a renal biopsy. At the time of renal biopsy her 24hr urine protein was 2232mg, κ:λ light chain ratio of 0.08, serum creatinine of 4.6mg/dL, an elevated serum IgG levels of 5471mg/dL (N: 1200-1480mg/dL). Bone marrow showed 21 per cent atypical plasma cells. On renal biopsy, glomeruli were unremarkable in light microscopy and Immunofluorescence. Tubules showed presence of acellular, eosinophilic, Periodic acid Schiff negative lamellated casts which were congophilic and demonstrated apple green birefringence under polarizer microscope (Figures 1a-c). Few of these casts were surrounded with epithelial reaction at the periphery (Figure 1d). Tubular epithelium showed cytoplasmic vacuoles and interstitium was oedematous with occasional lymphocytes and mild focal fibrosis. On Immunofluorescence (Figures 2a-d), tubular casts illustrated bright staining with IgG (4+). Similarly light chain studies showed λ (3+) positivity within the luminal casts and in the vacuoles of tubular epithelial cytoplasm. Vessels showed mild to moderate medial hypertrophy. Final pathological diagnoses included (i) Cast Nephropathy, (ii) AHL-Amyloidosis and (iii) Proximal tubulopathy with acute tubular necrosis, all primarily seen in tubules.

At follow up patient progressed to end stage renal disease over the next 8 months and is currently on maintenance haemodialysis and thalidomide.

Discussion

We present a rare case of renal failure in a patient with MM with three different intra-renal pathological findings: Cast nephropathy, amyloidosis (AHL type) and proximal tubulopathy.

Up to fifty percent of patients with MM and renal dysfunction have an identifiable intra-renal pathology.¹ The spectrum of renal lesions associated with monoclonal gammopathy is extensive and depend on the physiochemical properties of the immunoglobulin produced. Cast nephropathy is the most common pattern of renal injury in biopsied patients, seen in 30-50 per cent of

renal biopsies in MM. In cast nephropathy, excess light chains deposit within tubular lumens causing obstruction and injury. Light microscopy features show fractured periodic acid schiff negative casts with surrounding inflammatory cells².

Amyloidosis is the second most common pattern of renal injury in MM seen in 7-30 per cent of patients and amyloid deposits are usually noted along the vessels, glomeruli and rarely along the tubular basement membrane.² These are most often derived from monoclonal light chain but rarely are composed of heavy chain.^{3,4} Amyloidogenic light chains contain destabilizing mutations which decrease structural integrity and predispose to fibril formation. They also contain hydrophobic amino acid substitutions at exposed surfaces which predispose to aggregation and may contain domains more likely to be glycosylated and enhanced protein stability.⁵ Deposits in amyloidosis generally consist of light chain fragments, whereas deposits in light chain deposition disease usually consist of intact light chains. Light chains in amyloidosis have enhanced disulphide binding compared to light chains in light chain deposition disease, which may interfere with their clearance and metabolism.⁶ AHL amyloidosis, in which the amyloid fibrils are derived from fragments of the immunoglobulin heavy chain and light chain, is a rare entity. The pathogenesis of AH and AHL is unknown. The presence of a circulating complete immunoglobulin in most patients favours that the amyloid fibrils result from post-translational proteolysis of the monoclonal immunoglobulin. However, an abnormal biosynthesis of these immunoglobulin fragments, as demonstrated in light and heavy chain deposition disease, remains a possibility, particularly in AHL and the localized amyloidosis forms.⁷

The patho-physiology of intra-tubular amyloid is unclear because amyloid fibrils are large and unlikely to be filtered through the glomerular basement membrane. Possible mechanisms are fibril formation inside the tubule from either protein secreted by tubular cells or filtered light chains. Intra-tubular amyloidosis is a rare entity but should be considered when tubular casts or protein re-absorption-like droplets in tubular epithelial cells are PAS negative and are comprised of monoclonal light chains on immunofluorescence studies. Congo-red stains and electron microscopy are then required to confirm the diagnosis.

Light chain proximal tubulopathy is a form of proximal tubule injury secondary to increased filtration and subsequent uptake by tubular cells of pathogenic light chains. This rare disorder occurs when the free light chains

resist proteolysis and undergo homotypic polymerization within the endolysosomal system of the proximal tubular epithelium to form intracellular crystals, which are the distinguishing pathologic characteristics of this syndrome. The classic presentation is Fanconi syndrome clinically and on renal biopsy shows typical kappa-restricted intracytoplasmic crystals.⁸ Recently, the pathologic spectrum has been expanded to include noncrystalline morphology with 1/3rd cases showing λ restriction.⁹ International Kidney and Monoclonal Gammopathy Research Group currently recommend chemotherapy or stem cell transplant for Light chain proximal tubulopathy, to delay renal progression, and to minimize the risk of recurrence after renal transplantation.¹⁰

Physiologic properties of the abnormal light chains are thought to determine the pattern of renal injury in MM. Light chains involved in cast nephropathy have been referred to as 'tubulopathic' light chains as they obstruct tubular cells. In contrast, light chains in amyloidosis and LCDD have been termed 'glomerulopathic' light chains as they interact with mesangial cells within glomeruli and alter mesangial homeostasis.¹¹

The cause of multiple pathological patterns in patients of MM is not known till date. However, there are several hypotheses. First, a biclonal proliferative process may be involved in which more than one light chain causes damage.¹² Alternatively, the original light chain gene may mutate, giving rise to a second plasma cell clone.¹² This type of mutation has been seen with alkylating chemotherapy.¹³ A third explanation for concurrent light chain pathologies is that non-fibrillar proteins may serve as precursors to fibrils.¹³

Our patient, a diagnosed case of MM-IgG type presented with an acute deterioration of chronic renal failure on a background record of being treated with multiple chemotherapeutic drugs including alkylating drugs. Hence, there is possibility of mutation of the original light chain due to prior chemotherapy she had received during her relapsing and remitting course of disease in last 8 years.

There are reports of combination of histologic findings of plasma cell dyscrasia.¹⁴⁻¹⁶ To the best of our knowledge, our case is the first to describe intra-tubular amyloidosis (AHL-type) and proximal tubulopathy occurring in association with cast nephropathy. Another interesting feature of our patient's biopsy was the absence of glomerular deposits of amyloid.

Conclusion

Even though the physiologic properties of abnormal light chains are thought to determine the pattern of renal injury in multiple myeloma, pathophysiology appears to be more complex. Exposure to various chemotherapeutic drugs, especially alkylating agents may result in new light chain gene mutation resulting in secondary plasma cell clones which may be the basis for multiple injury patterns in myeloma kidney.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

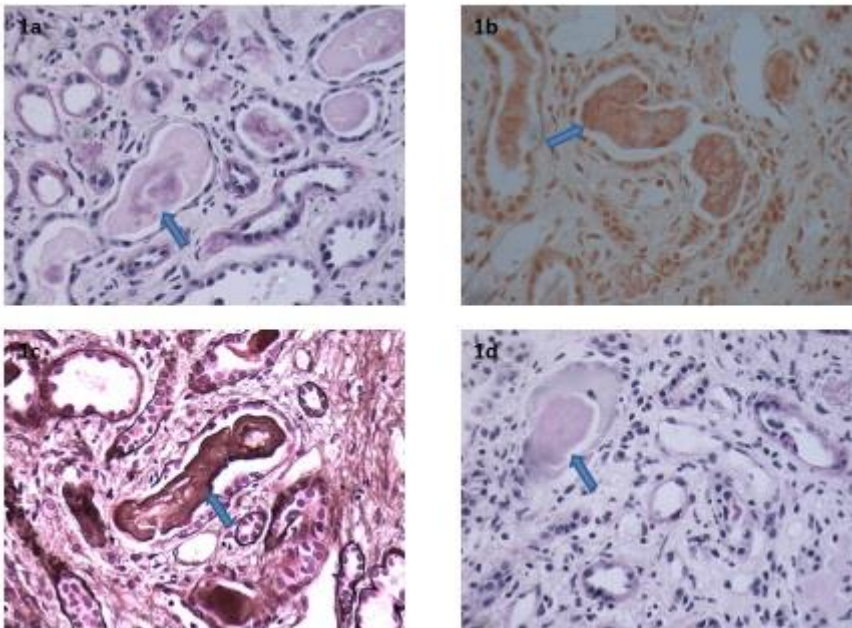
None

PATIENT CONSENT

The authors, *Rangaswamy D, Madken M, Vankalakunti M, Attur R, Nagaraju S*, declare that:

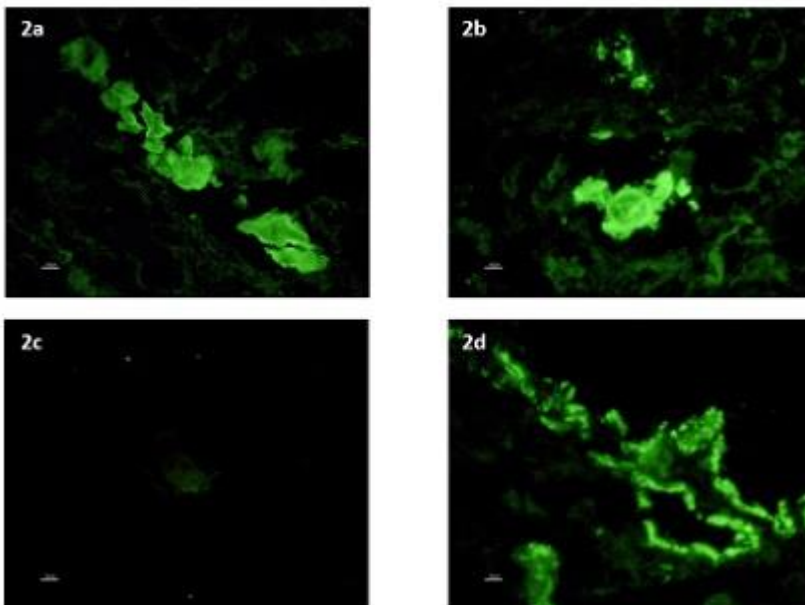
1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

Figure 1: Light Microscopic images of renal biopsy



- 1a: Waxy luminal cast that is weakly positive with PAS (PAS, 40x)
- 1b: Congophilic luminal cast (Congo red, 40x)
- 1c: Argyrophilic luminal cast (PASM, 40x)
- 1d: Few luminal cast that possessed epithelial reaction at periphery (PAS, 40x)

Figure 2: Immunofluorescence images of renal biopsy



- 2a: Tubular casts highlighted with FITC-IgG (3+) (20x)
- 2b: Tubular casts highlighted with FITC-Lambda (3+) (40x)
- 2c: Tubular casts that are negatively stained with FITC-Kappa (40x)
- 2d: Tubular cytoplasmic granules highlighted with FITC-Lambda (3+) (40x)