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Light chain proximal tubulopathy with lambda restriction presenting as acute kidney injury

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ABSTRACT

Monoclonal gammopathies can produce a variety of glomerular, tubular, vascular and interstitial lesions. The spectrums of renal lesions produced by these monoclonal gammopathies include AL/AH amyloidosis, light chain cast nephropathy or myeloma kidney and various proximal tubulopathies. Out of these, proximal tubule centered lesions are much less identified and diagnosed and light chain proximal tubulopathy (LCPT) is one among them. In LCPT the excess free light chains (mostly kappa type by immunofluorescence microscopy) in serum are filtered by the glomeruli and are reabsorbed by proximal tubules causing its damage. These monoclonal light chains when sequestered in the proximal tubules can give rise to crystalline and noncrystalline histological variants. Here we present a rare case of noncrystalline variant of LCPT with lambda light chain restriction who presented with renal insufficiency which on later investigations revealed to be multiple myeloma.

Case Report

Implication for health policy/practice/research/medical education:
Among the renal lesions of plasma cell dyscrasias, proximal tubule centred lesions are often overlooked and hence routinely missed during microscopic examination of a renal biopsy specimen. Knowledge about these lesions can be rewarding at times as these can lead the primary treating physician to the underlying disease process when clinical symptoms pertaining to it are absent and early treatment of which can influence the prognosis.

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Introduction

Intra-renal crystalline deposits of monoclonal immunoglobulin and/or light chain are an important cause of renal dysfunction in patients with multiple myeloma and other dysproteinemias (1,2). The most common immunoglobulin (Ig)-related crystalline nephropathy is light chain cast nephropathy characterized by crystalline precipitates of monoclonal light chain (either κ or λ) within distal tubules (3). Less commonly, Ig crystallization occurs intracellularly, within proximal tubular cells (light chain proximal tubulopathy [LCPT]), interstitial histiocytes (crystal-storing histiocytosis [CSH]), and podocytes, or intravascularly (crystalglobulinemia) (4).

The first description of LCPT causing Fanconi syndrome with needle shape crystals by electron microscopy (EM) found in the proximal tubular epithelial cell cytoplasm was reported in 1957 (5). As compared to LCPT due to kappa light chains, LCPT with lambda light chain restriction is less frequently reported. A recently published case series in 2016 showed that proteinuria, renal insufficiency and Fanconi syndrome were the common clinical presentations of LCPT (6). Many of these cases are easily missed on routine immunofluorescence (IF) microscopy.

Renal involvement may be the first manifestation of an underlying paraproteinemia. Hence, in this setting, renal biopsy interpretation with keen observation of inclusions on light microscopy along with light chain restriction on IF is important for the diagnosis of an underlying hematological malignancy, the early diagnosis of which can influence the prognosis as well as treatment decisions

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in these patients. Additional investigations like serum protein electrophoresis, free light chain assay, and other biochemical investigations would be helpful to confirm the diagnosis of the patient.

Case Presentation

A 53-year-old male patient presented with a history of bilateral lower limb swelling of 15 days duration. He is a known hypertensive on regular treatment for the past three years with a history of cerebrovascular accident (right temporo-parietal intraparenchymal hemorrhage) six months back. He had no history of fever/joint pain /skin rash/bone pain. There was also no history of any nonsteroidal anti-inflammatory drugs/native medicine intake. Clinical examination revealed pitting edema of bilateral lower limbs with pallor; however no organomegaly or lymphadenopathy was noted. Ultrasound abdomen revealed a normal kidney size of (right - 9.8 cm, left -10.2 cm) with normal corticomedullary differentiation and normal cortical echoes. Laboratory evaluation at the time of admission revealed renal failure with nephrotic range proteinuria (Tables 1 to 4).

In view of anemia and unexplained renal failure with nephrotic range proteinuria, with normal sized kidneys on ultrasonography, a renal biopsy was performed. On renal biopsy, light microscopy (LM) revealed 12 glomeruli with two of them showing mild mesangial expansion and one showing segmental sclerosis and periglomerular fibrosis. Remarkable findings were noted in the proximal tubules which included dilatation of the tubular lumen and epithelial damage in the form of loss of brush border, denudation of epithelial cells with intra-luminal debris, mitosis and regenerative changes with prominent nucleoli indicating tubular injury. Tubular intracytoplasmic vacuolations were prominently seen in many of the tubular cross sections. Crystalline inclusions within the proximal tubules were not observed on light microscopy (Figure 1).

Many of the proximal tubules displayed a distinct peritubular acellular homogenous eosinophilic material which showed variable positivity for periodic acid-Schiff stain (PAS), and Congo-red stain was negative. Interstitium showed patchy inflammation comprising of lymphocytes and plasma cells. Immunofluorescence was positive for lambda light chain in the proximal tubular basement membrane, and intracytoplasmic granules and negative for kappa light chain, immunoglobulins and complements in the glomerulus and tubular basement membrane. In view of cost constraints EM could not be done. Hence a diagnosis of LCPT (proximal tubulopathy associated with inflammatory reaction - acute tubulointerstitial variant) was made.

In view of renal biopsy findings of LCPT with lambda

Table 1. Complete hemogram and anemia work up

Complete blood count		Anemia work up	
Hemoglobin	7.9 g/dL	Serum iron	26.7 µg/dL
TLC	8700/µL	TIBC	167 µg/dL
DLC	N-54 , L-33, E-6 , M-4, B-3	Ferritin	1386 µg/dL
Platelet count	350 000/µL	Transferrin saturation	15.9%
Peripheral smear	Microcytic hypochromic RBCs, anisopoikilocytosis, tear drop cells and target cells	Vitamin B12	450 ng/mL
Viral serology (HIV/HBSAg/HCV)	Negative	Folate	18 µg/L

TLC, total leukocyte count; DLC, differential leukocyte count; HBSAg, Hepatitis B surface; antigen; HCV, hepatitis C virus; TIBC, Total iron binding capacity.

Table 2. Biochemical evaluation

Renal function tests		Liver function tests		Lipid profile	
BUN	20 mg/dL	Total protein	6.4 mg/dL	Total cholesterol	190 mg/dL
Creatinine	2.3 mg/dL	Albumin	2.7 mg/dL	TG	180 mg/dL
Sodium	142 meq/L	Globulin	3.7 mg/dL	HDL-C	39 mg/dL
Potassium	3.7 meq/L	T. bilirubin	0.3 mg/dL	LDL-C	117 mg/dL
Chloride	100 meq/L	D. bilirubin	0.05 mg/dL		
Bicarbonate	29 meq/L	AST	16		
Calcium	8.4 mg/dL	ALT	16		
Phosphorus	5.2 mg/dL	RBS	113 mg/dL		
Uric acid	8 mg/dL				

BUN, blood urea nitrogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol;AST, aspartate Transaminase; ALT, alanine Transaminase; RBS, random blood sugar.

Table 3. Urine microscopy

Urine analysis	
pH	5.5
Protein	2+
Glucose	-
Pus cells	1-2
RBC	2
Urine PCR -3.5	Spot protein - 273 mg/dL Spot creatinine - 76 mg/dL
24 hour urinary protein	3200 mg/24 hrs

Table 4. Myeloma work up

Free light chain assay	
Kappa	41
Lambda	1330
Kappa/lambda ratio	0.03
Serum protein electrophoresis	M band

light chain restriction, serum protein electrophoresis was performed with the suspicion of a paraproteinemia which revealed an M band (M spike). Following this, serum free light chain assay was done which showed very high lambda light chain levels of 1330 mg/dL (normal 5.7-26.3 mg/dL) and a mild increase in kappa light chain level of 41.9 mg/dL (normal -3.3-17.4 mg/dL) with a ratio of involved/uninvolved light chains 31.7 (0.26-1.65). Additionally a work up for Fanconi syndrome was conducted which was negative because urine analysis did not reveal any glycosuria and serum bicarbonate, phosphate, uric acid and potassium were within normal limits and fractional excretion of phosphate was within normal limits. The patient was advised for a bone marrow biopsy for confirmation of monoclonal gammopathy, which revealed multiple myeloma with bone marrow plasma cells of >30 %. However, he was unwilling for further treatment at our centre and was lost to follow up.

Discussion

Since the introduction of the term MGRS (monoclonal gammopathy of renal significance), the incidence of detection of various plasma cell dyscrasias with the help of a renal biopsy is on the rise. LCPT is one such rare entity usually associated with underlying plasma cell dyscrasias. The presence of LCPT is not only limited to multiple myeloma, but also seems to be associated with Waldenstrom macroglobulinemia and other hematological malignancies like non-Hodgkin's lymphoma namely diffuse large B cell lymphoma, or chronic lymphoid leukemia. Renal biopsy interpretation along with other ancillary tests may be useful for early detection and management of these cases.

Traditionally LCPT is classified into two major types based on EM namely, proximal tubulopathy with and without crystal formation. However, many times LCPT without crystals may be under-diagnosed if careful reading of light microscopy and immunofluorescence is not conducted (7). In resource restricted countries, often EM is not done as a routine, adding difficulty to the diagnosis and hence chance of missing the early detection.

In 2014 Herrera in his article suggested four different morphological types of proximal tubulopathies mainly based on the LM and IF and the same was confirmed by EM (8). They are 1. Proximal tubulopathy without cytoplasmic inclusions, 2. Proximal tubulopathy associated

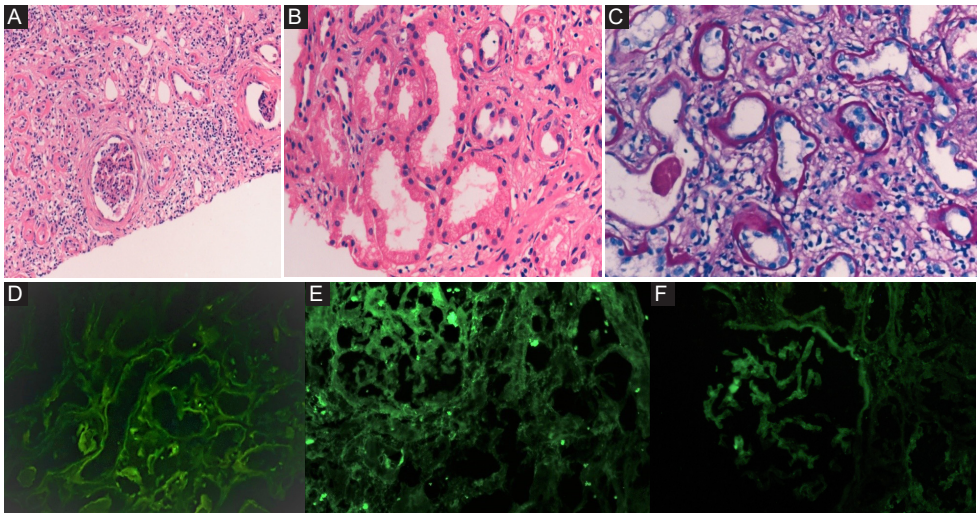

Figure 1. (**A**) Renal biopsy showing 2 glomeruli with periglomerular fibrosis, tubular atrophy and interstitial inflammation (H & E ×100). (B) Peritubular acellular material and proximal tubular injury (H&E ×200). (**C**) Variable Positivity for PAS in the peritubular acellular material (×200). (**D**) IF positive for lambda light chain in the tubular basement membrane (×100). (**E**) IF negative for kappa light chain in the tubular basement membrane (×100). (**F**) IF negative for IgG in the glomeruli and tubular basement membrane (×100).

with inflammatory reaction (acute tubulointerstitial variant), 3. Proximal tubulopathy with cytoplasmic inclusions and finally 4. Proximal tubulopathy with lysosomal indigestion/constipation variant.

It was originally thought that the distal tubules alone are affected in plasma cell dyscrasias especially in myeloma kidney. However, it took almost a century to understand the pathophysiology of the proximal tubular damage by the abnormal light chains. Herrera in his article explains in detail the handling of these physio-chemically abnormal light chains by the proximal convoluted tubules (PCT). The filtered abnormal light chains reach the PCT and are internalized as megalin and cubilin complex into the tubular epithelial cell. The endolysosomal enzymes are unable to degrade a large amount of abnormal light chains present in the PCT leading to their accumulation giving rise to four different morphological patterns of injury based on the defect in the above mentioned endolysosomal protein handling of these light chains (9,10).

In a recent case series published by Stokes et al in 2016, out of 46 patients with LCPT, 40(86.9%) patients had crystalline variants of LCPT. All crystalline LCPT cases in the study were kappa restricted since all of them showed features suggestive of acute tubular injury on renal biopsy with acute kidney injury present in 20% (8/40), Fanconi syndrome present in 43.4% (17/38), and nephrotic proteinuria present in 32.5% (13/40). Non-crystalline variant accounted for only about 13% (6/46) cases of LCPT in this series and only 2 out of 6 cases were lambda restricted. Acute kidney injury was present in 2/6 (33%) cases with nephrotic proteinuria present in 4/6 (66%) cases (6). In this case a diagnosis of LCPT (proximal tubulopathy - acute tubulointerstitial variant) was made considering Herrera's classification (2014) which is predominantly based on LM and IF findings. Moreover distal tubules did not show any fractured cast ruling out the possibility of myeloma cast nephropathy and LM and IF features of MIDD (monoclonal light chain deposit disease) were not present. However, based on the absence of prominent crystalline inclusions on light microscopy and lambda positivity on IF, a possibility of non-crystalline variant of LCPT with lambda light chain restriction was considered as diagnosis. The uniqueness of our case is the diagnosis of a probable non-crystalline LCPT variant with a rare lambda light chain restriction with absence of Fanconi syndrome despite extensive proximal tubular injury. Additionally, the final diagnosis of multiple myeloma was made following the workup done based on the renal biopsy findings which would otherwise not be thought of due to the absence of typical myeloma features in this patient like bone pain(which is one of the most common myeloma related symptom seen in 90% of the patients) and hypercalcemia. Therefore, while analyzing proximal tubule centered lesions, a high level of suspicion combined with careful interpretation of LM, IF and if possible EM along with other hematological workup is important as a collective approach in the early detection and management of the underlying hematological malignancy. We would also like to emphasize the importance of the division of LCPT into four light microscopic morphological patterns as per Herrera so that, molecular targeted therapies can be developed in the future.

Conclusion

In summary, for the treating clinician, LCPT poses an unusual diagnostic challenge as a major share of these patients won't have a prior history of hematological malignancies and the typical intracytoplasmic inclusions may not be visible by LM and may be missed on IF. Hence, prudent search into the cause of renal failure by detailed history and physical examination and careful microscopic examination of the biopsy specimen is mandatory to establish a diagnosis as one third of these patients, if treated with chemotherapy can attain complete or partial remission.

Authors' contribution

AT, RE and BG were the principal investigators of the study. SB and JM were included in preparing the concept and design. AT and BG revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Informed consent was obtained form the patient for publication of this report.

Conflicts of interest

The authors declare that they have no competing interests.

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