

Cast Nephropathy: Clinicopathologic Analysis of 4 Cases

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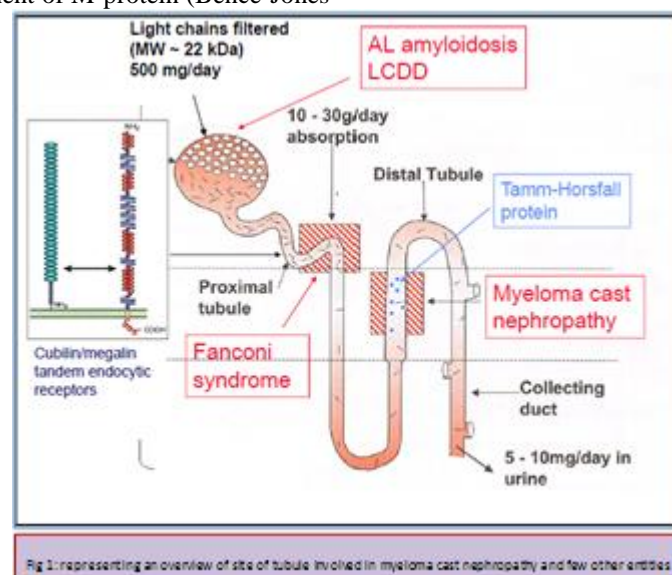
Abstract: Multiple myeloma is a malignancy of plasma cells. Myeloma Cast Nephropathy (myeloma kidney), refers to intrinsic Acute Kidney Injury (AKI) that results as the filtered light chain component of M-protein (Bence-Jones protein) exerts toxic & obstructive injury to tubules. A total of 4 cases diagnosed with cast nephropathy between Jan'2010-Apr'2014 were analysed retrospectively as per histopathological and clinical criteria. All 4 cases were between age 44-62 yrs, 3 were males & 1 female. 1 case showed light chain cast nephropathy with early features of acute tubulopathy. Second case showed evidence of light chain deposition disease with inflammatory tubulointerstitial nephritis alongwith light chain cast nephropathy. Rest 2 of the cases showed presence of cast nephropathy with superadded hypertension induced changes. Conclusion: Cast nephropathy is seen in 30 to 50% patients of multiple myeloma. The likelihood of underlying cast nephropathy is increased in cases of more profound AKI. Cast nephropathy can be misinterpreted as interstitial nephritis, amyloidosis, light chain deposition diseases, etc., hence vital for nephrologists to review the histology with pathologists to avoid misdiagnosis.

Keywords: Myeloma Kidney, Acute Kidney Injury, Cast Nephropathy, Bence Jones proteins, Tamm Horsfall protein

1. Introduction

Multiple myeloma is a clonal B-cell disease of slow proliferating plasma cells accompanied by monoclonal protein production and lytic bone lesion. There is overproduction of monoclonal Immunoglobulin; so called M-protein. Myeloma Cast Nephropathy (myeloma kidney), refers to intrinsic Acute Kidney Injury (AKI) that results as the filtered light chain component of M-protein (Bence-Jones

protein) exerts toxic & obstructive injury to tubules. Bence Jones protein cast nephropathy is characterised by prominent casts in tubules. Casts are usually large and "brittle," have fracture lines or are broken into many fragments often with geometric shapes, surrounded by tubular epithelium, neutrophils. While they are more common in distal tubules, cast may be formed in any segment of nephron, including Bowman's space.



2. Case Report

A total of 4 cases diagnosed with cast nephropathy between Jan'2010-Apr'2014 were analyzed retrospectively as per histopathological and clinical criteria. All 4 cases were between age 44-62 yrs, 3 were males & 1 female. 1 case showed light chain cast nephropathy with early features of acute tubulopathy. Second case showed evidence of light

chain deposition disease with inflammatory tubulointerstitial nephritis along with light chain cast nephropathy. Rest 2 of the cases showed presence of cast nephropathy with superadded hypertension induced changes. Bone marrow aspiration & biopsy confirmed the diagnosis of myeloma in all patients. The clinical, biochemical and radiological features of all the four cases along with associated lesions are presented in a tabular form in Table no. 1 as follows.

Parameters	Case 1	Case 2	Case 3	Case 4
Age (in yrs)	55	62	44	57
Sex	Female	Male	Male	Male
C/F	Fever, bone pain,	HTN, hypercalcemia, type II DM, proteinuria under evaluation	Fever, cough, difficulty in walking and grasping things, swelling of feet.	Hypertension, bone pain
Investigation	Renal function deranged. ESR:95 mm/hr. RBCs on urine microscopy.	Free kappa chain 8.03mg/L; free lambda chain 7138 mg/L(increased); Kappa-lambda ratio: 0.0011	ESR:86 mm/hr; microspherocytes & fragmented RBCs on P/S High proteinuria & RBCs on urine microscopy S/O Glomerulonephritis Protein electrophoresis: M band	ESR: 87mm/hr M band on protein electrophoresis Renal function deranged.
USG	B/L grade I hydronephrosis.	Hepatomegaly, B/L grade I renal parenchymal changes, multiple renal cysts.	Mild hepatomegaly.	Not significant
Clinical diagnosis	Multiple myeloma	Multiple myeloma-hypercalcemia ? Cast nephropathy	?ATN/CKD ? Nephritic syndrome	Accelerated hypertension

Table no. 1: clinical, biochemical & radiological features of 4 cases with cast nephropathy

The histopathological findings along with immunofluorescence and bone marrow aspiration & biopsy details of the cases are summarized in Table no. 2.

parameters	Case 1	Case 2	Case 3	Case 4
Renal biopsy (light microscopy)	6/21 glomeruli show increase in mesangial matrix. Tubules: patchy involvement with cystic dilatation, luminal fluffy colloid granular, RBC & WBC casts, fractured casts. Blood vessels: thickening & hyalinisation	1 /9 glomeruli is obsolescent, 1 shows focal mesangial hypercellularity. Tubules: patchy atrophy, focally few collecting ducts show angulated brittle casts with fracture planes & "jig-saw" puzzle appearance. Blood vessels: hyaline arteriosclerosis	4 /14 glomeruli shows glomerulomegaly with nodular hyalinosis, increased mesangial matrix & cells, thickened basement membrane. Tubules: focal atrophy with hyaline , light chain, cellular & RBCs casts. Blood vessels: dilatation.	Glomeruli: normal Tubules: hyaline casts, two tubules show fractured hyaline casts & 1 tubule shows multinucleate giant cells Blood vessels: hyaline arteriosclerosis
IF findings	Negative	Not performed as no glomeruli seen in th tissue sent for IF.	C3 deposits seen focally in Bowman's capsule segmental mesangial (2+) along with IgG.	Not done due to absence of glomeruli (medulla)
BMA & BMB	Not available	Consistent with myeloma	Consistent with multiple myeloma	Consistent with myeloma

Table no. 2: Histopathological features of 4 cases of cast nephropathy

Bence Jones protein cast nephropathy is characterised by prominent casts in tubules. Casts are usually large and "brittle," have fracture lines or are broken into many fragments often with geometric shapes, surrounded by tubular epithelium, neutrophils.

While they are more common in distal tubules, cast may be formed in any segment of nephron, including Bowman's space. In the present cases, typical fractured appearance, jig-saw puzzle appearance and angulated casts were noted which are highly specific for myeloma cast nephropathy (Fig 1-4). Hyaline arteriosclerosis was also noted in few of the vessels.

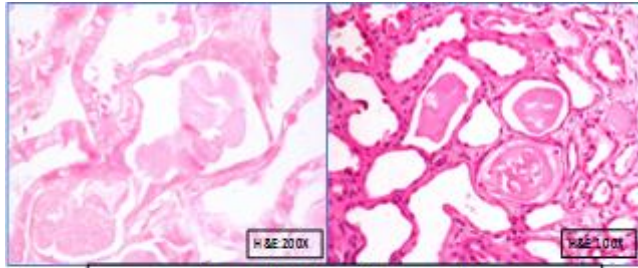


Fig 1: Renal tubules showing Fractured Cast

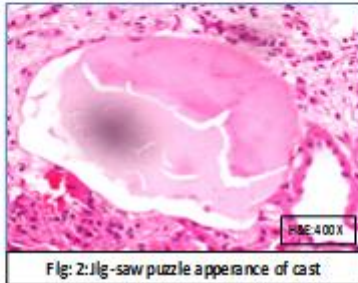


Fig 2: Jig-saw puzzle appearance of cast

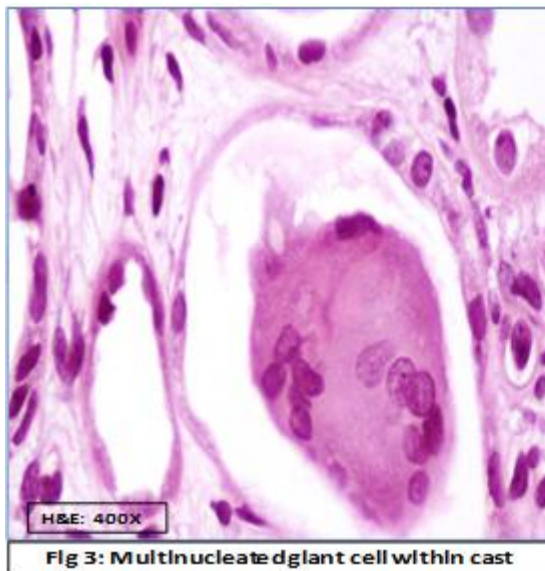


Fig 3: Multinucleated giant cell within cast

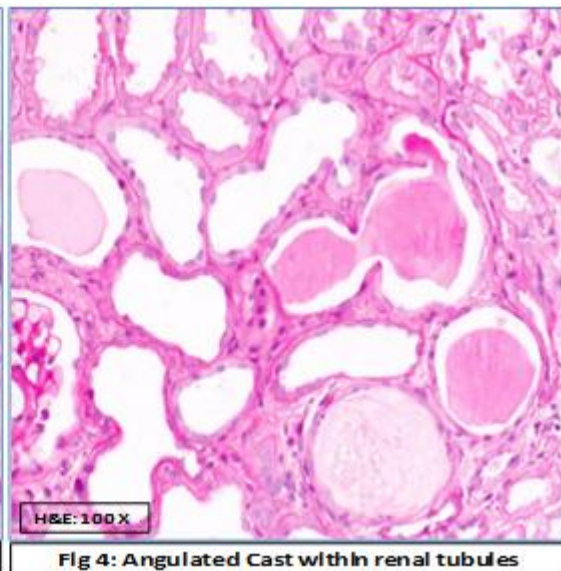


Fig 4: Angulated Cast within renal tubules

The final diagnoses based on clinical, biochemical and histopathological findings were made and summarized as:

Case 1: Light Chain (Myeloma) Cast Nephropathy With Early Features Of Acute Tubulopathy (Myeloma Related)

Case 2: Cast Nephropathy

Case 3: Light Chain Deposition Disease With Inflammatory Tubulointerstitial Nephritis & Light Chain Cast Nephropathy

Case 4: Cast Nephropathy With Superadded Hypertension Induced Changes.

3. Discussion

The diagnosis of Myeloma Cast nephropathy (MCN) is based on demonstration of tubular casts in distal nephron that are composed of immunoglobulin light chains, and light chains in cast is same as that in serum and urine. There can be numerous precipitating factors like hypercalcemia, dehydration, infection, contrast media, nephrotoxic drugs (NSAIDs, furosemide, aminoglycosides), acidic urine etc.

The mechanism behind cast formation is excessive light chain endocytosis in tubular cells. This occurs because of oxidative stress leading to activation of NF- κ B and MAP kinases. There is production of inflammatory cytokines and causing morphological changes. Myeloma casts leads to obstruction. Casts are associated with tubular rupture & when they rupture, they cause interstitial nephritis.

Extent of cast formation does not parallel the degree of interstitial fibrosis & tubular atrophy & despite role of casts in pathogenesis of tubulointerstitial lesion. Renal function

correlates with interstitial fibrosis and tubular atrophy not with cast formation.

The cast have reasonably typical tinctorial properties; PAS negative, eosinophilic, fuchsinophilic with Masson's trichrome; infrequently, Congo red positive. The staining is not uniform within the same cast or among all casts in the same kidney, but the above colors are more typical. The cast may be lamellated, contain crystals of a variety of shapes, and rarely at periphery have spicular appearance.

Patients with cast nephropathy are more likely to have hypercalcemia, severe anemia, advanced myeloma (Durie-Salmon stage 3) & light-chain myeloma compared with patients who have myeloma without renal failure

The differential diagnosis which can be considered in these type of cases are:

- Amyloidosis,
- Multiple myeloma,
- Light chains deposition disease,

- Waldenström's macroglobulinemia, Monoclonal gammopathy of undetermined significance,
- Fibrillary and immunotactoid glomerulopathy
- Cryoglobulinemias
- Diabetic Nephropathy.
- Interstitial nephritis

Patients with cast nephropathy present with renal insufficiency that can be severe (*i.e.*, serum creatinine 7 mg/dl). In up to 50% of patients, renal failure is acute in nature & often is attributed to a precipitating factor such as dehydration, infection, hypercalcemia or use of contrast medium or NSAID.

4. Conclusion

Cast nephropathy is seen in 30 to 50% patients of myeloma. The likelihood of underlying cast nephropathy is increased in cases of more profound AKI. The propensity of a particular myeloma light chain to produce cast depends on amount of Bence-Jones protein & its tendency to aggregate together with Tamm-Horsfall protein. Cast nephropathy can be misinterpreted as interstitial nephritis, amyloidosis, light chain deposition diseases, etc. Hence, vital for nephrologists to review the histology with pathologists to avoid misdiagnosis.

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