

# A Case of New-Onset Systemic Lupus Erythematosus With Serositis in a Maintenance Hemodialysis Patient

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**ABSTRACT:** A 61-year-old woman with a 4-year history of maintenance hemodialysis due to end-stage renal disease of unknown cause was admitted because of a recurrent fever and abdominal pain lasting for 3 months. She had rheumatoid arthritis as a complication and had taken sulfasalazine for over 4 years. Laboratory data revealed thrombocytopenia, hypocomplementemia, a high C-reactive protein level, and positivity for antinuclear antibody and anti-double strand DNA antibody. Gallium scintigraphy showed pericarditis, pleuritis, and peritonitis. Nonscarring alopecia was also noted. She was diagnosed as having systemic lupus erythematosus (SLE). Drug-induced lupus elicited by sulfasalazine was ruled out because the symptoms did not improve even after the discontinuation of the drug upon admission. Oral prednisolone treatment markedly improved her symptoms and laboratory data. However, she later died of sepsis arising from proctitis on day 71 of admission. This report underscores the necessity of considering new-onset SLE in patients with unexplained fever and serositis, including pleuritis, peritonitis, or pericarditis, even if they are receiving maintenance dialysis.

**KEYWORDS:** Systemic lupus erythematosus, hemodialysis, serositis, pleuritis, peritonitis, pericarditis

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## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multiple organ involvement, including the skin, joints, central nervous system, and kidneys.<sup>1</sup> SLE usually occurs in young and middle-aged women, with a decline in the incidence after menopause.<sup>2</sup> The results of previous studies have shown that the disease activity of SLE generally weakens after the initiation of dialysis therapy for end-stage renal disease.<sup>3,4</sup> Thus, only a few cases of new-onset SLE during maintenance dialysis therapy have been reported.<sup>5–8</sup> Here, we report a rare case of a 61-year-old woman who newly developed SLE with serositis, including pleuritis, peritonitis, and pericarditis, 4 years after the introduction of hemodialysis for end-stage renal disease.

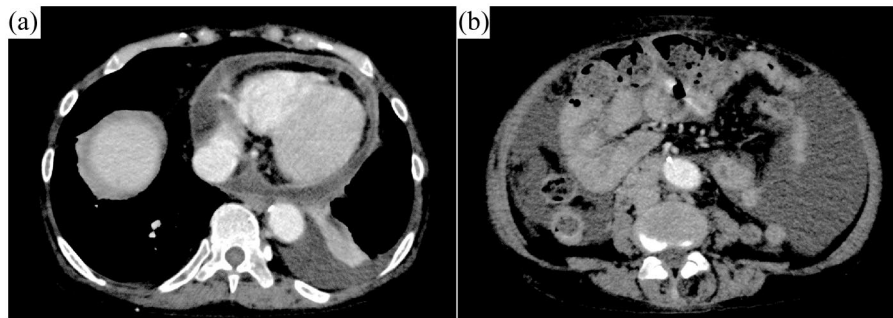
## Case Presentation

At the age of 29 years, the patient underwent a blood type-matched living donor kidney transplantation for end-stage renal failure of unknown cause. However, her renal function gradually worsened, and hemodialysis was introduced in February 2015 at the age of 56 years. She was also diagnosed as having rheumatoid arthritis in 2015, based on the presence of arthritis with morning stiffness in both hands and an elevated anti-cyclic citrullinated peptide antibody level (8.8 U/mL). She tested negative for anti-double strand DNA (anti-dsDNA) antibody, and her complement levels were normal. Thereafter, she had been treated with 2 drugs: prednisolone (PSL; 5 mg/day) and sulfasalazine.

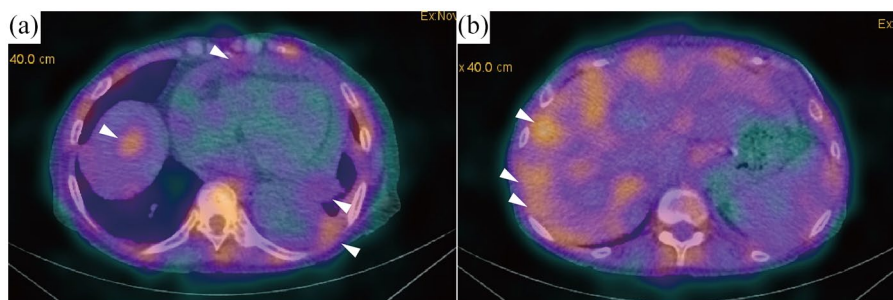
In August 2019, she developed a fever and abdominal pain. A laboratory examination revealed an elevated C-reactive protein (CRP) level of 26.24 mg/dL and a procalcitonin level of 24.24 ng/mL, and a computed tomography (CT) examination showed an increase in mesenteric fat tissue density and ascites. She was diagnosed as having peritonitis and was treated with antibiotics (meropenem) for 14 days. Her abdominal pain improved, and she was discharged once her CRP level had decreased to 0.47 mg/dL. However, 4 days later, she developed a fever again and visited our hospital. She was diagnosed as having recurrent peritonitis and was treated with antibiotics (meropenem and tazobactam/piperacillin) for 3 weeks. Her symptoms improved again, and she was discharged. However, 2 weeks after discharge, she was readmitted to our hospital because of repeated fever, abdominal pain, and dyspnea.

A physical examination on admission revealed a blood pressure of 70/47 mmHg, a heart rate of 159 beats per minute, an atrial fibrillation rhythm, and a body temperature of 37.3°C. The lung fields were clear to auscultation, and no neurological abnormalities were detectable. A contrast-enhanced CT examination showed the thickening of the pericardium, pericardial effusion, left pleural effusion, and ascites (Figure 1). Pleuritis, pericarditis, and peritonitis were suspected. A laboratory examination revealed the following results: white blood cell count, 6300/μL; CRP, 15.08 mg/dL; procalcitonin, 35.64 ng/mL; C3, 39 mg/dL; C4, 6 mg/dL; and CH50, <10 U/mL. The IgG level was elevated to 3529 mg/dL. Although these complement and immunoglobulin data were atypical for sepsis, her fever





**Figure 1.** Contrast-enhanced CT at the third admission showed the thickening of the pericardium, pericardial effusion, left pleural effusion, and ascites: (a) chest CT and (b) abdominal CT.



**Figure 2.** Gallium scintigraphy showed an abnormal uptake (shown in orange, arrowheads) in the pleura, pericardium, and peritoneum, including the liver surface.

had relapsed after stopping the antibiotics treatment. Therefore, she was diagnosed as having bacterial infection, and antibiotic treatment (meropenem) was re-initiated. Since her blood pressure remained low even after her atrial fibrillation rhythm returned to a sinus rhythm, hydrocortisone (200 mg/day) was also administered. On the next day, her blood pressure rose to 130/80 mmHg and her temperature fell to 36.5°C.

Subsequently, the following data were obtained: antinuclear antibody,  $\times 2560$  with homogenous pattern; anti-dsDNA antibody, 354 IU/mL; anti-SSA antibody,  $>1200$  U/mL; anti-SSB antibody, 2.0 U/mL; rheumatoid factor, 16 U/mL; anti-RNP antibody, 3.8 U/mL; anti-SM antibody, 1.2 U/mL; and circulating immune complex-C1q, 10.3  $\mu\text{g}/\text{mL}$ . Thrombocytopenia (82000/ $\mu\text{L}$ ) was also observed. Gallium scintigraphy showed an abnormal uptake in the pleura, pericardium, and peritoneum, including the liver surface (Figure 2). In addition, a dermatologist pointed out the presence of nonscarring alopecia. She was diagnosed as having SLE based on the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria.<sup>1</sup> She also fulfilled the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE<sup>9</sup> (Table 1). However, because the possibility of a bacterial infection could not be ruled out, she continued to receive antibiotic treatment. Her ascites was exudative and smears showed gram-negative bacilli, but no bacteria were detectable in cultures. Transthoracic echocardiography showed structures resembling vegetation on her mitral valve, but a transesophageal echocardiography revealed that these structures were Lambl's excrescences that were unassociated

with infective endocarditis. Blood culture tests and cultures of collected ascites samples repeatedly tested negative. She exhibited a fever and an increase in inflammatory markers even in the presence of antibiotics (Figure 3), suggesting that her fever was caused by serositis arising from SLE. On admission day 36, when the pericardial fluid was sampled, a fungus suspected of being *Aspergillus* was detected. Although it was unclear whether the fungal infection had contributed to the increased inflammatory response, she was treated with voriconazole before the initiation of high-dose steroid therapy. After confirming that her beta-D glucan level was not elevated, treatment with PSL (50 mg/day) was started on admission day 62. The inflammatory reaction rapidly improved after the initiation of PSL, and her anti-dsDNA antibody level decreased to 109 IU/mL. However, 1 week later, she once again experienced fever, abdominal pain, and a decreased blood pressure. A contrast-enhanced CT examination showed proctitis, and *Escherichia coli* was detected in blood cultures. Bacterial proctitis-induced septic shock was suspected. She was treated with antibiotics and vasopressors, but she died in January 2020. An autopsy was not performed.

## Discussion

We have described the case of a 61-year-old woman with end-stage renal disease who newly developed SLE 4 years after the initiation of maintenance hemodialysis therapy. The diagnosis of SLE was quite difficult in the present case because (1) sulfasalazine, a popular drug causing drug-induced SLE, had been prescribed to the patient; (2) the patient presented with fever

**Table 1.** Diagnosis of SLE, based on the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria.

ENTRY CRITERION		DATA	
Antinuclear antibodies		×2560	
ADDITIVE CRITERIA: CLINICAL DOMAINS AND CRITERIA		DATA	SCORE
Constitutional	Fever	38.4°C	2
Hematologic	Leukopenia	2700/μL	4
	Thrombocytopenia	82 000/μL	
	Autoimmune hemolysis	No	
Neuropsychiatric	Delirium	No	0
	Psychosis	No	
	Seizure	No	
Mucocutaneous	Non-scarring alopecia	Yes	2
	Oral ulcers	No	
	Subacute cutaneous OR discoid lupus	No	
	Acute cutaneous lupus	No	
Serosal	Pleural or pericardial effusion	Yes	5
	Acute pericarditis	No	
Musculoskeletal	Joint involvement	No	0
Renal	Proteinuria	N/A	0
	Renal biopsy lupus nephritis	N/A	
ADDITIVE CRITERIA: IMMUNOLOGY DOMAINS AND CRITERIA			
Antiphospholipid antibodies	Anti-cardiolipin antibodies	No	0
	Anti-β2GP1 antibodies	No	
	Lupus anticoagulant	No	
Complement proteins	Low C3	39 mg/dL	4
	Low C4	6 mg/dL	
SLE-specific antibodies	Anti-dsDNA antibody	354 IU/mL	6
	Anti-Smith antibody	No	
		Total score	23

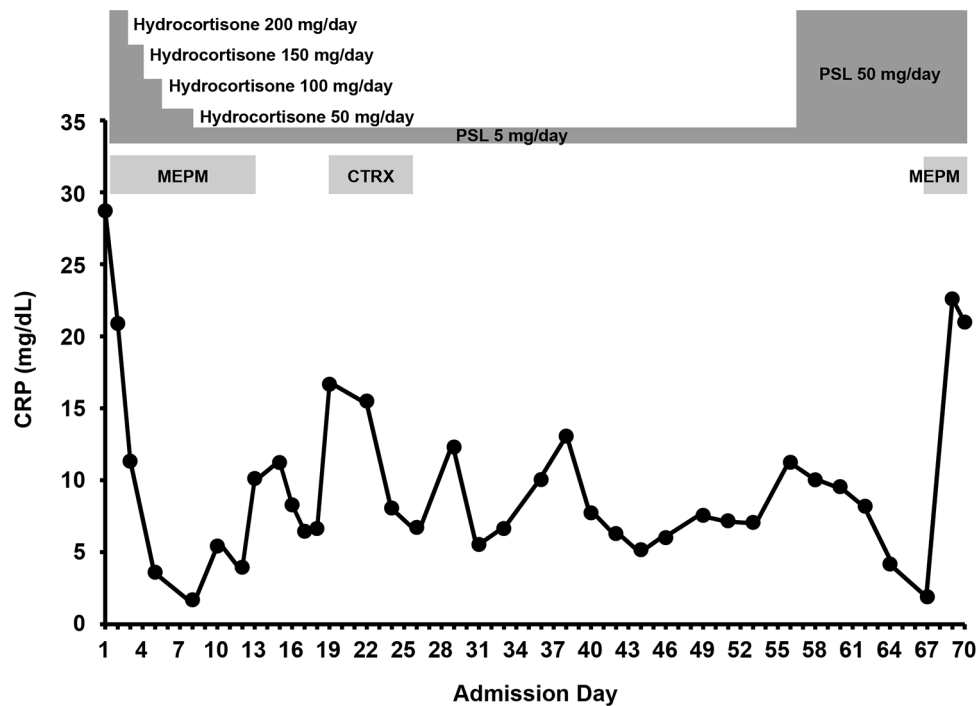
Abbreviation: N/A, not applicable.

and abdominal pain repeatedly and these symptoms were initially improved by antibiotics; and (3) some autoantibodies found in SLE are known to become false-positive in infectious conditions.

When elderly patients develop SLE-like symptoms, we must first consider the possibility of drug-induced SLE. Sulfasalazine, which had been used in this case, is a well-known drug that can cause SLE-like symptoms, although the incidence is 1% or less.<sup>10</sup> We ruled out the possibility of drug-induced SLE for the following reasons. First, in drug-induced SLE, the symptoms often improve within weeks after stopping

the suspected drug.<sup>11</sup> In the present case, her symptoms persisted for at least 2 months after stopping sulfasalazine. Second, anti-dsDNA antibody is rarely positive and hypocomplementemia is rarely observed in drug-induced SLE,<sup>10</sup> while the present case tested positive for anti-dsDNA antibody and hypocomplementemia was observed. For these reasons, we concluded that the patient had newly developed SLE 4 years after the initiation of hemodialysis therapy.

The patient exhibited 3 episodes of fever and abdominal pain before being diagnosed as having SLE. The first and second episodes were mainly caused by bacterial peritonitis. The



**Figure 3.** Clinical course during the third hospitalization.

Abbreviations: CRP, C-reactive protein; CTRX, ceftriaxone; MEPM, meropenem; PSL, prednisolone.

inflammatory markers, including serum procalcitonin levels, were extremely elevated, and the symptoms and the laboratory findings were rapidly improved by the treatment with antibiotics. The patient received 14 and 21 days of antibiotic treatment during her first and second hospitalizations, respectively. She therefore received a sufficient period of antibiotic treatment, given that the recommended duration of antibiotic treatment for spontaneous bacterial peritonitis in cirrhotic patients is 5 to 10 days.<sup>12</sup> On the other hand, the fever and abdominal pain at the time of the third admission were attributed to 2 causes: bacterial peritonitis and SLE. The smears of ascites showed gram-negative bacilli, and the ascites was exudative. In addition, the inflammatory markers, including the serum procalcitonin level, were quickly reduced by the antibiotics. These points suggested the existence of a bacterial infection. However, gallium scintigraphy showed pleuritis, pericarditis, and peritonitis. Although the antinuclear antibody levels in the pleural or ascites fluid were not measured in the present case, infection could not explain the systemic serositis. Instead, the serositis was considered to have been caused by a systemic autoimmune mechanism of SLE. The rapid decrease in the inflammatory response immediately after the third admission (Figure 3) was likely to have been caused by not only the improvement of infection in response to the antibiotics, but also by the decreased disease activity of SLE as a result of the increased steroid dose.

Before the start of PSL treatment, we paid close attention to the exclusion of infective endocarditis, since antinuclear antibodies, and other autoantibodies found in SLE are sometimes positive in cases with infective endocarditis.<sup>13</sup> Blood culture

tests were performed repeatedly without the use of antibiotics, but no bacteria were detected in the cultures. Regarding the structures attached to the mitral valve, we performed echocardiography repeatedly and found that the size of the structures did not change and that the valve was not destroyed. We thus concluded that these structures were unrelated to infection. Moreover, the patient had no rash characteristic of infective endocarditis, such as the Janeway rash or Osler's nodes. Based on these findings, we considered her unlikely to have had infective endocarditis.

The incidence and the trigger for new-onset SLE during maintenance dialysis therapy remain unknown. No information is available regarding how SLE might develop in these patients. Generally, SLE activity decreases after dialysis therapy is initiated.<sup>3,4</sup> Although the precise reason remains unknown, a decreased immune function in hemodialysis patients might be involved. Azotemia during dialysis is known to suppress immune responses.<sup>14</sup> The immune system of hemodialysis patients is also weakened by the functional repression of granulocytes, macrophages, antigen-presenting cells, and B lymphocytes.<sup>14</sup>

No consensus exists regarding the clinical characteristics of newly developing SLE after dialysis initiation. Several cases of new-onset SLE after dialysis initiation have been reported previously.<sup>5-8</sup> Hiyamuta et al<sup>8</sup> reported a 61-year-old woman who developed SLE 25 years after the initiation of dialysis. She presented with arthritis and pleuritis. Tsukamoto et al<sup>7</sup> reported a case of a 70-year-old man with diabetic nephropathy who developed SLE 4 years after the initiation of dialysis. He also

had arthritis and pleuritis. Peritonitis, pericarditis, and pleuritis were observed in the present case. Taken together, these findings suggest that patients who develop new-onset SLE after dialysis initiation are likely to exhibit serositis. However, patients with late-onset SLE diagnosed at the age of 50 years or older have also been reported to develop serositis, lung lesions, and Sjögren's syndrome more frequently.<sup>15</sup> It is unclear whether serositis is associated with the development of SLE after the introduction of hemodialysis or with the late development of SLE. The further accumulation of cases is necessary to solve this question.

In summary, we have described the case of a 61-year-old woman with end-stage renal failure who newly developed SLE 4 years after the initiation of maintenance hemodialysis therapy. The possibility of SLE in patients with unexplained pleuritis, peritonitis, or pericarditis, even after the initiation of hemodialysis, should be considered.

### Author Contributions

S.K., T.Y., N.Y., H.I., and M.O. were responsible for the clinical management of the patient and the preparation of the draft version of this manuscript. All the authors have read and approved the final version.

### Consent for Publication

Written informed consent was obtained from the family of the patient for the publication of this case report and any accompanying images.

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