Light Chain Crystal Podocytopathy in a Patient With Systemic Indolent B-Cell Lymphoma

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Kidney Int Rep (2020) 5, 373–376; https://doi.org/10.1016/j.ekir.2019.11.016
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INTRODUCTION

Paraproteinemia in association with a plasma cell dyscrasia or lymphoproliferative disorder can result in kidney injury through direct and indirect mechanisms.¹ Direct renal injury results from precipitation of monoclonal Igs and/or free light chains in the form of casts, fibrils, granular deposits, or crystals.² Among these patterns of renal injury, light chain cast nephropathy is most commonly responsible for kidney dysfunction, in which light chain precipitants are found in the distal convoluted tubular lumen.³ Less commonly, intracellular light chain crystals can form a group of renal disorders known as crystalline nephropathy. These crystals, most often within proximal tubular epithelial cells where filtered light chains are reabsorbed, lead to tubular injury and renal dysfunction (light chain proximal tubulopathy [LCPT]) that usually manifests as Fanconi syndrome.⁴ Other intrarenal intracellular inclusions are even less commonly found in podocytes (light chain crystal podocytopathy [LCCP]), interstitial histiocytes (crystal-storing histiocytosis), endothelial cells, mesangial cells, and intervacularly (crystalglobinemia).³,⁴ There are only a handful of reported cases of LCCP, in which patients present with proteinuria and renal insufficiency, and with concomitant LCPT.⁵,⁶ No previous cases have described this phenomenon in the setting of lymphoma (as opposed to plasma cell dyscrasia).

We report a case of a 64-year-old man with marginal zone lymphoma and IgG kappa paraproteinemia who presented with a gradual decline in kidney function and was found to have 7.2 g/24 h of proteinuria. His kidney biopsy revealed LCCP and interstitial infiltration by lymphoma. His proteinuria and renal insufficiency responded to treatment of his underlying lymphoproliferative disorder.

CASE PRESENTATION

A 64-year-old man was referred to nephrology because of proteinuria and renal insufficiency. He had a diagnosis of atypical chronic lymphocytic leukemia with IgG kappa paraproteinemia for 10 years until his progressive lymphadenopathy prompted an axillary lymph node biopsy, confirming a diagnosis of an indolent B-cell lymphoma most in keeping with marginal zone lymphoma. His bone marrow biopsy demonstrated a clonal population of B cells with bright expression of kappa light chain, and cytogenetics was positive for trisomy 12. His medical profile otherwise included coronary artery disease with previous angioplasty, hypertension controlled on 2 agents, and dyslipidemia.

Before starting treatment for lymphoma, urine testing revealed 7.2 g of protein in 24 hours, consisting of 2.5 g of albumin, 1.9 g of free kappa light chains, and 1.2 g of IgG kappa. Serum laboratory studies are summarized in Table 1. Several years before these laboratory results, creatinine was 0.9 mg/dl (estimated glomerular filtration rate 93 ml/min per 1.73 m²) and urine dipstick was positive for protein at 0.3 g/l. He was negative for antinuclear antibody, and testing for human immunodeficiency virus as well as viral hepatitis B and C was negative.

Three cores of renal parenchyma were received for light microscopy. There were 36 glomeruli, including 5 globally sclerosed, 2 with segmental scars, and a few shrunken. Some glomeruli showed mildly increased luminal mononuclear cells, with no increase in
mesangial matrix or cellularity. The majority of glomeruli contained periodic acid–Schiff–positive podocyte inclusions, either as resorption droplets or crystals, which varied from segmental to global in distribution. There was widespread interstitial infiltration by small lymphoid cells. Interstitial fibrosis and tubular atrophy were mild, arteriolar hyalinosis was mild to moderate, and arterial sclerosis was severe (Figure 1).

Routine immunofluorescence on frozen tissue was negative. Immunofluorescence on paraffin sections after protease digestion revealed cytoplasmic podocyte staining for kappa with no staining for lambda, though no tubular staining was seen. Immunohistochemistry on paraffin sections for CD3 and CD20 showed the vast majority of interstitial lymphoid cells to be B cells with 10-fold less staining for T cells. Immunohistochemistry for kappa and lambda showed 10% to 15% of these cells to stain for kappa with virtually no lambda staining, as well as tubular cytoplasmic droplet staining greater for kappa compared with lambda.

Electron microscopy demonstrated mildly wrinkled and normal-thickness glomerular basement membranes, and no immune-type electron-dense deposits or tubuloreticular inclusions. Several podocyte cell bodies contained numerous hexagonal or rhomboidal crystals. The podocyte foot processes were completely effaced in cells with crystals and elsewhere showed moderate effacement. Some tubular epithelial cells contained similar crystals but not enough to merit a diagnosis of LCPT (Figure 1).

The diagnosis is kappa light chain crystal podocyt-opathy with interstitial infiltration by B-cell lymphoma.

The patient was started on monthly cycles of rituximab and bendamustine for his lymphoma, leading to a significant drop in his serum monoclonal IgG kappa protein, as well as an improvement in renal function and proteinuria (Table 1).

DISCUSSION

We outlined the case of a 64-year-old man with LCCP whose proteinuria and renal insufficiency improved with

| Test              | Results before treatment | Results 6 mo after treatment | Reference |
|-------------------|--------------------------|-------------------------------|-----------|
| Hemoglobin (g/dl) | 9.9                      | 9.5                           | 13.7–18.0 |
| White blood cells (x10^3/μl) | 30,000                   | 5000                          | 4000–11,000 |
| Lymphocytes (x10^3/μl) | 25,000                   | 130                           | 700–3500  |
| Platelets (x10^3/μl) | 75                       | 101                           | 150–400   |
| Protein (g/dl)    | 11.3                     | 7.7                           | 6.3–8.0   |
| Creatinine (mg/dl) | 1.7                      | 1.4                           | 0.6–1.4   |
| Sodium (mEq/l)    | 138                      | 139                           | 133–145   |
| Potassium (mEq/l) | 3.9                      | 3.6                           | 3.5–5.0   |
| Chloride (mEq/l)  | 103                      | 101                           | 98–111    |
| Bicarbonate (mEq/l) | 27                      | 28                            | 21–31     |
| Calcium (mg/dl)   | 8.8                      | 9.2                           | 8.4–10.4  |
| Magnesium (mEq/l) | 0.9                      | 0.9                           | 0.6–1.1   |
| Phosphate (mg/dl) | 5.0                      | 3.7                           | 2.5–4.6   |
| IgG (g/l)         | 4300                     | 2080                          | 680–1800  |
| IgA (g/l)         | 20                       | 20                            | 60–420    |
| IgM (g/l)         | 10                       | 10                            | 40–300    |
| 24-h urine protein (g) | 7.2                     | 3.1                           | <0.150    |

Conversion factors for units: serum creatinine in mg/dl to μmol/l, ×88.4; serum total calcium in mg/dl to mmol/l, ×0.25; serum phosphate in mg/dl to mmol/l, ×0.323; serum IgG, IgA, and IgM in mg/dl to g/l, ×0.01.

Figure 1. The biopsy shows a marked lymphoid infiltrate in many areas of cortex (a, periodic acid–Schiff [PAS], original magnification ×1.6) staining predominantly for B-cell markers (not shown) consistent with lymphoma. The glomeruli show varying PAS-positive material in podocytes that resolves as cytoplasmic crystals on ultrastructural examination (b, original magnification ×3000).
treatment of his underlying hematological disorder. As rare as this entity is, our case is particularly unique because it is the only one described in the setting of a paraproteinemia due to a lymphoma, which also explained the finding of lymphomatous interstitial infiltration.

A variety of Ig-associated renal diseases has been characterized in the setting of lymphoproliferative disorders, such as light chain cast nephropathy and amyloidosis. Light chains are taken up by cells of the kidney, typically proximal tubular cells, and may form crystalline inclusions that result in injury. The monoclonal protein in most patients with light chain–associated nephropathy is kappa, which can aggregate intracellularly by resisting proteolytic clearance. For example, variability in the V domain of the kappa chain in patients with LCPT was found in vitro to confer resistance to proteolytic degradation by cathepsin B in the lysosome, resulting in self-reactivity and crystallization. However, the determinants of crystal localization in other cell types are unknown, although it is the intrinsic light chain properties that are likely most responsible, as evidenced by a recurrent case of LCCP in a recipient of 2 kidney transplants, in which case both allografts demonstrated identical podocyte and proximal tubular cell crystal localization.

A summary of previously reported cases of LCCP is shown in Table 2. Multiple myeloma was the commonest hematological disorder, and most patients presented with proteinuria and renal insufficiency. Proteinuria in LCCP is a combination of albuminuria with or without nephrotic syndrome due to podocyte injury, as well as Bence Jones proteinuria. However, when significant albuminuria is present in LCCP, coexisting focal segmental glomerulosclerosis or another pattern of glomerulosclerosis must also be considered. Focal segmental glomerulosclerosis was the commonest coexisting pattern of glomerular injury on light microscopy in our review. Though our finding of interstitial lymphoid infiltration was explained by the lymphoma, other LCCP cases have shown reactive interstitial mononuclear inflammation or interstitial histiocytes in the setting of crystal-storing histiocytosis. Nearly all cases demonstrated crystalline inclusions in cells other than podocytes, including endothelial cells, mesangial cells, and especially proximal tubular epithelial cells, the latter accounting for the occasional finding of tubular injury on light microscopy. Treatment of the underlying monoclonal gammopathy (clone-directed systemic therapy, with or without hematopoietic stem cell transplant) generally led to improved renal parameters, as was seen in our patient. Crystalline nephropathy has a highly variable prognosis, largely depending on the activity of the underlying lymphoproliferatic disorder.

Most reported cases of LCCP demonstrated kappa chain restriction, though immunofluorescence was

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Table 2. Summary of reported cases of LCCP

| Reference            | Age, sex | Underlying hematologic disorder | Other pathological features |
|----------------------|----------|---------------------------------|----------------------------|
| Carstens et al., 1989 | 57, M    | IgG k multiple myeloma          |                            |
| Yamamoto et al., 1991 | 71, M    | IgG k multiple myeloma          | Interstitial histocyte infiltration |
| Matsuyama et al., 1994 | 40, F    | IgG k MGRS                      | FSGS                       |
| Kasvi et al., 2003    | 52, F    | IgG k multiple myeloma          | Global glomerulosclerosis, interstitial monoclonal inflammatory cell infiltration |
| Popa et al., 2004     | 51, M    | IgG k multiple myeloma with systemic crystal-storing histiocytosis | Interstitial histocyte infiltration |
| Tomioka et al., 2004  | 46, F    | IgG k multiple myeloma          | Interstitial histocyte infiltration |
| Keller et al., 2005   | 56, M    | IgG k multiple myeloma          | Acute tubular necrosis, mild interstitial monoclonal inflammatory cell infiltration |
| Nasr et al., 2006     | 54, F    | IgG k multiple myeloma          | Collapsing FSGS (pamidronate related), mild interstitial monocytic and lymphocytic infiltration |
| Elliott et al., 2010  | 53, M    | IgG k MGRS                      | Tubular injury             |
| Aklesh et al., 2014   | 45, M    | IgG k multiple myeloma          | Collapsing gammopathy, global glomerulosclerosis, acute tubular injury, nonspecific chronic inflammatory cell infiltration |
| Jeon et al., 2015     | 52, F    | IgG k multiple myeloma          | FSGS, mild lymphocytic infiltration of interstitium |
| Hoelbeek et al., 2016 | 62, F    | IgG k plasma cell dyscrasia with type I cryoglobulinemia | Glomerular macrophage infiltration, mesangiocapillary proliferative pattern of glomerular injury |
| Lee et al., 2016      | 66, F    | IgG k multiple myeloma          | FSGS, tubular injury, tubular casts, interstitial histocyte infiltration |
| Stokes et al., 2016   | n = 3    |                                 | Acute tubular injury        |
| Wang et al., 2016     | 71, F    | IgG k multiple myeloma          |                            |
| Khoshghi et al., 2017 | 29, M    | IgG k MGRS                      | FSGS, tubular injury        |
| Yang et al., 2017     | 51, M    | IgG k MGRS                      | FSGS                       |
| Present case          | 64, M    | Marginal zone lymphoma and IgG k paraproteinemia | Global glomerulosclerosis, interstitial lymphoid cell infiltration |

F, female; FSGS, focal segmental glomerulosclerosis; M, male; MGRS, monoclonal gammopathy of renal significance; MM, multiple myeloma.

*Transplant recipients.
Though LCCP most commonly occurs as a consequence of a plasma cell neoplasm, LCCP usually presents as proteinuria and renal insufficiency, and improves with treatment of the underlying lymphoproliferative disorder. LCCP is often falsely negative when compared with immunohistochemistry. This observation may be a consequence of tightly packed paraprotein arrays that are inaccessible to the Ig used in staining protocols. However, even if immunohistochemical methods do not demonstrate light chain restriction, crystal nephropathy cannot be excluded because antisera may fail to recognize light chains that may be partially degraded. Therefore, electron microscopy is needed to visualize crystalline inclusions, and then if needed, immunoelectron microscopy can confirm the diagnosis, though its cost and complexity limit its availability.

Although all other reported cases of LCCP were secondary to a plasma cell dyscrasia, ours was due to marginal zone lymphoma. On the other hand, pure LCPT has been rarely associated with lymphoma. Lymphoproliferative disorders are a well-known cause of proteinuric glomerular disease, and marginal zone lymphoma has been described in association with minimal change disease, but not with LCCP.

**CONCLUSION**

We report a case of a 64-year-old man with marginal zone lymphoma who underwent a kidney biopsy because of proteinuria and renal dysfunction, was found to have LCCP along with lymphomatous interstitial infiltration, and improved with treatment of his lymphoproliferative disorder. This case adds to the short list of previously published cases of LCCP and is the first to describe a patient whose underlying hematological disorder was a lymphoma rather than a plasma cell dyscrasia (Table 3). Electron microscopy is essential for the diagnosis to identify crystals and because of false negatives on immunostaining. This review also highlights the importance of investigating for a lymphoproliferamctic disorder in patients discovered to have intrarenal crystalline deposits.

**DISCLOSURE**

All the authors declared no competing interests.

**AUTHOR CONTRIBUTIONS**

Research idea and study design were carried out by AK, RJ, MS, and CTC; data acquisition and data analysis/interpretation were carried out by FK and AK; and supervision and mentorship was carried out by AK, RJ, AP, and CTC. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author’s own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

**Supplemental References.**

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**Table 3. Teaching points**

- Crystalline nephropathy is a type of monoclonal Ig-associated renal disease characterized by the presence of light chain intracellular crystals.
- Intracellular light chain intracellular inclusions can form inside proximal tubular cells (LCPT) or even more rarely within podocytes (LCCP).
- LCPT usually presents as proteinuria and renal insufficiency, and improves with treatment of the underlying lymphoproliferamctic disorder.
- Though LCCP most commonly occurs as a consequence of a plasma cell neoplasm, lymphoma can also be etiological, in which case lymphomatous interstitial inflammation must be sought on renal histology.
- The diagnosis of LCCP relies on electron microscopy to identify crystals because of the possibility of false-negative immunostaining.

LCCP, light chain crystal podocytopathy; LCPT, light chain proximal tubulopathy.