

## PAPER DETAILS

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## Light Chain Cast Nephropathy Presenting with Asymptomatic Proteinuria

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### Abstract

Kidney disease is a common complication of monoclonal gammopathies including multiple myeloma. Patients with multiple myeloma and other monoclonal gammopathies can present with a variety of kidney manifestations that depend upon the pathologic monoclonal proteins involved and the compartments of the kidney that are targeted. The most common clinical findings include acute or subacute kidney injury, chronic kidney disease, albuminuria or nephrotic syndrome and electrolyte abnormalities. The spectrum of kidney impairment ranges from mild to severe acute kidney injury (AKI) requiring hemodialysis. Most patients presenting with AKI have light chain cast nephropathy. 58-year-old female patient was referred to our clinic due to proteinuria. We aimed to represent a light chain cast nephropathy patient presenting with asymptomatic, non-nephrotic range proteinuria and whom were eventually treated with autologous stem cell transplantation. Light chain cast nephropathy should be kept in mind at the differential diagnosis of patients presenting with asymptomatic non-nephrotic range proteinuria especially whom were treated with anti-proteinuric medications. Kidney biopsy should not be deferred during the diagnostic process.

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**Keywords:** Light Chain, Cast Nephropathy, Asymptomatic Proteinuria.

### Introduction

Kidney disease is a common complication of monoclonal gammopathies including multiple myeloma. Patients with multiple myeloma and other monoclonal gammopathies can present with a variety of kidney manifestations that depend upon the pathologic monoclonal proteins involved and the compartments of the kidney that are targeted. Approximately 20 to 50 percent of patients

with multiple myeloma present with an elevated serum creatinine at the time of diagnosis.<sup>1-5</sup> The spectrum of kidney impairment ranges from mild to severe acute kidney injury (AKI) requiring hemodialysis. Most patients presenting with AKI have light chain cast nephropathy. Hypercalcemia is the most common electrolyte abnormality in patients with multiple myeloma (>10%, at the time



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of diagnosis).<sup>2</sup> Other electrolyte disorders include pseudohyponatremia and partial or complete Fanconi syndrome resulting in abnormalities such as renal tubular acidosis, hypouricemia, hypophosphatemia, aminoaciduria, renal phosphate wasting, and glycosuria. Laboratory tests used in the evaluation of monoclonal plasma cell disorders are serum free light chain (FLC) assay, serum protein electrophoresis and immunofixation, urine protein electrophoresis and immunofixation. The serum FLC assay is more sensitive than the urine protein electrophoresis for detecting FLCs.<sup>6</sup> We aimed to represent a light chain cast nephropathy patient presenting with asymptomatic, non-nephrotic range proteinuria and emphasize the importance of kidney biopsy for the patients even though indications are not certain.

## Case Report

A 58-year-old female patient was referred to our clinic due to proteinuria. She was operated for breast cancer 7 years ago. She received radiotherapy and chemotherapy after the operation, and she was being followed in remission for the last 5 years. She was diagnosed with essential hypertension and she was receiving enalapril plus lercanidipine combination since then. The patient's blood pressure was 130/80 mmHg; pulse was 77 beats/min; temperature was

37°C. No pathology was detected at her physical examination. In the laboratory tests, her renal function results and albumin levels were normal. Proteinuria was detected (++) in the dipstick urine test and 1.2 gr/day in the 24-hour urine sample. All laboratory tests which were performed in the patient's application are presented in Table 1. After detection of non-nephrotic range proteinuria, the levels of complement and autoimmune markers were found to be negative. All immunoglobulins were quantitatively diminished in plasma protein electrophoresis and immunofixation electrophoresis whereas monoclonal IgA protein was detected qualitatively. Kappa and lambda light chains detected in urine protein electrophoresis. Urine protein level was detected as 1.480 g/day quantitatively. Quantitative excretion of albumin fraction was detected as 1301.1 mg/L. Kappa light chain concentration was 2.89 mg/dL (0-0.9); lambda light chain concentration was 2.72 mg/dL (0-0.7) in urine immunofixation electrophoresis. Details of associated laboratory tests are presented at Table 2. We performed kidney biopsy because of the persistent proteinuria above 1g/day under angiotensin converting enzyme (ACE) inhibitor therapy. Histopathological examination of the biopsy material revealed that 3 of 32 glomeruli were global sclerotic, also mesangial expansion was detected at 6 glomeruli. Lymphoplasmacytic

**Table 1.** Laboratory Results

Lab Test	Results
Glucose (mg/dL)	93 (74-106)
Urea (mg/dL)	25 (17-43)
Creatinine (mg/dL)	0.66 (0.66-1.09)
Na (mmol/L)	138 (137-146)
K (mmol/L)	4 (3.5-5.2)
Cl (mmol/L)	101 (101-109)
Ca (mg/dL)	10.2 (8.8-10.6)
P (mg/dL)	3.7 (2.6-4.5)
Total Protein (g/L)	7.2 (6.6-8.3)
Albumin (g/dL)	4.1 (3.5-5.2)
Hb (g/dL)	10.7 (11.2-15.7)
Hct (%)	33.7 (34.1-44.9)
WBC (x10 <sup>3</sup> /μl)	7.27 (3.98-10.04)
Plt (x10 <sup>3</sup> /μl)	497 (180-370)
MCV (fL)	78.8 (79.4-94.8)
Blood Gas (venous)	PH:7.316 PCO <sub>2</sub> :59.1 HCO <sub>3</sub> :26
Dipstick Urine Test	Erythrocyte (-) protein (+)
Proteinuria (g/day)	1.2
AST (U/L)	12 (0-35)
ALT (U/L)	8 (0-35)

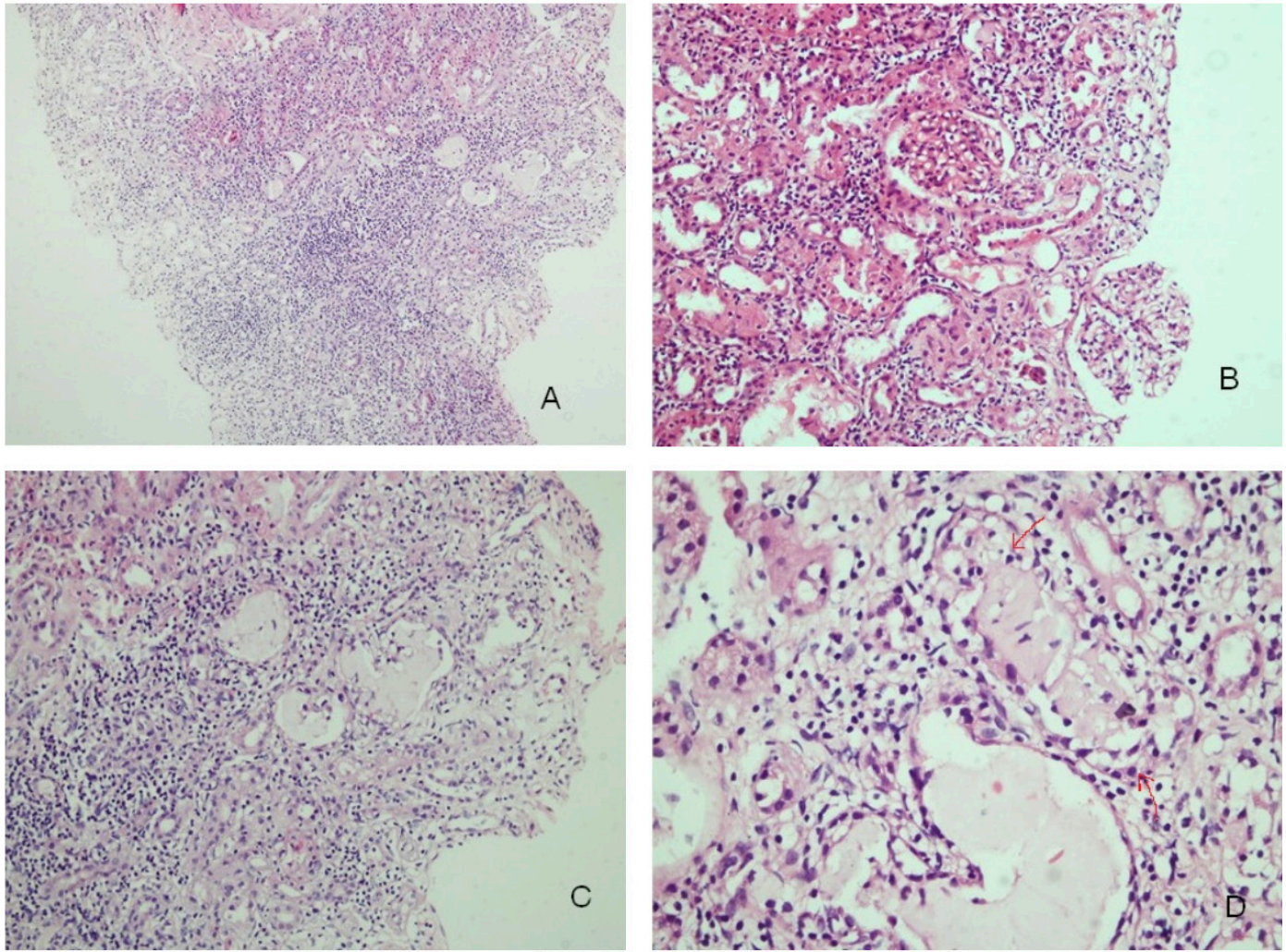
Na: Sodium; K: Potassium; Cl: Chlorine; Ca: Calcium; P: Phosphorus; WBC: white blood cells, Hb: Hemoglobin; Hct: Hematocrit; Plt: Platelet; MCV: Mean Corpuscular Volume; AST: Aspartate Transaminase; ALT: Alanine Aminotransferase

**Table 2.** Autoimmune Markers and other Laboratory Results

Lab Test	Results
ANA	NEGATIVE
p-ANCA	NEGATIVE
c-ANCA	NEGATIVE
C <sub>3</sub> (mg/dL)	167(90-180)
C <sub>4</sub> (mg/dL)	33.4(10-40)
IgG (g/L)	6.12 (7-16)
IgA (g/L)	0.65 (0.7-4)
IgM (g/L)	0.28 (0.4-2.3)
PEF	Albumin: 54.4% (40-65); alpha-1: 3.7% (1.5-4.2); alpha-2: 17.9 % (8.3-16.6); beta: 14% (8.5-17.9); gamma: 10% (9.5-20.7)
IEFs <sub>s</sub>	Whole immune globulins diminished quantitatively; monoclonal IgA protein detected qualitatively.
IEF <sub>u</sub>	Urine kappa concentration 2.89 mg/dL; urine lambda concentration 2.72 mg/dL. Urine protein level is detected as 1.480 g/day quantitatively.
Kappa l.c (mg/L)	25.8(6.7-22.4)
Lambda l.c (mg/L)	>58.6(8.3-27)

ANA: Anti-Nuclear Antibody; ANCA: Anti Neutrophil Cytoplasmic Antibody; C<sub>3</sub>: Complement 3; C<sub>4</sub>: Complement 4; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IgA: Immunoglobulin A; PEF: Protein Electrophoresis; IEF<sub>s</sub>: Immune fixation on electrophoresis; Kappa l.c: Kappa Light Chain; Lambda l.c: Lambda Light chain





**Figure 1. a)** Massive tubulointerstitial nephritis at the medullar zone, **b)** Interstitial inflammation at the cortical zone, near normal glomerular structure, **c)** Cast material at the eosinophilic distal tubules in the medullar region, **d)** Cast material surrounded by histiocytic reaction at the distal tubules shown with arrows.

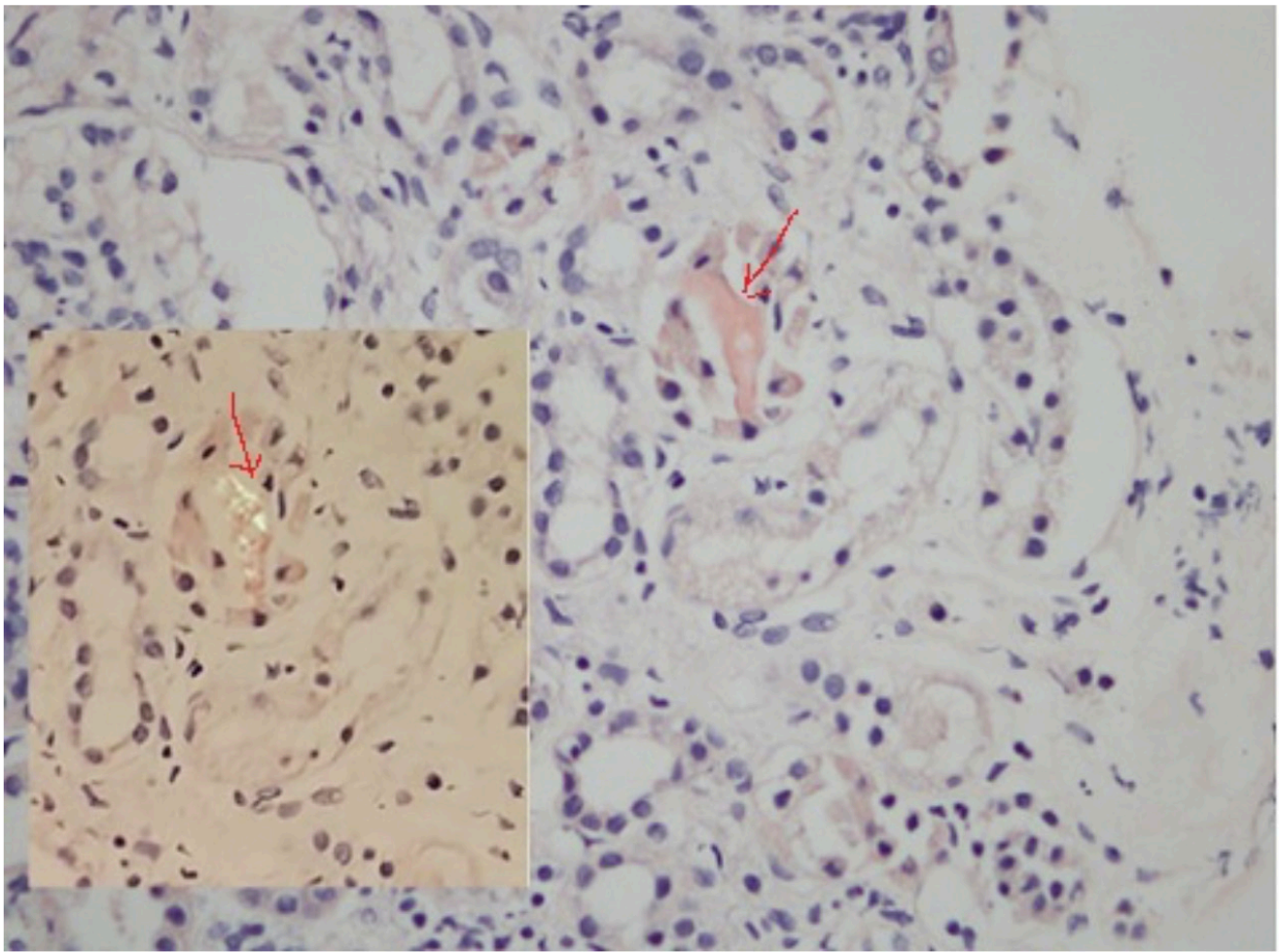
inflammatory infiltration including diffuse eosinophils were detected at tubulointerstitial area. Intertubular cast structures were detected predominantly at distal tubules but also at proximal tubules. Amyloid staining was positive with Kongo red at one of those cast structures. Interstitial fibrosis-tubular atrophy (IFTA) was presented at %10 of cortical area. C4d was determined granular positive by immunohistochemical method. Positive C4d staining supports the diagnosis of amyloid accumulation. The pathological images are presented at Figure 1 and Figure 2. After that result the patient referred to the hematology department for treatment and follow up arrangements.

Bone marrow biopsy was performed and reported as follows: cellularity is 55%, plasma cells at interstitium is increased. Histochemical examination revealed amyloid accumulation

is negative with Kongo Red and reticular fiber degree I. Neoplastic plasma cells were positive with IgG and lambda at immunohistochemical examination. CD138 (+) plasma cells were about 30 % and distributed at interstitium. Neoplastic plasma cells were negative with CD3, cyclin D1, and c-myc. Interstitial lymphoid cells revealed partially T lymphocyte phenotype with CD3 and B lymphocyte phenotype with CD20 and CD19.

The bone marrow biopsy was reported as plasma cell disorder and patient were diagnosed as multiple myeloma. Patient treated with autologous stem cell transplantation after 4 cures chemotherapy and is still being followed up in nephrology, hematology clinics with normal kidney functions and proteinuria <1000 mg/day.





**Figure 2.** Kongo Red (+) cast material in the distal tubule, histiocytic accumulation shown with arrow and at the small figure bifragent view under polarized light microscope.

## Discussion

Biopsy indications are not certain for patients with normal renal functions and proteinuria ranges between 1 g/day and nephrotic range ( $>3.5$  g/day). Most clinicians prefer to follow up those patients especially if renal functions are normal. Our case differs from other similar cases by representation asymptotically even though light chain cast nephropathy lies under. We performed kidney biopsy at our patient because of the persistent proteinuria greater than 1 g/day even after using more than a 6-month period (7 years) of ACE inhibitor. The whole basic laboratory workup was normal at the presentation of our case. The overall goal of evaluation of a patient with kidney disease and a monoclonal protein is to determine whether a monoclonal protein is involved in the pathogenesis of the kidney disease. Kidney biopsy is required to establish this association and to guide therapy in many cases unless contraindicated. Laboratory testing of monoclonal proteins can

assist with narrowing the differential diagnosis and plays an important role in monitoring the response to treatment. We performed serum protein electrophoresis and immunofixation before the biopsy procedure. Hypogammaglobulinemia was detected at serum protein electrophoresis. After detecting cast nephropathy at the kidney biopsy sample, bone marrow aspiration and biopsy were performed. Serum FLC assay and urine protein electrophoresis and immunofixation were also performed.

Light chain cast nephropathy should be strongly suspected in any patient presenting with unexplained kidney impairment over a period of less than six months and an elevated FLC level of  $\geq 1500$  mg/L. By contrast, light chain cast nephropathy is uncommon in patients with low ( $<500$  mg/L) serum FLC concentrations.<sup>7-9</sup> We detected low levels than expected in our case.

The extent to which the serum FLC ratio is abnormal may also distinguish light chain cast nephropathy from other lesions associated with myeloma. In one study, patients with light chain

cast nephropathy had much higher ratios compared with patients with either amyloidosis or light chain deposition disease (LCDD).<sup>10</sup>

After bone marrow biopsy, our case was diagnosed as multiple myeloma which referred with light chain cast nephropathy. Although most patients presenting with AKI have light chain cast nephropathy, we did not find any laboratory results compatible with kidney injury at the time of diagnosis. If we had had delayed the biopsy due to the normal laboratory results kidney failure might have ensued. It is known that, once kidney involvement occurs, the complication risk rises and the chance for cure diminishes.

The importance of our case is that, although whole laboratory results were not high enough as expected at those cases, we diagnosed by kidney biopsy which was not definitely indicated. After that, patient was treated appropriately with autologous stem cell transplantation owing to early detection of the disorder by kidney biopsy which is not often performed in most cases with asymptomatic proteinuria.

As a conclusion, we aimed to emphasize that light chain cast nephropathy should be kept in mind at the differential diagnosis of patients presenting with asymptomatic non-nephrotic range proteinuria especially whom were treated with ACE inhibitors longer than 6 months. Kidney biopsy should be performed at appropriate cases confidentially.

### Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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