CASE REPORT

Light Chain Proximal Tubulopathy with Crystalline Cast Nephropathy: Two Case Reports

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ABSTRACT

Light chain proximal tubulopathy (LCPT) is a rare kidney disorder whereby monoclonal free light chains damage proximal renal tubule. Combined LCPT and crystalline light chain cast nephropathy (LCCN) is even rarer, with fewer than 20 cases reported globally. We describe two cases: Case 1, a 41-year-old man with acute kidney injury (AKI), nephrotic range proteinuria, and multiple myeloma; Case 2, a 28-year-old man with AKI and nephrotic syndrome but lacking evidence of serum paraprotein or plasmacytosis as well as absence of atypical lymphoid cells, both, in blood and bone marrow examinations . Renal biopsies showed intracytoplasmic crystalline inclusions and casts in distal tubules, with no demonstrable amyloid deposition (negative Congo red stain). Immunofluorescence and immunohistochemical studies revealed monoclonal Lambda light chain restriction in casts and variably within the epithelium . This represents the first reported case series of simultaneous LCPT and crystalline LCCN in Malaysia, emphasizing the importance of accurate diagnosis for proper patient management and haematological evaluation.

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INTRODUCTION

Light chain proximal tubulopathy (LCPT) represents a rare entity among paraprotein-related kidney diseases, marked by the infiltration of monoclonal light chains (LC) into proximal renal tubular epithelial cells, instigating tubular dysfunction and injury (1).

The pathogenesis of LCPT involves the endocytosis and accumulation of toxic monoclonal light chains within proximal tubular cells. In cases where crystalline deposits form, mechanical disruption of cellular structures occurs, leading to oxidative stress, mitochondrial dysfunction, and apoptotic cell death. Non-crystalline deposits can similarly impair lysosomal function, contributing to progressive tubular damage and eventual atrophy.

The co-occurrence of LCPT with crystalline light chain cast nephropathy (LCCN) is an even rarer phenomenon, with fewer than 20 documented cases reported worldwide. LCCN, characterized by the formation of crystalline casts composed of monoclonal LC within renal tubules, contributes to tubular obstruction and subsequent renal impairment (1). The formation of casts in LCCN results in physical obstruction of the distal nephron, leading to tubular dilatation and back-

leak of glomerular filtrate. This process induces a pro-inflammatory response characterized by macrophage and neutrophilic infiltrations. The release of cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), drives interstitial inflammation, promoting fibrosis and progressive scarring of the renal parenchyma. Renal biopsy remains the cornerstone for diagnosing LCPT and LCCN, unveiling intracytoplasmic crystalline inclusions within proximal tubular epithelial cells and noticeable crystalline and non-crystalline casts within distal tubules (1).

In this context, we present two intriguing cases of combined LCPT and LCCN, underscoring the rarity and diagnostic complexity of this dual pathology. These cases underscore the crucial need to identify the diverse renal manifestations linked to monoclonal gammopathies and the imperative for a comprehensive diagnostic approach in patients with paraprotein-associated renal dysfunction.

Further research efforts are warranted to unravel the underlying pathophysiological mechanisms and devise targeted therapeutic approaches for managing this rare manifestation of renal associated paraproteins .

CASE REPORT

Case 1 is a 41-year-old man who presented with acute kidney injury (AKI) and nephrotic range proteinuria. The renal biopsy in case 1 showed focal intracytoplasmic crystalline inclusions within proximal tubular epithelial cells and prominent crystalline and non-crystalline casts within the distal tubules as seen in Figure 1 (a and b). Immunofluorescence (IF) and immunohistochemical (IHC) studies revealed dominant monoclonal Lambda light chain (LC) staining within the intratubular casts and proximal tubular epithelium (Figure 1c and 1d). These findings are characteristic of LCCN, which is commonly associated with multiple myeloma.

Further work-up confirmed the diagnosis of Immunoglobulin D-Lambda Multiple Myeloma and temporary haemodialysis was required. He was started on antimyeloma agents (Bortezomib, Thalidomide & Dexamethasone) which led to some improvement in kidney function. In LCCN, excess monoclonal light chains form casts in the distal tubules, causing notable kidney damage. Improvement in kidney function after antimyeloma treatment emphasizes the need to treat the underlying blood disorders to reduce renal-associated conditions.

Case 2 is a 28-year-old man presented with nephrotic syndrome and AKI. Serum protein electrophoresis/immunofixation, serum free light chain and bone marrow examinations revealed lack of evidence of paraprotein, plasmacytosis or atypical lymphoid cells. Renal biopsy in case 2 also showed focal intracytoplasmic crystalline inclusions within proximal tubular epithelial cells and prominent crystalline and non-crystalline casts within the distal tubules as shown in Figure 2 (a-d). Notably, no nodular glomerulosclerosis, mesangial expansion, or global glomerular involvement typical of monoclonal immunoglobulin deposition disease (MIDD) were observed. Similar to case 1, Congo red stain for amyloid deposition was negative. The IF and IHC studies demonstrated Lambda LC restricted staining within the intratubular casts and proximal tubular epithelium depicted by Figure 2 (e-f). Unfortunately, both patients were lost to follow-up subsequently.

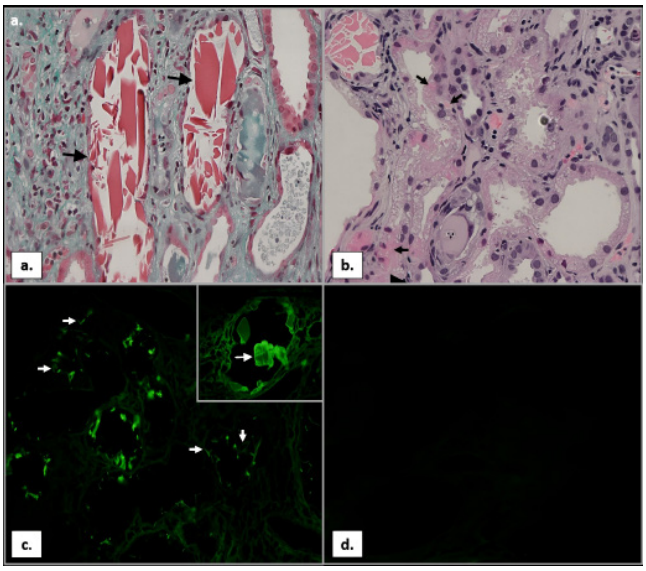

Figure 1: Case 1. (a) Distal tubules distended with crystalline casts of various geometric shapes, ranging from rectangular, rhomboidal, polygonal to needle-shaped (black arrow) (Masson Trichrome immunohistochemical stain, 400x magnification). (b) Proximal tubules displaying tubular injury with coarse cytoplasmic vacuolization and eosinophilic intracytoplasmic crystalline inclusions (black arrow) (Hematoxylin & Eosin, H&E, 400x magnification). IF performed on protease digested paraffin sections demonstrating the intraluminal crystalline casts (picture insert), intracytoplasmic reabsorption droplets and needle-shaped crystals (white arrows) that stained exclusively for (c) λ-LC (Immunofluorescence, 400x magnification), but not for (d) κ-LC (Immunofluorescence, 400x magnification).

Despite the lack of ultrastructural studies for both cases, the available biopsy findings and staining results provide substantial evidence for the diagnoses of LCCN and LCPT. The simultaneous occurrence of focal intracytoplasmic crystalline inclusions and casts in both proximal and distal tubules is a rare but notable finding, emphasizing the complex interplay between these two pathologies.

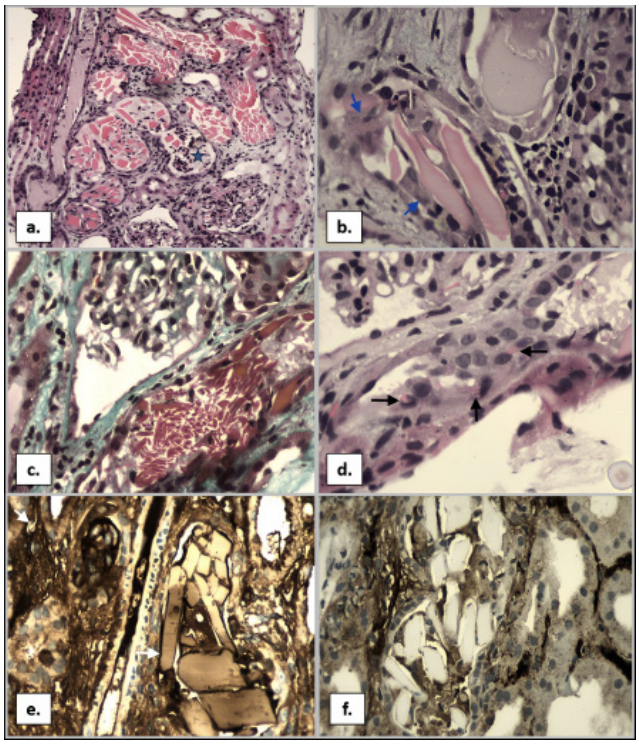

Figure 2: Case 2. (a-c) Obstructed distal tubules filled with crystalline and noncrystalline casts. The crystalline casts appear strongly eosinophilic on (a) H&E (200x magnification) and brightly fuchsinophilic on (c) MT stain (Masson Trichrome, 400x magnification). Intratubular aggregates of neutrophils (star) and giant cells reaction (blue arrows) surrounding the tubular casts were also present. (d) Eosinophilic intracytoplasmic crystalline inclusions (black arrows) within the proximal tubular epithelial cells (H&E, 400x magnification). (e) IHC for λ-LC showed intense staining (white arrows) within the intraluminal crystalline casts and tubular epithelial cells (Immunohistochemical stain, 400x magnification). (f) IHC for k-LC was negative (Immunohistochemical stain, 400x magnification).

DISCUSSION

LCCN, or myeloma cast nephropathy, is a primary renal disease associated with paraproteinemia, often presenting with a crystalline appearance and frequently leading to AKI. Approximately 90% of cases meet the criteria for multiple myeloma (1). When bone marrow analysis does not reveal a clonal haematological disorder, imaging studies are warranted to investigate localized plasmacytoma or lymphadenopathy indicative of low-stage or low-grade lymphoma (2).

LCPT poses diagnostic challenges due to its crystalline and non-crystalline forms, especially in patients without a history of haematolymphoid disease. Intracytoplasmic crystals may not be visible by light microscopy or routine immunofluorescence, necessitating additional steps such as protease digestion for the unmasking of monoclonal LC via IF done on paraffin sections (3). Cases of LCPT without crystal formation can be even more elusive, with LC restriction observed on IF as the primary notable finding, emphasizing the importance of careful interpretation of Kappa and Lambda IF stains on renal biopsy (4).

In LCCN, the excessive secretion of monoclonal light chains leads to the formation of casts in the distal tubules, causing significant renal impairment. The improvement in kidney function following antimyeloma therapy highlights the importance of treating the underlying haematological malignancy to alleviate renal complications. LCPT, on the other hand, involves LCs resistant to lysosomal degradation, promoting self-aggregation and crystallization within proximal tubular cells. Due to inherent biochemical differences, these two pathologies seldom coexist (1,3).

Renal biopsy remains crucial for diagnosing LCPT and LCCN, revealing intracytoplasmic crystalline inclusions within proximal tubular epithelial cells and noticeable crystalline and non-crystalline casts within distal tubules. Immunofluorescence and immunohistochemical studies are essential for identifying the presence of monoclonal light chains within the renal tissue.

While LCCN is typically associated with multiple myeloma, cases without evidence of clonal hematological disorders pose diagnostic challenges, necessitating further investigations such as imaging studies to explore localized plasmacytoma or lymphadenopathy. LCPT, characterized by LCs resistant to lysosomal degradation, adds another layer of complexity, especially in patients without a history of haematolymphoid disease (4).

The literature emphasizes the critical role of renal biopsy in diagnosing both LCCN and LCPT. In LCCN, biopsy findings typically include crystalline casts within distal tubules, identifiable through immunofluorescence studies showing monoclonal light chains. For LCPT, the renal biopsy might reveal intracytoplasmic crystalline inclusions within proximal tubular cells which demonstrate light chain restriction in immunofluorescence. These diagnostic tools are essential for identifying the underlying pathology and guiding appropriate treatment strategies.

Moreover, while LCCN is often linked to multiple myeloma, cases without clear evidence of a clonal haematological disorder necessitate further investigations, such as imaging studies, to identify localized plasmacytoma or lymphadenopathy. This approach highlights the importance of a thorough and multifaceted diagnostic process when initial tests do not conclusively indicate a haematologic malignancy. In Case 2, such additional investigations could have provided crucial insights into the patient's condition, potentially identifying an underlying localized or low-grade lymphoid disorder.

Recent advancements in the understanding of LCPT and LCCN emphasize the critical role of advanced diagnostic modalities, including immunoelectron microscopy and

specialized immunofluorescence, in detecting subtle and diagnostically challenging cases. Crystalline LCPT, predominantly associated with κ light chains, remains the most frequently encountered variant; however, increased recognition of non-crystalline forms, often λ-restricted, has refined diagnostic accuracy and expanded the pathological spectrum. In the context of LCCN, the implementation of targeted therapies aimed at suppressing monoclonal light chain production has demonstrated efficacy in mitigating renal injury and preserving renal function. Early and precise diagnosis remains paramount in facilitating timely intervention and optimizing patient outcomes (5).

In summary, the comparison of these two cases with the literature on LCCN and LCPT illustrates the diagnostic and therapeutic complexities of renal diseases associated with paraproteins. Case 1 exemplifies a typical presentation of LCCN associated with multiple myeloma, responding well to targeted antimyeloma therapy. Conversely, Case 2 highlights the challenges of diagnosing LCPT or similar conditions in the absence of evident haematologic disease, further complicated by the patients' loss to follow-up. These cases underscore the necessity of comprehensive diagnostic evaluations, including renal biopsies and additional imaging studies, to accurately diagnose and effectively manage paraprotein-related kidney diseases.

CONCLUSION

In conclusion, the co-occurrence of light chain proximal tubulopathy (LCPT) and crystalline light chain cast nephropathy (LCCN) represents a rare and diagnostically challenging entity among paraprotein-related kidney diseases. The presented cases underscore the importance of recognizing the diverse renal manifestations associated with monoclonal gammopathies in which there is a necessity for a comprehensive diagnostic assessment in such patients.

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REFERENCE

1. Meng C, Wang L, Zhang Y, Zhou F. Light chain proximal tubulopathy: A case report and literature review. Exp Ther Med. 2019; 18(4):3019-3025. DOI:10.3892/etm.2019.7879.
2. Lin J, Markowitz GS, Valeri AM, Kambham N, Sherman WH, Appel GB, D'Agati VD. Renal monoclonal immunoglobulin deposition disease: the spectrum of the disease. Journal of the American Society of Nephrology. 2001; 12(7):1482-1492.
3. Leung N, Bridoux F, Hutchison CA, Nasr SH, Cockwell P, Ferdman JP, Dispenzieri A, Song KW, Kyle RA, et. al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood. 2012; 120(22):4292-4295.
4. Stokes MB, Valeri AM, Herlitz L, Khan AM, Siegel DS, Markowitz GS, et al. Light chain proximal tubulopathy: clinical and pathological characteristics in the modern treatment era. Journal of the American Society of Nephrology. 2016; 27(5):1555-1565.
5. Lin Y, Xing G, Hu R, Liu S, Li G, Zhang P, et al. Clinicopathological characteristics of light chain proximal tubulopathy: a multicentre case series. J Clin Pathol. 2024; doi: 10.1136/jcp-2024-209620.