Nephrotic Syndrome Developed in a Patient with Acute Promyelocytic Leukemia Treated with Daunomycin

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Dear Sir,

Nephrotic syndrome (NS) is an unusual but well-recognized complication of malignant diseases [1,2]. Among the hematological neoplasms, lymphocytic leukemia and lymphoma have a known association with NS, while its occurrence in the acute myelogenous leukemia (AML) appears to be exceedingly rare [2]. To the best of our knowledge, there have been only two reports in the literature [3, 4]. We report here a case of acute promyelocytic leukemia (APL) associated with NS. The development of NS was coincidental with the administration of chemotherapy in this case.

A 32-year-old Japanese woman presented at our hospital with progressive fatigue and gingival bleeding which had developed 2 weeks earlier. Until then she had been in excellent health with no history of renal disease or drug exposure. The physical examination was normal except for anemic conjunctiva and purpuric lesions scattered on the upper chest. The hematocrit was 21.4%, WBC $34.1 \times 10^9/l$ with 12% blast cells and 70% promyelocytes, and the platelet count was $22 \times 10^9/l$. Coagulation studies demonstrated that the patient had disseminated intravascular coagulation (DIC). Urinalysis showed trace amounts of protein, and the sediment was normal. Serum albumin was 4.5 g/dl, urea nitrogen 16.3 mg/dl, and creatinine 0.6 mg/dl. The bone marrow aspirate showed increased cellularity with 13.2% myeloblasts and 82.4% promyelocytes. The

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Fig. 1. a Light micrograph of a glomerulus showing minor abnormalities. HE. $\times 200$. b Electron micrograph showing widespread detachment of epithelial cells from GBM. $\times 8,000$.

Serum albumin was 3.0 g/dl on the 15th hospital day. Thus, the patient developed NS during the course of chemotherapy for APL. Anticoagulant therapy had little effect on her severe DIC, and the patient died on the 16th day because of massive hemorrhage into both lungs.

Histopathological studies on the kidney were obtained at autopsy, and revealed minor glomerular abnormalities (fig. 1a). The capillary lumen was patent, and there was no evidence of intravascular coagulation in the glomerulus. Immunofluorescence diagnosis of APL associated with DIC was made, and BHAC-DMP therapy (BHAC 300 mg/day, DNR 60 mg/day, 6-MP 50 mg/day, prednisolone 30 mg/day) was administered from the 1st to the 8th hospital days. On the 5th hospital day, moderate proteinuria (1.05 g/day) was noted. Urinary protein excretion was increased on the 13th hospital day (9.38 g/day), and reached 17.5 g/day on the 15th hospital day. The albumin/total protein ratio in the urine was 53%, indicating the poor size selectivity of proteinuria.

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Immunofluorescence studies revealed no deposits of immunoglobulin or complement in the glomeruli. As shown in figure 1b, however, a striking feature was the detachment of the epithelium from the glomerular basement membrane (GBM). Such alterations were widely distributed and associated with the swelling of endothelial cells.

While a chance association between NS and leukemia cannot be excluded in the present case, the temporal relationship between the chemotherapy and the development of NS raises the possibility of a role of antileukemic drugs in the renal injury. Among the cytotoxic drugs used to treat patients with AML, anthracyclines are of special interest, since a single injection of adriamycin or daunomycin into rats induces a nephropathy characterized by massive proteinuria with NS [5, 6]. While the mechanism of anthracycline-induced NS in rats is unknown, Whiteside et al. [6] showed that

epithelial detachment from GBM was associated with the development of massive proteinuria in adriamycin nephrosis. In this regard, it is intriguing that the prominent histologic feature in our patient was the widespread detachment of epithelial cells from the GBM. As pointed out by Thompson et al. [4], however, the dose of daunomycin used for treatment of leukemia is generally lower than that administered to rats to induce NS. Moreover, the extremely low number of reported cases makes it difficult to establish a definite cause-and-effect relationship between daunomycin and NS in human beings. Nevertheless, the structural alteration of epithelial cells observed in our case would be enough to account for protein leakage to nephrotic levels. Poor size selectivity of protein excretion in the urine is a point in favor of such structural damage. Thus, a causative role of daunomycin cannot be excluded in the present case.

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