Clinical Study

Light Chain Proximal Tubulopathy: Expanding the Pathologic Spectrum with and without Deposition of Crystalline Inclusions

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Light chain proximal tubulopathy (LCPT) is an uncommon form of renal disease associated with dysproteinemias. It is characterized by intracytoplasmic deposition of crystallized mostly kappa monoclonal light chains in proximal tubules (PTs). Crystals are located within lysosomes by electron microscopy (EM). Rare lambda LCPT cases without crystals by EM were described. Retrospectively, we reviewed clinical, light microscopic (LM), immunofluorescence (IF), and EM findings in 9 cases (8 males, 1 female; mean age 57 years (38–81)) with multiple myeloma. LM showed abundant cytoplasmic droplets in PT cells in all cases. Droplets were also present in the podocytes, endothelial and parietal cells in one case. IF revealed staining of crystals with kappa in 3 and lambda in 6. EM showed electron dense rectangular, rhomboid, or needle shaped crystals in PT cells in 3 cases (33%), one of which had crystals in podocytes and interstitial cells. Six lambda LCPT cases showed no crystals by EM (67%). This may reflect differences in the physicochemical properties of light chains. The mechanisms of crystal accumulation in these cells and the significance of this finding are unknown.

1. Introduction

The kidney is affected in a variety of dysproteinemias, the pathogenesis, and the morphology, which varies depending on the etiology [1]. The common morphological presentation of the affected kidney includes myeloma cast nephropathy, monoclonal immunoglobulin deposition disease, and amyloidosis. Another unique entity which is less frequently reported as case reports and small case series is light chain proximal tubulopathy (LCPT) [2].

The first description of LCPT causing Fanconi syndrome (FS) with needle shape crystals by EM found in the PT epithelial cell cytoplasm was reported in 1957 [3]. Subsequently less than 100 cases of LCPT described in the English language literature as case reports and small case series [4–6]. The largest series with 17 cases was reported by Maldonado et al. in 1975 [7].

In LCPT the excessive light chains (LCs), mostly kappa type by IF, are excreted through the kidney and are reabsorbed in the PT cells leading to tubular damage, less frequently resulting in acquired FS. The association of the LCPT with lambda LC is rarely described in the English language literature [6,8].

The excessive LC absorbed by the cytoplasm of PT cells result in formation of crystalline structures which can be detected by IF and EM. The crystals are electron dense usually rhomboid, square, or rectangular in configuration and found in the lysosomes of PT cells by EM. Rarely, crystals can be seen in glomerular cells including podocytes and as well as in interstitial cells and histiocytes in the kidney [9–15]. Our case series with 3 kappa and 6 lambda-type LCPT is adding more information to existing literature with light, IF and EM findings.
2. Materials and Methods

The renal database of the Department of Pathology, University of Arkansas for Medical Sciences and Louisiana State University Health Sciences Center was searched retrospectively for a diagnosis of LCPT from 2004 to 2010. The selection of cases was based on the presence of eosinophilic intracytoplasmic droplets on hematoxyline-eosin (h&e) by LM, either kappa or lambda LC-restricted staining of droplets by IF, and intracytoplasmic needle, rhomboid, oval to round, rectangular or square electron dense crystals by EM. A total of 9 cases were found and the clinical history, LM, IF and EM findings were noted. The renal biopsies were fixed in 10% buffered formalin and routinely processed for LM. Three micron serial sections for LM were stained for h&e, periodic acid-Schiødt (PAS), Jones Methenamine Silver (JMS), Masson's trichrome and Congo red. IF was performed on Michel's fixed tissues and 3 micron duplicate frozen sections stained with direct IF method using FITC-conjugated polyclonal rabbit anti-human antiserum against immunoglobulins (G, A, M) complement 3 (C3), complement 1q (C1q), kappa, lambda, fibrinogen, albumin and Thioflavin-T (Dako Corporation, Carpenteria, CA,USA). The scale of 0 to 3+ grading was used to document any staining in the glomeruli, basement membranes, tubules, interstitium and vessels. EM was performed on 10% buffered formalin or 3% glutaraldehyde fixed samples that were processed according to standard protocol, and examined in a digital electron microscope (UAMS-JEOL, JEM1010, Japan; LSUHSC- Hitachi, H-7650, Japan).

3. Case Presentations

A total of 9 cases have met the inclusion criteria for the diagnosis of LCPT. Eight patients were male and one was female with an age range of 38 years to 81 years with a mean of 57 years. All patients presented with proteinuria ranging from 2 to 5 grams/24 hour and creatinine values ranging from 144.44 Mmol/L to 433.16 Mmol/L with an average value of 229.84 Mmol/L. One patient had FS and one presented with acute renal failure. The clinical and pathological findings are summarized in Table 1. Five to 23 glomeruli were available for LM. Glomeruli were unremarkable in 8 cases. Only one patient had cytoplasmic eosinophilic droplets in all glomeruli affecting podocytes and parietal cells (Figure 1(a)). None of the cases had crescents. Global glomerulosclerosis was present in a mean of 31% of glomeruli (range, 2% to 50%). In 2 cases, 1 glomerulus with focal segmental glomerulosclerosis (1 NOS, 1 collapsing variant) was identified. All cases (100%) displayed characteristic eosinophilic, PAS negative cytoplasmic droplets in PT cells (Figure 1(b)). Scattered distal and collecting tubules and interstitial cells also showed similar cytoplasmic droplets in a segmental pattern in one case (Figure 1(c)). Droplets were bright pink with Masson's trichrome (Figure 1(d)). The degree of interstitial fibrosis with proportional tubular atrophy ranged from mild in 1 case to moderate in 4 cases. There was no significant interstitial fibrosis in 4 cases. Focal mild lymphoplasmacytic interstitial infiltrate was present in 5 cases. All cases showed multiple foci of acute tubular injury. Six cases demonstrated mild to moderate vascular intimal thickening. Arterioles showed hyalinosis in 3 cases. Only one case with AL-type amyloidosis showed Congo red positive staining of mesangium and vessels.

Seven to 15 glomeruli were present for IF evaluation in 9 cases. All cases (100%) showed strong (3+), multifocal granular intracytoplasmic LC immunoreactivity [3 kappa (33%) and 6 lambda (67%)] (Figure 2). Only one case exhibited glomerular staining involving podocytes and parietal cells with kappa LC. Focal interstitial staining was present in 2 cases with kappa. One case had concurrent kappa-type light chain deposition disease with linear kappa staining of glomerular and tubular basement membranes. Vascular wall staining was not seen. All immunoglobulins and complements were negative in 9 cases. One case with amyloidosis had Thioflavin-T and lambda positivity of the mesangium and vessel walls. One to 2 glomeruli were available for EM in each case. The characteristic EM

Table 1: Clinical and morphological findings in 9 cases with light chain proximal tubulopathy.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/sex</th>
<th>MM diagnosis before biopsy</th>
<th>LM: cytoplasmic granularity in</th>
<th>IF: cytoplasmic granular staining</th>
<th>EM: cytoplasmic crystals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54/M</td>
<td>MM</td>
<td>PT, DT, podocyte, parietal cells</td>
<td>Kappa linear staining in gbm and tbm</td>
<td>PT, podocytes, parietal, interstitial cells. Granular deposits along gbm and tbm</td>
</tr>
<tr>
<td>2</td>
<td>60/M</td>
<td>MM</td>
<td>PT</td>
<td>Lambda</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>38/M</td>
<td>MM; FS</td>
<td>PT</td>
<td>Lambda</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>51/M</td>
<td>MM</td>
<td>PT + amyloid</td>
<td>Lambda</td>
<td>None; amyloid fibrils</td>
</tr>
<tr>
<td>5</td>
<td>58/M</td>
<td>MM</td>
<td>PT</td>
<td>Kappa</td>
<td>PT</td>
</tr>
<tr>
<td>6</td>
<td>55/M</td>
<td>MM</td>
<td>PT</td>
<td>Lambda</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>59/F</td>
<td>MM</td>
<td>PT</td>
<td>Lambda</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>58/M</td>
<td>MM</td>
<td>PT + LCCN</td>
<td>Lambda + casts</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>63/M</td>
<td>MM</td>
<td>PT + LCCN</td>
<td>Lambda + casts</td>
<td>None</td>
</tr>
</tbody>
</table>

findings were seen in 3 cases with kappa LCPT (33%) as intracytoplasmic electron dense rhomboid, oval to round, rectangular, and square-shaped crystals located in lysosomes of PT cells (Figure 3). One of the 3 kappa LCPT cases also had sparse small crystals in the glomeruli involving podocytes, mesangium, and interstitial cells. Another kappa LCPT case exhibited crystals in the interstitial cells in addition to PT cells. In 6 cases with lambda LCPT (67%), no crystals were identified in any location in the kidney. Only one of them showed prominent endolysosomes. The available segments of vessels were unremarkable. The degree of foot process effacement ranged from mild in 4 cases to moderate-marked in 5 cases. There were dark granular deposits in the glomerular and tubular basement membranes in one case with concurrent light chain deposition disease (LCDD). One case with amyloidosis exhibited characteristic amyloid fibrils in the mesangium and arteriolar walls.
4. Discussion

The renal involvement secondary to plasma cell dyscrasias (PCD) is a significant prognostic factor for patients [16]. In the majority of cases the excessive abnormal LC proteins deposit as fibrils, tubular casts, or basement membrane precipitates and can manifest as amyloidosis, cast nephropathy and LCDD, respectively [1, 16–18]. The increasing understanding regarding the type and structure of LC protein and the compartment which it involves gives us a better perspective of understanding of the disease pathogenesis. The LCPT is an uncommonly reported disease occurs in PCD patients and less than 100 cases reported in the literature. Patients may have varied clinical presentations such as proteinuria, kidney failure, FS, or osteomalacia [1]. The disease condition is considered to be reversible once the underlying etiology is corrected. LCPT patients may develop FS which is a disorder of the proximal tubule transport system leading to aminoaciduria, glycosuria, phosphaturia, bicarbonate, and uric acid wasting [2]

The LCPT is a unique entity in which the LC crystals of mostly kappa type are deposited in the cytoplasm of the PT cells and detected as intracytoplasmic droplets by LM and IF and electron dense crystals of a variety of shapes by EM in majority of cases [19–25]. Although crystals accumulate predominantly in PT cells, rare case reports described the presence of crystals in the glomeruli and interstitial cells [9–14, 24]. Glomerular crystals may be detected by LM, IF and EM in podocytes, mesangial, endothelial and parietal cells [6, 9, 11–14, 24]. Interstitial cells and histiocytes in the interstitium may contain crystals and they can be detected by LM, IF, and EM [10, 12, 14, 24].

A few case series demonstrated that the majority of LCPT cases without crystals by EM proved to be of lambda LC type. All cases of lambda LCPT in our series did not show crystals by EM, supporting the existing literature. Larsen et al. published the largest case series of 10 LCPT without crystal deposition and 9 of 10 cases had lambda light chain restriction [6]. In their series, Kapur et al. reported 3 of 5 cases with no crystals, and instead, PT cells had prominent phagolysosomes. However, by immunoelectron microscopy, the lysosomal content showed LC restriction in 2 cases studied [25]. The definite method of confirmation in these cases is by immunogold labeling but is available only in selected places. Such cases might reflect more light on the pathogenesis because they might represent a stage ahead of the crystal deposition stage in which the cells of the proximal tubules are shed because of the toxic effects of the crystals, and it is not possible to identify the crystals on EM studies. For a crystal to be visualized it has to aggregate in a specific structure to be visualized. It is also possible that in early stages of the disease the accumulated light chains cannot be visualized because they have not formed crystals to be detected by EM. Moreover, findings may suggest that physical and chemical properties of kappa and lambda LC quite differ from each other.

It has been demonstrated by Nasr et al. in cases where IF performed on frozen tissue was not successful for showing restriction of either kappa or lambda LC in cytoplasmic droplets, IF on formalin-fixed, paraffin embedded, pronase-digested tissue appeared to work [26]. In our series the intracytoplasmic droplets were positive by IF in all cases.

The LCPT cases occasionally have FS which is caused by the deposition of predominantly kappa LC in the cytoplasm of proximal tubules which interferes with the reabsorptive capacity of the tubular cells. Kinetic studies showed that V domain of the kappa LC in most of FS patients is responsible for resistance of kappa LC to proteolysis in the lysosomes of PT cells resulting in aggregation and crystal formation [27–31]. In our series one of 3 cases with kappa LCPT had FS and crystals by EM supporting this evidence.

It is rare for lambda LC to cause LCPT with FS. Only a few case reports have been reported of lambda LCPT with FS in English language literature. In these cases EM showed needle-like crystals in PT cells [8, 32, 33]. Another case report of animal experiment showed deposition of lambda LC in tubular cells of mice after repeated injections of urine from a patient with myeloma associated FS caused by lambda LC. In this brief report, similar to our findings, no crystals were seen in mice kidney tubular cells [34]. None of our 6 cases with lambda LCPT had FS. Only one of them showed prominent endolysosomes by EM. The occurrence of LCPT has been described in diseases other than PCD including chronic lymphocytic leukemia [35], well-differentiated lymphocytic lymphoma [32], Waldenstrom’s macroglobulinemia [36], and diffuse large B-cell lymphoma of the spleen [5]. All cases in our series had a diagnosis of multiple myeloma at the time of kidney biopsy.

Four cases in our series had concurrent diseases with LCPT including light chain deposition disease in case 1, amyloidosis of AL lambda chain type in case 4 and light chain cast nephropathy in cases 8 and 9. Such associations have been described in the literature [25]. Two cases had concurrent focal segmental glomerulosclerosis (FSGS), collapsing variant in case 2 and NOS variant in case 6 along with LCPT. However, it is difficult to suggest pathogenetic relationship between crystalline inclusions and FSGS. Only one case report by Matsuyama et al. described the concurrent FSGS with LCPT with crystalline inclusions in the glomerular podocytes in a patient with monoclonal gammopathy. They postulated that it is possible that the crystalline inclusions damage the podocytes and produce secondary FSGS [11].

In summary cases of LCPT with lambda LC without crystals by EM are more common than cases of LCPT with lambda LC with crystals. In such a case without crystals by EM, based on LM findings which they may be subtle and characteristic IF findings one can make a diagnosis of LCPT and can have a significant clinical impact.

Our results are in concordance with few reports highlighting the EM differences in cases of kappa and lambda LCPT. Our cases depict the variability of the clinical presentation, LM, IF, and EM findings in LCPT. More have to be elucidated in the biology of the kappa and lambda LC to understand the disease pathogenesis.
Acknowledgment

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References


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