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Lambda light chain crystalline proximal tubulopathy with probable light chain cast nephropathy and clonal plasma cell infiltrate – uncommon manifestations of a rare form of multiple myeloma

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ABSTRACT

Light chain proximal tubulopathy (LCPT) is an uncommon renal disease characterized by the accumulation of monoclonal light chains within proximal tubular epithelial cells, with or without crystal formation. We report a rare case of lambda LCPT with crystals. Renal biopsy showed substantial acute tubular injury with unusual cytoplasmic changes affecting proximal tubules. In addition, abnormal tubular casts suggested concomitant light chain cast nephropathy. A clonal plasma cell infiltrate was present in the tubulointerstitial compartment. Immunofluorescence demonstrated strong staining for lambda light chain in tubular epithelial cells. Despite the absence of discernible crystals on light microscopy (LM), they were readily identified when ultrastructural evaluation was undertaken. Crystalline inclusions demonstrated positive immunogold labelling for lambda.

Implication for health policy/practice/research/medical education:

Histopathological recognition and accurate diagnosis of light chain proximal tubulopathy is very important as it may be the first sign of an underlying serious hematological condition for which early treatment is needed.

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Introduction

Renal dysfunction is increasingly recognized in patients with monoclonal gammopathy, resulting from clonal proliferation of B-lymphocytes or plasma cells and subsequent overproduction of monoclonal immunoglobulins. Diseases such as AL amyloidosis, light chain cast nephropathy and monoclonal immunoglobulin deposition disease are some of the more common disorders involving accumulation of abnormal proteins or immunoglobulin deposits in their various forms within the kidney. Light chain proximal tubulopathy (LCPT) is characterized by presence of monoclonal light chains

within proximal tubular epithelial cells, with or without crystal formation. It is important that LCPT not be overlooked as an underlying plasma cell dyscrasia may not be suspected clinically at the time of biopsy in many patients (1). In fact, only 0.5% of patients known to have multiple myeloma also had concomitant LCPT in one study (2). The concept of monoclonal gammopathy of renal significance (MGRS) was introduced in 2012 (3) and renal manifestations of a monoclonal gammopathy can be the first signs of an underlying neoplastic hematological condition. Based on a few recent large LCPT case series (1,4-6), there were more cases with

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crystals (59.7%) compared to those without. Kappa light chain was detected in the great majority of cases having crystalline inclusions. We report a case of lambda LCPT with crystals, highlighting some unusual light microscopic and ultrastructural features.

Case Presentation

A 60-year-old gentleman of Indian descent presented to Changi General hospital upon referral by his general practitioner for anemia. He had consulted his doctor for dyspnea which had persisted for a few months. A complete blood count found a haemoglobin level of 6.8 g/dL. Prior to this presentation, he had no significant medical history except reflux symptoms, for which an esophagogastroduodenoscopy found nothing untoward. He was treated with a brief course of gastric motility agents and a proton-pump inhibitor. He was normotensive, non-diabetic and had no known renal conditions or any significant family history. Investigations disclosed significant renal impairment with a serum urea of 28.0 mmol/L and creatinine of 741 $\mu\text{mol/L}$ (estimated glomerular filtration rate 6 mL/min/1.73 m²). There was no electrolyte derangement and serum total calcium was within the normal range at 2.49 mmol/L. Serum bicarbonate was 12 mmol/L and a gap acidosis was present. This was attributed to uremia as serum lactate and ketones were normal, and no exogenous substances were suspected. Liver function test was normal. Anemia was attributed to chronic kidney disease. Urine microscopy was unremarkable. Urine dipstick revealed 1+ protein and a 24-hour urine collection quantified proteinuria to be 2.78g/day. Ultrasound scan showed normal sized but echogenic kidneys. Further work-up showed positive anti-nuclear antibody at 1:160 dilution (homogenous pattern), although the extractable nuclear antigen panel was negative. Anti-double stranded DNA and anti-phospholipase A2 receptor antibodies were also negative. A kidney biopsy was performed for a definitive diagnosis. At the same time, the myeloma screen revealed a normal serum kappa free light chain (FLC) concentration of 17.3 mg/L (3.3–19.4 mg/L) while lambda FLC was elevated at 144 mg/L (5.7–26.3 mg/L). An IgM Lambda monoclonal band measuring 5 gm/L was detected on serum immunofixation; urine immunofixation demonstrated a lambda monoclonal band. Marked plasmacytosis (>90%) was demonstrated on the bone marrow aspirate with flow cytometry showing them to be cytoplasmic lambda light chain restricted CD138/38/56 (partial) positive and CD45/19/20/117 negative monoclonal plasma cells, clinching the diagnosis of plasma cell myeloma. The bone marrow trephine biopsy confirmed plasmablastic multiple myeloma (MM). FISH analysis on CD138 selected plasma cells demonstrated t(11;14) and trisomy

11, whilst cytogenetic analysis revealed complex structural abnormalities involving multiple chromosomes. Further, allele specific PCR for Myd88 L265P mutation was negative. PET-CT disclosed multiple areas of increased FDG uptake in the axial and proximal appendicular skeleton, some associated with bony lytic lesions.

The renal biopsy procured two cores of renal cortical and one core of corticomedullary tissue with 44 glomeruli. Three glomeruli (7%) were globally sclerosed. There was focal periglomerular fibrosis. Most of the remainder were fairly unremarkable apart from showing slight capillary wall wrinkling. There was no significant mesangial expansion or hypercellularity. No nodular transformation of mesangial regions was seen. Capillary loops were mostly single contoured, patent and not significantly thickened, devoid of endocapillary hypercellularity and fibrin thrombi. A cellular crescent was present. No necrotizing lesions were found. Occasional glomeruli were involved by NOS-type (not otherwise specified) segmental sclerosis. Mild podocyte hypertrophy was encountered. There were no crystalline inclusions, fuchsinophilic immune deposits or argyrophilic basement membrane spikes.

Acute tubular injury was substantial, with cytoplasmic vacuolation, apical blebbing, epithelial flattening and desquamation. Many proximal tubular epithelial cells were also swollen and packed with pale, vacuolated cytoplasmic inclusions that had a peculiar hue on trichrome stains (Figures 1A, 1B and 1C). Sloughed, swollen epithelial cells filled the lumen of a number of tubules. No convincing cytoplasmic or luminal crystals were present, despite a thorough search. Several tubules also had PAS-negative casts, at times “fractured” and having sharp edges. These casts appeared polychromatic on trichrome stains (Figures 2A and 2B). Moderate tubular atrophy with mild but not insignificant interstitial fibrosis was observed. There was moderately extensive lymphoplasmacytic inflammation. Immunostains highlighted a preponderance of CD3+T-lymphocytes and a smaller population of CD20+ B-cells. By in-situ hybridisation, some plasma cells exhibited lambda light chain restriction (Figures 2c and d). No atypical lymphoid cells were discerned. Mild arteriolar hyalinosis and arterial sclerosis were noted. No vasculitis or thrombotic microangiopathy was evident. No congophilic material (amyloid) was detected in any of the renal compartments. Tubular basement membranes were not substantially thickened.

On immunofluorescence microscopy, glomeruli were negative for all immunoreactants, namely IgG, IgA, IgM, C3, C1q, C4, kappa light chain, lambda light chain, fibrinogen and albumin. Tubular basement membranes were also unremarkable. However, proximal tubular epithelial cells stained very intensely for lambda light chain (Figure 1D), with trace staining for kappa in a

minority of these cells (image not shown). No abnormal tubular casts were found on the frozen section H&E slide.

Electron microscopic examination showed segmental thickening and wrinkling of the glomerular basement membrane (GBM). Podocyte foot process effacement was significant, affecting at least 60% of peripheral capillary wall surface area, associated with microvillous transformation of podocyte cytoplasm. There were no conventional amorphous or organized non-crystalline

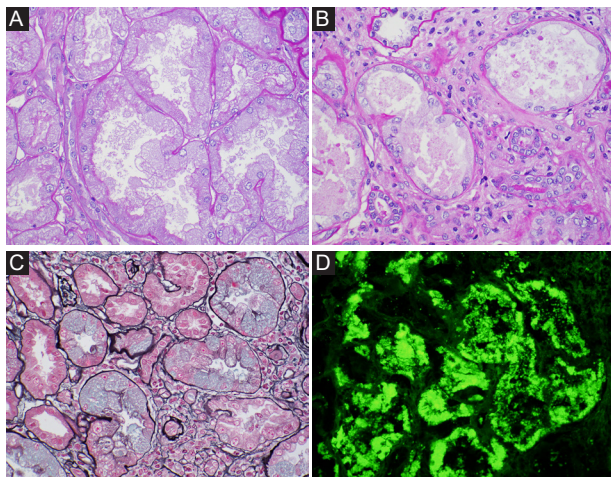


Figure 1. Light and immunofluorescence microscopy images of proximal tubules. (A) Swollen epithelial cells with vacuolated cytoplasm and apical blebbing (Periodic acid-Schiff, $\times 400$). (B) Epithelial flattening and desquamation (Periodic acid-Schiff, $\times 400$). (C) Cytoplasmic inclusions with a greenish hue on the trichrome stain (Masson-silver, $\times 400$). (D) Strong staining for lambda in epithelial cells (Anti-Lambda FITC, $\times 400$).

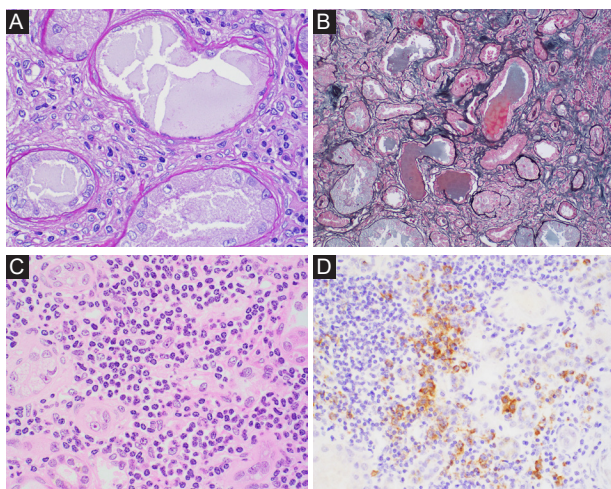


Figure 2. Light microscopy and immunohistochemistry images. (A) Abnormal tubular casts (Periodic acid-Schiff, $\times 600$). (B) These casts were polychromatic on the trichrome stain (Masson-silver $\times 200$). (C) Lymphoplasmacytic tubulointerstitial infiltrate (Hematoxylin & eosin, $\times 600$). (D) Plasma cells showed lambda light chain restriction (Lambda in-situ hybridization $\times 400$).

deposits in any location including extraglomerular sites. In particular, fine powdery subendothelial and tubular basement membrane deposits were absent, ruling out monoclonal immunoglobulin deposition disease. The cytoplasm of many proximal tubular epithelial cells contained crystalline inclusions, generally rhomboid in shape (Figure 3A). There were large and abnormally shaped lysosomes in a minority of tubular cells, a number of which had internal crystalline inclusions (Figures 3B and 3C). Spillage or release of crystals into the lumina of several tubules was attributable to epithelial cell rupture (Figure 3D). In the interstitial compartment, scattered histiocytic cells also revealed intracytoplasmic crystals. On higher resolution, some of the crystals displayed internal geometric lucencies or parallel linear arrays (Figures 3E and 3F). Immuno-electron microscopy (immunogold

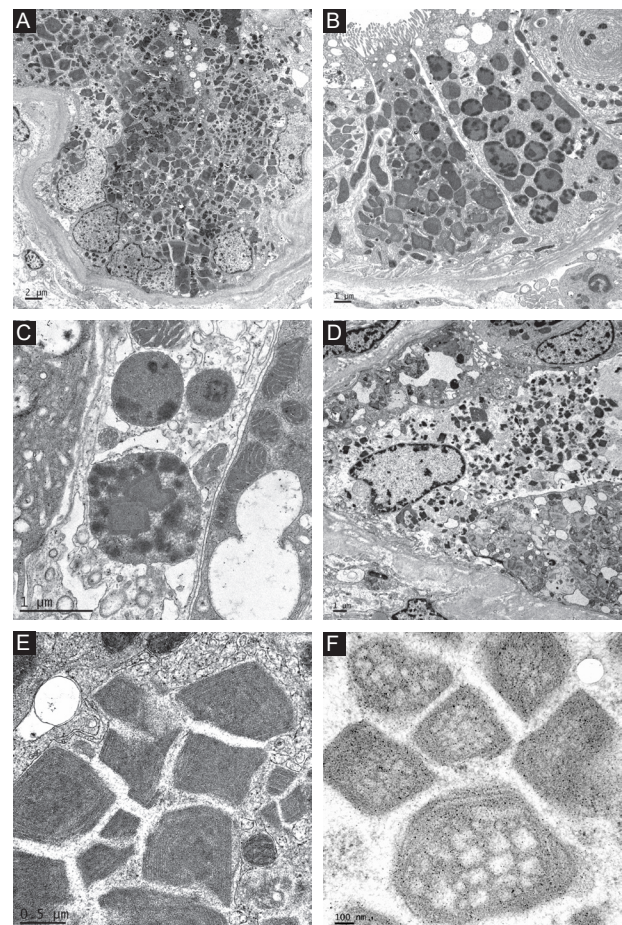


Figure 3. Transmission electron microscopy images (Uranyl acetate and lead citrate). (A) Proximal tubular epithelial cells packed with rhomboid crystals. (B) Abnormal lysosomes next to crystalline inclusions. (C) Lysosomes also contained light chain crystals. (D) Spillage of crystals from damaged epithelial cells into tubular lumen. (E) Crystals featured linear and at times concentric internal arrays. (F) Immunogold labelling for lambda; some crystals had geometric internal lucencies.

labelling) was performed and crystalline inclusions labelled strongly for lambda light chain only (Figure 3F). There was less obvious labelling for this light chain in a number of lysosomes. The Bowman's space of one glomerulus had a small number of crystals.

The patient was commenced on hemodialysis. Chemotherapy comprising daratumumab, bortezomib, cyclophosphamide and dexamethasone was initiated with a view to subsequent autologous stem cell transplantation. He tolerated chemotherapy well and showed symptomatic improvement as well as significant recovery in hemoglobin level and renal function. First disease reassessment showed that the M band had completely disappeared but there was a remarkable increase in serum lambda FLC concentration to >1000 mg/L. Hence, cyclophosphamide was replaced by lenalidomide in his chemotherapy regime.

Discussion

LCPT is a MGRS-defining entity but most patients will not meet the criteria for MM at the time of diagnosis. According to the consensus statement published by the International Kidney and Monoclonal Gammopathy Research Group (IKMG), only 12% to 33% of LCPT cases had underlying MM (7). LCPT is caused by build-up of abnormal light chains in proximal tubular cells. Under normal physiological conditions, FLCs are filtered through the GBM and reabsorbed by proximal tubular epithelial cells through specialized receptors, endocytosed and transported to lysosomes for degradation. However, excess immunoglobulin light chains produced by a clonal population of plasma cells often have mutations in the variable (V_L) region which confer resistance to degradation. As a result, excessive light chains accumulate within the cytoplasm and lysosomes, causing cell injury (8). Lysosomes are thought to play an important role in the processing of light chains. In fact, there have been experiments demonstrating the central role of lysosomes in AL amyloidogenesis through the acquisition of a macrophage phenotype in transformed mesangial cells (9). Supersaturation and unique physicochemical properties predispose to crystallization. In the absence of crystalline inclusions, some cases with excess FLC in tubular cells represent physiologic trafficking rather than target organ damage. Crystalline LCPT involves kappa light chain most of the time, in particular the V_k1 subgroup, with only rare examples showing lambda-restricted intracytoplasmic crystals. Some authors have postulated that V_L region mutations introduce additional hydrophobic or apolar amino acid domains to the structure of FLCs, enhancing crystal formation (10,11). The rarity of lambda compared to kappa-restricted disease remains enigmatic. To our knowledge, 9 cases with lambda restriction have been reported in the literature (1,4,11-16). Five had underlying

MM, one had smoldering myeloma, one was diagnosed as monoclonal gammopathy of undetermined significance, one case was lymphocytic lymphoma and the underlying hematological condition was unclear in the last case. Many of the crystals seen in our patient's kidney resided in the cytoplasm of proximal tubular epithelial cells, with fewer present in lysosomes. They were mostly rhomboid in shape and had internal geometric lucencies or linear arrays. Additionally, a small number of abnormal or mottled lysosomes were observed next to the crystals. Apart from proximal tubules and histiocytes, light chain crystals have been detected in podocytes, bone marrow plasma cells and even hepatocytes (17).

Changes noted on light microscopy (LM) mirrored those described in the literature. Features of acute tubular injury were rather non-specific but swollen tubular cells with unusual vacuolation and discoloration pointed to the presence of abnormal substances (crystals or lysosomes) within those cells. This case reemphasizes the observation that crystals may not be apparent on LM even if they are conspicuous under electron microscopy. Abnormal lysosomes can give rise to similar cellular changes indistinguishable from crystals on LM. As alluded to previously, abnormal casts resembling light chain or Bence Jones casts were noted only in the LM sample and involved very few tubules. Hence, light chain restriction could not be confirmed in these casts by immunofluorescence. Immunohistochemistry was not pursued as it is not uncommon to have non-specific higher intensity staining for kappa in renal tissue, likely resulting from reduced clearance in the setting of impaired renal function. We believe that as tubular cells became severely damaged, cytoplasmic contents including crystals were released into tubular lumina. Spontaneous crystallization of Bence Jones casts can occur but is rare, as binding to uromodulin and lack of lysosomal processing in the extracellular luminal environment may impede crystal formation. Urinary back-flow from renal tubules can result in crystals appearing within the Bowman's space. It has been pointed out that some monotypic light chains reabsorbed by tubular cells were mainly V region fragments not easily recognized by commercially available antibodies (8). Demonstration of light chain restriction can be made more sensitive through the use of pronase-digested immunofluorescence staining, or immunohistochemistry by the antigen retrieval technique. In the series by Larsen et al, fewer LCPT cases were found to have crystals (1). This in contrast to the greater number of biopsies with crystals documented to date. The lack of sensitivity of frozen tissue immunofluorescence for detection of light chain restriction might have contributed to underreporting when crystals were not seen. On the other hand, one must be careful not to interpret higher

intensity staining for any particular immunoglobulin light chain alone as evidence of LCPT, especially if there are no abnormal cellular inclusions, significant tubular injury or biochemical features of Fanconi syndrome.

A clinical feature quite unique to LCPT with crystals is Fanconi syndrome, said to be rare in the absence of crystalline inclusions. Unfortunately, this was not formally investigated in our patient but hallmarks of this syndrome include aminoaciduria, normoglycemic glycosuria, hyperphosphaturia with hypophosphatemia and uricosuria. In isolated LCPT, slowly progressive renal failure and subnephrotic proteinuria are to be expected. However with concomitant light chain cast nephropathy and tubulointerstitial inflammation like in this case, renal function would have and indeed deteriorated much more rapidly. Renal involvement in MM is an independent predictor of poor outcome (18). IgM myeloma is an exceptionally rare entity and accounts for <0.5% of all MM cases (19). Given the potential diagnostic similarity with lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) but a very different clinical approach to management, differentiating these two distinct diseases becomes crucially important (20). In our patient, the morphology and immunophenotype of the abnormal plasma cells on the bone marrow aspirate and trephine biopsy, presence of t(11;14) on FISH and cytogenetics as well as the negativity of Myd88 mutation confirmed the diagnosis of IgM myeloma unequivocally. It is uncertain if IgM MM truly has a more aggressive course and a worse overall outcome than IgG or IgA MM. Since most of the data have come from small case series, many quote a median survival of approximately 36 months (21) but a report of the largest cohort of cases suggested that the overall survival is no different to non-IgM myelomas diagnosed and treated contemporaneously. However, it is clear that IgM MM definitely has a poorer overall outcome compared to LPL/WM. In addition, IgM MM appears to have poor clinical outcome in the context of high-dose therapy (22). At the present time, treatment guidelines recommend the same therapeutic approach for IgM, IgG and IgA myelomas.

Conclusion

In summary, we have illustrated the renal pathology and clinical characteristics of LCPT secondary to a rare form of MM. The renal biopsy can be the sentinel investigation that alerts clinicians to an underlying life-threatening illness.

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Conflicts of interest

There were no conflicts of interest.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. The patient gave the consent to publish as a case report.

Authors' contribution

YN and HL wrote the paper and provided the pathological findings. CC is the nephrologist managing the patient's renal condition. MRTG and CN are hematologists treating the patient. All authors read and signed the final paper.

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