

# Myeloma-Associated Fanconi Syndrome Due to $\lambda$ -Light Chain Crystal Deposition

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**Multiple myeloma is uncommonly complicated with Fanconi syndrome, due to the deposition of light chains in renal tubular epithelial cells. A 76-year-old man with  $\lambda$ -Bence Jones type multiple myeloma had adult Fanconi syndrome. Electron microscopy showed that rhomboid, high-density substances of various sizes, were accumulated in the proximal tubular epithelial cells on renal biopsy. Immunoelectron microscopy demonstrated that these crystals were  $\lambda$ -light chains. The deposition of  $\kappa$ -light chain in patients with myeloma-associated Fanconi syndrome has been known. This is the 1st report showing the deposition of  $\lambda$ -light chain in renal proximal tubular epithelial cells.**

**Key words:** Fanconi syndrome; immunoelectron microscopy; multiple myeloma

Multiple myeloma is complicated with various renal disorders, and their onset closely involves the presence of immunoglobulin light chains. Fanconi syndrome, a renal disorder, is characterized by generalized aminoaciduria, hypophosphatemia, renal diabetes and metabolic acidosis, due to impaired reabsorption of various substances in the proximal renal tubules, which is thought to result from proximal renal tubular damage by light chain immunoglobulins (Orfila et al., 1991; Lajoie et al., 2000; Gu et al., 2003). There have been several reports on morphological changes in these proximal renal tubules, including electron-microscopic observations of crystalline structures in the cytoplasm (Costanza and Smoller, 1963; Maldonado et al., 1975; Thorner et al., 1983; Chan et al., 1987; Truong et al., 1989; Uchida et al., 1990; Yonemura et al., 1997; Marlowitz et al., 2000; Minemura et al., 2001). We recently

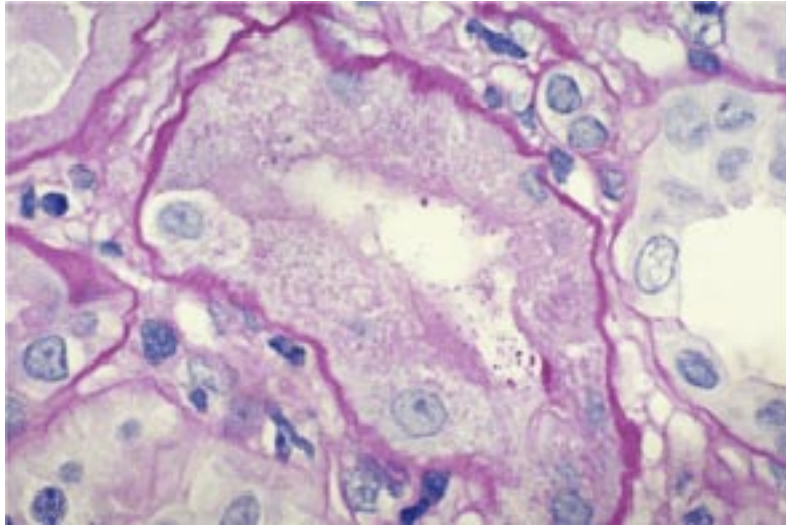
encountered a patient with Fanconi syndrome associated with  $\lambda$ -Bence Jones type multiple myeloma, and could demonstrate the deposition of  $\lambda$ -light chains in the proximal renal tubules by immunoelectron microscopy.

## Patient Report

A 76-year-old man sustained a fracture of the left femoral neck in March 1999. Admitted to a local hospital, he was diagnosed as having osteomalacia. Proteinuria was revealed on admission, and the reaction level gradually increased thereafter. In June 2002, the patient was referred and admitted to our University Hospital for further examination. He had a history of partial gastrectomy for stomach ulcer at 39 years of age.

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Abbreviations: FBS, fasting blood sugar; OGTT, oral glucose tolerance test



**Fig. 1.** Proximal tubular epithelial cells are swollen, containing numerous fine granules (periodic acid-Schiff stain) (original magnification,  $\times 1000$ ).

His blood pressure on admission was 140/84 mmHg, and his pulse rate was 52/min and regular. There were no abnormalities in the chest, abdomen and nervous system. In addition to pain in the back during movement, mild edema of the lower extremities was noted.

Laboratory findings were as follows: white blood cell count,  $4,100/\text{mm}^3$ ; Hb, 9.3 g/dL; hematocrit, 27.6%; platelet,  $14.8 \times 10^3 /\text{mm}^3$ ; Na, 147 mEq/L; K, 3.2 mEq/L; Cl, 122 mEq/L; Ca, 8.3 mg/dL; P, 2.2 mg/dL; blood urea nitrogen, 14 mg/dL; Cr, 1.66 mg/dL; uric acid, 1.6 mg/dL; total protein, 5.0 g/dL; albumin, 3.2 g/dL; alkali phosphatase, 1,413 IU/L; fasting blood sugar (FBS), 80 mg/dL; immunoglobulin G, 514 mg/dL; immunoglobulin A, 64 mg/dL; immunoglobulin M, 46 mg/dL;  $\lambda$ -Bence Jones protein, + (by protein fractionation and serum and urine immunoelectrophoresis); creatinine clearance, 30.2 mL/min and 75-g oral glucose tolerance test (OGTT), normal. Blood gas analysis revealed metabolic acidosis: partial pressure of  $\text{O}_2$ , 102.8 mmHg; partial pressure of  $\text{CO}_2$ , 38.1 mmHg; pH, 7.265; bicarbonate, 16.7 mmol/L and base excess,  $-9.1$  mmol/L.

Urinalysis showed 1+ for protein, negative for occult blood and 4+ for glucose. Taken together with the FBS and 75-g OGTT results, these findings suggested renal diabetes. Daily urinary protein excretion was 2.3 g, about 70% of which was Bence Jones protein. Urinary amino acid analysis showed generalized aminoaciduria. Calculated

tubular phosphate reabsorption was 28.5%, rate of bicarbonate excretion was 15.8% and fractional excretion of uric acid was 70.7%.

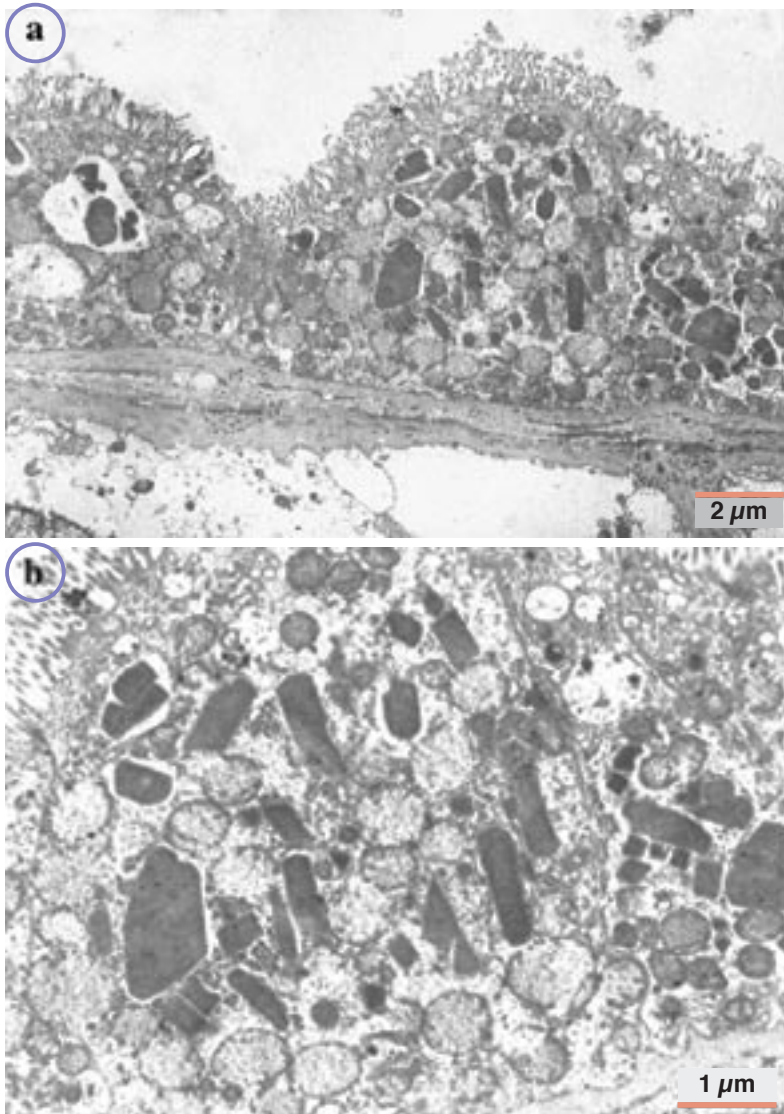
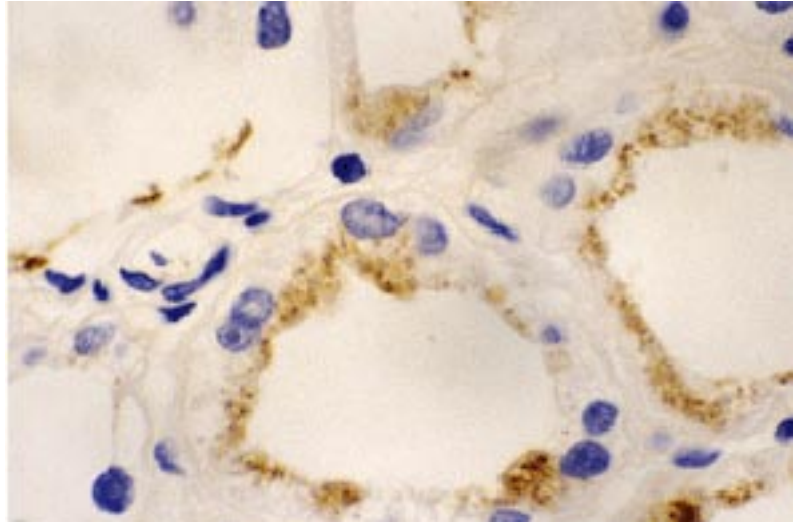
Bone marrow examination showed 22% plasma cells including markedly atypical, binucleate or vacuolated forms. These findings led us to a diagnosis of Fanconi syndrome associated with  $\lambda$ -Bence Jones type multiple myeloma.

Light microscopy showed no pathological changes in 35 renal glomeruli. Interstitial fibrosis and cell infiltration were noted in some areas, and proximal renal tubular cells were swollen, containing numerous fine granules (Fig. 1). No abnormalities were observed in the distal renal tubules. No amyloid deposition was found by Congo-red staining.

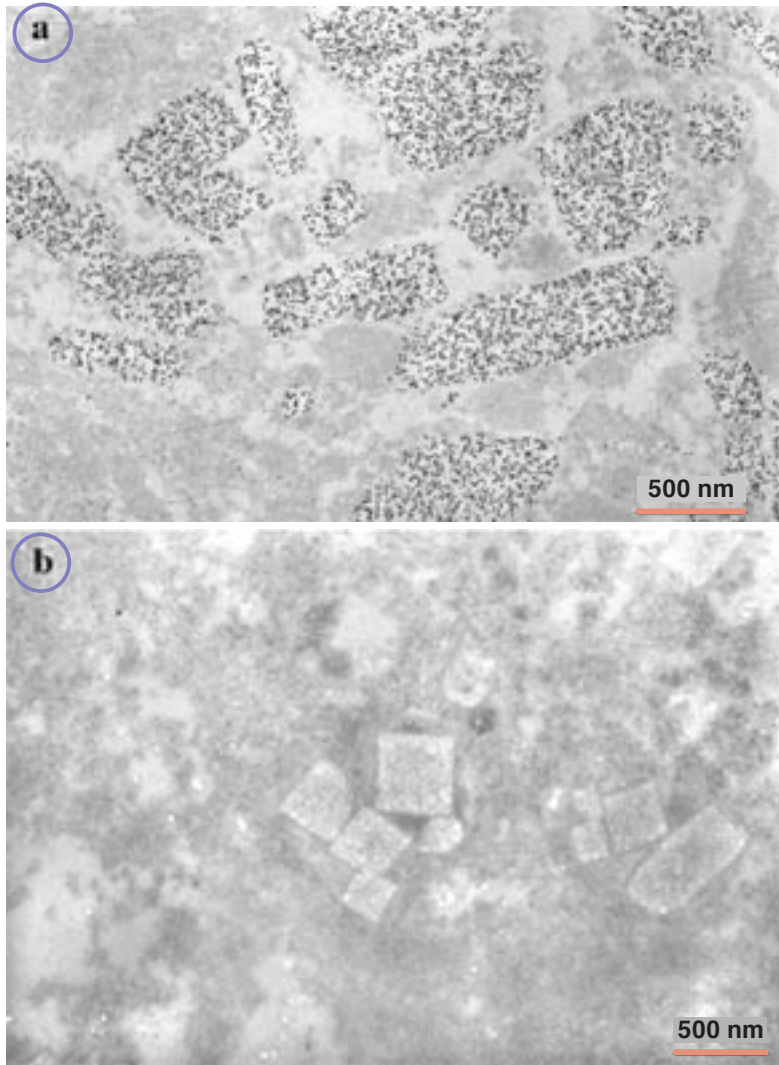
Immunofluorescence staining showed no deposits of immunoglobulins or complements. Immunoperoxidase staining demonstrated the presence of  $\lambda$ -light chains in the cytoplasm of proximal tubular epithelial cells (Fig. 2). No  $\kappa$ -light chains were present. There was no deposition of  $\lambda$ - or  $\kappa$ -light chains in the distal tubules.

Transmission electron microscopy showed that rhomboid, high-density substances of various sizes, partially enveloped in endoplasmic reticulum-like structures, were accumulated in the proximal tubular epithelial cells. The remaining organelles were decreased, for example mitochondria (Figs. 3a and b).

**Fig. 2.** Immunoperoxidase staining for  $\lambda$ -light chain shows positivity in the cytoplasm of proximal tubular epithelial cells (peroxidase-antiperoxidase stain) (hematoxylin counterstain,  $\times 1000$ ).



**Fig. 3.** Low- (a) and high-power (b) electron photomicrographs of proximal tubular epithelial cells. These cells contain a large number of crystals, several of which seem to be within membrane bound structures interpreted as phagolysosome.



**Fig. 4.** Immunoelectron micrographs for  $\lambda$  (a) and  $\kappa$  (b).  $\lambda$ -Light chain protein is demonstrated in these crystals by presence of electron-dense gold particles (a).  $\kappa$ -Light chain protein is not seen in crystals (b).

To demonstrate that these crystals were  $\lambda$ -light chains, we performed immunoelectron microscopic examination using anti- $\lambda$ - or anti- $\kappa$ -chain antibody as the primary antibody followed by the gold-labeled secondary antibody, and detected numerous  $\lambda$ -chains in the crystals, indicating that  $\lambda$ -chains were the main component of the crystals (Fig. 4a). No  $\kappa$ -chains were detected (Fig. 4b).

### Discussion

Sirota and Hamerman (1954) first reported that Fanconi syndrome complicated multiple myeloma. Although Fanconi syndrome occurs as an inherited or acquired disorder, few studies have reported

its association with myeloma (Matsuyama et al., 1994). Fanconi syndrome has been reported to be caused by  $\kappa$ -chains in a majority of patients (Costanza et al., 1963; Maldonado et al., 1975; Truong et al., 1989; Uchida et al., 1990; Yonemura et al., 1997; Isobe et al., 1998; Minemura et al., 2001) and by  $\lambda$ -chains in only 2 patients (Matsuyama et al., 1994; Marlowitz et al., 2000). Although the ratio of  $\kappa$ - to  $\lambda$ -light chains involved in the onset of multiple myeloma is 1.5:1,  $\kappa$ -chains cause Fanconi syndrome in an overwhelmingly large number of patients. To explain this observation, it has recently been postulated that changes in the V-domains of light chains are closely involved in their deposition in renal tubules, and that  $\kappa$ -chains frequently belong to a subgroup that is easily aggregated and



deposited (Aucoutrier et al., 1993; Matsuyama et al., 1994).

Some studies have reported that electron microscopic observation of proximal renal tubules demonstrates the presence of rhomboid- or needle-shaped crystals (Costanza et al., 1963; Maldonado et al., 1975; Thorner et al., 1983; Chan et al., 1987; Truong et al., 1989; Uchida et al., 1990; Yonemura et al., 1997; Marlowitz et al., 2000; Minemura et al., 2001). Also, a few studies have detected similar crystals in renal glomeruli or bone marrow plasma cells (Silva et al., 1983; Thorner et al., 1983). The shape of the crystals observed in the present patient was similar to that seen in  $\kappa$ -light chain myeloma, suggesting that there is no difference between the  $\kappa$ - and  $\lambda$ -light chains in the process of crystal formation or the mechanism of renal tubular damage.

Also, immunohistochemical studies have demonstrated the deposition of light chains in the proximal renal tubular epithelial cells (Uchida et al., 1990; Marlowitz et al., 2000; Minemura et al., 2001). However, since it was difficult to identify the light chains in the crystals by light microscopy, Truong et al. (1989) observed these crystals immunoelectron-microscopically, and showed that they were mainly composed of  $\kappa$ -light chains (Costanza and Smoller, 1963). Subsequently, Lajoie et al. (2000) made a similar report. We first demonstrated with immunoelectron microscopy that the main component of the crystals was  $\lambda$ -light chains. Because of the paucity of patients with  $\lambda$ -chain myeloma-associated Fanconi syndrome, only 1 such patient has been analyzed immunohistochemically (Marlowitz et al., 2000); thus, the present patient represents a valuable case.

Physical injury due to light-chain deposition, the toxicity of light chains themselves or chemical damage to renal tubules by lysosome enzymes during the catabolism of light chains in the proximal renal tubules has been implicated in the mechanism for the development of Fanconi syndrome as a complication of multiple myeloma (Orfila et al., 1991; Lajoie et al., 2000; Gu et al., 2003). In the electron microscopic images in this patient, the normal structure was so markedly destroyed by crystals composed of  $\lambda$ -chains that the crystals appeared to

cause direct physical injury, leading to tubular dysfunction. Further studies are necessary to find out whether these morphological changes are related to the clinical severity of the condition, and whether treatment can improve the tissue structure.

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