中文題目：近端腎小管病變可以是原發性澱粉樣蛋白沈積症的表現

英文題目：Proximal renal tubulopathy can be a manifestation of AL amyloidosis

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***Introduction**:*

Light chain or primary amyloidosis is a rare disease caused by misfolded amyloid light chain (AL) protein deposition at extracellular spaces of systemic vital organs. The most frequent involved organs are the kidney and the heart. The common clinical manifestation of amyloidosis with kidney involvement is nephrotic syndrome; however, the association between amyloidosis and proximal renal tubulopathy is unclear. Here, we reported an amyloidosis patient presented with Fanconi syndrome, which is the demonstration of proximal tubulopathy.

Case presentation:

A 57-year-old, non-smoker female has a clinical history of hepatitis C virus (HCV) infection for 7 years with normal levels of liver function tests and abdominal echo serial follow-up revealed chronic liver parenchymal disease and normal kidney size. Before she got clinical symptoms, she had a level of 1.0-1.5 mg/dl of serum creatinine, 93-139 ml/min/1.73 m^2 of eGFR and negative for proteinuria by urine dipsticks. Foamy urine, urinary frequency and 2 + proteinuria of urine dipsticks had developed one month before she received HCV genotype 1b eradication with sofosbuvir and velpatasvir. After sustained viral response (SVR) achieved, which defined as HCV RNA undetectable 12 weeks post-therapy, her proteinuria deteriorated to the 2,009 mg/g of urinary total protein-to-creatinine ratio (UPCR, normal range < 150 mg/g). Additionally, the patient's laboratory test results (Table 1) showed 1.3 mg/dL of serum uric acid (UA, normal range 2.3-6.6 mg/dL in female), 2.7 mg/dL of serum phosphate (PO_4^{3-}, normal range 2.5-5.0 mg/dL), 10.1 mg/dL of serum calcium (Ca^{2+}, normal range 8.6-10.3 mg/dL), 4.7 g/dL of serum albumin level (normal range 3.5-5.7 mg/dL), 1.0 mg/dL of serum creatinine, 61 ml/min/1.73 m^2 of eGFR and complete blood count was within normal limits.

The results of biochemistry and gas analysis of serum and urine (Table 1) showed 16,694 ng/mL of urinary β2-microglobulin level (β2-M, normal range 0-300 ng/mL), normal serum anion gap (AG, 12.6 mEq/L) metabolic acidosis, normoglycemia with an elevated urinary glucose level (428 mg/dl), an elevated fractional excretion of phosphate ($F_EPO_4^{3-}$, 24.2%) and hypouricemia with an elevated fractional excretion of uric acid (F_EUA, 54.9%). All the results illustrated the Fanconi syndrome (proximal renal tubular dysfunction). Additionally, the testing results of positive urine anion gap (UAG, 22.92 mEq/L), lower urine osmolal gap (UOG, 65.78 mOsm/kg H_2O), lower estimated urinary NH_4^+ (32.89 mEq/L) and inadequate ability to acidify urine pH to below 5.5 (Table 1).

Immunology studies showed normal results for C3, C4, ANA, rheumatoid factor, antibodies against DNA, SSA/Ro and SSB/La and normal serum levels of IgG (1102.70 mg/dL), IgA (246.65 mg/dL), and IgM (101.58 mg/dL), which has a normal range of 700-1600, 70-400, and 40-230 mg/dL, respectively. Blood levels of heavy metals including lead, mercury, chromium, cadmium and copper were all within normal limits. There was neither concomitant Chinese herbal treatment nor history of familial disease. Although her serum protein electrophoresis (PEP) (Figure 1), urine PEP (Figure 2) and serum immunofixation electrophoresis (IFE) did not detect specific pattern of monoclonal gammopathy, urine IFE revealed the monoclonal kappa light chain (Figure 3). Abdominal fat pad biopsy and bone marrow trephine biopsy were performed. Eosinophilic amorphous substance was present in the dermis and subcutis of abdominal skin specimen and the Congo red stain exhibited apple-green birefringence under polarized light (Figure 4), which was consistent with amyloidosis. There was neither amyloid-like substance nor plasmacytosis in the bone marrow. The serum free light chain assay showed significant pathological levels of kappa (204 mg/L) and lambda (13.9 mg/L) free light chains with abnormal kappa/lambda ratio (14.68, normal range 0.26-1.65). Echocardiogram demonstrated a preserved left ventricular ejection fraction (LVEF) of 77 %. Cardiac biomarkers revealed 0.01 ng/mL of high sensitive troponin I level (normal range < 0.026 ng/mL) and 16 pg/mL of B-type natriuretic peptide (BNP, normal range < 100 pg/mL). Systemic evaluation did not discover autonomic nervous system, gastrointestinal tract or heart involvement. The patient had received melphalan and dexamethasone combination therapy for six months. Partial improvement in Fanconi syndrome was observed (Table 2). However, her hematologic and renal response of AL amyloidosis remained in stable disease.

Discussion:

AL amyloidosis is the most common type of systemic amyloidosis and the diagnosis requires histopathological amyloid tissue proof and demonstration of plasma cell dyscrasia. Fanconi syndrome can be linked to plasma cell dyscrasia, drug toxicity, autoimmune disorders, heavy metal intoxication, vitamin D deficiency or Chinese herbal nephropathy. Monoclonal gammopathy of plasma cell dyscrasia can be illustrated by the PEP, IFE of serum and/or urine plus abnormal serum free light chain ratio. Confirmation of systemic amyloid deposition is not necessary from the affected organ and specimens are mostly obtained from abdominal fat pad and the bone marrow biopsy. All clinical pictures established the diagnosis of systemic AL amyloidosis with kidney involvement and ruled out kappa light chain myeloma along with other etiologies of Fanconi syndrome.

Conclusion:

Systemic AL amyloidosis has various symptoms since the disease can involve multiple organs in the body. We reported a rare case of amyloidosis and proximal renal tubulopathy (Fanconi

syndrome) is an indication of diagnosis. AL amyloidosis and other plasma cell dyscrasias should be in the lists of clinical differential diagnosis of proximal renal tubular dysfunction. Fanconi syndrome, including hypouricemic hyperuricosuria, hyperphosphaturia, normoglycemic glucosuria, normal anion gap metabolic acidosis and an elevated level of urinary β2-microglobulin, can be the early clues of AL amyloidosis.