

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

Keitaro Noguchi, Chishio Munemura, Satoko Maeda, Satoru Yamamoto, Yoshikazu Murawaki, Toshiyuki Kaidoh\* and Shinichi Morino†

*Division of Medicine and Clinical Science, Department of Multidisciplinary Internal Medicine, \*Division of Morphological Analysis, Department of Functional, Morphological and Regulation Science, School of Medicine and †Laboratory of Electron Microscopy, Tottori University Faculty of Medicine, Yonago 683-8503 Japan*

**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

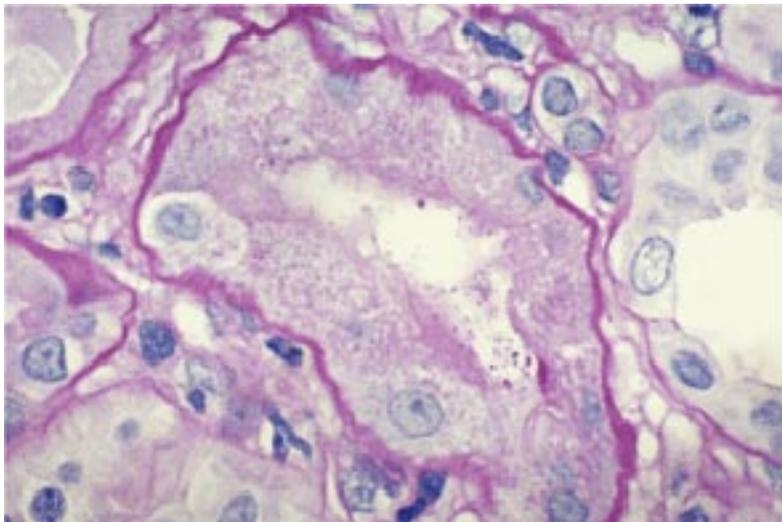
encountered a patient with Fanconi syndrome associated with  $\lambda$ -Bence Jones type multiple myeloma, and could demonstrate the deposition of  $\lambda$ -light chains in the proximal renal tubules by immunoelectron microscopy.

## 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%.

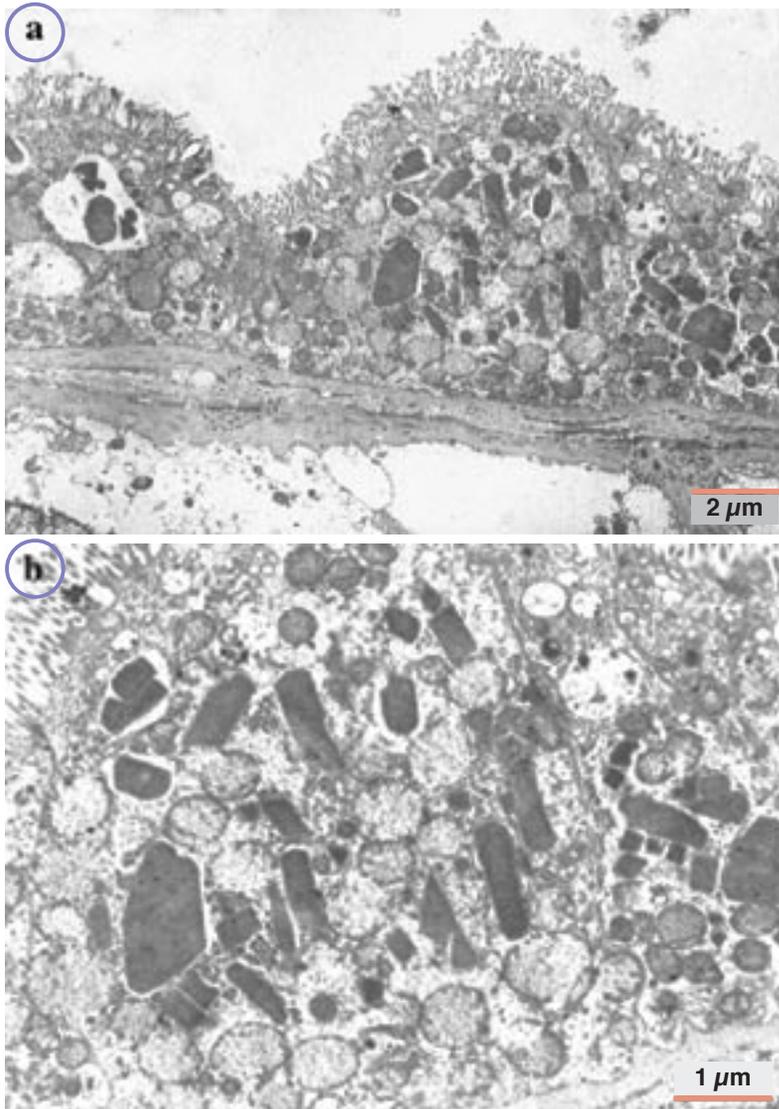
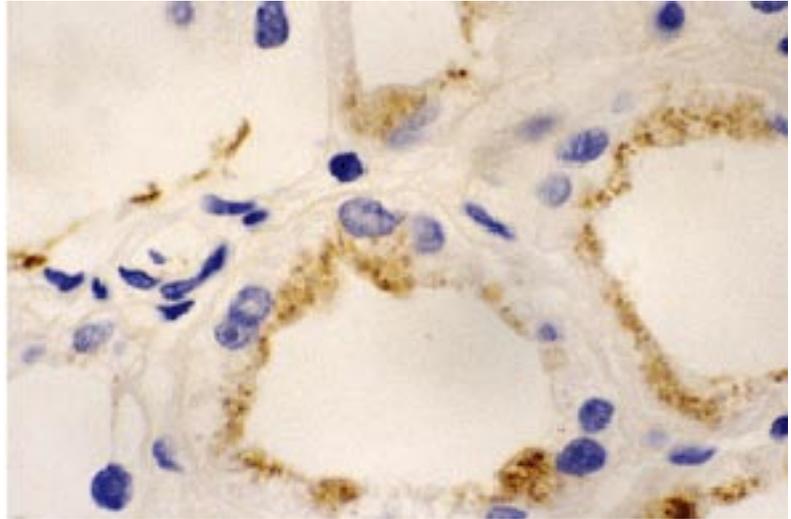
Bone marrow examination showed 22% plasma cells including markedly atypical, binucleate or vacuolated forms. These findings led us to a diagnosis of Fanconi syndrome associated with  $\lambda$ -Bence Jones type multiple myeloma.

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.