Case Report

Tubulointerstitial Nephritis and Uveitis Syndrome in Two Siblings

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TANAKA, H., WAGA, S., NAKAHATA, T., SUZUKI, K., ITO, T., ONODERA, N., IWAMI, S., MONMA, N. and ITO, E. Tubulointerstitial Nephritis and Uveitis Syndrome in Two Siblings. Tohoku J. Exp. Med., 2001, 194 (1), 71–74 — Two Japanese sisters with persistent uveitis showed significant increased levels of urinary β-2 microglobulin. A percutaneous renal biopsy performed in the younger sister revealed tubulointerstitial nephritis (TIN) with helper/inducer T cell infiltrates. Also, abnormal 67-gallium accumulation in the kidneys, suggesting TIN, was observed in the other one at the same time. Although patients with the syndrome of tubulointerstitial nephritis and uveitis (TINU) have been reported to date, its occurrence in siblings has rarely been seen. Both of them shared same human leukocyte antigen (HLA) DR6, suggesting the potential association between HLA-DR6 and TINU. ——— helper/inducer T cell infiltration; HLA-DR6; siblings; tubulointerstitial nephritis and uveitis syndrome; urinary β-2 microglobulin

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The tubulointerstitial nephritis and uveitis syndrome (TINU) is characterized by the association of idiopathic tubulointerstitial nephritis and concomitant uveitis. It was first described as a new syndrome in 1975 by Dobrin et al. (1975). Thereafter, similar cases had been reported by the name of TINU. However, its occurrence is still uncommon in children and adolescents (Morino et al. 1991; Yoshioka et al. 1991; Igarashi et al. 1992; Takemura et al. 1999; Vohra et al. 1999). We too encountered two female siblings with TINU. So far it has rarely been reported regarding TINU in siblings (Morino et al. 1991).
CASE REPORTS

Patient 1

A Japanese girl aged 11.5 years with a month history of anterior uveitis in the right eye was referred to our hospital because of suspicion of having a systemic disease. She had no history of exanthema, arthralgia, fever of unknown origin or disabilities. Despite administration of topical steroids, the uveitis persisted.

Although physical examination and chest x-ray were unremarkable, urinary \( \beta_2 \)-microglobulin (\( \beta_2 \)MG) increased to 5205 \( \mu \)g/liter (normal < 150 \( \mu \)g/liter). Urinalysis showed a specific gradient of 1.020, pH 6.5, protein 28 mg/100 ml, erythrocyte sediments 5/high powered field (HPF), leukocyte sediments 30/HPF without eosinophils and a sterile culture. Serum creatinine was 0.8 mg/100 ml. Laboratory tests revealed no abnormal findings. Serum immunoglobulins were as follows: IgG, 1630 mg/100 ml; IgA, 273 mg/100 ml; IgM, 171 mg/100 ml and IgE, 15 U/ml. Neither hypocomplementemia nor anti-nuclear antibody (ANA) were present. T cell subset in peripheral blood were as follows: CD4, 49.8%; CD8, 18.3% and CD4: CD8 ratio 2.72. Creatinine clearance was 93.1 ml/minutes.

A percutaneous renal biopsy was performed with taking the informed consent from the patient's parents. Portions of 7 glomeruli were seen by light microscopy of periodic acid-Schiff-stained sections. Glomeruli showed only a mild mesangial hypercellularity. There were mononuclear cell infiltrates associated with focal tubular atrophy in the interstitium (Fig. 1). No polymorphonuclear cells or eosinophils were observed. Immunofluorescence showed no evidence of immune complex deposition. Electron microscopy showed no electron dense deposits. Thus, the diagnosis of TINU was made. The mononuclear cells infiltrating the interstitium were characterized by enzyme immunohistochemistry using monoclonal antibodies (i.e., CD3, pan T cells; CD4, helper/inducer T cells; CD8, suppressor/cytotoxic T cells, CD11c, monocytes/macrophages; CD20, pan B cells). We observed that helper/inducer T cells (CD3- and CD4-positive cells) were prominent. No B cells or suppressor/cytotoxic T cells were observed.

Because no causative events for tubulointerstitial nephritis (TIN), such as drugs or infection, had not been documented during the clinical course of uveitis, the diagnosis of TINU was made. Then, she was observed closely with topical steroids administration. Although urinary \( \beta_2 \)MG fluctuated ranging from 751 \( \mu \)g/liter to 2518 \( \mu \)g/liter, she did not

Fig. 1. Marked mononuclear cell infiltration and focal tubular atrophy in the interstitium. Glomeruli showed mild mesangial hypercellularity (periodic acid-Schiff stain, \( \times \) 200).
complain of any disabilities. The uveitis gradually subsided. Serum creatinine remained within the normal values during the clinical course. Urinary $\beta_2$MG showed a tendency to decrease without medication.

**Patient 2**

A Japanese adolescent aged 17.5 years and the elder sister of Patient 1, referred to our hospital because her younger sister had been diagnosed as having TINU. Since a year before, she had been treated with topical steroids administration for the bilateral persistent uveitis. However, she had no history of exanthema, arthralgia, fever of unknown origin or disabilities.

Physical examination and chest x-ray were unremarkable. Urinalysis showed a specific gradient of 1.015, pH 7.5, protein 12 mg/100 ml, erythrocyte sediments 0/HPF, leukocyte sediments 4/HPF without eosinophils and a sterile culture. Laboratory tests except for urinary $\beta_2$MG revealed no abnormal findings. Serum creatinine was 0.6 mg/100 ml. Neither hypocomplementemia nor ANA were present. Urinary $\beta_2$MG increased to 437 $\mu$g/liter. A 67-gallium scintigram for tubulointerstitial lesion (Shibasaki et al. 1991) performed at the initial presentation disclosed a mildly increased accumulation in both kidneys. Because no causative events for TIN had not been documented during the clinical course of uveitis, she was observed closely under the diagnosis of possible TINU. Urinary $\beta_2$MG fluctuated ranging from 179 $\mu$g/liter to 397 $\mu$g/liter following the next 6 months. Because of a mild increase in the levels of urinary $\beta_2$MG, a percutaneous renal biopsy was not done.

Thereafter, she did not complain of any disabilities, and the uveitis gradually subsided. Serum creatinine remained within the normal values during the clinical course.

**Human leukocyte antigen (HLA) of the patients**

Evaluation of HLA-DR antigens of the patients revealed DR6 and DR9 in Patient 1, and DR4 and DR6 in Patient 2, respectively.

**DISCUSSION**

Although the cause of TINU remains to be elucidated, it is assumed to be a systemic disease associated with alteration in cell-mediated immunity (Yoshioka et al. 1991; Gafter et al. 1993; Vohra et al. 1999). Of the immunohistological studies in TINU patients, it has been reported that the interstitial infiltrating cells are mainly suppressor/cytotoxic T cells associated with monocytes/macrophages to date (Yoshioka et al. 1991; Kobayashi et al. 1998; Takemura et al. 1999). However, Yano et al. (1991) reported a case of TINU with prominent helper/inducer T cells subset infiltrates.

In our patient, the interstitial infiltrating cells were mainly helper/inducer T cells subset. It has been reported that no relationship is found between the duration from the onset of the disease to renal biopsy and the interstitial mononuclear cell involvement (Kobayashi et al. 1998). Further, we observed recently a TINU patient who showed persistent helper/inducer T cells involvement over 6 months, which was confirmed by the repeated renal biopsies (unpublished data). These observations suggest that the infiltrating T cells subset in a proportion of TINU patients may not show a transition with time. Hence, it is considered that heterogeneity regarding the interstitial infiltrating T cells subset may exist in TINU patients. Further studies regarding infiltrating T cells in TINU patients should be done.

So far Gafter et al. (1993) reported a high frequency of HLA-DR6 antigen in TINU patients. However, to the best of our knowledge, no sibling cases have been reported in the literature except for a report described by Morino et al. (1991). Although they described two female Japanese siblings with acute TIN, uveitis occurred in only one of them during the clinical courses. In contrast, both of our patients showed persistent uveitis concomitant
increased levels of urinary β₂MG, and one of them (Patient 1) showed biopsy-proven TIN. Because 67-gallium scintigram has been reported as a useful examination in the acute stage of TIN in order to see interstitial cell infiltration (Shibasaki et al. 1991), the abnormal 67-gallium accumulation in the kidneys as well as the increased levels of urinary β₂MG in Patient 2 strongly suggested that she had TIN at the initial presentation.

Although complete evaluation of HLA in the present cases were not done, both of them shared same HLA, DR6, as in the previous report (Gafer et al. 1993). It has been reported that pathogenesis of TINU might be associated with certain HLA haplotypes in a proportion of patients (Morino et al. 1991; Gafer et al. 1993). Further studies are needed to ascertain the potential association between HLA and TINU in the future.

Takemura et al. (1999) reported that long-term outcome of TINU patients is favorable. In our patients, increased levels of β₂MG and uveitis seemed to subside spontaneously with time, suggesting a favorable outcome without systemic corticosteroids administration (Takemura et al. 1999). However, Kobayashi et al. (2000) reported recently that TINU patients required a longer period of time for the improvement. Thus, careful follow-up and close observation are warranted to confirm long-term outcome of our patients.

References


