New-onset systemic lupus erythematosus in a long-term hemodialysis patient with acute pleuritis and pneumonitis

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Received: 23 May 2014 / Accepted: 20 October 2014 / Published online: 7 November 2014
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Abstract A 61-year-old woman, with a 25-year history of maintenance hemodialysis due to end-stage renal disease of unknown causes, was admitted because of systemic joint pain and inflammatory response of unknown etiology that persisted for 1 month. Laboratory data on admission revealed leukocytopenia, lymphocytopenia, high serum C-reactive protein, and positivity for antinuclear antibody (ANA) and anti-double strand DNA. After admission, she progressively developed cough and dyspnea. A chest radiograph revealed bilateral ground glass opacity and pleural effusion. A thoracentesis revealed lupus erythematosus cells, suggesting lupus pleuritis. A chest computed tomography showed a pattern of diffuse alveolar damage compatible with acute lupus pneumonitis. She fulfilled the American Rheumatism Association diagnostic criteria for systemic lupus erythematosus (SLE). Methylprednisolone pulse therapy followed by oral prednisone treatment improved the clinical symptoms and laboratory abnormalities. ANA was negative 25 years earlier when she first started hemodialysis and she had neither clinical nor serological abnormalities related to SLE during the last

25 years. Further, she had neither received drugs that can cause drug-induced SLE, nor had a history of ultraviolet ray exposure, pregnancy, blood transfusion, trauma and smoking. This report suggests that new-onset SLE can develop in patients undergoing long-term dialysis. Hence, when we encounter dialysis patients with arthralgia and/or respiratory disorders, we should consider the possibility of new-onset SLE.

Keywords Arthralgia · Hemodialysis · LE cells · Lupus pleuritis · Lupus pneumonitis · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that typically affects multiple organs [1]. Patients with SLE usually presents with cutaneous (malar rash, discoid rash, photosensitivity), hematological (leukocytopenia and thrombocytopenia), serosal (pleural and pericardial effusion), mucosal (oral/nasopharyngeal ulcer), and renal (lupus nephritis) involvements. Some of the SLE patients with lupus nephritis eventually develop end-stage renal disease (ESRD), and may require renal replacement therapy.

Previous reports have shown that clinical and serological activity of SLE usually burns out after initiation of chronic renal replacement therapy [2, 3]. In some cases, reactivation of SLE does occur in patients under chronic dialysis treatment [4, 5]. However, the onset of SLE long after the initiation of renal replacement treatment has been rarely reported.

Herein, we present the rare case of a patient with ESRD who presented with arthralgia, leukocytopenia, pleuritis,

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and pneumonitis and abruptly developed SLE for the first time after 25 years of maintenance hemodialysis therapy.

Case report

A 61-year-old woman was admitted to our hospital with arthralgia persisting for 1 month and inflammatory response of unknown etiology. Twenty-five years earlier, she was first diagnosed with extremely decreased kidney function of unknown etiology, and had undergone maintenance hemodialysis therapy ever since. Because her bilateral kidneys were already atrophied at that time, she did not undergo kidney biopsy. She tested negative for antinuclear antibody (ANA) and did not present skin or joint symptoms at the time hemodialysis therapy began.

She had no family history of collagen-vascular diseases or past history of hypertension, diabetes mellitus, and other diseases that could cause arthritis. She had undergone parathyroidectomy for secondary hyperparathyroidism 6 years ago and carpal tunnel release for carpal tunnel syndrome 5 years ago. She had no history of blood transfusion. She was hospitalized due to sepsis of unknown etiology 3 years ago, and had been treated by oral antibiotics for persistent elevation of serum C-reactive protein level until long after hospital discharge.

On admission, she was alert, with a blood pressure of 94/54 mmHg, heart rate of 94 bpm, and body temperature of 36.8 °C. Oxygen saturation by pulse oximetry was 96 % (room air). There was no malar rash, discoid rash, oral ulcers, or photosensitivity. Arthralgia of shoulder and hip joints was noted. Table 1 summarizes the laboratory tests

Table 1 Results of laboratory tests conducted on admission

Complete blood count		Immunological studies	
Hemoglobin	7.7 g/dL	Immunoglobulin G	1725 mg/dL
Hematocrit	25.3 %	Immunoglobulin A	396 mg/dL
White blood cells	2,690/ μ L	Immunoglobulin M	45 mg/dL
Lymphocyte	231/ μ L (8.6 %)	C3	92 mg/dL
Platelets ($\times 10^3$)	261/ μ L	C4	35 mg/dL
Serum biochemistry		CH50	60 U/L
Total protein	6.3 g/dL	Rheumatoid factor	8 U/mL
Albumin	2.5 g/dL	Anti-CCP antibody	(–)
Blood urea nitrogen	55 mg/dL	Antinuclear antibody	2560 $\times$
Creatinine	5.15 mg/dL	Anti-dsDNA antibody	59.7 U/mL
Uric acid	5.8 mg/dL	Lupus anticoagulant	(–)
Total bilirubin	0.1 mg/dL	Anti-cardiolipin antibody	(–)
Glucose	95 mg/dL	Anti-Smith antibody	(–)
C-reactive protein	13.0 mg/dL	Anti-SS-A antibody	(–)
Calcium	8.6 mg/dL	Anti-SS-B antibody	(–)
Phosphorus	4.1 mg/dL	MPO-ANCA	<1.0 U/mL
Sodium	139 mmol/L	PR3-ANCA	<1.0 U/mL
Potassium	4.8 mmol/L	Infectious studies	
Chloride	103 mmol/L	Procalcitonin	0.8 ng/mL
Aspartate aminotransferase	36 U/L	β -D-glucan	(–)
Alanine aminotransferase	13 U/L	HBs antigen	(–)
Lactate dehydrogenase	337 U/L	HCV antibody	(–)
Alkaline phosphatase	309 U/L	Treponema pallidum latex agglutination	(–)
Amylase	88 U/L	Interferon- γ release assays	(–)
Creatine kinase	179 U/L	Endocrinological studies	
Iron	25 μ g/dL	Plasma cortisol	12.0 pg/mL
Unsaturated iron binding capacity	159 μ g/dL	Plasma ACTH	18.5 μ g/mL
Ferritin	152.8 ng/mL		

Titers of ANCA were measured using the following assays; MPO-ANCA (STACIA MEBLuxTM TEST MPO-ANCA, normal range ≤ 3.5 U/mL) and PR3-ANCA (STACIA MEBLuxTM TEST PR3-ANCA, normal range ≤ 3.5 U/mL). ACTH adrenocorticotrophic hormone, Anti-CCP antibody anti-cyclic citrullinated peptide antibody, Anti-dsDNA antibody anti-double stranded DNA antibody, HBs antigen hepatitis B surface antigen, HCV hepatitis C virus, MPO-ANCA myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA proteinase 3 anti-neutrophil cytoplasmic antibody

Fig. 1 Chest radiograph and computed tomography during admission. Chest radiographs on admission (**a**), on the 17th hospital day (**b**), and on the 44th hospital day (**c**) are shown. Bilateral ground glass opacity, observed in the radiograph on the 17th hospital day (**b**), disappeared after treatment with prednisolone (**c**). A chest computed

tomography on the 17th hospital day (**d**, **e**) revealed a pattern of diffuse alveolar damage and thickened interlobular alveolar septa (**d**) with a small pleural effusion (**e**), indicative of lupus pneumonitis and pleuritis

results. Briefly, leukocyte count was 2,490/ μ L (lymphocyte count 231/ μ L); hemoglobin, 7.7 g/dL; and platelet count, 26.1×10^4 / μ L. Among the serum biochemical parameters, C-reactive protein was 13.0 mg/dL; albumin, 2.5 g/dL; blood urea nitrogen, 55 mg/dL; and creatinine, 5.15 mg/dL. All other biochemical parameters were compatible with the results obtained generally by patients undergoing hemodialysis. Immunological workup results were complement (C) 3, 92 mg/dL; C4, 35 mg/dL; erythrocyte sedimentation rate, 95/105 mm; a high titer ANA of 1:2,560 with homogenous pattern; and a high titer of anti-double strand DNA (anti-dsDNA) of 59.7 U/mL (Normal <10 U/mL). Lupus anticoagulant, anti-cardiolipin antibody, anti-SS-A antibody, anti-SS-B antibody, and anti-Smith antibody were all negative. Serum procalcitonin level was 0.8 ng/mL (Normal <0.5 ng/mL). A series of blood cultures were negative for microorganisms including *Mycobacterium tuberculosis*. An interferon gamma release test was also negative. Chest radiograph (Fig. 1a) and computed tomography on the first hospital day showed no evidence of infectious diseases or malignancies.

On the 10th hospital day, she progressively developed dyspnea, cough, and low-grade fever (37.2 °C). Oxygen saturation by pulse oximetry decreased to 92 % (room air) and arterial oxygen pressure was 68.1 mmHg (room air). A chest radiograph revealed bilateral ground glass opacity in

the lungs (Fig. 1b). Because bacterial or atypical pneumonia was suspected at that time, empiric antibiotic therapy with sulbactam/ampicillin (1.5 g/day) and minocycline (200 mg/day) was started. However, respiratory symptoms did not improve and bilateral pleural effusion increased rapidly.

On the 17th hospital day, a thoracentesis was performed. Culture of the pleural effusion was negative, while microscopic examination of the pleural effusion disclosed the presence of inclusion body-like cells phagocytosed by neutrophils, indicative of lupus erythematosus (LE) cells and lupus pleuritis (Fig. 2). Finally, she fulfilled 5 out of 11 American Rheumatism Association diagnostic criteria for SLE (arthritis, pleuritis, leukocytopenia, positive ANA, and positive anti-dsDNA), and was diagnosed with new-onset SLE. Laboratory data showed high titer of surfactant protein A of 62.9 ng/mL (Normal <43.7 ng/mL) and surfactant protein D of 261 ng/mL (Normal <110 ng/mL). A chest computed tomography revealed patterns of diffuse alveolar damage such as bilateral ground glass opacity, thickened interlobular alveolar septa, and bilateral pleural effusion, all compatible with lupus pneumonitis and pleuritis (Fig. 1d, e). Serum procalcitonin was almost negative and sputum culture was also negative for all microorganisms, including *Mycobacterium tuberculosis*. Hence, bacterial pneumonitis and other diagnosis were less likely

Fig. 2 May-Giemsa staining of the cells from pleural fluid. Cells from pleural fluid stained by May-Giemsa method presented inclusion body-like cells phagocytosed by neutrophils, suggestive of LE cells, a characteristic finding in systemic lupus erythematosus. Yellow arrows show the LE cells

based on the serological results. On the 18th hospital day, methylprednisolone pulse therapy (1 g/day $\times$ 3 days) was started and followed by oral prednisolone (50 mg/day) administration.

The clinical course is shown in Fig. 3. Both arthralgia and respiratory symptoms rapidly disappeared by the 24th hospital day. Serum C-reactive protein level decreased to almost normal range. The titers of ANA and anti-dsDNA also decreased. A chest radiograph on the 44th hospital day

showed a significant improvement (Fig. 1c). Because the activity of SLE was well-controlled, the dose of prednisolone was tapered to 30 mg/day and the patient was discharged on the 45th hospital day. At 7 months after discharge, she remains free of SLE-related symptoms and is still receiving 12.5 mg/day of oral prednisolone treatment.

Discussion

We described a rare case of a patient with ESRD who developed SLE for the first time after 25 years maintenance hemodialysis therapy. Physical findings and laboratory results (arthritis, leukocytopenia, lymphocytopenia, positive ANA and anti-dsDNA, LE cells in the pleural effusion) led to the diagnosis of SLE. Prednisolone treatment almost completely resolved her abnormal biochemical parameters, arthritis, pleuritis, and pneumonitis.

There are a few reports of patients that developed SLE after the initiation of hemodialysis. Hernandez-Jaras et al. [6] described an 18-year-old woman with new-onset SLE that occurred 2 years after the initiation of hemodialysis treatment for renal disease of an unknown cause. She developed oral ulcers, seizure, pericardial effusion, pancytopenia, positive ANA, and positive anti-dsDNA. At 2 months after the initiation of prednisolone 1.5 mg/kg/day, she improved clinically and serologically. Kasama et al. [7] reported a case of a 36-year-old man who developed SLE 4 years after the initiation of hemodialysis therapy for membranoproliferative glomerulonephritis. He presented dyspnea, fever, pleural chest pain, small joint pain, photosensitivity, positive ANA, positive anti-dsDNA,

Fig. 3 Clinical course during the hospitalization. ABPC/SBT ampicillin/sulbactam, MINO minocycline, mPSL methylprednisolone, PSL prednisolone, CRP C-reactive protein, Anti-dsDNA anti-double strand DNA, C-Xp chest X-ray radiograph

and positive Coomb's test. Pleuritis was suggested by the chest radiograph. A diagnosis of SLE was made and he was successfully treated with high-dose corticosteroids. Lee et al. [8] reported a case of a 41-year-old woman who developed new-onset SLE 6 years after the initiation of hemodialysis for unknown causes. She presented non-erosive arthritis, leukocytopenia, positive ANA, and positive anti-dsDNA. After the diagnosis of SLE was confirmed, prednisolone was initiated at 20 mg/day and her symptoms resolved rapidly. All of these cases developed SLE within 10 years. To our knowledge, there are no such reports of new-onset SLE in patients on dialysis for more than 20 years as in the current case.

The immune system in patients undergoing hemodialysis is reported to be impaired because of the combination of immunological defects; decreased phagocytic function of granulocyte and monocyte/macrophage, defective in the antigen capacity of antigen-presenting cells, and reduced numbers and antibody producing capacity of B lymphocyte [9]. Because autoimmune-related diseases are closely related to the activity of immune system, it is easy to understand that hemodialysis patients are less likely to develop autoimmune-related diseases. Actually, there are few reports regarding other autoimmune-related diseases that newly developed after dialysis initiation. This may be simply because under-publication. However, Gagnon et al. [10] reported high incidence of positive autoantibody such as rheumatoid factor, anti-DNA antibody, ANA, and anti-smooth muscle antibody in maintenance dialysis patients. These results indicate that hemodialysis patients can develop autoimmune-related diseases including SLE.

So why did the patient develop SLE long after the initiation of hemodialysis therapy? SLE is a chronic autoimmune disease characterized by microvascular inflammation with auto-antibodies that can affect various organs. When this patient started dialysis, she did not present any symptoms of SLE such as skin rash, photosensitivity, oral ulcers, or arthritis. ANA was also negative. Although she had a history of treatment with levothyroxine, aspirin, warfarin, lansoprazole, and alfacalcidol, these drugs are not included in the common drugs that could induce SLE. In addition, she had not had any known factors that could lead to the development of SLE, such as viral infection, exposure to ultraviolet ray, pregnancy, trauma, blood transfusion, and smoking. Of note, Pisetsky et al. [11] reported that bacterial infection can trigger the development of SLE. Given that she had a history of treatment with antibiotics for chronic inflammation related to persistent bacterial infection, it is possible that chronic inflammation was partly involved in the onset of SLE in this case. However, further case series studies are necessary to determine the mechanism of how SLE can develop long after the initiation of dialysis treatment.

Another distinctive manner of this patient is that she developed SLE at a relatively older age compared with the other reported cases. The incidence of late onset SLE is usually low. Actually, the elderly patients account for only 12–18 % of the total SLE population [12, 13]. In addition, late onset SLE may have a different clinical course with insidious development or non-specific symptom compared with younger patients, which made the diagnosis of SLE challenging. In the present case, the first symptom of this patient was joint pain, but the degree of the symptom was relatively mild and did not lead to the diagnosis. Several reports show that skin manifestations, photosensitivity, and nephritis were less frequent in patients with late onset SLE patient than in patients who developed SLE at their younger ages [12]. By contrast, serositis and lung involvement are more common in late onset SLE [12, 14]. These results were in line with the manifestation in the present case that the patient had no skin symptom but developed pleuritis and pneumonitis.

Pulmonary manifestations of SLE can have a wide spectrum including, pleuritis, pneumonia, pulmonary embolism, pneumothorax, and pulmonary hemorrhage [15]. Pleuritis is the most common pulmonary manifestation of SLE, occurring in 45–60 % of patients with SLE [16] and it is one of the diagnostic criteria for SLE by the American Rheumatism Association. Laboratory data of SLE patients with pleuritis are often characterized by strong C-reactive protein response, in contrast to patients without pleuritis [17]. Our patient also presented high titer of C-reactive protein despite the absence of infection, which is compatible with the course of lupus pleuritis.

Acute lupus pneumonitis (ALP) is uncommon, and it occurs in 1–4 % of patients with SLE [16]. The clinical presentation of ALP is characterized by fever, cough, and dyspnea of sudden onset that can be life-threatening in many cases. The diagnosis of ALP is made only after infectious and other etiologies are excluded. Because there are no controlled studies for the treatment of ALP, the following recommendations are based on personal experience and case reports. The mainstay of ALP treatment is systemic corticosteroids (prednisolone 1–1.5 mg/kg/day in divided doses) [18]. In patients with severe initial presentation, intravenous pulse corticosteroids (i.e., methylprednisolone 1 g/day for several days) are preferred [9]. The clinical course of our patient is consistent with the course of ALP. As in a previous report [19], our patient underwent methylprednisolone pulse therapy (1 g/day $\times$ 3 days), followed by oral prednisolone (50 mg/day), and had a dramatic improvement. To our knowledge, this is the first report of ALP in a patient on dialysis.

The presence of LE cells is highly specific for SLE [20] and that remains an important diagnostic finding. In the present case, we found LE cells in the patient's

pleural fluid, which led to the diagnosis of SLE. Auto-antibodies penetrate the cell membrane and bind to the nucleoproteins, which leads to the denaturation of cells, forming hematoxylin bodies. Then, the hematoxylin bodies are phagocytosed by neutrophils, forming LE cells [21, 22].

In summary, we described the case of patient who developed SLE long after the initiation of hemodialysis, and was successfully treated by prednisolone. This report emphasizes that SLE can develop in patients on long-term dialysis. Therefore, when we encounter dialysis patients with arthritis and/or respiratory disorder, SLE should be considered as one of the potential differential diagnoses.

Acknowledgments We thank Edanz Editing (<http://www.edanzediting.co.jp/>) for carefully reading and preparing our manuscript.

Conflict of interest Honoraria: Kazuhiko Tsuruya (Kyowa Hakko Kirin Co., Chugai Pharmaceutical Co.), Research funding: Kazuhiko Tsuruya (Kyowa Hakko Kirin Co., Chugai Pharmaceutical Co., Fuso Pharmaceutical Industries, MSD K.K., Takeda Pharmaceutical Co.), Endowed department: Kazuhiko Tsuruya (Baxter).

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