Nephrotic Syndrome Associated with Recombinant Interleukin-2

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Dear Sir,

Adoptive immunotherapy using recombinant interleukin-2 (rIL-2) has recently been demonstrated to have antitumor effects in man. Adverse effects have included an apparent increase in capillary permeability (vascular leak syndrome) and a decrease in glomerular flow rate [1, 2]. To our knowledge, nephrotic syndrome (NS) associated with rIL-2 has not been reported. We would like to report a case of NS with human rIL-2 treatment.

An 81-year-old woman was treated with human rIL-2 for a recurrence of malignant hemangioepithelioma. The diagnosis was first established in March 1984 after skin biopsy of a purpuric mass on the forehead. Initially she was treated with electron beam radiation (total 8,000 rad) and adriamycin (30 mg, 2 times intravenously) between March 23 and May 18, 1984. In April 1988, purpura recurred in the jaw. Despite of electron beam radiation therapy (total 11,600 rad) from July 15 to September 4, 1988, her purpura extended progressively. After obtained informed consent, human rIL-2 therapy (molecular weight 15,000 and isoelectric point 7.7, Takeda Chemical Industries, Japan) was started. She received a daily dose of 500 units rIL-2 intravenously beginning on September 5, 1988, and the dose was increased to 1,500 units/day. The maintenance therapy (1,500 units 3 times a week) was instituted. Later on, her condition was maintained with normal levels of serum albumin and creatinine without proteinuria. After the 16th week of rIL-2 therapy urinary frequency developed and edema ensued. Urinalysis revealed only a few white blood cells per high-power field but gave 3 + proteinuria. Marked proteinuria (more than 3.5 g/24 h with approximately 86% albumin) persisted and serum albumin fell to 2.6 g/dl. Her white blood cell count was 4,800/mm³ with 38% eosinophils. The level of serum creatinine was 1.2 mg/dl (fig. 1). The result of serum immunoelectrophoresis was normal and the titer of serum antinuclear antibody was less than 1:20. The concentrations of C3 and C4 were normal and the Clq-binding assay for circulating immune complexes disclosed a negative result. Anti-interleukin-2 antibodies could not be detected. Following the discontinuation of rIL-2 therapy, her proteinuria and edema subsided. Serum albumin reached a level of 3.4 g/dl by the end of the 4th week. She is currently in remission of her NS and her purpura has not got

larger. The patient continued to be treated with indomethacin (25–50 mg/day) for lumbago both during the nephrotic and the remission phases.

Nonsteroidal anti-inflammatory drugs have been known as a cause of NS, but the proteinuria in our patient disappeared despite the continued treatment with indomethacin. Endogenous antigen released by the tumor might also contribute to the development of NS. Although we could not reveal her renal pathology, we thought that the NS seemed to be related to rIL-2 therapy because the proteinuria disappeared with no additional therapy after the discontinuation of rIL-2. Lane et al. [3] reported that 1 out of 12 patients with acquired immunodeficiency syndrome treated with rIL-2 developed proteinuria. The mechanisms by which rIL-2 induces proteinuria remain unclear. Kawaguchi et al. [4] suggested that protein excretion might be increased by means of reduction of anionic sites after administration of a massive dose of human rIL-2 (1.7 x 10⁶ units) in rats. Cotran et al. [5] suggested that rIL-2 therapy might stimulate endogenous production of other lymphokines and monokines, and these in turn served as a stimulus for activation of endothelial cells, which resulted in vascular leakiness to macromolecules. And also, Averbuch et al. [6] reported a case of NS occurring during therapy with recombinant leukocyte A interferon. In minimal change NS, mononuclear cells were reported to release a factor which caused changes in glomerular permeability [7]. Thus, rIL-2 in our patient might have an effect on glomerular permeability directly or indirectly, resulting in proteinuria and hence NS. Further studies should follow.

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Hisanaga/Kawagoe/Yamamoto/Kuroki/Fujimoto/Tanaka/Kurokawa
rIL-2 therapy

1500 U x 3/week

Indomethacin 25–50 mg/day

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Serum creatinine, mg/dl 1.0

Urinary protein

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Edema

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Fig. 1. Clinical course in a patient with malignant hemangioepithelioma treated with rIL-2.

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