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Chronic Lupus Peritonitis Is Characterized by the Ascites with a Large Content of Interleukin-6

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Systemic lupus erythematosus (SLE) is an autoimmune disease and can cause multi-organ damage. Peritoneal involvement, also called lupus peritonitis, is a rare but sometimes fatal manifestation. Deposition of immune complexes consisting of immunoglobulin G and complement is considered to be involved in the pathogenesis of lupus peritonitis; however, it remains unknown whether inflammatory cytokines contribute to the pathology of this manifestation. Here we present two patients with treatment-resistant lupus peritonitis: a 37-year-old woman with a 26-year history of SLE who had been treated with prednisolone and cyclophosphamide followed by azathioprine and a 65-year-old woman with a 33-year history of SLE who had been treated with prednisolone alone. Both patients were admitted to our department because of abdominal distention. Computed tomography scans showed massive ascites. Ascitic fluid examinations of both patients showed leukocytosis with no evidence of malignancy or infection. After eliminating other causes for ascites, they were diagnosed with lupus peritonitis. Despite the intensified immunosuppressive therapy, they died of uncontrolled peritonitis several months after admission. Examinations of the ascites at admission also revealed a large content of interleukin (IL)-6, compared with other inflammatory cytokines, IL-1β and tumor necrosis factor-α. In fact, the ascitic IL-6 levels of these two patients were 12,389 pg/mL and 5,486 pg/mL, much higher than their serum IL-6 levels of 36 pg/mL and 140 pg/mL, respectively. We therefore suggest that IL-6 may contribute to the pathogenesis of lupus peritonitis and that the inhibition of IL-6 signaling may provide a novel therapeutic strategy for lupus peritonitis.

Keywords: ascites; cytokine; interleukin 6; lupus peritonitis; systemic lupus erythematosus
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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies and multi-organ damage (Tsokos 2011). Serositis is one of the major organ involvements and observed in 10%-30% of lupus patients (Man and Mok 2005; Al Arfaj and Khalil 2009). Pleural and pericardial involvements are common; however, peritoneal serositis, which is also called lupus peritonitis, is rare (Man and Mok 2005; Prasad et al. 2012; Zhou et al. 2014).

Lupus peritonitis is classified into two types (Kawashiri et al. 2012); the acute type, which occurs with abdominal pain and responds well to corticosteroid therapy, and the chronic type, which usually responds poorly to corticosteroids and requires additional immunosuppressive agents, such as cyclophosphamide or azathioprine (Provenzano et al. 1993; Kawashiri et al. 2012).

The exact mechanism of lupus peritonitis remains unclear; however, deposition of immune complexes is considered to be involved in the pathogenesis of this condition (Pott Junior et al. 2012). Inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, may also play a role in the pathogenesis of lupus peritonitis; however, to our knowledge, ascitic cytokine profiles in lupus peritonitis have not been reported. Here we present two cases of treatment-resistant chronic lupus peritonitis, and our cases suggest that IL-6 may contribute to the pathology of lupus peritonitis.

Clinical Courses

A 37-year-old woman presented with a two-month history of painless abdominal distension, termed Patient 1. She was diagnosed with SLE based on the presence of antinuclear antibody (ANA), anti-DNA antibody, pleuritis, nephritis, and thrombocytopenia 26 years ago, and she had been treated with prednisolone (PSL) and intravenous cyclophosphamide therapy (IVCY) followed by azathio-

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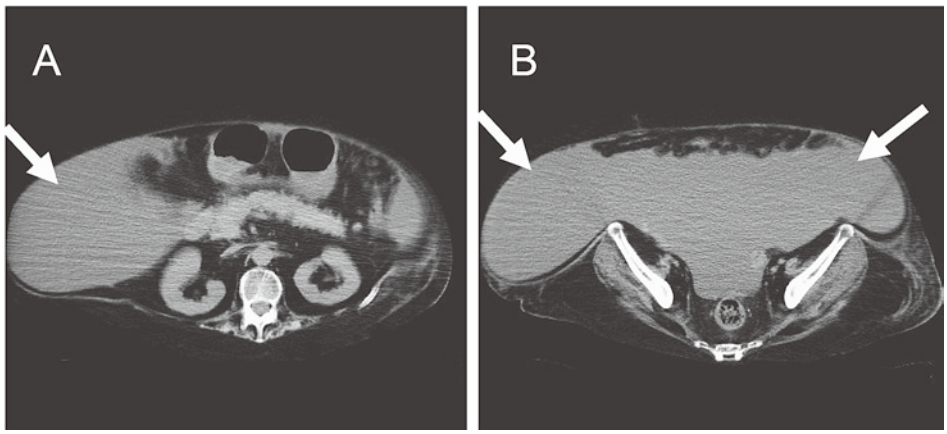

Fig. 1. Abdominal CT scan of Patient 1.
CT scan of Patient 1 revealed massive ascites (arrows).

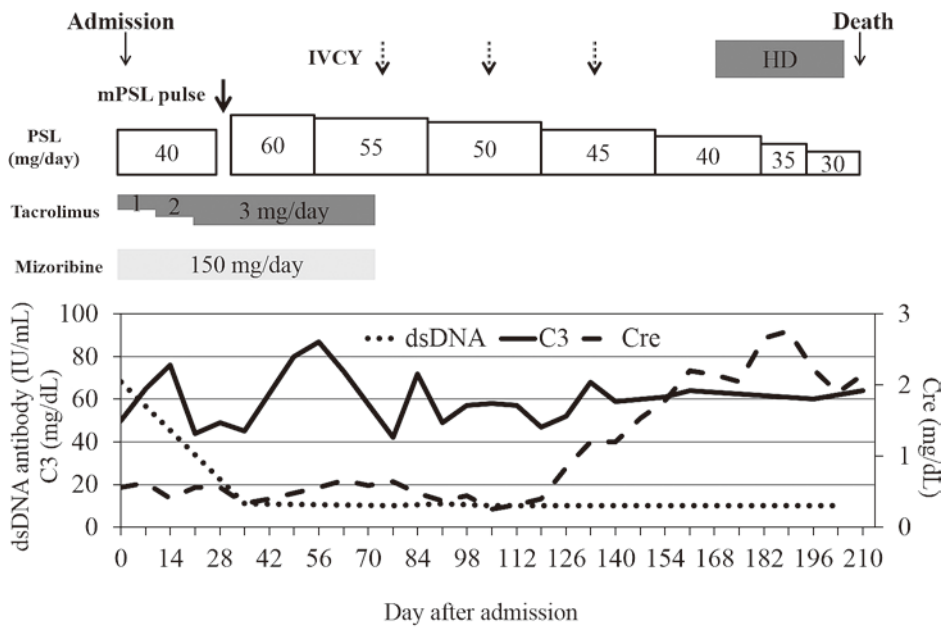

Fig. 2. Clinical course of Patient 1.
Clinical course of Patient 1 showed that combination of an increased dose of prednisolone and immunosuppressive agents was not effective, and the patient died of respiratory failure seven months after admission.
IVCY, intraveneous cyclophosphamide; mPSL, methylprednisolone; HD, hemodialysis.

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On admission, her blood pressure was 129/80 mmHg, body temperature was 37.0°C, heart rate was 111 beats/min, and oxygen saturation level (SpO2) was 96%. A computed tomography (CT) scan demonstrated massive ascites (Fig. 1). Ascitic fluid was exudative when the Light criteria (Light 2002) was adopted to ascites, and its examination revealed leukocytosis with no signs of malignancy or infection (Table 1). Laboratory tests showed an elevation of anti-DNA antibodies, hypocomplementemia, and proteinuria of non-nephrotic range (Table 1). Further investigations excluded other causative disorders, such as right-sided heart failure and liver cirrhosis. Thus, we made a diagnosis of lupus peritonitis and administered an increased dose of PSL combined with antibiotics, diuretics, and immunosuppressive agents. We initially used the combination of tacrolimus and mizoribine because these agents did not have the risk of infertility and secondary malignancies; however, since the combination was not effective, the patient received IVCY (500 mg every four weeks) again. Although the SLE disease activity index (SLEDAI) decreased from 18 to 9 (Bombardier et al. 1992), Patient 1 died of respiratory failure due to increased intra-abdominal pressure seven months after admission (Fig. 2).

Another patient, a 65-year-old woman, presented with a one-month history of painless abdominal bloating, termed Patient 2. She was diagnosed with SLE based on the presence of ANA, malar rash, pleuritis, and nephritis 33 years

Table 1. Laboratory findings of the two patients.

	Patient 1	Patient 2	
Complete blood cell counts			
WBC	7,500	4,200	/mL
Seg	80	85	%
Lym	10	8	%
Mon	10	6	%
Eos	0	0	%
Bas	0	0	%
RBC	399×10^4	278×10^4	/mL
Hb	13.5	8.9	g/dL
MCV	98.7	94.9	fl
Hct	39.3	26.4	%
Ret	2.5	1.4	%
Plt	11.6×10^4	13.9×10^4	/mL
Ascitic Fluid			
total cells	475	75	cells/mm^3
polynuclear	325	25	cells/mm^3
mononuclear	150	50	cells/mm^3
TP	3	3.1	g/dL
LDH	111	88	IU/L
ADA	13.1	4.6	IU/L
Urinalysis			
protein	(1+)	(2+)	
	1.92	1.21	g/g・cr
occult.blood.	(−)	(−)	
<sediment>			
WBC	5-9	10-29	/HPF
Cast	5-9	5-9	/LPF
Biochemistry			
T.Bil (0.3-1.2)	0.6	0.5	mg/dL
ALP (115-330)	323	132	IU/L
γ-GTP (10-47)	358	13	IU/L
AST (8-38)	35	12	IU/L
ALT (4-43)	69	9	IU/L
LDH (117-205)	360	199	IU/L
TP (6.7-8.1)	5.6	5.7	g/dL
Alb (4.2-5.3)	2.7	2.8	g/dL
BNP (< 18.4)	27.3	145.6	pg/mL
HbA1c (4.8-6.2)	5.4	5.3	%
Procalcitonin (< 0.4)	0.06	0.05	ng/mL
β-D-glucan (< 10)	11	< 4	pg/mL
Na (136-145)	141	136	mEq/L
K (3.5-5.1)	3.8	5.3	mEq/L
Cl (98-107)	106	107	mEq/L
BUN (8-20)	20	54	mg/dL
Cr (0.32-0.84)	0.56	3	mg/dL
C3 (83-140)	50	74	mg/dL
C4 (14-37)	8.2	30.2	mg/dL
CH50 (23-46)	20.6	41.8	U/mL
ANA (< 79)	640	< 79	fold
dsDNA Ab (< 12)	68	2.2	IU/mL
Sm Ab (< 6.9)	< 5	< 5	index
RNP Ab (< 14.9)	6.9	37.6	index
SS-A Ab (< 9.9)	110	26.3	index
SS-B Ab (< 14.9)	< 5	< 5	index
Lupus anticoagulant	(−)	(−)	
β2GP1 Ab (< 1.2)	< 1.2	< 1.2	U/mL
Cardiolipin (< 10)	10	8	U/mL
SAA (< 7.9)	220.7	273.5	mg/mL
CRP (< 0.3)	0.4	3.9	mg/dL
Quantiferon	(−)	(−)	

ago, and she had been treated with PSL alone.

On admission, her blood pressure was 120/64 mmHg, body temperature was 36.8°C, heart rate was 96 beats/min, and SpO2 was 96%. A CT scan revealed marked accumulation of ascites (Fig. 3). Laboratory findings showed positive result for anti-RNP antibody, slight decrease of C3, proteinuria of non-nephrotic range, and renal dysfunction (Table 1). Ascitic fluid examination showed leukocytosis with no evidence of malignancy or infection (Table 1). After ruling out other causes for ascites, we administrated an increased dose of PSL (40 mg/day) with antibiotics and diuretics, although we did not use immunosuppressive agents because of renal dysfunction; however, massive ascites and the SLEDAI (14 on admission) did not improve. Patient 2 died of prerenal failure due to intravascular volume depletion two months after admission (Fig. 4).

Although autopsy was not performed, ascitic cytokines at admission were examined after the death of both patients to explore cytokine profiles in chronic lupus peritonitis. The results indicate that IL-6 was considerably accumulated among the inflammatory cytokines, which were measured at Bio Medical Laboratories (Kawagoe, Saitama, Japan).

Discussion

In this report, we described two cases of treatment-resistant lupus peritonitis. Lupus peritonitis should be diagnosed only after eliminating all the other possible causes for ascites, such as peritoneal carcinomatosis, hepatocellular carcinoma, peritoneal tuberculosis, bacterial or fungal peritonitis, nephrotic syndrome, protein-losing enteropathy, severe malnutrition, portal hypertension, liver cirrhosis, and congestive heart failure (Schousboe et al. 1988). Considerable attention should be paid to this diagnostic procedure. In our cases, we repeated ascitic tap several times in both patients and found no signs of infection or malignancy. Repeated blood cultures, laboratory tests, and other examinations also showed no evidence of other causes for ascites except lupus peritonitis. Thus, we made a diagnosis of lupus peritonitis in both patients.

Chronic lupus peritonitis is usually observed in established lupus patients (Prasad et al. 2012). Disease activity does not always correlate with its manifestation (Schousboe et al. 1988; Kaklamanis et al. 1991). No particular autoantibodies are associated with it (Prasad et al. 2012). On review of the literature, the mortality rate is relatively high (3/16, 19%) (Ito et al. 2002). In both our cases, the patients had a long duration of SLE and their initial manifestations included both pleuritis and nephritis. Positive autoantibodies were different; however, SLEDAI scores were high in both patients. These findings are consistent with previous reports (Schousboe et al. 1988; Kaklamanis et al. 1991; Ito et al. 2002; Prasad et al. 2012).

Previous reports on ascitic fluid examination in patients with chronic lupus peritonitis have shown mixed white blood cell counts, with mononuclear and polynuclear cells ranging from 10/mm^3 to 1,630/mm^3, anti-DNA anti-

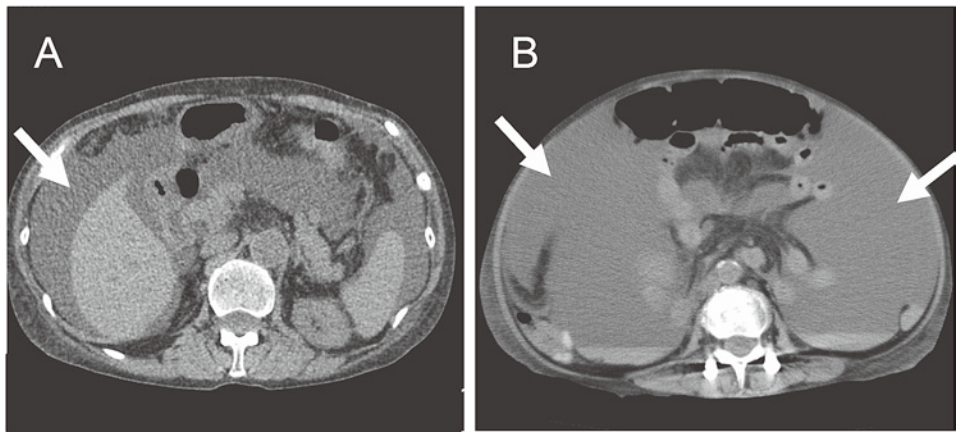

Fig. 3. Abdominal CT scan of Patient 2.
CT scan of Patient 2 demonstrated marked accumulation of ascites (arrows).

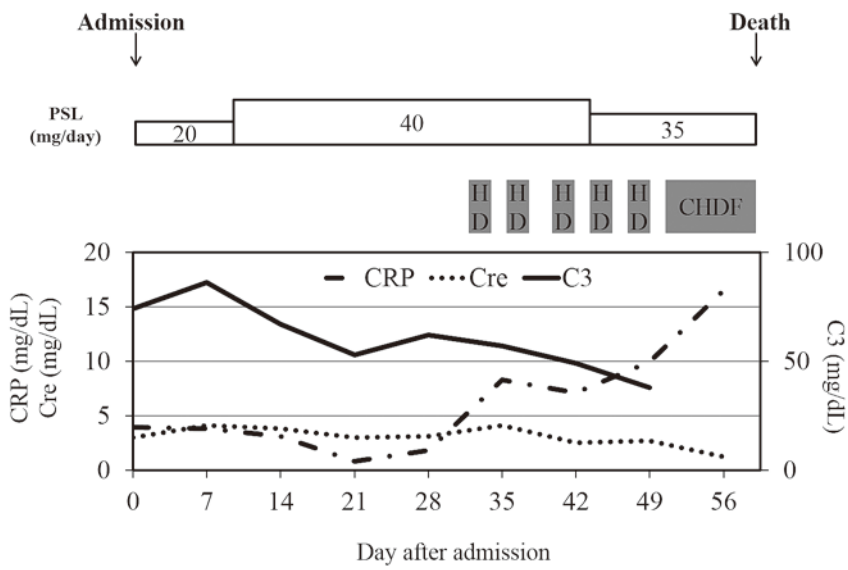

Fig. 4. Clinical course of Patient 2.
Clinical course of Patient 2 showed that an increased dose of prednisolone did not improve massive ascites, and the patient died of prerenal failure two months after admission.
CHDF, continuous hemodiafiltration; HD, hemodialysis; PSL, prednisolone

bodies, immune complexes, and low complement levels (Schousboe et al. 1988; Ito et al. 2002). Peritoneal pathological examination has demonstrated infiltrations of mononuclear or polynuclear leukocytes around the vessels and deposition of immunoglobulin G and complement have been detected with evidence of vasculitis (Schocket et al. 1978; Okamoto et al. 1981). These findings suggest that depositions of immune complexes and concomitant vasculitis contribute to the pathogenesis of lupus peritonitis.

Ascitic cytokines in lupus peritonitis have not been reported. Our patients indicated the accumulation of IL-6 in the ascitic fluid, and the concentration ratio of ascites to serum was high compared with TNF-α and IL-1β (Table 2). IL-6 is a pleiotropic cytokine produced by various cell types, including T cells, B cells, monocytes, fibroblast, keratinocytes, endothelial cells, mesangial cells, and some tumor cells (Nishimoto and Kishimoto 2006). IL-6 has a wide range of biological activities in immune regulation, hematopoiesis, inflammation, and oncogenesis (Kishimoto 2010). IL-6 is also involved in endothelial cell permeability (Desai et al. 2002; Wei et al. 2013; Goldman et al. 2014).

Riche et al. (2013) reported that ascitic TNF-α, IL-1, and IL-6 levels were all increased in bacterial peritonitis caused by gastrointestinal disorders and that the ranges of ascitic cytokines were 90-882 pg/mL (TNF-α), 1,180-22,670 pg/mL (IL-1), and 22,859-328,410 pg/mL (IL-6). Yamamoto et al. (2011) also reported that ascitic TNF-α, IL-1β, and IL-6 significantly increased in patients who developed peritonitis compared with patients who did not after colorectal surgery. Compared with these previous reports, the ascitic cytokine profiles in our patients seem to

Table 2. Cytokine profiles of the two patients.

Patient 1	serum (normal, pg/mL)	ascites (normal, pg/mL)	the ratio of ascites to serum
TNF-α	3.6 (< 2.8)	2.1	0.58
IL-1β	0.2 (< 0.2)	0.2	1
IL-6	36 (< 8)	12,389	344.1
Patient 2			
TNF-α	51.7 (< 2.8)	1.5	0.029
IL-1β	0.2 (< 0.2)	7	35
IL-6	140 (< 8)	5,486	39.2

be different from bacterial peritonitis. Among the inflammatory cytokines, only IL-6 level was elevated in our cases. Although IL-6 accumulates in ascites of hepatic and malignant origin (Andus et al. 1992), the pathological condition in which only IL-6 level increases among inflammatory cytokines has not been reported. Thus, we propose a novel IL-6-mediating mechanism of chronic lupus peritonitis. First, deposition of immune complexes from an unknown origin causes inflammation of the peritoneum. Second, mononuclear or polynuclear cells infiltrate the peritoneum and produce IL-6. Finally, IL-6 increases vascular permeability and cause massive ascites. Therefore, inhibition of IL-6 signaling using tocilizumab, an anti-IL-6 receptor antibody, may be a useful therapeutic approach for this condition.

In conclusion, we have presented two patients with treatment-resistant chronic lupus peritonitis. Ascitic fluid examinations revealed that IL-6 was selectively accumulated, the cytokine profiles of which were different from bacterial peritonitis. These findings suggest that IL-6 may be involved in the pathogenesis of lupus peritonitis, and the inhibition of IL-6 signaling may be a novel therapeutic strategy for this condition.

Conflict of Interest

The authors declare no conflict of interest.

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