

## **Interesting case seminar: Native kidneys**

### **Case Report:**

#### **Proximal tubulopathy and light chain deposition disease presented as severe pulmonary hypertension with right-sided cardiac dysfunction and nephrotic syndrome.**

Bauerova L.

Department of Pathology, the First Faculty of Medicine and General Teaching Hospital, Charles University Prague

(nephropathology training: Department of Clinical and Transplant Pathology, IKEM)

### **Clinical history:**

A 47-year-old woman was admitted to the hospital for severe dyspnea, fatigue, subfebrilia and peripheral edema. She suffered from Crohn disease which was diagnosed 12 years ago, now in a long term remission without therapy. Her present disease started 2 months ago with fatigue, back and muscle pain, and progressive dyspnea. She also complained of peripheral edema, which was slowly progressing. Physical and laboratory examination revealed pulmonary hypertension with right-sided heart dysfunction, nephrotic proteinuria (8-19g/day) and mild anemia (hemoglobin 104g/l). Kidney function was slightly decreased with a serum creatinine level of 138 $\mu$ mol/l (1,5mg/dl). Monoclonal protein IgG kappa at a very high level was identified in the serum (24 500 mg/l), and in the urine. The radiological skeletal bone survey revealed discrete lytic lesions in the skull. A biopsy specimen of the bone marrow confirmed the diagnosis of multiple myeloma.

A kidney biopsy was performed with clinical diagnosis of amyloidosis, which was assumed to be an etiology of her nephrotic syndrome, cardiac and pulmonary dysfunction.

### **Renal biopsy findings:**

The biopsy sample for IF contained 3 glomeruli which were negative for immunoglobulins, C3, C1q complement components and also for kappa, lambda light chains. Only very weak unspecific linear positive staining along the capillary walls for IgG was recognized during repeated examinations. All proximal tubules contained a massive number of protein droplets which showed kappa positive staining (Fig. 1). The tubular basement membranes also showed semi-linear kappa positive staining. In light microscopy all proximal tubules had epithelial cells with granular eosinophilic abundant cytoplasm; there were no casts in their lumina (Fig.2, 3). The tubular basement membranes had discrete segmental PAS positive thickening corresponding with immunofluorescence staining (Fig.4). There were 10 glomeruli with a slight increase of PAS positive mesangial matrix. Also, GBM were focally segmentally slightly thickened, and this thickening was PAS positive (Fig. 5). No crescent, no sclerotic lesions were observed. Congo red staining was negative.

Prominence of the lysosomal system with variably sized and shaped lysosomes appeared at the ultrastructure level together with dense linear granular deposits along the tubular basement membranes and also along several segments of the glomerular capillary walls.

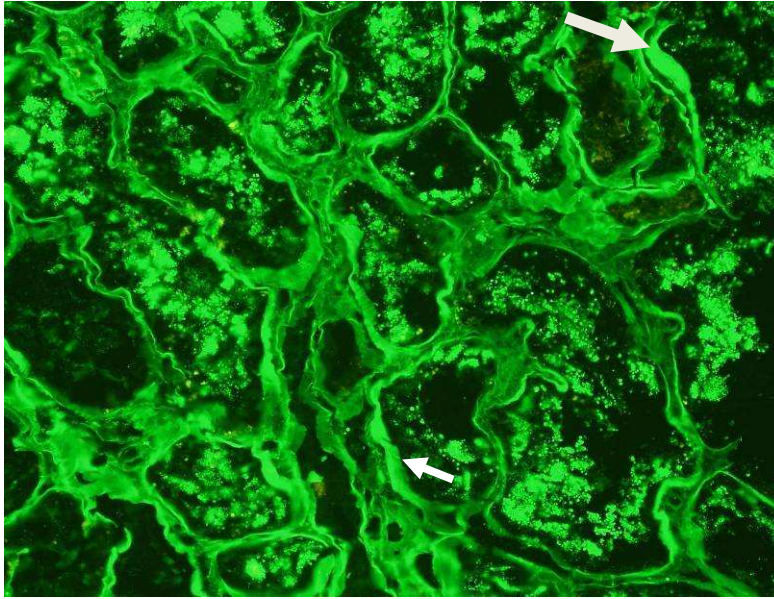


Fig.1. The immunofluorescence microscopy reveals a massive number of kappa positive protein droplets in the tubular epithelial cells and also semi-linear positive thickening of the tubular basement membranes (arrows).

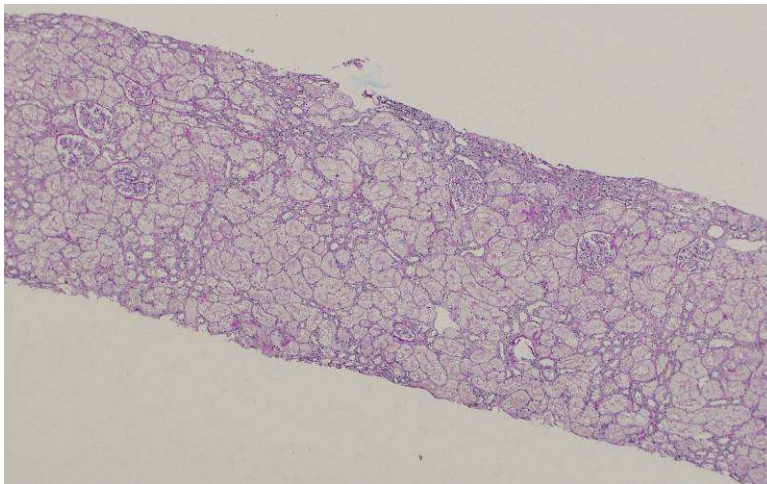


Fig. 2. This low-power image of the renal cortex shows well-preserved parenchyma without signs of tubular atrophy and without protein casts.

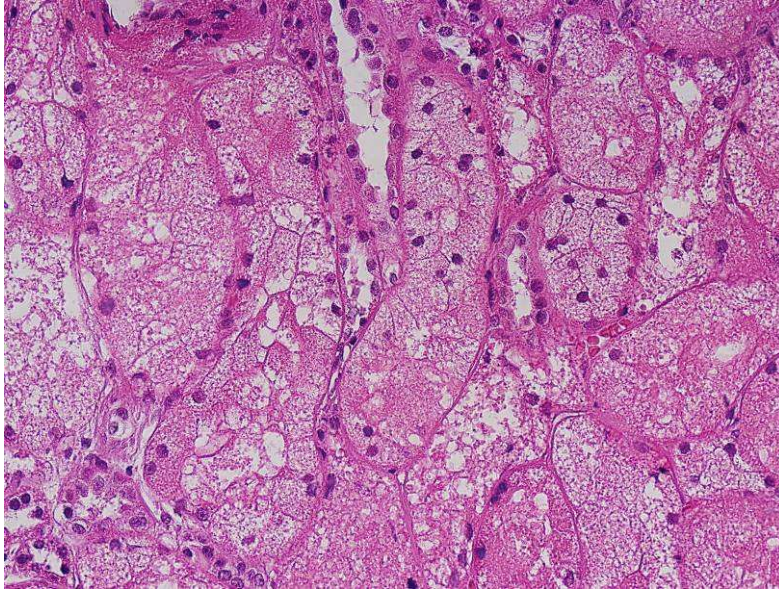


Fig.3. The high-power image of H&E shows proximal epithelial cells with abundant granular cytoplasm.

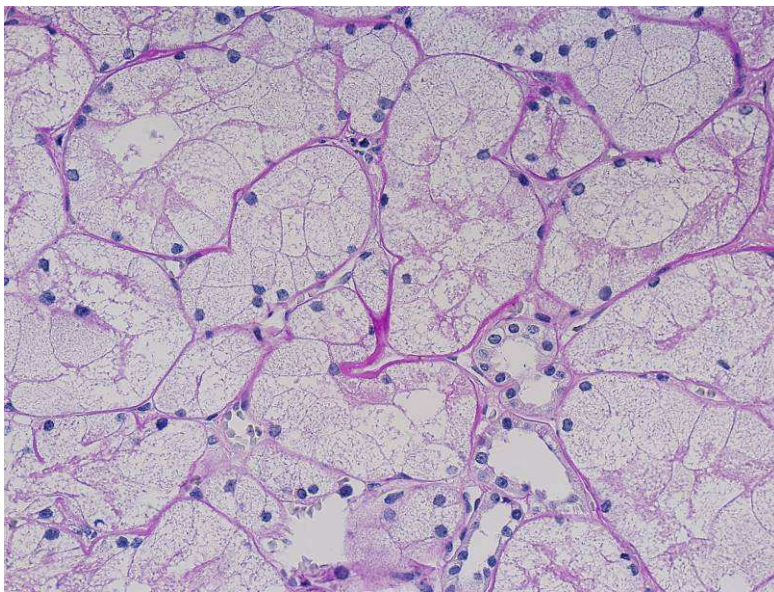


Fig.4. This image depicts the kidney cortex with segmental PAS positive thickening of the tubular basement membranes and proximal epithelial cells with abundant granular cytoplasm.

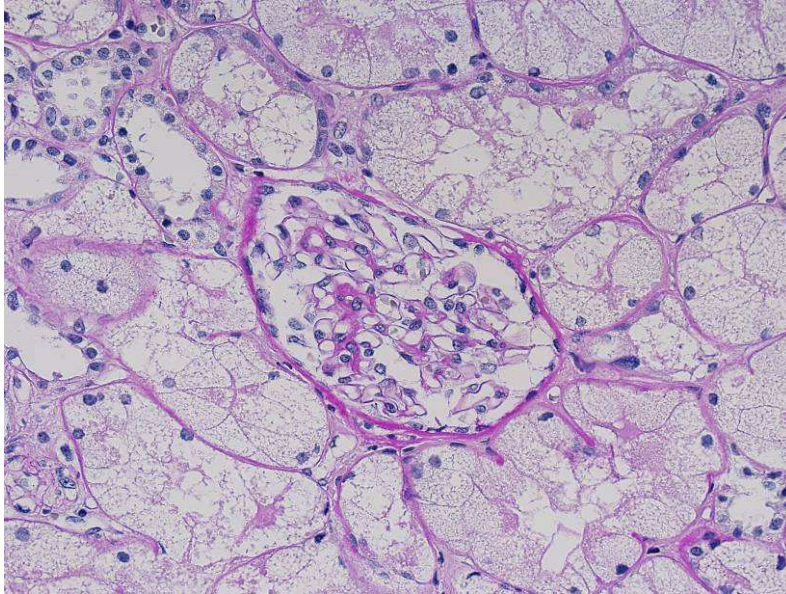


Fig.5. This glomerulus reveals mild segmental PAS positive thickening of GBMs, and proximal tubules with the same morphological features as in the preceding figures.

#### Diagnosis:

The diagnostic conclusion was proximal tubulopathy and LCDD as a complication of multiple myeloma.

#### Differential diagnosis of kidney involvement associated with plasma cell dyscrasia:

- Amyloidosis
- Monoclonal Ig deposition disease
  - a) LCDD, LHCD, HCDD
  - b) Proliferative GN with monoclonal IgG deposits
- Light chain cast nephropathy (myeloma kidney)
- Proximal tubulopathy (with or without Fanconi Syndrome)
- Other renal lesions (Other renal pathology not associated with plasma cell dyscrasia can be seen in the renal biopsies of individual patients, e.g., „previous“vascular nephrosclerosis, FSGS, etc.)

#### Discussion:

Renal pathology associated with the presence of a paraprotein can be quite diverse and nephrotoxic light chains (LCs) can affect the various renal compartments. One group of nephrotoxic LCs is associated with glomerular damage (such patients may develop amyloidosis or LCDD), and the second group produces predominantly tubular damage. When LCs are excessively absorbed by proximal tubular cells (receptor-mediated endocytosis, cubilin/megalin complex), the result is proximal tubulopathy (with or without Fanconi syndrome). When other LCs lead to distal nephron obstruction, it is called LC cast nephropathy (myeloma kidney).

**Light/heavy chain (AL) amyloidosis** represents the most frequent cause of nephrotic syndrome in patients suffering from multiple myeloma. Diagnosis of amyloidosis is based on the detection of deposits in a tissue with the determination of the type of amyloid. Congo red stain continues to be the gold standard for detection of amyloid deposits. Small deposits especially in 2-3 um thin sections

may not be visible in bright light. In such cases, Congo red itself is not diagnostic and other techniques such as immunofluorescence, immunohistochemistry and ELMI are necessary. Deposits of amyloid are frequently very focal and irregularly distributed in the different compartments of kidney tissue; therefore multiple sections may need to be examined. In differential diagnosis of AL amyloid the main problem is represented by the various types of hereditary amyloidoses. The kidney may be involved in all types of hereditary amyloidoses. Hereditary amyloidoses are not as rare as they were once considered to be, and also a family history of amyloidosis is often missing. Although, there are data concerning an increasing number of cases of hereditary amyloidoses (10% in the USA, 16% in the UK), they are still believed to be underdiagnosed (1).

**Monoclonal Ig (Light/heavy-chain) deposition disease (LCDD)** of the kidney is defined as deposition of monotypic light chains within glomeruli and along the tubular basement membranes (TBM).

Approximately 25% of patients with LCDD suffered from multi-organ involvement (lungs, heart, and liver). In the kidney LCDD generates a wide spectrum of pathological findings which may resemble many diseases including minimal change NS, diabetic glomerulosclerosis, membranoproliferative GN, amyloidosis or nonspecific tubular atrophy with interstitial fibrosis (2). In my opinion, the most challenging is diagnosis of LCDD in patients with long-term diabetes, and also subtle and early cases which require use of a variety of diagnostic techniques. IF is highly sensitive and specific for diagnosis in the majority of cases. However, exceptional cases can be IF negative. In some instances, the light/heavy chains are so abnormal that the commercially available antibodies cannot detect them in deposits. ELMI is very helpful for diagnosis (3).

**Proliferative GN with monoclonal IgG deposits** represents a rare form of renal involvement associated with monoclonal gammopathy which mimics immune-complex GN. In a series of 37 patients analyzed by Nasr et al., the most common histological pattern was membranoproliferative GN, and at the time of presentation 49% had nephrotic syndrome, 68% had renal insufficiency, and 77% had hematuria (4). Deposits were detected in glomeruli by IF, and they showed IgG, C3, C1q positive staining and light chain restriction for kappa or lambda. In ELMI, the deposits were granular and localized mainly in the mesangium and in the subendothelial space. Monoclonal IgG3 was identified in the glomeruli of 2/3 of patients. Of the 4 subclasses of human IgG, IgG3 has the greatest complement-fixing capacity, which can activate complement cascade with inflammatory mediators and promote glomerular leukocyte infiltration and proliferation as the morphological features of glomerulonephritis.

**Light chain cast nephropathy (myeloma kidney).** The typical clinical presentation is acute renal insufficiency which can be precipitated by episodes of dehydration, infections, exposure to contrast media, or loop diuretics. In light microscopy, the typical morphological features are represented by refractile casts in the tubular system, most commonly in the distal tubules and collecting ducts. The casts are dense, eosinophilic and often fragmented with jagged edges. In addition, there is a reaction of the surrounding tubular cells and polymorphonuclears are often found around the casts. In practice, the number of casts may be quite variable in a biopsy specimen, and no guidelines exist which address how many tubular casts should be present to make such a diagnosis.

**Proximal tubulopathy (with or without Fanconi syndrome)** Light chain proximal tubulopathy associated with plasma cell dyscrasia is an uncommon entity (5). Two morphological patterns were recognized which correlate with the presence or absence of Fanconi syndrome. The presence of intracytoplasmic crystals in the proximal tubular cells was associated with Fanconi syndrome. In the non-Fanconi type, the cytoplasm of the proximal tubular cells may be granular and eosinophilic due to an abundance of lysosomes. The great majority of cases reported in the literature have been

associated with kappa light chains. Morphological features of the proximal tubular cells with abundant granular cytoplasm can be easily overlooked. On the other hand, early diagnosis is important because LC proximal tubulopathy is reversible when the secretion of LC s is suppressed.

#### **Patient's follow-up**

She was treated with 4 courses of chemotherapy (bortezomib, dexamethason and cyclofosamid) and her pulmonary and cardiac function returned to the normal range during 4 weeks of therapy. Her kidney function improved with a serum creatinine level of 70 $\mu$ mol/l (0.6mg/dl) and proteinuria of 0.7g/day. The serum  $\beta_2$  – microglobuline level decreased from 9.7 to 3.28mg/l.

The patient achieved partial remission with stable renal function, and she is preparing for autologous stem cell transplantation.

#### *References:*

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