Cytokine dynamics in a 14-year-old girl with tubulointerstitial nephritis and uveitis syndrome

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Abstract Tubulointerstitial nephritis and uveitis (TINU) syndrome, which was first described in 1975, has been reported in more than 130 patients, mostly in adolescent or young women. Although data concerning the etiologic background of this inflammatory disease are limited, several humoral factors, including cytokines, have been reported in association with the disease. Here, we report a case of TINU in a 14-year-old girl, whose renal and ophthalmological improvement was associated with the decrease of serum levels of tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), and interleukin-8 (IL-8). This suggests the presence of T-cell-mediated immunity in this unique syndrome.

Keywords Cytokine dynamics · TINU · TNF- α · IFN- γ · IL-8

Introduction

Tubulointerstitial nephritis and uveitis (TINU) syndrome was first described in 1975 by Dobrin et al. [1] by presenting two adolescent female patients with acute eosinophilic interstitial nephritis, anterior uveitis, and non-caseating granulomas in the bone marrow and lymph nodes.

Although data concerning the etiologic background of TINU were limited [2], several factors have been proposed as candidate molecules involved in the pathogenesis of TINU syndrome [3–5]. Tanaka et al. [6] suggested that T-lymphocytes were involved in the pathogenesis of TINU syndrome, because the majority of cells that infiltrated the interstitium of the kidneys were T-lymphocytes. Considering the role of T-lymphocytes in cytokine-mediated allergic reactions [7], some cytokines can naturally be a promising class of candidate molecules that might be involved in the pathogenesis of TINU syndrome [5]. Thus, it should be of value to investigate the dynamics of cytokines produced by T-cells in patients with TINU syndrome.

To the best of our knowledge, this is the first report to describe the dynamics of the cytokines produced by T-cells in a patient with TINU syndrome. We selected three cytokines, tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), and interleukin-8 (IL-8), all of which were related to T-cell activation [8–10], and IFN- γ was shown to have effects on patients with non-infectious uveitis [11].

Case report

A 14-year-old girl was referred to our hospital with a 1-month history of mild proteinuria and a 4-month history of weight loss (5 kg). She had no family history of renal diseases or autoimmune diseases. She had noticed progressive visual impairment over the year prior to admission without associated blurred vision, photophobia, or ophthalmalgia.

Her physical examination showed a height of 156.3 cm, weight of 45.3 kg, and blood pressure of 106/68 mmHg. There was no systemic edema. Her bulbar conjunctivas

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were inflamed. A slit-lamp examination showed keratic precipitates on the left side. A chest X-ray examination showed no infiltrative shadows. The laboratory data were as follows: no evidence of pancytopenia, serum C-reactive protein (CRP) 0.7 mg/dL, serum creatinine (s-Cr) 0.8 mg/dL, serum albumin (s-Alb) 3.7 g/dL, serum calcium 9.5 mg/dL, serum angiotensin-converting enzyme (ACE) 12.2 mU/mL, IgG 1991 mg/dL, bicarbonate 23.2 mmol/L, erythrocyte sedimentation rate 46 mm/h, serum complement component 3 186 mg/dL, complement component 4 35 mg/dL, and 50 % hemolytic unit of complement level 59.5 U/mL. Immunological studies including anti-streptolysin O, anti-neutrophil cytoplasmic antibodies, hepatitis B virus, hepatitis C virus antigens, cryoglobulin screening test, anti-double-stranded DNA IgG antibody, anti-Sjögren's syndrome A antibody, and anti-Sjögren's syndrome B antibody were all negative. Urinalysis showed an elevated urinary β_2 -microglobulin (U- β_2 MG) of 9,762 μ g/L, non-nephrotic proteinuria (0.24 g/day), and normoglycemic glycosuria. A renal biopsy showed mononuclear cell infiltration in the renal tubules and interstitium (Fig. 1), normal glomeruli, and no tubulointerstitial fibrosis or tubular atrophy. The fluorescent antibody stainings for IgG, IgA, IgM, C3, and C4 were negative.

The patient was diagnosed with TINU syndrome. She was treated for left anterior uveitis with eye drops that contained steroids and an anticholinergic agent without systemic treatments since day 7. Though she had no aggravation of subjective symptoms, uveitis was exacerbated bilaterally on day 28. Uveitis was recovering gradually with topical treatment and cured on day 84 (Fig. 2).

We examined serum cytokine levels using the BioPlex® multiple suspension array system (Bio-Rad).

Fig. 1 Mononuclear cells (arrows) infiltrated in renal tubules and the interstitium

The results of the cytokine studies are shown in Fig. 2. Elevated serum TNF- α , IL-8, and IFN- γ were all decreased along with the disease course, which suggested the relation of these cytokines to the disease pathogenesis.

The level of TNF- α decreased to below the detection limit in 7 days, when the indicators for renal involvement started to improve. In contrast, the serum IL-8 and IFN- γ levels seemed to decrease gradually along with the improvement of renal indicators. The serum IFN- γ and U- β_2 MG levels moved in opposite directions until day 15. Transient aggravation of uveitis at around day 15 seemed to be preceded by the transient re-elevation of the serum IFN- γ level. After that, both serum IFN- γ and U- β_2 MG levels decreased, and the uveitis condition improved. There was no recurrence of TINU syndrome for 4 years after this episode.

We also examined the serum IL-2, IL-4, and IL-10 levels. Both serum IL-2 and IL-4 levels were below the detection limit from day 1 to day 204. Due to the sensitivity, we could not make a definitive conclusion as to whether these cytokines had some relation with the status of TINU syndrome. Although the serum IL-10 level decreased before the improvement of status of TINU, we could not find references which suggested some association between the serum IL-10 level and the status of TINU or non-infectious uveitis.

This study protocol was approved by the ethics committee of Jichi Medical University, and informed consent was obtained from the patient.

Discussion

Our data suggested that there was some association between the status of TINU syndrome and the serum levels of TNF- α , IFN- γ , and IL-8.

Potential roles of TNF- α , IFN- γ , and IL-8 in TINU syndrome

The possible association of TNF- α with tubulointerstitial injury

In this patient, the serum levels of TNF- α and creatinine showed similar time courses (Fig. 2). Torii et al. [12] showed that TNF- α induced an increase in plasminogen activator inhibitor 1 (PAI-1) protein secretion. PAI-1 is reported to be an acceleration factor of renal interstitial fibrosis [13, 14]. The s-Cr level increases when the renal interstitium is injured [15]. Because renal interstitial fibrosis is part of the pathophysiology of TINU syndrome, these facts suggested that TNF- α can play some role in the development of TINU syndrome.

Fig. 2 Serial observations of urinary β_2 -microglobulin (U- β_2 MG), serum creatinine (s-Cr), the urinary protein/urinary creatinine ratio (UP/UCr), serum cytokine levels, and uveitis condition. The units for U- β_2 MG (open squares [$\mu\text{g/L}$]) are indicated on the left axis, while those for the UP/UCr (open triangles) and serum creatinine level

(open circles [mg/dL]) are indicated on the right axis. The units for the serum TNF- α (filled circles [pg/mL]), serum IL-8 (filled triangles [pg/mL]), and IFN- γ (filled squares [pg/mL]) levels are shown on the right axis

The possible association of IL-8 with the UP/UCr ratio

The serum levels of IL-8 and the urinary protein to creatinine ratio (UP/UCr ratio) showed similar time courses (Fig. 2). IL-8 is a chemokine, responsible for activating T-cells and recruiting them to sites of inflammation [8, 9]. Renal tubular epithelial cells are capable of synthesizing IL-8 [8]. IL-8 production by tubular epithelial cells is regulated by a variety of proinflammatory cytokines, most notably TNF- α and IFN- γ [8, 16].

Garin et al. [17] reported that the in vivo infusion of IL-8 increased ³⁵sulfate uptake by the glomerular basement membrane (GBM), and it also augmented the urinary albumin to creatinine ratio. This suggested that IL-8 may induce albuminuria by altering the metabolism of sulfated compounds in the GBM. We also reported previously that the serum IL-8 level was associated with the UP/UCr ratio

[18]. Tang et al. [19] reported that there was a tubuloglomerular “cross-talk” mechanism in the state of proteinuria, in which IL-8 could be an important initial signal in directing circulating leukocytes into the renal interstitium. That report might explain the interstitial changes which we observed in the proteinuria condition.

The possible association of IFN- γ with the U- β_2 MG level and uveitis

Interstitial nephritis is induced by mononuclear cells, including T-cells, which infiltrate the interstitium following IFN- γ stimulation [10]. This suggested the mechanism that an increased level of U- β_2 MG might cause an elevation in the IFN- γ levels. Then, the elevation of the IFN- γ level might have caused the exacerbation of uveitis observed in the patient described in the present study [11].

It is generally believed that tubulointerstitial nephritis in TINU syndrome is a self-limited disease [20]. Therefore, elevated U- β_2 MG and serum cytokine levels were improved without systemic treatments.

The inflammatory cytokine levels examined by us do not increase specifically only in TINU syndrome and we might see a secondary phenomenon of T-cell activation; however, our data suggested that there was some association between the status of TINU syndrome and the serum levels of TNF- α , IFN- γ , and IL-8.

This study was a retrospective study. Accordingly, we need to collect and analyze more data regarding cytokine dynamics in TINU syndrome following cohort studies to confirm our results.

Conclusion

We treated a 14-year-old girl with tubulointerstitial nephritis and uveitis (TINU) syndrome. Serum tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), and interleukin-8 (IL-8) levels were associated with the status of TINU syndrome. Our report provided an interesting starting point for gaining a better understanding of the pathophysiology of TINU syndrome.

Conflict of interest The authors have declared no conflict of interest.

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