Kidney International, Vol. 46 (1994), pp. 455–460

Detection of urinary interleukin-8 in glomerular diseases

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Detection of urinary interleukin-8 in glomerular diseases. To clarify the mechanism of neutrophil infiltration in glomerulonephritis, both urinary and plasma levels of a potent neutrophil chemotactic cytokine, interleukin-8 (IL-8), were measured in 40 healthy volunteers and 96 patients with various renal diseases. The plasma IL-8 levels were less than 16 pg/ml. The urinary IL-8 levels were elevated in several renal diseases including IgA nephropathy (17 of 43), acute glomerulonephritis (4 of 6), lupus nephritis (11 of 15), purpura nephritis (2 of 4), membranoproliferative glomerulonephritis (1 of 1), and cryoglobulinemia (2 of 2). IL-8 was detected immunohistochemically in diseased glomeruli, suggesting its local production. Elevated urinary IL-8 levels during the acute phase or exacerbations were found to be decreased during spontaneous or steroid pulse therapy-induced convalescence in all patients examined. The urinary IL-8 levels were higher in patients with glomerular leukocyte infiltration than in those without infiltration. Collectively, local production of IL-8 in diseased glomeruli might be involved in the pathogenesis of the glomerular diseases and measurement of IL-8 in the urine might be useful for monitoring the glomerular diseases.

Glomerular hypercellularity in the acute phase of glomerular diseases is caused predominantly by intraglomerular polymorphonuclear leukocyte and mononuclear cell infiltrations. However, the precise mechanism causing the infiltration of polymorphonuclear leukocytes remains to be investigated. Accumulating evidence indicates that inflammatory cytokines, such as interleukin-1 (IL-1) [1], tumor necrosis factor-α (TNF-α) [1] and interleukin-6 (IL-6) [2], may play an important role in the pathogenesis of glomerular diseases and are involved in the acute exacerbations [3]. Recent studies indicated that the urinary excretion of IL-6 reflected its local production, either by cells resident in the glomeruli or by infiltrating cells [4, 5]. The results suggested that the measurement of the urinary excretion of IL-6 was useful for evaluating the renal damage and monitoring the disease activities.

We observed that a novel neutrophil chemotactic cytokine, interleukin-8 (IL-8) [6], played a causative role in neutrophil infiltration in acute inflammation [7]. IL-8, originally described as a secreted product from LPS-stimulated human peripheral blood monocytes [8], is also secreted by various types of non-leukocytic cells, including dermal fibroblasts [9] and endothelial cells [10]. Furthermore, recent studies indicated that IL-8 was produced by mesangial cells [11] or renal epithelial cells [12] in response to lipopolysaccharide, IL-1, or TNF-α.

To examine the possibility that locally-produced IL-8 participates in the pathophysiology of the acute phase of glomerular disease by recruiting leukocytes, particularly, neutrophils, we determined here both urinary and plasma levels of IL-8 in patients with various renal diseases. We also investigated the relationship between IL-8 levels and disease activity.

Methods

Patients

Forty healthy volunteers and 96 patients with primary or secondary glomerular diseases were evaluated in this study. The patients in this study were chosen randomly. There were 70 males and 66 females with a median age of 39.7 years (range 4 to 82 years). The clinical profiles of normal volunteers and patients are summarized in Table 1. Among these patients, 88 patients had the diagnosis verified by renal biopsy, while 6 acute glomerulonephritis (AGN) patients and 2 lupus nephritis patients were clinically diagnosed without pathological analyses. Patients of AGN showed the symptoms of acute nephritic syndrome, such as hematuria and edema, after the streptococcal infections. Renal biopsies were not carried out since their symptoms resolved without special medication within a few weeks. Urinary tract infections and pyuria were negated in all cases by means of bacterial cultures and/or the microscopic findings since urinary tract infection itself is associated with increased urinary IL-8 levels [13]. Whenever possible, patients did not receive any immunosuppressive agents before collecting samples. However, 17 patients (1 cryoglobulinemia, 13 lupus nephritis patients, and 3 IgA nephropathy patients) were in a clinically active state and were treated with methylprednisolone pulse therapy (500 mg/day, 3 days) during this study. This study was approved by the Drug Ethics Committee of Kanazawa University Hospital. All renal biopsies were performed with the consent of the patients.

Pathological studies

Eighty-eight kidney specimens were obtained by renal biopsy. Two observers, without knowledge of the clinical course, examined the renal tissue under light microscopy to establish the diagnosis by standard pathological methods. For the lupus nephritis patients, World Health Organization (WHO) criteria were used for the light microscopic classification of the major forms and the active lesions of lupus nephritis [14]. The "activity index (AI)" of the histological appearance was also calculated according

Received for publication November 8, 1993
and in revised form March 11, 1994
Accepted for publication March 14, 1994

Table 1. Patients' profiles with respect to diagnosis, the presence of glomerular leukocyte infiltration, glomerular expression of IL-8 and urinary IL-8 levels

Diagnosis	No. of patients (male:female)	Age years (mean)	Glomerular leukocyte infiltration	Glomerular expression of IL-8	Urinary IL-8 levels pg/mg · creatinine
Healthy volunteers	40 (20:20)	4–75 (40.0)	ND	ND	0
IgA nephropathy	43 (22:21)	16–70 (39.0)	9/26 (35%)	3/25 (12%)	80.6 ± 42.0
with acute exacerbation or onset	15 (3:12)	16–70 (32.3)	4/4 (100%)	2/3 (67%)	203.4 ± 116.5
without acute exacerbation or onset	28 (19:9)	16–60 (42.5)	5/22 (23%)	1/22 (5%)	14.8 ± 12.3
AGN	6 (3:3)	4–8 (5.0)	ND	ND	63.4 ± 37.8
MPGN	1 (1:0)	62	1/1	1/1	175.0
MCNS	3 (2:1)	32–63 (52.6)	0/3 (0%)	0/3 (0%)	0
FGS	10 (6:4)	17–63 (37.8)	0/10 (0%)	0/10 (0%)	0
MN	12 (10:2)	45–67 (58.6)	0/12 (0%)	0/12 ((0%)	0
Lupus nephritis	15 (3:12)	16–53 (33.4)	5/12 (41%)	1/7 (14%)	98.1 ± 38.7
Purpura nephritis	4 (2:2)	4–72 (38.7)	1/4 (25%)	0/0	47.7 ± 27.8
Cryoglobulinemia	2 (1:1)	59–82 (70.5)	1/1	1/1	108.6 ± 105.7
Total	136 (70:66)	4–82 (39.7)	17/69	6/59	

Abbreviations are: AGN, acute glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; MCNS, minimal change nephrotic syndrome; FGS, focal glomerulosclerosis; MN, membranous nephropathy; ND, not done. Values are mean ± SEM.

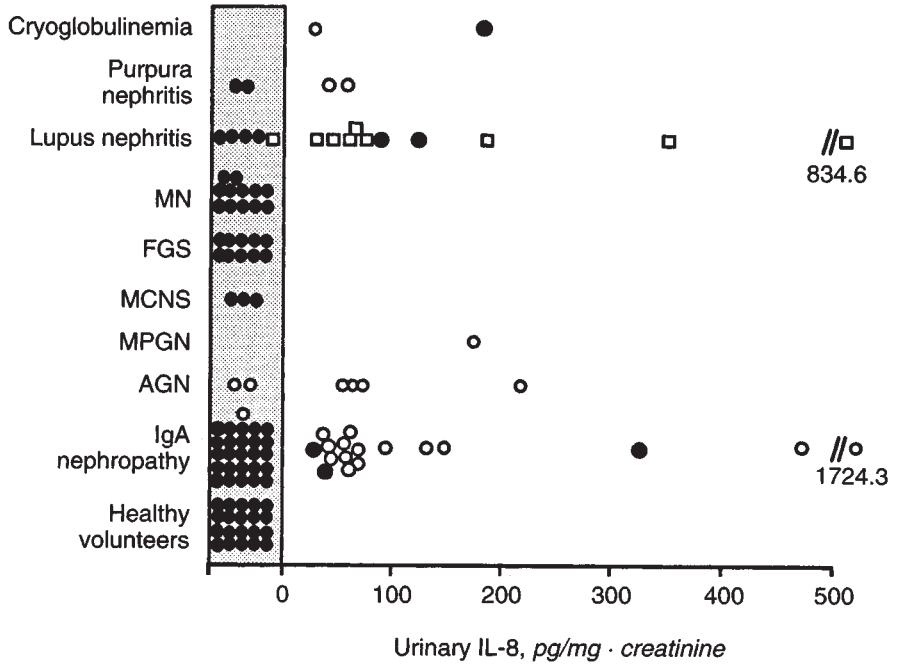

Fig. 1. *Urinary IL-8 levels in patients with various renal diseases.* Open circles indicate the patients with acute exacerbation or onset while closed ones indicate those without acute exacerbation or onset. For lupus nephritis patients, (□) indicates patients with more than 6.0 of activity index.

to the methods of National Institute of Health (NIH) described by Austin et al [15].

Immunohistochemical studies

The presence of IL-8 protein was demonstrated immunohistochemically on fresh tissue specimens by using the indirect avidin-biotinylated peroxidase complex method with a specific murine monoclonal anti-human IL-8 (clone WS-4) antibody [16]. A polyclonal mouse IgG antibody that had been absorbed with both human liver powder and immunoglobulin was used as the negative control. Two immunohistochemistry observers were totally blind to urinary IL-8 levels and the clinical course.

Urinary and plasma IL-8 measurements

Spontaneously-voided midstream urines and plasma were collected at the same time. All of the 96 cases were not receiving any treatment, and from 69 cases, urine and plasma were collected on the morning of renal biopsy. Ten ml of the each urine was spun at 200 × *g* for five minutes, and the supernatant was used for this ELISA. The specimens were kept at −70°C until the measurement of IL-8. Both urinary and plasma IL-8 levels were determined by ELISA, using a monoclonal antibody (clone WS-4) as a capture and a rabbit antibody as a second antibody essentially as previously described [16], except that the dilution buffer was changed to 1% BSA (Sigma Chemical Co., St. Louis, Missouri, USA) in PBS containing 0.05% Tween 20. This system is highly

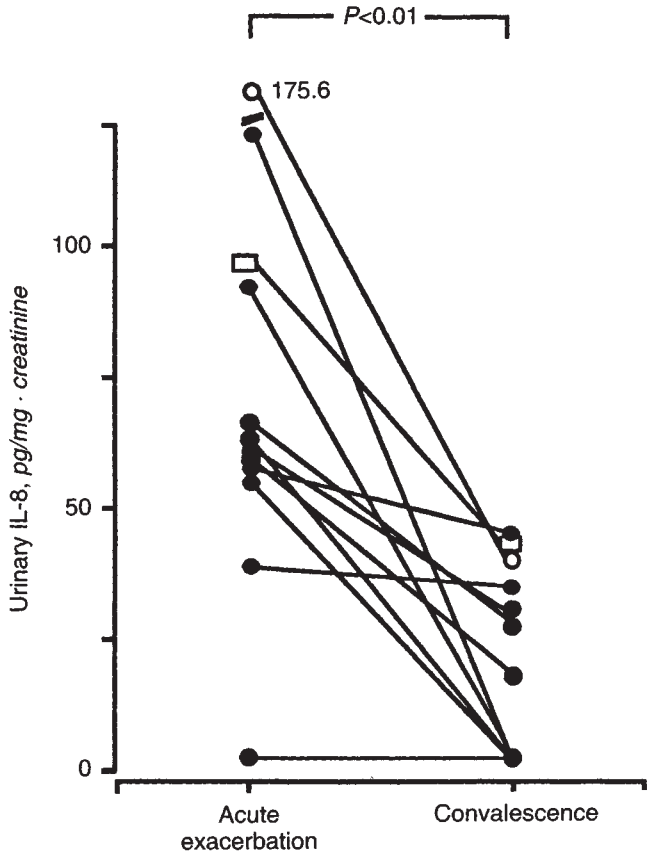

Fig. 2. *Comparison of urinary IL-8 levels in several diseases at acute onset or exacerbation with those at convalescence.* Symbols are: (●) IgA nephropathy; (○) MPGN; (□) purpura nephritis.

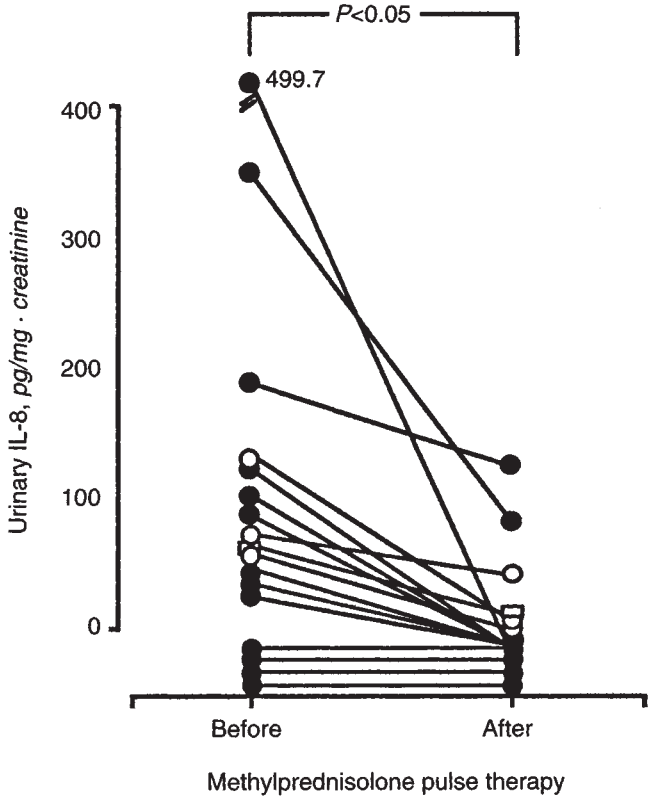

Fig. 3. *Alteration of urinary IL-8 levels following methylprednisolone pulse therapy in 17 patients.* Symbols are: (○) IgA nephropathy; (●) lupus nephritis; (□) cryoglobulinemia.

specific for IL-8, since there was no cross reactivity with other chemokines including platelet basic protein, platelet factor 4, growth related gene and monocyte chemotactic and activating factor. The recovery rate was confirmed to be more than 95% up to 10 ng/ml in this ELISA system. IL-8 was very stable [16] and the *in vitro* generation of IL-8 in urine samples containing cells could be excluded in this system, since the supernatants were obtained immediately after the collection of urine. All assays were performed at least in duplicate. The detection limit of this ELISA system for IL-8 was less than 16 pg/ml. Urinary IL-8 level was standardized by the amount of creatinine in the urine.

Statistics

Statistical significance was analyzed using Student's *t*-test for paired or unpaired data while correlation coefficiency was tested using Pearson's and Spearman's equations for parametric and nonparametric data, respectively. $P < 0.05$ was accepted as statistically significant.

Results

Urinary and plasma IL-8 levels

Plasma IL-8 levels from normal volunteers and patients fell below the detection limit of ELISA. No detectable levels of IL-8 were found in the urine of any of the healthy volunteers as previously described [13]. Similarly, IL-8 could not be detected in the urine from the minimal change nephrotic syndrome (MCNS), focal glomerulosclerosis (FGS), and membranous nephropathy patients. In contrast, elevated urinary IL-8 levels were detected in 17 out of 43 cases of IgA nephropathy (39.0%), prominently in 14 out of 15 cases showing acute onset or exacerbation (93.3%), in 4 of 6 cases of AGN (66.6%), in 11 of 15 cases of lupus nephritis (73.3%) and in 2 of 4 cases of purpura nephritis (50%). It was also detected in 1 of 1 case of membranoproliferative glomerulonephritis (MPGN) and 2 of 2 cases of cryoglobulinemia (Fig. 1). As for thirteen lupus nephritis patients who experienced renal biopsies, glomerular appearance was classified on optical microscopy as focal proliferative lupus nephritis (PLN, WHO Class III) in two patients, diffuse proliferative lupus nephritis (DPLN, WHO Class IV) in eight, and membranous lupus nephritis (MLN, WHO V) in three. All patients with DPLN and one with PLN showed detectable level of urinary IL-8, whereas urinary IL-8 was not detected in any patients with MLN. The activity index ranged from 0 to 18 (mean 6.5 ± 1.3, mean ± SEM, $N = 13$), and specimens given as activity index of more than 6.0 were considered to be active (Fig. 1).

Urinary IL-8 levels at acute onset or exacerbation

Acute onset or acute exacerbation, manifested by macroscopic hematuria and/or an abrupt increase in urinary protein, was observed in 25 patients with IgA nephropathy (15 cases), AGN (6 cases), MPGN (1 case), purpura nephritis (2 cases) and cryoglobulinemia (1 case) (Fig. 1, open circles). In all cases except one with IgA nephropathy and 2 with AGN, urinary IL-8 levels were

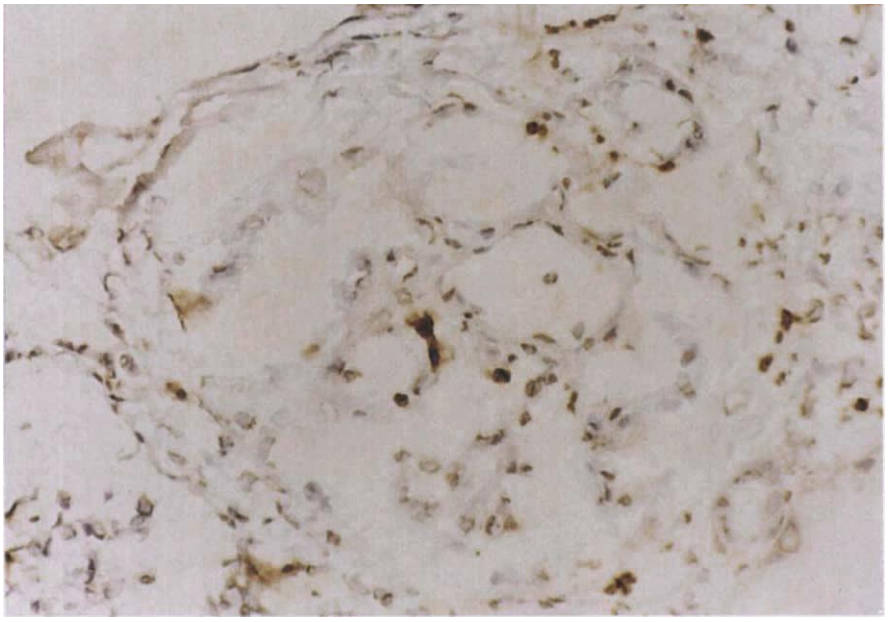

Fig. 4. *Immunohistochemical examination.* Expression of IL-8 protein in renal tissues was detected using a specific monoclonal anti-human IL-8 antibody as described in the **Methods**. The sections were observed under light microscopy at × 320 magnification. A representative result from one cryoglobulinemia patient is shown here. IL-8-positive cells were detected in glomerular capillaries.

increased. In 12 patients whose clinical courses could be followed by sequential urine sampling, urinary IL-8 levels decreased as the disease resolved (73.6 ± 5.9 pg/mg creatinine vs. 25.1 ± 6.4 pg/mg creatinine, $P < 0.01$; Fig. 2). Urinary IL-8 levels remained elevated in 7 patients including 5 with IgA nephropathy, 1 with MPGN and 1 with purpura nephritis even after the improvement of clinical signs as evidenced by decreased urinary protein excretion and improved urinary sediments.

Effects of methylprednisolone pulse therapy on urinary IL-8 levels

Seventeen patients (including 13 lupus nephritis patients, 3 IgA nephropathy patients and 1 cryoglobulinemia patient) were treated with methylprednisolone pulse therapy (500 mg/day, 3 days) during this study. Urinary IL-8 levels were elevated in 13 of these patients at the start of therapy (Fig. 3). All patients showed significant clinical improvement at four to eight weeks after the initial pulse therapy as judged by physical findings and renal functions. Concomitantly with the resolution of disease, urinary IL-8 levels decreased in 13 patients who showed elevated urinary IL-8 levels at the start of the therapy (98.4 ± 32.7 pg/mg creatinine vs. 19.3 ± 8.2 pg/mg · creatinine, $P < 0.05$; Fig. 3).

IL-8 is produced locally in renal tissues

Local production of IL-8 in renal tissues was suggested by elevated urinary level as opposed to undetectable plasma level of IL-8 in patients with the various types of renal diseases that we examined. To directly examine whether cells within the glomeruli produced IL-8, renal tissues from 59 patients were examined immunohistochemically for the presence of antigenic IL-8. In the glomeruli from patients with undetectable urinary IL-8 levels, IL-8 was not detected immunohistochemically (Table 1). IL-8-positive cells were detected in glomerular capillaries (Fig. 4) when immunostaining was performed on specimens obtained from patients with IgA nephropathy, MPGN, lupus nephritis and cryoglobulinemia (Table 1). The staining was specific to IL-8, since control antibody did not give a positive staining (data not shown). These results favored the notion that IL-8 was produced locally in glomeruli of patients with glomerular lesions.

Possible involvement of IL-8 in leukocyte infiltration into glomeruli

Since evidence is accumulating that IL-8 is essential for leukocyte infiltration in acute inflammation [7], we examined the relationship between leukocyte infiltration in glomeruli and urinary IL-8 levels in 69 patients whose urines were collected at the time of renal biopsy. The urinary IL-8 levels were elevated in 14 out of 17 patients with leukocyte infiltration in glomeruli whereas only 6 out of 52 patients without leukocyte infiltration showed elevated urinary IL-8 levels (Fig. 5).

Discussion

This study showed that the levels of immunoreactive IL-8 were elevated in urine from patients with primary or secondary glomerular diseases compared with healthy volunteers. Based on immunoblotting analysis on urine from patients with urinary tract infection [13], urinary IL-8 was presumed to be intact, rather than a degradation product without biological functions. Despite the presence of IL-8 in urine, plasma IL-8 levels failed to elevate above the detection limit, suggesting that IL-8 was produced locally in the diseased renal tissue. This assumption is supported by observations that resident cells, such as mesangial cells [11] and endothelial cells [10] and epithelial cells [12] and leukocytes could produce IL-8 *in vitro*. Immunohistochemical analyses confirmed that immunoreactive IL-8-positive cells were found in the capillaries of the diseased glomeruli. However, in 28 out of 34 patients with detectable urinary IL-8, IL-8 was not detected by immunohistochemical study in renal tissue obtained by renal biopsies. This might be partially because we could not fully observe IL-8-positive cells in the limited number of glomeruli obtained by renal biopsy specimen. In addition, the detection of the IL-8-positive cells

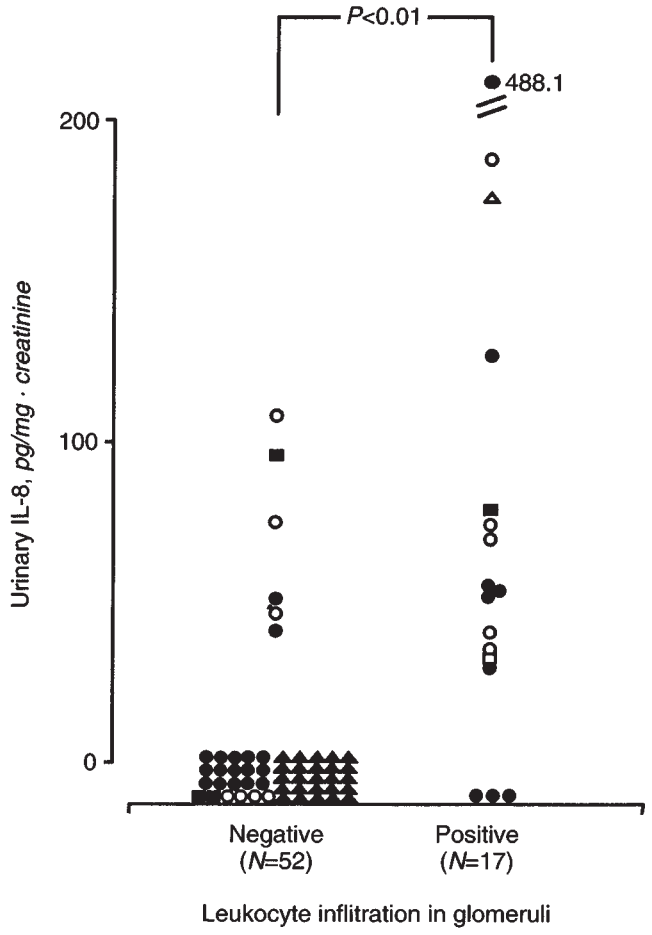

Fig. 5. *Relationship between leukocyte infiltration in glomeruli and urinary IL-8 levels.* Symbols are: (○) lupus nephritis; (●) IgA nephropathy; (■) purpura nephritis; (□) cryoglobulinemia; (△) MPGN; (▲) MCNS, FGS, MN.

might be limited due to the low sensitivity of this immunohistochemical method.

Elevated urinary IL-8 levels were observed in patients with IgA nephropathy, AGN, purpura nephritis, cryoglobulinemia, MPGN and lupus nephritis, but not in patients with MCNS, FGS and membranous nephropathy. The most noticeable difference was that glomeruli from the former group showed the infiltration of polymorphonuclear cells and/or mononuclear cells and the proliferation of mesangial cells, whereas those from the latter group did not. In this study, the urinary IL-8 levels were increased in 14 out of 15 IgA nephropathy patients with acute onset or exacerbation, conditions in which polymorphonuclear leukocytes and mononuclear cells in glomeruli are often observed [17]. Moreover, we often observed infiltration of polymorphonuclear leukocytes into glomeruli that stained positively with anti-IL-8 antibody in immunohistochemical analyses (data not shown). As for thirteen lupus nephritis patients who experienced renal biopsies, all patients with DPLN and one with PLN showed detectable level of urinary IL-8, whereas urinary IL-8 was not detected in any patients with MLN. These results suggest that IL-8, produced in the glomeruli, promotes the infiltration of leukocytes, particularly neutrophils into glomeruli in the process of renal injury.

IL-8 is known to promote neutrophil adhesion to endothelium *in vitro* [18, 19] and to cause the release of reactive oxygen metabolites [20] and degranulation of neutrophils [21]. Thus, it is possible that neutrophil activation by IL-8 produced in diseased glomeruli was also involved in glomerular injury. Thus, the measurement of urinary IL-8 may detect the local inflammatory events, particularly those related to both infiltration and activation of leukocytes, in the diseased glomeruli.

The efficacy of pulse therapy with a corticosteroid has been established on lupus nephritis [22], IgA nephropathy [23], and cryoglobulinemia [24] as judged by improvement of the prognosis. However, the precise mechanism of the effects of glucocorticoids on glomerular injury remains to be investigated. In this study, urinary IL-8 levels decreased markedly in all patients after treatment with pulse therapy. Glucocorticoids have been shown to suppress IL-8 production at the transcriptional level in a human fibrosarcoma cell line [25]. Although it is not clear at the moment whether similar effects are exerted on mesangial, endothelial, or epithelial cells, it is tempting to speculate that one of the pharmacological actions of glucocorticoids might be the inhibition of IL-8 production by activated resident cells and infiltrating mononuclear cells. If this is the case, agents, which specifically inhibit IL-8 production or block its biological functions, could be used along with steroid pulse therapy.

Acknowledgments

We gratefully acknowledge Dr. I. Ma for her technical assistance and Dr. Y. Ko for his technical advice of measuring IL-8 by ELISA. We also acknowledge Drs. R. Sumita, K. Ohta, G. Ohta, Y. Noda, S. Takeda, K. Ohta, Y. Ishida, H. Iida, M. Kurosaki and S. Aoki for their help in collecting samples. We would like to express our gratitude to Dr. B. W. Nielsen (University of Aarhus) for critical review of this manuscript.

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