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CASE REPORT

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A case of renal involvement in persistent immune activation caused by chlamydial salpingitis

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Abstract A 24-year-old woman presented with renal insufficiency, macrohematuria, and mild urinary protein. Polyclonal hypergamma-globulinemia, thrombocytosis, increased concentration of serum, and urinary interleukin (IL)-6 all indicated persistent immune activation caused by a *Chlamydia trachomatis* infection of the fallopian tube. Gynecological treatment with levofloxacin was effective both for the renal symptoms and other immunological parameters. First and second renal biopsy specimens showed an immune-complex glomerulopathy with extensive interstitial infiltration of many types of inflammatory cells, including plasma cells. Thus, we conclude that chlamydial salpingitis must be considered as one causative disease factor for renal involvement by means of its persistent immune activation effects.

Keywords *Chlamydia trachomatis* · Salpingitis · Immunecomplex glomerulopathy · Interleukin-6 · Levofloxacin

Introduction

Chlamydia trachomatis infection is a leading cause of sexually transmitted disease, resulting in female tubal infertility. Although treatment with antibiotics may reduce patient symptoms, such as lower abdominal pain and pyrexia, *C. trachomatis* has not been recovered from tubal or endometrial tissues [5, 19]. Because persistent infections have been proposed as a source of antigen for the stimulation of the host immune system, repeated exposure to chlamidial antigens is thought to contribute to the occurrence of immune-complex-type nephropathy. Here, we describe a patient with renal involvement in persistent immune activation, which might be associated with fallopian infection with *C. trachomatis* (salpingitis).

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Clinical history

A 24-year-old woman was admitted to our hospital in October 1996 for investigation of macrohematuria, which had appeared three or four times per month since April 1996. At 23 years of age, she had experienced a first occurrence of macrohematuria on only one day during the fourth month of her third pregnancy, but no events thereafter. Urological examinations were normal, and she was hospitalized for the purpose of further examination by internists. Physical examinations were normal and superficial lymphadenopathy, hepatosplenomegaly, skin rash, and edema were not observed. There had been some gynecological problems in her past medical history. At 19 years of age, a medical abortion was performed (3 months into her first pregnancy). From 20 years of age, she had been repeatedly suffering lower abdominal pain, continuing for 7 days after every menstruation. At 21 years of age and 23 years of age, she contracted gestational toxicosis, and proteinuria occurred from 37 weeks in each pregnancy but immediately resolved after delivery of a healthy child.

Laboratory data (Table 1) showed four distinctive features: (1) microcytic anemia; (2) evidence of persistent immune stimulation, i.e., polyclonal gamma-globulinemia, thrombocytosis, activation of the coagulation and fibrinolytic systems, slightly elevated C-reactive protein (CRP) and a high erythrocyte sedimentation rate (ESR), additional examination revealing a high titer of serum interleukin (IL)-6; (3) hypolipidemia; and (4) renal insufficiency indicated by urinary protein of 1.61 g/day, creatinine clearance 73.4 ml/min, urinary red blood cell (RBC) sedimentation >100/HPF, and other sedimentations. To investigate the causative pathogenesis, we had performed further tests as follows: anti-nuclear antibody (Ab), ds-DNA Ab, rheumatoid factors, anti-neutrophil cytoplasmic Ab, and anti-cardiolipin Ab, which were all negative. Other anti-virus Abs, including hepatitis B virus, hepatitis C virus, human immunodeficiency virus, Epstein-Barr virus, and cytomegalovirus, were also negative. Bone marrow aspiration revealed no malignancy and no plasmacytosis. After performance of renal biopsy, the patient left the hospital.

At this time, there was no hindrance in her daily life; she was treated with dipylidamole 300 mg/day and warfarin 3 mg/day. From gynecological history and examination, she was diagnosed

as suffering from chlamydial salpingitis. An increased titer of *C. trachomatis* antibodies was measured using an enzyme-linked immunosorbent assay [ELISA; Sero IPALISA (Savyon Diagnostics Ltd); immunoglobulin (Ig)A, 1.54 (normal range <0.9); IgM, 1.0 (normal range <0.9)]. The new quinolone antibiotic levofloxacin (LVFX) 300 mg/day was administered for 2 weeks, resulting in the (temporary) disappearance of the macrohematuria.

In May 1997, the patient felt severe lower abdominal pain and pyrexia and was readmitted to hospital. The laboratory data were very similar to the findings at the first admission, except for an increase of CRP (9.4 mg/dl), decrease of platelet counts (35.4×10^4/μl), and worsening of renal function (serum creatinine 1.4 mg/dl, creatinine clearance 28.5 ml/min.). Gynecological echographs showed moderate effusion in Douglas's pouch, and she was diagnosed with acute pelvic inflammation caused from worsening of the salpingitis and was again administered LVFX for 2 weeks (Fig. 1). Together with a decrease of CRP, the abdominal pain and pyrexia were relieved. On the 11th day in the hospital, a second renal biopsy was taken. From the 23rd day, she was treated with oral prednisolone and intravenous heparin infusion followed by oral warfarin. Platelet counts and γ-globulin gradually decreased but remained outside the upper limit of the normal range. Creatinine clearance also improved. However, the levels of urinary protein and urinary sediment of red blood cells (RBCs) were persistent. Serum and urinary IL-6 showed high titers at the beginning of hospitalization and improvement later.

As of July 1999, tapered prednisolone (10 mg/day) and warfarin (1.5 mg/day) has been prescribed continuously, but chlamydial infection is still apparent serologically (IgA 3.02, IgG 0.58), and renal functions are slowly worsening (serum creatinine is 2.5 mg/dl). Also, the patient had the characteristic laboratory findings of blood and urine.

Pathologic findings

A sufficiently long specimen (1.8 cm length, cortex:medulla=2:1) was obtained at first biopsy, but only four glomeruli were located (Fig. 2). Each glomerulus appeared to show an increase of mesangial cells and matrix and endocapillary proliferation. Thickness of the glomerular basement membrane (GBM) was normal. One glomerulus demonstrated fibrous crescent. In the cortex, scattered interstitial nephritis with infiltrating cells consisting of lymphocytes, eosinophils, plasma cells, and neutrophils was observed. Immunofluorescence (IF) revealed deposits of IgM and C3c in the glomeruli with a granular pattern, but IgA, IgG, C1q and fibrinogen were negative. Electron microscopy (EM) showed a small number of subepithelial deposits in the GBM, the effacement of the foot processes of glomerular epithelial cells, and invasion of neutrophils into the glomerulus (electron micrograph not shown).

Additional findings were documented in the second renal biopsy specimen (Fig. 3). A sufficiently long specimen was again obtained, but only five glomeruli were located. All glomeruli appeared to show endocapillary proliferation and broad, extended interstitial nephritis with the same infiltration of cells as the first biopsy specimen. Lymphocytes, neutrophils, eosinophils, and monocytes were found to be attached along the endothelial cells of small arteries, which were located in the region of interstitial nephritis (so-called "endocapillaritis"). IF showed deposition of IgA and C3c in a mesangial pattern, but the deposition of IgM was only seen at sclerotic glomeruli.

Table 1 Laboratory findings of first admission. *CBC* complete blood cell count, *WBC* white blood cell, *RBC* red blood cell, *Hb* hemoglobin, *Htc* hematocrit; *Plt* platelet; *TP* total protein, *Alb* albumin, *GOT* glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase, *LDH* lactate dehydrogenase, *TG* triglyceride, *BUN* blood urea nitrogen, *Cr creatinine*, *u-FDP*urinary fibrin/fibrinogen degradation products, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *Ig* immunoglobulin, *Ab* antibody, *IL* interleukin, *SG* specific gravity, *HF* high power field, *WF* wide power field, *LF* low power field

	Findings at first admission	Normal range
CBC		
WBC	7000/ml	3600–9100
RBC	318×10^4/ml	374–502
Hb	7.4 g/dl	11.1–15.3
Htc	22.6%	33.2–45.3Plt
67.6×10^4/ml	13.0–37.0	
Blood chemistry		
TP	8 g/dl	6.5–8.0
Alb	3.46 g/dl	3.8–5.5
GOT	7 IU/l	11–35
GPT	2 IU/l	4–30
LDH	245 IU/l	220–440
γ-GTP	6 IU/l	4–62
Ch-E	338 IU/l	256–613
Total cholesterol	81 mg/dl	130–250
TG	33 mg/dl	55–130
BUN	17.2 mg/dl	8.0–19.0
Cr	0.9 mg/dl	0.8–1.3
Na	138 mEq/l	136–148
K	4.4 mEq/l	3.6–5.0
Cl	107 mEq/l	98–109
Fibrinogen	438 mg/dl	150–400
u-FDP	74.4 mg/ml	<0.1
Serological test		
CRP	2.2 mg/dl	<0.3
ESR	128 mm/h	3–15
IgG	2870 mg/dl	738–1244
IgA	950 mg/dl	93–296
IgM	258 mg/dl	46–453
CH50	61 U/ml	31.3–46.3
C3	52 mg/dl	45–95
C4	40 mg/dl	15–55
Anti-nuclear Ab	40(homo) dilution	–
Anti-ds-DNA Ab 2	IU/ml	<10
IL-6	9.2 pg/ml	<4
Urinary Protein	1.61 g/day	<0.15
Creatine clearance	73.4 ml/min	89.5–129.9
Urinalysis		
pH	6	
SG	1.015	
Protein	2+	–
Glucose	–	–
Occult	3+	–
Keton	–	–
Sediment		
RBC	>100/HF	
WBC	6–10/HF	
Cast		
Granular	5–10/WF	
Epithelial	1–5/LF	
Hyaline	0–1/WF	

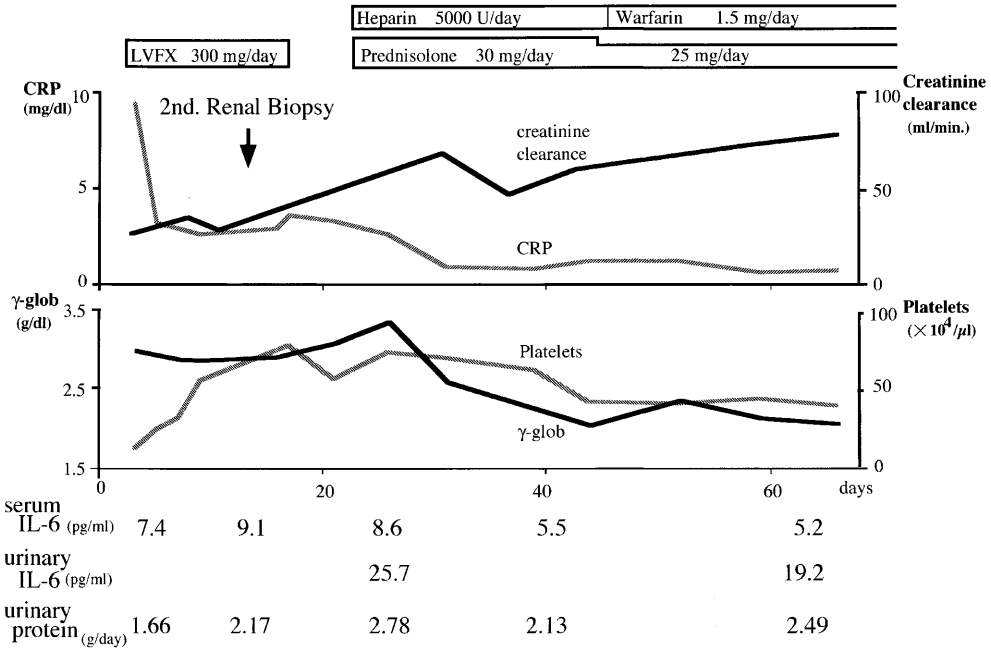

Fig. 1 Clinical course of second admission. In May 1997, acute pelvic inflammatory disease resulted from chlamydia salpingitis. Serial readings of the patient's creatinine clearance, C-reactive protein level (CRP), platelets, and γ-globulin are plotted against time. Serum and urinary interleukin (IL)-6 concentrations and urinary protein are shown. Levofloxacin, prednisolone, heparin, and warfarin treatment is also shown. All indices improved, but platelets and γ-globulin did not return to normal range

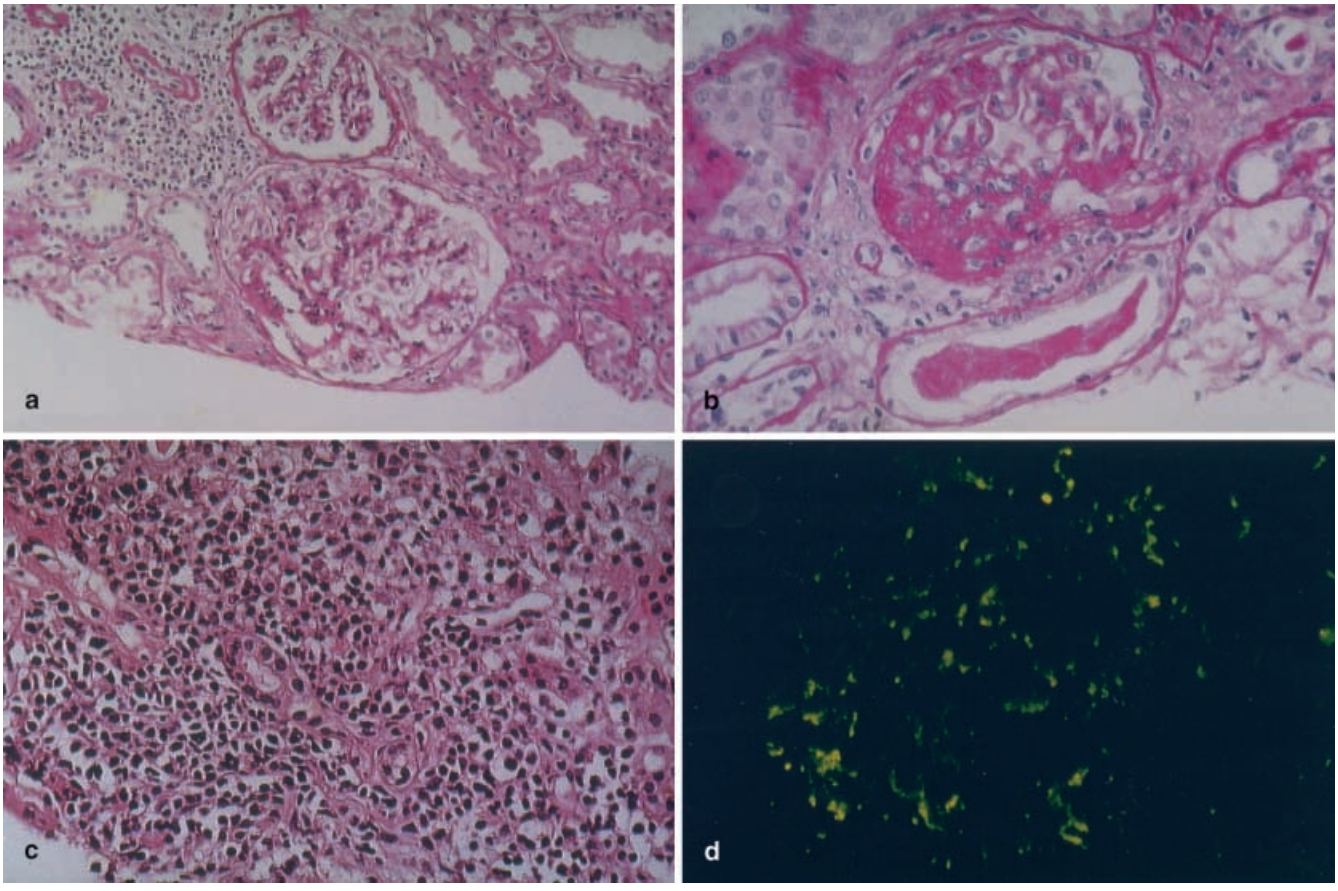

Fig. 2 Renal histology of first renal biopsy. **a**, **b** Four glomeruli were obtained. Each glomerulus appeared to show mesangial proliferation but no thickening of glomerular basement membrane. One glomerulus demonstrated segmental sclerosis and fibrous crescent. **c** Scattered interstitial nephritis with infiltrating cells consisting of lymphocytes, eosinophils, plasma cells, and neutrophils. **d** Immunofluorescence (IF) staining showed deposits of immunoglobulin (Ig)M and C3c in glomeruli with a granular pattern. **a** periodic acid–Schiff (PAS) staining, ×160; **b** PAS staining, ×200; **c** PAS staining, ×200; **d** IF using anti-human IgM mouse monoclonal antibody, ×400

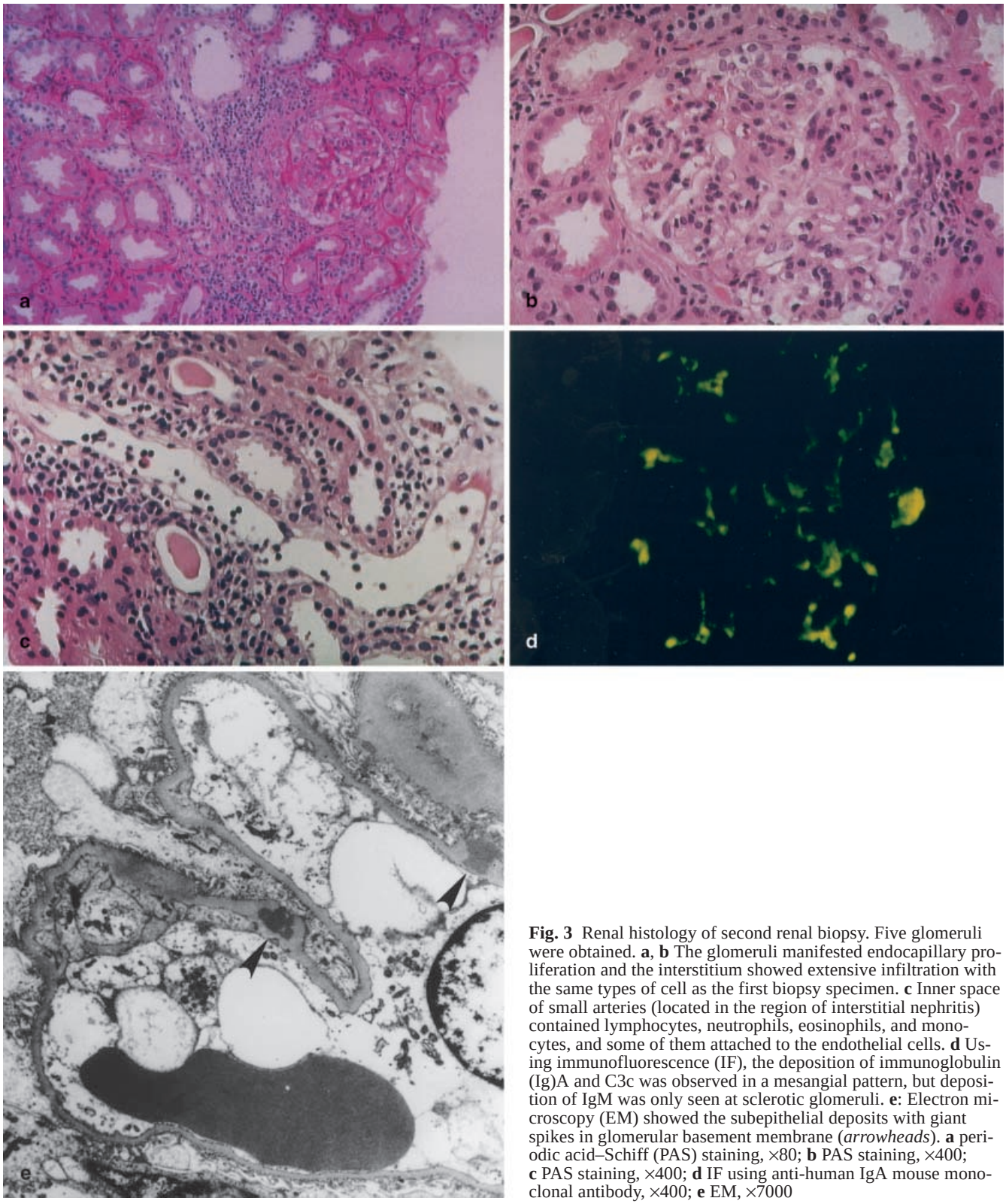

Fig. 3 Renal histology of second renal biopsy. Five glomeruli were obtained. **a**, **b** The glomeruli manifested endocapillary proliferation and the interstitium showed extensive infiltration with the same types of cell as the first biopsy specimen. **c** Inner space of small arteries (located in the region of interstitial nephritis) contained lymphocytes, neutrophils, eosinophils, and monocytes, and some of them attached to the endothelial cells. **d** Using immunofluorescence (IF), the deposition of immunoglobulin (Ig)A and C3c was observed in a mesangial pattern, but deposition of IgM was only seen at sclerotic glomeruli. **e**: Electron microscopy (EM) showed the subepithelial deposits with giant spikes in glomerular basement membrane (*arrowheads*). **a** periodic acid–Schiff (PAS) staining, ×80; **b** PAS staining, ×400; **c** PAS staining, ×400; **d** IF using anti-human IgA mouse monoclonal antibody, ×400; **e** EM, ×7000

IgG and fibrinogen was negative. EM showed dense deposits at paramesangial and increased amounts of subepithelial deposits with giant spikes at GBM.

Discussion

We report a case of renal involvement during persistent *C. trachomatis* infection. Gynecologists using physical examination, echograph, and detection of anti-*C. trachomatis* antibodies diagnosed chlamydial salpingitis. Because high titers of IL-6 and polyclonal gamma-globulinemia were detected, differential diagnosis was required to exclude a certain category of diseases such as Crow-Fukase syndrome and Castleman's disease, which are also associated with over-expression of IL-6. However, bone marrow aspiration and other physical examination ruled out these diseases. Therefore, we considered chlamydia salpingitis as the disease responsible for the renal insufficiency.

Does *C. trachomatis* affect the pathogenesis of nephropathy?

To the best of our knowledge, there is no reference in the literature describing an association between renal involvement and *C. trachomatis* infection. As for *C. psittasi*, which is the same Chlamydia genus, some case reports have noted the occurrence of nephropathy after an acute respiratory organ infection and endocarditis [4, 9, 11, 12, 16]. In these cases, the renal histology showed interstitial nephritis, acute tubular necrosis, and mesangial or endocapillary proliferative glomerulonephritis. We interpreted these histological findings as being similar to our case.

The patient's medical history indicated the possibility that subclinical and persistent *C. trachomatis* infection had preceded the occurrence of the first macrohematuria because the symptoms of menstruation-associated lower abdominal pain occurred from the age of 20 years. Extensive sexual activity and abortion during the teens are considered as risk factors for sexually-transmitted infection with *C. trachomatis* [5, 17]. If able to cause the development of nephropathy, fallopian infection of *C. trachomatis* cannot be ignored in this context.

The meaning of distinctive laboratory data

We hypothesize the presence of persistent inflammation, which was documented by many laboratory data, such as marked increase in platelet count, polyclonal gammaglobulinemia, CRP, erythrocyte sedimentation rate, and hypercoagulation. In fact, high levels of serum and urinary IL-6 in each clinical investigation were outside the normal range. Furthermore, antibiotics and immunosuppressive (steroidal) therapy induced a parallel improvement in IL-6 titers and inflammatory parameters. As for marked hypolipidemia, it is becoming clear that hyper-IL-6 states reduce lipogenesis [1, 3]. Thus, we interpreted this to indicate a strong association between occurrence of persistent inflammation induced by chronic infection of *C. trachomatis*.

Newer aspects of persistent infection of *C. trachomatis* have been reported [2, 15]. IL-6 and interferon-γ, which are locally produced in infected tissues, favor the persistent infection of host cells. Under these circumstances, *C. trachomatis* might continuously divert the host immune system and sometimes cause a chronic strong inflammatory response. In this case, treatment with LVFX, which is the gold standard in therapy of chlamydial salpingitis, was effective in reducing the severity of inflammation, but chlamydia infection persists locally.

Analysis of renal histology

When the two renal tissue images were compared, endocapillary proliferative changes, glomerular dense deposits, and increased hump-like materials were added. Also glomerular deposition of immunoglobulins and complement was observed in both biopsies. This evidence suggests that immune-complex-mediated glomerulopathy had occurred.

The glomerular deposition of Ig class changed from IgM (granular pattern) into IgA (coarse in mesangial area) over time. There is a possibility that this histological finding reflected seroconversion during *C. trachomatis* infection because IgM production occurs early in the immune response to *C. trachomatis* and IgA occurs after acute or chronic responses or the recurrence of infection [7, 13]. To seek direct evidence of *C. trachomatis*, we performed immunohistochemical assays on renal tissues using anti-*C. trachomatis* mouse monoclonal Ab (Biomeda, Foster, Calif.) and DNA polymerase chain reaction on extracts from urinary sediment cells, but no such evidence was obtained. However, it remains possible that the deposited immune complexes might consist partly of *C. trachomatis*.

IL-6 is a cytokine that influences the terminal differentiation of B cells to plasma cells, but its role in renal pathology is obscure. Urinary levels of IL-6 are thought to be a marker for the interstitial damage of IgA nephropathy and active lupus nephritis [10, 14]. Suematsu reported that in a transgenic mouse model, over-expression of IL-6 causes mesangial proliferation and plasma cell infiltration into the interstitium [18] but recently other investigations reported that IL-6 over-expression led to reduced renal function without mesangial proliferation and interstitial nephritis [8]. Because our case showed massive interstitial infiltration with many types of inflammatory cells and endocapillaritis of small arteries, we assume that the existence of humoral factors such as IL-6 play a key role in renal damage.

In summary, we conclude that renal involvement in this case was associated with chlamydial salpingitis.

However, important questions remain open. For example, the second renal biopsy tissue might take overlap of IgA nephropathy into consideration, and *C. trachomatis* might be one of causative pathogens of the IgA nephropathy. At any rate, we should recognize *C. trachomatis* as one of the latent pathogens causing renal dysfunction.

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