HLA Class II Display by Circulating T Lymphocytes in Nonsteroidal Anti-Inflammatory Nephritis Induced by Drugs

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CD11b, and moreover, stained by 12 or 13 antibodies. Therefore, the renal interstitium was infiltrated by cytotoxic T cells expressing HLA class II antigen. Consequently, prednisolone treatment was started with 30 mg per day. After 2 weeks of prednisolone therapy, blood urea nitrogen and creatinine levels returned to normal, being 19 and

Dear Sir,

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported increasingly as causes of renal dysfunction [1-3]. In spite of the abundant clinical data available to characterize the natural history of nephritis with or without nephrotic syndrome, there has been limited information concerning immunopathogenic mechanisms [4].

Renal biopsies performed by several groups have demonstrated a predominance of cytotoxic T cells in the interstitium [5, 6], while some biopsies taken early in the acute phase have shown significant infiltration by helper T cells [7]. Even when the predominant lymphocyte subset expressed in the interstitium has varied among groups, it has been speculated that cell-mediated immune mechanisms may be involved in the pathogenesis of NSAID-induced interstitial nephritis.

We had a 56-year-old male manifesting an acute renal failure without the nephrotic syndrome. He had taken diclofenac sodium 200-300 mg daily in the past 4 weeks because of persistent shoulder pain. On admission, blood urea nitrogen was 36 mg/dl, and serum creatinine was 2.6 mg/dl. A first renal biopsy was performed in the 4th week of hospitalization (fig. 1) to determine the indication of steroid treatment for the persistent renal dysfunction. It revealed interstitial nephritis, and the lymphocyte subpopulations within the interstitial inflammatory infiltrates confirmed that, in good accordance with previous reports [5, 6], 90% of them were T cells with a CD4+/CD8+ ratio of 1:4. These CD8+ cells were also positive to

Fig. 1. Percentage distribution of expression of HLA class II in T cells. 12 = (I2+)-CD 19+; 13 = (I3+)-CD 19+; M = control

mean value of (I2+)-(CD19+); ■ = control mean value of (I3+)-(CD19+). Steroid dose (prednisolone) started at 30 mg daily and decreased as follows: 20 mg daily, 20 mg every other day, 10 mg every other day.

1.2 mg/dl, respectively. At this point, a second biopsy still demonstrated mild interstitial infiltration of T cells, but the CD4+/CD8+ ratio improved to 1:1. In addition, no infiltrating cell was positive to CD 11b, 12, or 13 antibodies.

The circulating lymphocyte responses during the process of interstitial nephritis

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Table 1. Positive percentage of monoclonal antibodies in peripheral blood after the 4th week of hospitalization (= week 0 of steroid treatment)

have been rarely focused on [8]. Interestingly, before prednisolone therapy, the immunological characterization of circulating lymphocytes was similar with that of renal interstitium. That is, the CD4+/CD8+ ratio was low and 12 or 13 positive cells were increased (table 1). However, the distribution of HLA class II antigen in the peripheral blood involves not only activated T cells but also B cells [9]. In order to estimate the approximate percentage of HLA-class-II-positive activated T cells, the quantity of CD19 positive cells, the B-cell-associated monoclonal antibody, was subtracted from that of 12+ or 13+. Although no significant alterations were observed in B cells, the percentage of both, (I2+)-(CD19+) and (I3+)-(CD19+), was noticeably increased (fig. 1). According to steroid-induced clinical remission, activated CD8+ T cells expressing 12 or 13 antigen gradually disappeared from the peripheral blood.

Both T and B cell activation in the local lymphoid tissue was reported following organ transplantation, and activated T cells enter the graft from the blood [10]. Therefore, peripheral lymphocyte subsets in this case might demonstrate that activated T cells, but not B cells, recognize the interstitial damage produced by nonimmune causes, including NSAIDs, and modulate consequent immune processes. Involvement of other factors including renal prostaglandin synthesis inhibition [11] was not yet neglected, and further studies will be necessary to show differences from other causes of interstitial nephritis. Nonetheless, the findings of the present case raise the possibility that cell-mediated immunity plays a role in the pathogenesis of NSAID-induced interstitial nephritis.

References

- Garella S: Drug-induced renal disease. *Hosp Pract* [Off J] 1993;28:129-140. Fries JF, Williams CA, Bloch DA: The relative toxicity of nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 1991;34:1353-1360. Welton A, Hamilton CW: Nonsteroidal antiinflammatory drugs. Effect on kidney function. *J Clin Pharmacol* 1991;31:588-598. Meyers CM, Kelly CJ: Immunopathogenic mechanisms of interstitial nephritis; in Pusey CD (ed): *Immunology of Renal Diseases*. Dordrecht, Kluwer Academic Publishers, 1991, pp 271-288. Stachura I, Jayakumar S, Bourke E: T and B lymphocyte subsets in fenoprofen nephropathy. *Am J Med* 1983;75:9-16. Bender WL, Whelton A, Beschoner WE, Darwish MO, Hall-Craggs M, Solez K: Interstitial nephritis, proteinuria, and renal failure caused by nonsteroidal antiinflammatory drugs. *Am J Med* 1984;76:1006-1012.

Cheng HF, Nolasco F, Cameron JS, Hidreth G, Neild GH, Hartley B, Neill G: HLA-DR display by renal tubular epithelium and phenotype of infiltrate in interstitial nephritis. *Nephrol Dial Transplant* 1989;4:205-215. Watson AJ, Dalbow MH, Stachura I, Fragola JA, Rubin MF, Watson RM, Bourke E: Immunologic studies in cimetidine-induced nephropathy and polymyositis. *N Engl J Med* 1983;308: 142-145.

Yamada Y, Kanbayashi H, Endo Y: A study of differential expression of HLA class II antigens in human lymphocytes. *Jpn J Clin Pathol* 1991; 39:379-382.

Mann R, Zakheim B, Dayman M, McCafferty E, Michaud L, Nelson EG: Murine interstitial nephritis. Long term cultured L3T4+ T cell lines transfer delayed expression of disease as I-A-restricted inducers of the effector T cell repertoire. *J Immunol* 1985;135:286-293. Murray MD, Brater DC: Renal toxicity of the nonsteroidal anti-inflammatory drugs. *Annu Rev Pharmacol Toxicol* 1993;33:435-465.

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Circulating Lymphocyte Subsets in the Interstitial Nephritis Induced by Diclofenac Sodium