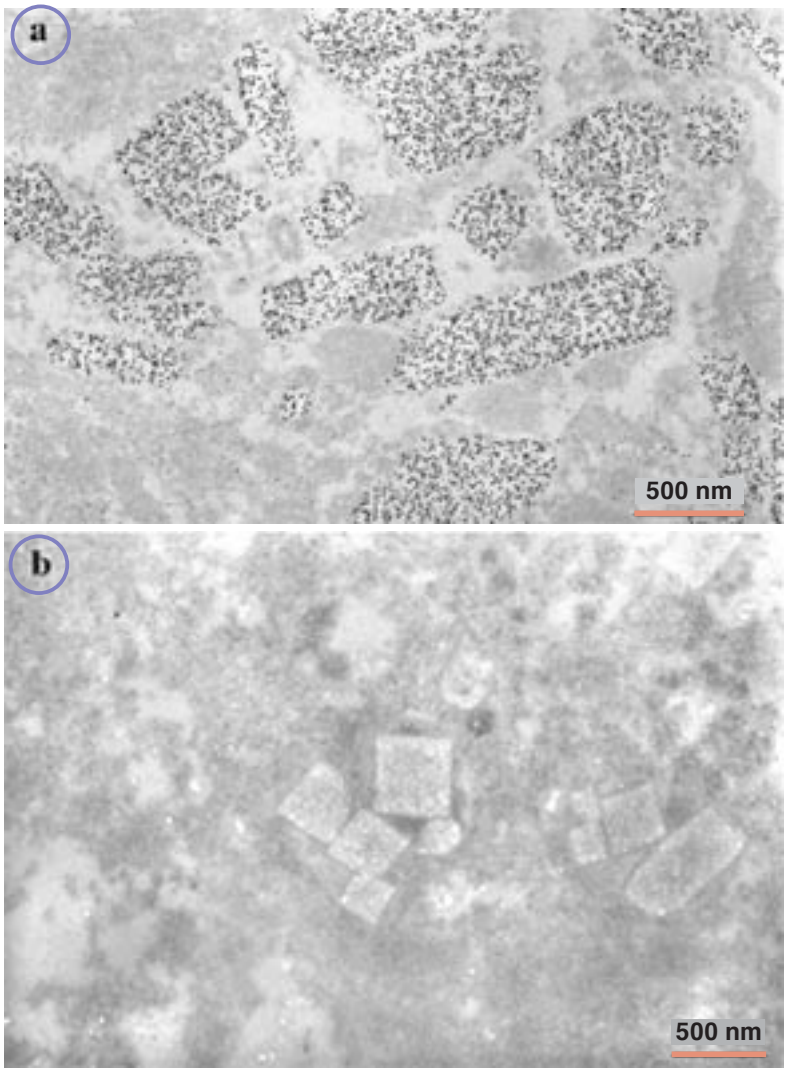

Fig. 4. Immunoelectron micrographs for λ (**a**) and κ (**b**). λ-Light chain protein is demonstrated in these crystals by presence of electron-dense gold particles (**a**). κ-Light chain protein is not seen in crystals (**b**).

To demonstrate that these crystals were λ-light chains, we performed immunoelectron microscopic examination using anti-λ- or anti-κ-chain antibody as the primary antibody followed by the gold-labeled secondary antibody, and detected numerous λ-chains in the crystals, indicating that λ-chains were the main component of the crystals (Fig. 4a). No κ-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 κ-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 λ-chains in only 2 patients (Matsuyama et al., 1994; Marlowitz et al., 2000). Although the ratio of κ- to λ-light chains involved in the onset of multiple myeloma is 1.5:1, κ-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 κ-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 κ-light chain myeloma, suggesting that there is no difference between the κ- and λ-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 κ-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 λ-light chains. Because of the paucity of patients with λ-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 λ-chains that the crystals appeared to cause direct physical injury, leading to tubular dysfunction. Further studies are necesary 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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