KI REPORTS
KIReports.org

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

Fareed Kamar[1], Melvin Silverman[2], Rohan John[3], Christopher T. Chan[2], Anca Prica[4] and Abhijat Kitchlu[2]

[1]Department of Medicine, Division of Nephrology, Cumming School of Medicine, University of Calgary, Calgary, Canada; [2]Department of Medicine, Division of Nephrology, University of Toronto, Toronto, Canada; [3]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada; and [4]Division of Medical Oncology and Hematology, University of Toronto, Toronto, Canada

Correspondence: Abhijat Kitchlu, Toronto General Hospital, University Health Network, 8th Floor, 8N-842, Toronto, ON, Canada, M5G 2C4. E-mail: abhijat.kitchlu@uhn.ca

Received 29 September 2019; revised 14 November 2019; accepted 25 November 2019; published online 6 December 2019

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

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 intravascularly (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 m^2) 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

Table 1. Laboratory investigations before and after treatment

Test	Results before treatment	Results 6 mo after treatment	Reference
Hemoglobin (g/dl)	9.9	9.5	13.7–18.0
White blood cells (/μl)	30,000	5000	4000–11,000
Lymphocytes (/μl)	25,000	130	700–3500
Platelets ($\times 10^3$/μl)	75	101	150–400
Protein (g/dl)	11.3	7.7	6.3–8.0
Albumin (g/dl)	3.0	3.9	3.3–4.8
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.

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 podocytopathy 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

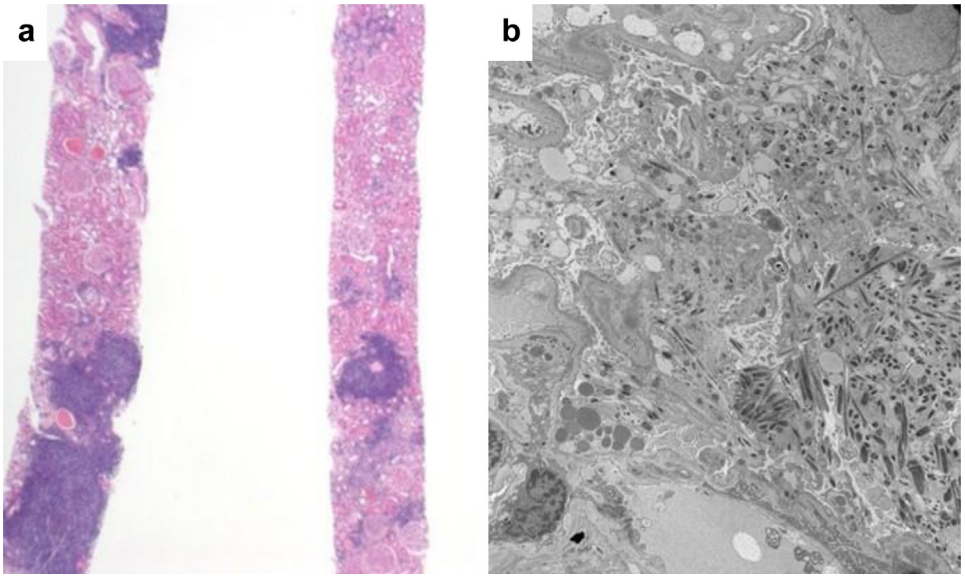

Figure 1. The biopsy shows a marked lymphoid infiltrate in many areas of cortex (a, periodic acid–Schiff [PAS], original magnification ×1.6) staining predominantly for B-cell markers (not shown) consistent with lymphoma. The glomeruli show varying PAS-positive material in podocytes that resolves as cytoplasmic 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 lymphoplasmacytic disorders, such as light chain cast nephropathy and amyloidosis.[1] Light chains are taken up by cells of the kidney, typically proximal tubular cells, and may form crystalline inclusions that result in injury.[5] The monoclonal protein in most patients with light chain–associated nephropathy is kappa, which can aggregate intracellularly by resisting proteolytic clearance.[2] 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,[7] resulting in self-reactivity and crystallization.[8] 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.[6]

A summary of previously reported cases of LCCP is shown in Table 2.[9,S1–S11] 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.[9] 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.[4–6,9,S3,S4,S9,S11] Though our finding of interstitial lymphoid infiltration was explained by the lymphoma,[S12] other LCCP cases have shown reactive interstitial mononuclear inflammation[9,S4,S7,S9] or interstitial histiocytes in the setting of crystal-storing histiocytosis.[4,S2,S5,S6] 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,[2,4,5,9,S6,S8,S10,S13] as was seen in our patient. Crystalline nephropathy has a highly variable prognosis, largely depending on the activity of the underlying lymphoplasmacytic disorder.[2]

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

Table 2. Summary of reported cases of LCCP

Reference	Age, sex	Underlying hematologic disorder	Other pathological features
Carstens *et al.*, 1989[S1]	57, M	IgG κ multiple myeloma	—
Yamamoto *et al.*, 1991[S2]	71, M	IgG κ multiple myeloma	Interstitial histiocyte infiltration
Matsuyama *et al.*, 1994[S3]	40, F	IgG κ MGRS	FSGS
Kowalewska *et al.*, 2003[S4]	52, F	IgG κ multiple myeloma	Global glomerulosclerosis, interstitial mononuclear inflammatory cell infiltration
Papla *et al.*, 2004[S5]	51, M	IgG κ multiple myeloma with systemic crystal-storing histiocytosis	Interstitial histiocyte infiltration
Tomioka *et al.*, 2004[S6]	46, F	IgG κ multiple myeloma	Interstitial histiocyte infiltration
Keller *et al.*, 2005[S7]	56, M	IgG κ multiple myeloma	Acute tubular necrosis, mild interstitial mononuclear inflammatory cell infiltration
Nasr *et al.*, 2006[9]	54, F	IgG κ multiple myeloma	Collapsing FSGS (pamidronate related), mild interstitial monocytic and lymphocytic infiltration
Elliott *et al.*, 2010[S8]	53, M	IgG κ MGRS	Tubular injury
Akilesh *et al.*, 2014[5]	45, M	IgG κ multiple myeloma	Collapsing glomerulopathy, global glomerulosclerosis, acute tubular injury, nonspecific chronic interstitial inflammation
Jeon *et al.*, 2015[S9]	52, F	IgG κ multiple myeloma	FSGS, mild lymphocytic infiltration of interstitium
Hoelbeek *et al.*, 2016[2]	62, F	IgG κ plasma cell dyscrasia with type I cryoglobulinemia	Glomerular macrophage infiltration, mesangiocapillary proliferative pattern of glomerular injury
Lee *et al.*, 2016[4]	66, F	IgG κ multiple myeloma	FSGS, tubular injury, tubular casts, interstitial histiocyte infiltration
Stokes *et al.*, 2016[3] (cases not individually detailed)	n = 3	—	Acute tubular injury
Wang *et al.*, 2016[S10]	71, F	IgG κ multiple myeloma	—
Khalighi *et al.*, 2017[6,a]	29, M	IgG κ MGRS	FSGS, tubular injury
Yang *et al.*, 2017[S11,a]	51, M	IgG κ MGRS	FSGS
Present case	64, M	Marginal zone lymphoma and IgG κ paraproteinemia	Global glomerulosclerosis, interstitial lymphoid cell infiltration

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

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).
■ LCCP usually presents as proteinuria and renal insufficiency, and improves with treatment of the underlying lymphoplasmacytic 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.

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.[S8] 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.[S8] 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.[S14]

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.[3] Lymphoproliferative disorders are a well-known cause of proteinuric glomerular disease,[S12] and marginal zone lymphoma has been described in association with minimal change disease,[S15,S16] 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 lymphoplasmacytic 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.

REFERENCES

1. Sethi S, Rajkumar SV, D'Agati VD. The complexity and heterogeneity of monoclonal immunoglobulin-associated renal diseases. *J Am Soc Nephrol*. 2018;29:1810–1823.
2. Hoelbeek J, Duivenvoorden R, de Boer OJ, et al. Unique renal manifestation of type I cryoglobulinemia, with massive crystalloid deposits in glomerular histiocytes, podocytes, and endothelial cells. *Am J Clin Pathol*. 2016;145:282–285.
3. Stokes MB, Valeri AM, Herlitz L, et al. Light chain proximal tubulopathy: clinical and pathologic characteristics in the modern treatment era. *J Am Soc Nephrol*. 2016;27:1555–1565.
4. Lee EJ, Lee SY, Park SY, et al. Crystalline podocytopathy and tubulopathy without overt glomerular proteinuria in a patient with multiple myeloma. *Kidney Res Clin Pract*. 2016;35:259–262.
5. Akilesh S, Alem A, Nicosia RF. Combined crystalline podocytopathy and tubulopathy associated with multiple myeloma. *Hum Pathol*. 2014;45:875–879.
6. Khalighi MA, Revelo MP, Abraham JD, et al. Light chain podocytopathy mimicking recurrent focal segmental glomerulosclerosis. *Am J Transplant*. 2017;17:824–829.
7. Leboulleux M, Lelongt B, Mougenot B, et al. Protease resistance and binding of Ig light chains in myeloma-associated tubulopathies. *Kidney Int*. 1995;48:72–79.
8. El Hamel C, Thierry A, Trouillas P, et al. Crystal-storing histiocytosis with renal Fanconi syndrome: pathological and molecular characteristics compared with classical myeloma-associated Fanconi syndrome. *Nephrol Dial Transplant*. 2010;25:2982–2990.
9. Nasr SH, Preddie DC, Markowitz GS, et al. Multiple myeloma, nephrotic syndrome and crystalloid inclusions in podocytes. *Kidney Int*. 2006;69:616–620.