

## Thrombopoietin and interleukin-6 levels in Henoch-Schönlein purpura

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**Background and Purpose:** Depending on the severity of the illness, thrombocytosis is found in about 60% to 70% of patients with Henoch-Schönlein purpura (HSP). Whether thrombocytosis is the result of an inflammatory reaction mediated by thrombopoietin (TPO) or other inflammatory cytokines such as interleukin (IL)-6 remains unknown.

**Methods:** Thirty two patients who met the diagnostic criteria for HSP were included. They were divided into two groups — HSP patients with thrombocytosis (n = 14) and those without thrombocytosis (n = 18) with a platelet count of 400,000/ $\mu$ L. Eight normal healthy controls were also included. TPO and IL-6 serum levels during the acute phase were measured by enzyme-linked immunosorbent assay.

**Results:** Patients with platelet counts greater than 400,000/ $\mu$ L in the acute stage had significantly lower TPO levels than patients with platelet counts lower than 400,000/ $\mu$ L ( $310 \pm 65.6$  pg/mL vs  $608 \pm 97.8$  pg/mL,  $p=0.013$ ). However, HSP patients with or without thrombocytosis had similar TPO levels as the healthy controls ( $441 \pm 176$  pg/mL,  $p=0.89$  and  $0.29$ , respectively). IL-6 serum levels were significantly elevated in HSP patients during the acute stage of HSP ( $28.6 \pm 61.7$  pg/mL vs  $3.16 \pm 1.35$  pg/mL,  $p=0.049$ ). In patients with complications of glomerulonephritis or gastrointestinal hemorrhage (n = 12), IL-6 levels were significantly lower than in those without such complications ( $8.07 \pm 3.79$  pg/mL vs  $40.9 \pm 16.9$  pg/mL,  $p=0.007$ ).

**Conclusions:** This study showed that thrombocytosis in HSP patients is a type of inflammatory reactive thrombocytosis, and that IL-6 may also play a role in the pathogenesis of HSP.

**Key words:** Henoch-Schoenlein purpura, interleukin-6, nephritis, thrombocytosis, thrombopoietin

### Introduction

Henoch-Schönlein purpura (HSP) is the most common systemic small vessel vasculitis affecting children. Its clinical features have been well documented and include non-thrombocytopenic palpable purpura, arthritis, bowel angina, gastrointestinal (GI) bleeding, and nephritis. Though the cause has not been well understood, it is clear that widespread leukocytoclastic vasculitis caused by immunoglobulin A (IgA) deposition in the vessel walls may play an important role in the pathogenesis of HSP [1]. Our recent nationwide survey on the epidemiological characteristics of childhood HSP showed an annual incidence of 12.9 (11.8-13.4)

per 100,000 children <17 years of age [2]. Except for rare extended GI or renal involvement, the long-term prognosis is generally good.

Thrombocytosis is found in about 60% to 70% of HSP patients in the acute stage, which might be related to the severity of the illness [3,4]. Thrombocytosis can be classified into primary (clonal) and secondary (reactive) forms. While clonal thrombocytosis is noted in myeloproliferative diseases, reactive thrombocytosis is observed in stressful or inflammatory states, such as infection, trauma, and malignancy. The thrombocytosis of HSP is believed to be a type of inflammation-triggered thrombocytosis but this has never been established.

Thrombopoietin (TPO), c-Mpl ligand, a 332-amino acid glycoprotein produced by the liver, kidneys, marrow stroma, and several other tissues, is a cytokine that stimulates megakaryocyte proliferation and maturation. TPO is considered to play a key role in the regulation of

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platelet production, but the regulation of TPO blood levels is complex. TPO is constitutively produced and is primarily regulated by the receptor-mediated uptake of platelets and by the hepatocyte and stromal cell responses to thrombocytopenia or the mediators of inflammation [5,6].

Interleukin-6 (IL-6) is a pleiotropic cytokine that has a wide variety of biological functions in the immune or inflammatory response of the host to various stimuli. IL-6 can induce thrombocytosis and it is also one of the cytokines that is abnormally increased in various autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus, and various vasculitis syndromes such as Kawasaki disease and giant cell arteritis [7-9]. However, TPO and IL-6, which are the major regulators of platelet production, have not been studied so far in HSP patients in terms of disease activity.

The aim of the present study was to measure the serum levels of TPO and IL-6 in HSP patients in order to evaluate whether or not there is a relationship between the expression of these cytokines and thrombocytosis. To clarify the role of TPO and IL-6 in the pathogenesis of HSP, we also compared these parameters to different clinical aspects and disease severities.

## Methods

### Patients

A total of 32 previously healthy Chinese children (18 boys and 14 girls) with acute onset and/or active presentation of HSP at the National Taiwan University Hospital were included in this study. The diagnosis was confirmed based on the American College of Rheumatology 1990 criteria [10] during the period from December 1998 to November 2003. Informed consent and institutional approval were obtained for this study.

All the patients underwent laboratory and physical investigations at the acute stage and their blood samples were collected and analyzed for a complete blood count with differential count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulins, antinuclear antibody, and complement 3 and 4 levels. All the patients were followed-up regularly and the clinical presentations were recorded until they were asymptomatic. The study also included 8 normal healthy children as controls. Serum samples of the patients and controls were stored at  $-20^{\circ}\text{C}$  before testing.

### Serum TPO and IL-6 assay

TPO serum levels of the 32 HSP patients and 8 healthy controls were determined by a commercial

enzyme-linked immunosorbent assay (ELISA) kit (Quantikine; R&D Systems, Minneapolis, MN, USA). The procedure was performed in accordance with the instructions of the manufacturer. The minimal detectable level of TPO in this assay was 15 pg/mL.

IL-6 serum levels were detected by another commercial ELISA kit (DuoSet ELISA development system; R&D Systems). The assay was performed as per the manufacturer's instructions for general ELISA. The minimal detectable level of the IL-6 assay was 0.7 pg/mL.

### Statistical analysis

For statistical analysis, HSP patients were divided into the high platelet count group and the normal platelet count group, using the cut-off of 400,000/ $\mu\text{L}$ . We also compared the serum levels of TPO and IL-6 with regard to different disease characteristics to elucidate any differences between these cytokines and disease severities.

As these values were not normally distributed, we performed non-parametric analysis of variance using the Mann-Whitney test for comparing the groups. Linear regression analyses were used for correlation studies. A value of  $p < 0.05$  was considered statistically significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows (SPSS, Chicago, IL, USA) software and the results were expressed as mean  $\pm$  standard error.

## Results

### Clinical presentations and courses

The study included 18 boys and 14 girls, with a mean age of 5.9 years (range, 1-10 years). Table 1 summarizes

**Table 1.** Clinical characteristics of patients with Henoch-Schönlein purpura

Symptoms and signs	No. of patients (%)
Purpura over lower extremities and/or buttocks	32 (100)
Abdominal pain with/without SOB	21 (65.6)
Gastrointestinal hemorrhage <sup>a</sup>	7 (21.9)
Arthritis/arthralgia	20 (62.5)
Extremities edema	11 (34.4)
Glomerulonephritis	8 (25)
Previous URI	16 (50)
Prolonged disease course >2 months	13 (40.6)

Abbreviations: SOB = stool occult blood; URI = upper respiratory infection

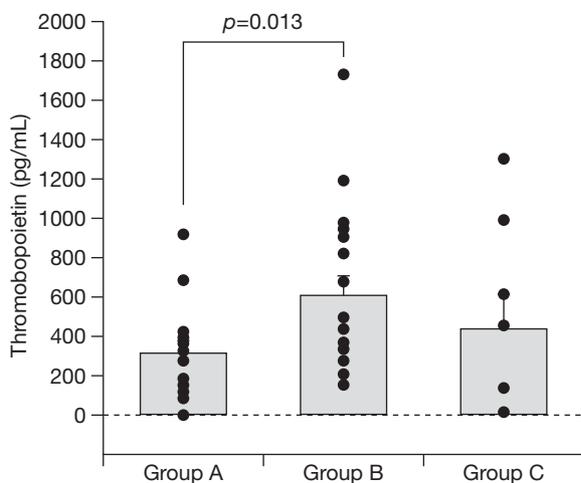
<sup>a</sup>Gastrointestinal hemorrhage defined as SOB of 2+ or greater.

the clinical characteristics of the 32 patients. We defined GI hemorrhage as occult blood in stool more than or equal to 2+. Glomerulonephritis was defined as the presence of hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen), pyuria (>5 leukocytes per high-power microscopic field in a centrifuged specimen), or proteinuria ( $\geq 30$  mg/dL).

All the patients presented with the characteristic palpable purpuric lesions of HSP. Abdominal pain was noted in 21 of 32 patients (65.6%). One-third of them had GI hemorrhage and only 1 patient had intussusception initially, followed by perforation. Arthritis or arthralgia occurred in 20 of 32 patients (62.5%); the ankles, followed by the knee joints, were the most common joints involved. Bipedal edema was noted in 11 of the 32 patients, and 3 of them also had edema of the upper limbs, face, or scrotum. Eight patients (25%) developed glomerulonephritis — 7 within 2 weeks after purpura was noted. Despite the combined treatment of non-steroidal anti-inflammatory drugs and short-term steroids or azathioprine depending on the disease severity, 13 patients (40.6%) had a prolonged disease course of more than 2 months, defined by the duration of the anti-inflammatory drug given.

### Correlation between platelet count and TPO concentration

The platelet counts of our HSP patients ranged from 259,000 to 693,000/ $\mu$ L, with a median value of



**Fig. 1.** Thrombopoietin (TPO) levels in Henoch-Schönlein purpura patients. Group A: 14 patients with thrombocytosis (platelet count >400,000/ $\mu$ L); Group B: 18 patients without thrombocytosis; Group C: 8 healthy controls. The average TPO level of group A is significantly lower than that of group B ( $p=0.013$ ).

380,500/ $\mu$ L. If thrombocytosis was defined as a platelet count over 400,000/ $\mu$ L (the upper limit of the normal value in our central lab), 14 of the 32 (43.8%) HSP patients would be considered as having thrombocytosis in the acute stage.

In order to identify the effects of thrombocytosis, the 32 HSP patients were divided into those HSP patients with thrombocytosis (high platelet counts,  $n = 14$ ) and those without thrombocytosis (normal platelet counts,  $n = 18$ ), with a cut-off platelet count of 400,000/ $\mu$ L. Patients with high platelet counts in the acute stage had significantly lower TPO levels than patients with normal platelet counts ( $310 \pm 65.6$  pg/mL vs  $608 \pm 97.8$  pg/mL,  $p=0.013$ ). However, HSP patients with or without thrombocytosis had similar TPO levels to healthy controls ( $441 \pm 176$  pg/mL,  $p=0.89$  and  $0.29$ , respectively) [Fig. 1].

### Correlation between platelet count and IL-6 concentration

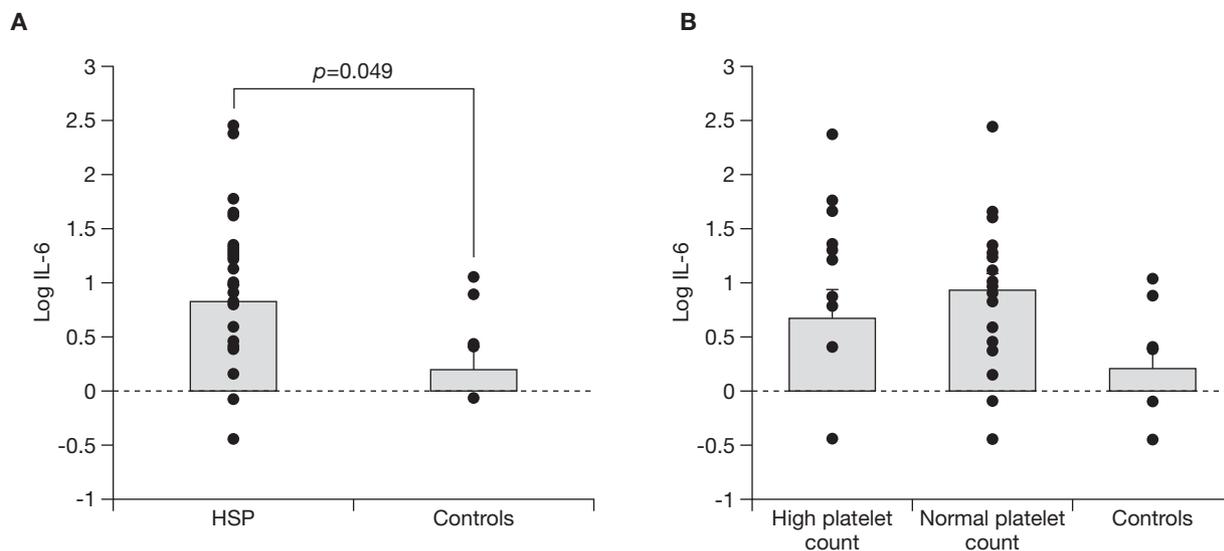
In the HSP patients, there was no difference between the IL-6 levels of the high platelet count group and the normal platelet count group ( $29.8 \pm 16.7$  pg/mL vs  $27.7 \pm 14.9$  pg/mL,  $p=0.92$ ). In contrast, the serum IL-6 levels were significantly higher in our patients than in the healthy controls ( $28.6 \pm 61.7$  pg/mL vs  $3.16 \pm 1.35$  pg/mL,  $p=0.049$ ) [Fig. 2].

### Correlation between IL-6 concentration and disease characteristics

IL-6 levels were undetectable in 6 of 32 patients. Of these 6 patients, 2 had glomerulonephritis, 2 had GI hemorrhage, and 2 had both complications. As depicted in Fig. 3, the blood IL-6 levels in HSP patients with nephritis were relatively but not significantly lower than those of patients without nephritis ( $7.06 \pm 3.48$  pg/mL vs  $35.8 \pm 14.3$  pg/mL,  $p=0.06$ ). Furthermore, blood IL-6 levels in HSP patients with GI hemorrhage were also slightly lower than those of patients without GI hemorrhage ( $10.1 \pm 5.94$  pg/mL vs  $33.8 \pm 13.8$  pg/mL,  $p=0.1$ ). Taken together, 12 of the 32 HSP patients with complications of either nephritis or GI hemorrhage had significantly lower serum IL-6 levels than those without internal organ involvement ( $8.07 \pm 3.79$  pg/mL vs  $40.9 \pm 16.9$  pg/mL,  $p=0.007$ ).

### Discussion

HSP is believed to be an immune-mediated systemic inflammatory disease of unknown etiology. In our



**Fig. 2.** Interleukin-6 (IL-6) concentration in patients versus healthy controls. (A) Comparison of the IL-6 levels of 32 Henoch-Schönlein purpura (HSP) patients and 8 healthy controls. The serum IL-6 levels in our patients were significantly higher than in the healthy controls ( $p=0.049$ ). (B) In HSP patients, there was no difference between the IL-6 levels of the high platelet count group ( $n = 14$ ) and the normal platelet count group ( $n = 18$ ) [ $p=0.92$ ].

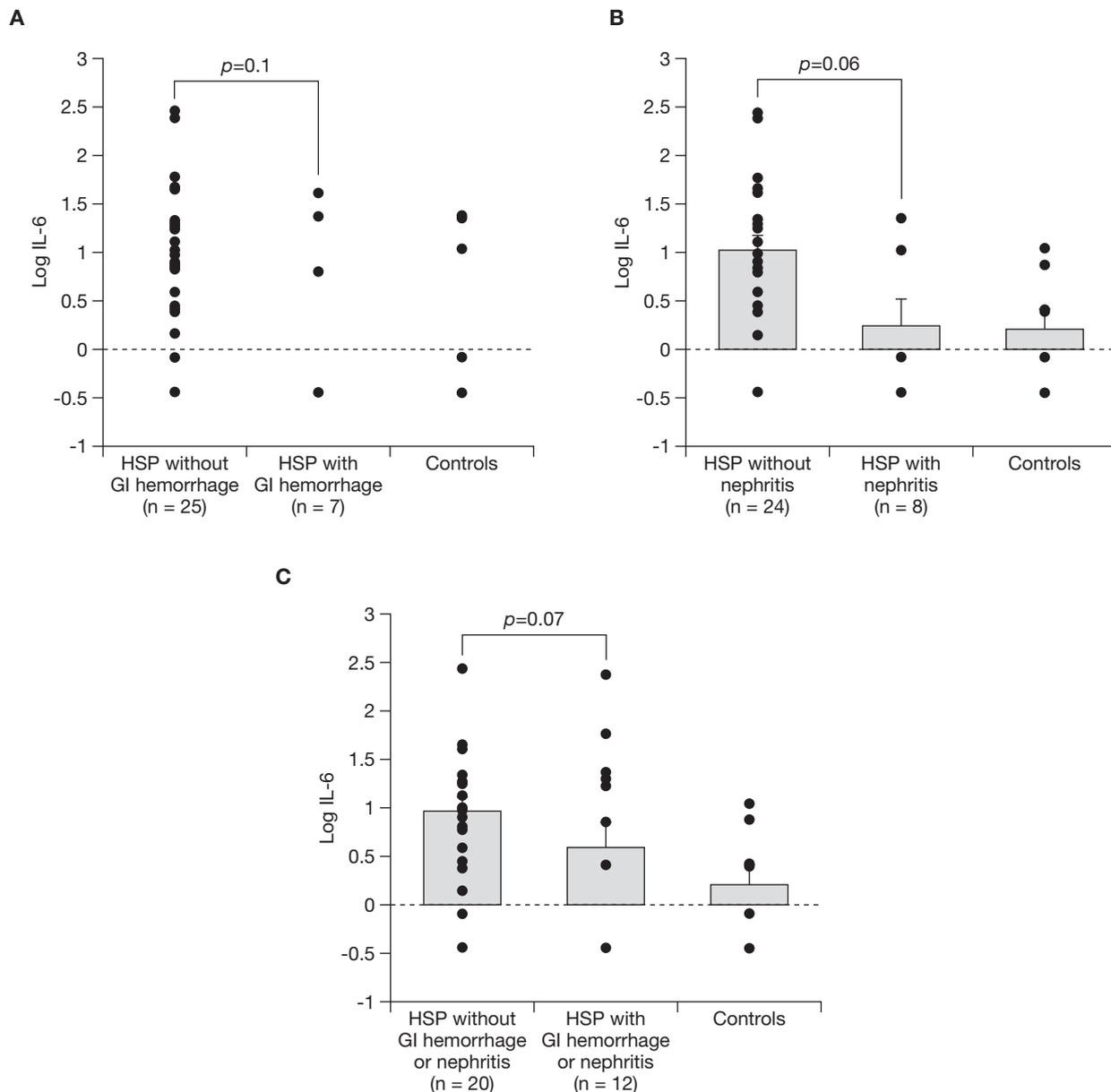
previous study, elevation of leukocytes, neutrophil percentage, platelet counts, ESR, and CRP at the onset of HSP reflected the nature of the acute inflammatory process [11]. We also found that cytokines such as tumor growth factor-beta, tumor necrosis factor (TNF)-alpha, and IL-8 may play an important role in the pathogenesis of such small vessel vasculitis [11-13]. Besbas et al revealed that TNF, and a less intense IL-1 and IL-6 staining, was significantly increased in the affected skin during the acute phase. However, the serum IL-6 levels were not checked [14]. In clinical practice, thrombocytosis was noted in many but not all inflammatory diseases. The exact mechanisms underlying the inflammatory, autoimmune, and neoplastic forms of thrombocytosis are still unclear.

As stated previously, thrombocytosis in general can be divided into clonal thrombocytosis and reactive thrombocytosis, but the differential diagnosis of these two entities may be clinically difficult. In 1998, Wang et al demonstrated that TPO levels may be helpful in distinguishing the two types of thrombocytosis. They found that TPO levels were significantly higher in clonal thrombocytosis than in reactive thrombocytosis, although both had similar levels in normal healthy controls [15]. In reactive thrombocytosis, it was well established that RA patients with normal platelet counts had TPO levels comparable with healthy controls, while RA patients with marked thrombocytosis had a significant reduction of TPO levels [16].

In the present study, we demonstrated that HSP patients with or without thrombocytosis had TPO levels similar to healthy controls, but patients with high platelet counts had significantly lower TPO levels than patients with normal platelet counts. Although the number of healthy controls was small, our results were consistent with 2 previous studies and implied that the thrombocytosis of HSP was the reactive thrombocytosis. TPO had been reported to be elevated in reactive thrombocytosis and to act as an acute phase reactant that correlated with ESR, fibrinogen, CRP, and IL-6. However, the sample size was small and the correlation was weak [17].

By serial measurements of TPO along with platelet counts and other cytokines, many studies found that an elevation of TPO preceded thrombocytosis in several different conditions of reactive thrombocytosis [18-20]. Folman et al also showed that the levels of IL-6, and not IL-11 or TNF, increased before the rise in TPO concentration in postoperative thrombocytosis [20]. These findings did not contradict the theory that TPO is primarily regulated by the receptor-mediated uptake of platelets.

It is possible that in chronic states, TPO production was increased secondary to some acute phase reactants, followed by the increase in platelet count due to the stimulation by TPO. When the platelet count was high, TPO was consumed by a receptor-mediated uptake of platelets and megakaryocytes, resulting in a decrease in



**Fig. 3.** Interleukin-6 (IL-6) concentration and disease characteristics. (A) Henoch-Schönlein purpura (HSP) patients with gastrointestinal (GI) hemorrhage ( $n = 7$ ) had slightly lower serum levels of IL-6 than patients without GI hemorrhage ( $10.1 \pm 5.94$  pg/mL vs  $33.8 \pm 13.8$  pg/mL,  $p=0.1$ ). (B) Patients with nephritis ( $n = 8$ ) had relatively but not significantly lower serum levels of IL-6 than patients without nephritis ( $7.06 \pm 3.48$  pg/mL vs  $35.8 \pm 14.3$  pg/mL,  $p=0.06$ ). (C) Twelve out of 32 HSP patients with either nephritis or GI hemorrhage had significantly lower serum levels of IL-6 than those without internal organ involvement ( $8.07 \pm 3.79$  pg/mL vs  $40.9 \pm 16.9$  pg/mL,  $p=0.007$ ).

serum levels of this cytokine. As in our present study, a cross-sectional measurement of serum TPO and IL-6 levels revealed that TPO concentrations tend to be negatively correlated with the platelet counts, but these levels remained the same in healthy controls; IL-6 concentration levels in HSP patients were significantly higher than those in healthy controls, irrespective of platelet counts.

In previous studies, serum IL-6, an important pro-inflammatory cytokine, was found to be elevated in patients with reactive thrombocytosis [21]. Subsequent animal and humoral studies demonstrated that IL-6-induced thrombocytosis in mice was accompanied by increased TPO mRNA steady-state expression in the liver and elevated TPO plasma levels [22]. Administration of IL-6 to cancer patients resulted in a

corresponding increase in TPO levels and platelet counts [22]. With these findings, it could be hypothesized that IL-6 acts as an acute phase reactant that increases secondary to the inflammatory response of HSP, which is triggered by some unknown etiology. It is still unknown whether IL-6 stimulates thrombopoiesis through TPO or other mediators, or if IL-6 acts on the hematopoietic progenitor cells directly and the concentration of TPO merely follows the dynamic changes in platelet mass.

An incidental but important finding of our study reveals that HSP patients with renal involvement had significantly lower serum IL-6 levels than the other HSP patients, almost similar to normal healthy controls. This was also true of patients with GI hemorrhage. It is surprising that an acute phase reactant that is elevated to an average extent in our HSP patients would become significantly lower in more severely complicated cases. To rule out the effects of possibly stronger anti-inflammatory medication used in complicated cases before the blood samples were collected, we reviewed the clinical courses of these patients and found only one of them transferred to our clinic on the 45th day of the disease onset and after prolonged use of oral prednisolone.

On the other hand, the samples were tested for other acute phase reactants, such as CRP and ESR, but the levels were not suppressed in these complicated patients (data not shown). Despite the minor, but still possible influence, the phenomena can be explained by one of two possibilities: first, IL-6 was consumed during the specific process of systemic and local inflammation; or second, IL-6 had protective effects against the disease status developing nephritis or GI hemorrhage.

IL-6 plays an important role in immune regulation and inflammation as well as in autoimmune diseases. Not surprisingly, increased circulating IL-6 levels were noted in many other types of vasculitis, such as Kawasaki disease, giant cell arteritis, and SLE with vasculitis [7-9]. Recent *in vivo* and *in vitro* studies have demonstrated that IL-6 promoted angiogenesis by stimulating endothelial cell proliferation and morphological differentiation into capillary-like structures [8]. By this function, the protective effects of elevated IL-6 in the development of disease-related ischemic events in giant-cell arteritis can be explained.

In HSP, we have no evidence to conclude that ischemia secondary to small vascular inflammation plays a role in the pathogenesis of nephritis and GI hemorrhage. However, we also cannot rule out this

possible mechanism. Some researchers believe that HSP is a severe systemic form of IgA nephropathy (IgAN) and results in imbalances in serum IL-6 such that its soluble receptor plays a role in the progression of IgAN and HSP nephritis [23]. It was reported that urine IL-6 levels reflect the activity of IgAN and higher urinary fractional excretion of IL-6 predicted a worse prognosis [24]. We recently collected the urine samples of our HSP patients in the acute stage to determine whether IL-6 lost from urine occurred concurrently with the development of HSP nephritis. Anti-IL-6 receptor antibody is proven to be effective in treating RA in humans and ameliorates murine lupus nephritis [9]. Before the use of this strategy to control autoimmune diseases becomes widespread, further studies to clarify the role of IL-6 in the pathogenesis of HSP are needed.

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