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CASE REPORT

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Successful plasmapheresis in alveolar hemorrhage associated with systemic lupus erythematosus

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Abstract The case of an 18-year-old Japanese man with systemic lupus erythematosus (SLE) complicated by alveolar hemorrhage is described. The patient presented with fever, butterfly rash, and polyarthralgia, and was diagnosed with SLE. He suddenly developed alveolar hemorrhage during steroid pulse therapy. Treatment with plasmapheresis was initiated, with prompt clearing of the chest radiograph. This experience suggests that the prompt initiation of plasmapheresis should be considered for SLE patients with life-threating alveolar hemorrhage resistant to conventional immunosuppressive therapies.

Key words Alveolar hemorrhage · Plasmapheresis · Systemic lupus erythematosus (SLE)

Introduction

Noninfectious pleuropulmonary complications frequently occur in systemic lupus erythematosus (SLE) patients. Of these, alveolar hemorrhage is generally life-threatening.[1,2] Although various treatments, including high-dose steroids and cytotoxic agents, have been used to treat this serious complication, the mortality rates have been reported to be as high as 70%–90%,[3–5] and there is no uniformly recommended therapeutic strategy. Here, we described the case of a man with SLE who developed alveolar hemorrhage. He was successfully treated with a combination of plasmapheresis and high-dose corticosteroids.

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Case report

An 18-year-old Japanese man was referred to our hospital with hemoptysis and progressive anemia. In April 1999, he developed fever, butterfly rash, and polyarthralgia. He was diagnosed with SLE on the basis of the butterfly rash, photosensitivity, arthritis, pancytopenia, high antinuclear antibody (ANA), and high anti-double-strand DNA antibody (anti-dsDNA Ab), and was admitted to a regional hospital on May 1, 1999. After admission, he was treated with oral prednisolone (30 mg/day). Since his symptoms did not improve, he then received steroid pulse therapy (methylprednisolne 1000 mg/day for 3 successive days) at that hospital. After this steroid pulse therapy, he reported hemoptysis on May 20, 1999. He was referred to this department for treatment of the hemoptysis on May 22, 1999.

Physical findings on admission were as follows: body temperature 37.4°C, respiration rate 22/min, blood pressure 130/60 mmHg, and heart rate 88 beats/min. His palpebral conjunctiva was slightly anemic. Breath sounds were diminished in both lower lungs. Hepatosplenomegaly, leg edema, and joint swelling were not observed.

Laboratory data on admission are shown in Table 1. His peripheral blood showed leukopenia (WBC 2500/μl) and thrombocytopenia (platelets 7.7×10^4/μl). Rapid progression of the anemia (hemoglobin level fell from 13.2 to 10.6 g/dl in 36 h) was observed. Serological studies showed that ANA (>X1280 Ho, SP), anti-ssDNA Ab (>400 AU/ml), anti-dsDNA Ab (>400 IU/ml), anti-phospholipid antibodies (anti-cardiolipin β2-glycoprotein-I (4.5 U/ml), anticardiolipin antibodies (24 U/ml)), and circulating immune complex level (C1q: 18.8 μg/ml) were elevated. C3 (34 mg/dl), C4 (4 mg/dl), and CH50 (<12 U/ml) were markedly depressed. Anti-neutrophil cytoplasmic antibodies (ANCA), including antibodies to myeloperoxidase (MPO), proteinase-3 (PR-3), and anti-glomerular basement membrane (GBM) antibody, were negative. Arterial blood gas analysis in room air revealed mild hypoxemia (pH 7.469, $PaCO_2$ 40.5 mmHg, PaO_2 80.4 mmHg, HCO_3^- 29.0 mEq/l, BE

Table 1. Laboratory findings on admission

Urinalysis		ESR	25 mm/h
Protein	(−)		
Sugar	(−)	Serological studies	
Ketone	(−)	CRP	0.1 mg/dl
Occult blood	(−)	IgG	1030 mg/dl
		IgA	151 mg/dl
Feces		IgM	79.6 mg/dl
Occult blood	(−)	C3	34 mg/dl
		C4	4 mg/dl
		CH50	<12 CH50U/ml
Peripheral blood		Immune complex (C1q)	18.8 g/ml
WBC	2500/μl	Immune complex (C3d)	11.5 g/ml
Stab.	5%	RF	<10 IU/ml
Seg.	59%		
Ly	29%	FANA	>×1280 (Ho, SP)
Mono	3%	Anti-DNA antibody	>400 IU/ml
		Anti-ssDNA antibody	>400 IU/ml
RBC	369×10^4/μl	Anti-dsDNA antibody	(−)
Hgb	10.6 g/dl	Anti-RNP antibody	(−)
Ht	33.2%	Anti-Sm antibody	4.5 U/ml
Platelets	7.7×10^4/μl	Anti-CL-β2GP1	24 U/ml
		Anti-cardiolipin antibody	(−)
Blood coagulation		Lupus anticoagulant	(−)
PT	92.3%	Anti-MPO antibody	(−)
APTT	31.9 s	C-ANCA	(−)
Fibrinogen	264 mg/dl	Anti-GBM antibody	(−)
FDP	3.3 mg/dl		
		Anti-CMV	(−)
Biochemistry			
TP	6.9 g/dl	Anti-EBV VCA-IgG	320
Alb	4.0 g/dl	VCA-IgM	10>
TBil	0.9 mg/dl	EADR-IgG	10>
AST	31 IU/l	EBNA	1240
ALT	19 IU/l	Anti-HSV IgM	(−)
LDH	524 IU/l	Anti-HZV IgM	(−)
ALP	178 IU/l		
γ-GTP	20 IU/l	Arterial blood gas analysis	
ChE	137 IU/l	pH	7.469
Tchol	137 mg/dl	$PaCO_2$	40.5 Torr
BUN	21 mg/dl	PaO_2	80.4 Torr
Cr	1.0 mg/dl	HCO_3	29.0 mmol/l
FBS	4.2 md/dl	BE	4.3 mmol/l
Na	141 mEq/l	SaO_2	96.5%
K	4.4 mEq/l		
Cl	107 mEq/l		

RBC, red blood cells; PT, prothrombin time; APTT, activated partial thromboplastin; FDP, fibrinogen degradation products; TP, total protein; Alb, albumin; TBil, total bilirubin; AST, L-asparate:2-oxoglutarate aminotransferase; ALT, L-alanine:2-oxoglutarate aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl-transpeptiase; ChE, cholinesterase; Tchol, total cholesterol; BUN, blood urea nitrogen; Cr, creatinine; FBS, fasting blood sugar; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CH50, 50% hemolitic complement activity; RF, rheumatoid factor; MPO, myeloperoxidase; ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; HZV, herpes zoster virus; VCA, virus capsid antigen; EADR, early antigen diffuse and restricted; EBNA, Epstein–Barr nuclear antigen

4.3 mEq/l, SaO_2 96.5%). Initial sputum and blood cultures were negative.

Radiographic studies showed diffuse alveolar infiltrates compatible with alveolar hemorrhage (Fig. 1). It was suggested that the alveolar hemorrhage might be steroid resistant in this case, because the pulmonary complication had occurred in spite of high doses of steroids, including steroid pulse therapy. Therefore this patient was treated with intensive plasmapheresis by the single-filtration method (3 l/day) to remove any pathogenic autoantibodies as rapidly as possible. Plasmapheresis was followed by intravenous methylprednisolone pulse therapy (1000 mg/day, for 3 successive days). X-ray and computed tomography (CT) findings then showed a significant resolution, and there was no infiltrating shadow in the bilateral lung fields on May 30 (9 days after admission) (Fig. 2). Figure 3 shows the clinical course of the patient. Since the episodes of alveolar hemorrhage were recurrent, plasmapheresis was reinstituted and his symptoms improved. The patient was discharged on July 14 without further complications.

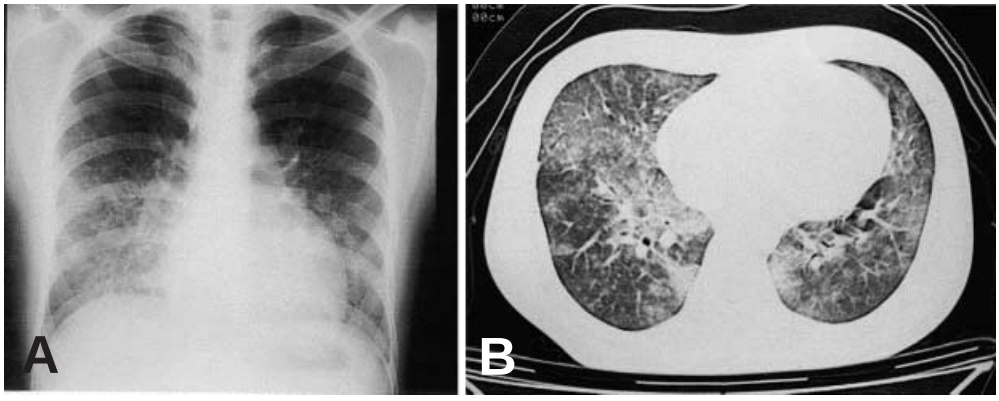

Fig. 1. **A** Chest radiography and **B** computed tomography on admission

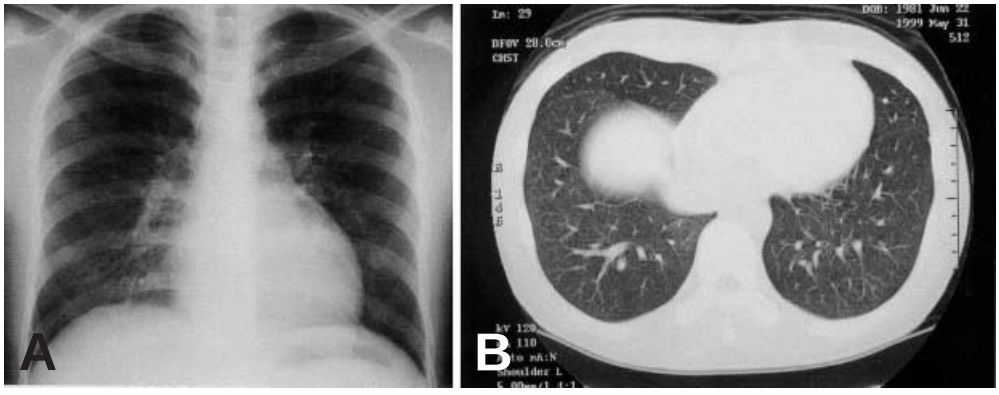

Fig. 2. **A** Chest radiography and **B** computed tomography on day 9 after admission

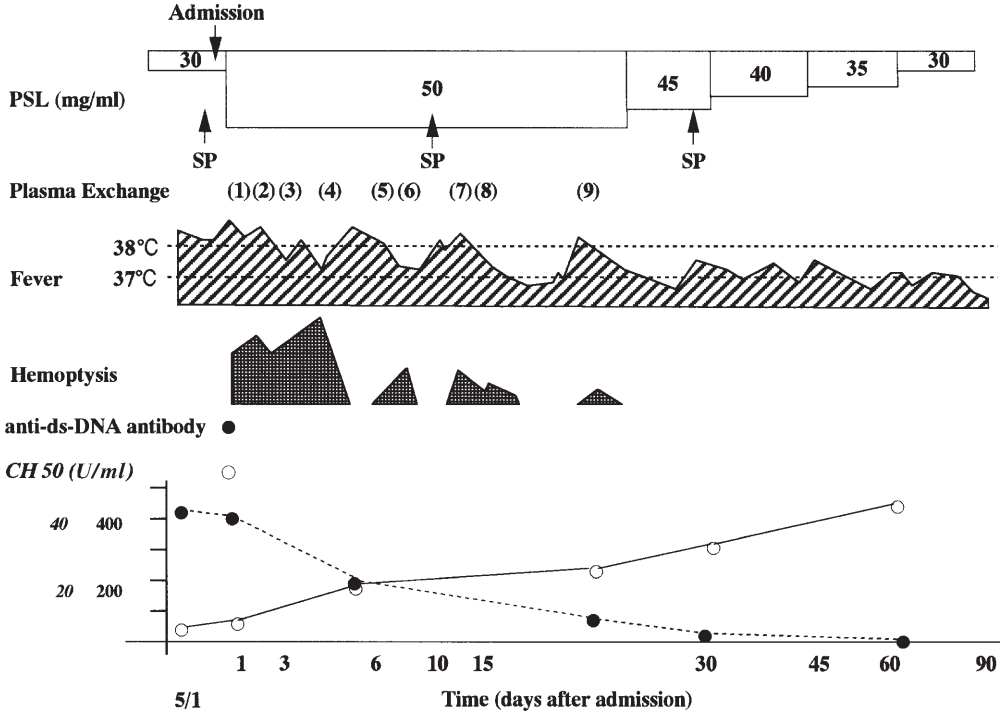

Fig. 3. The clinical course of this case. *PSL*, prednisolone; *SP*, steroid pulse therapy

Discussion

Diffuse alveolar hemorrhage is an uncommon but lethal complication of SLE.[1,2] Although various treatments have been used for this complication, the survival rate after alveolar hemorrhage in SLE is still the same as in previous reports.[3–5] In the present case, alveolar hemorrhage was suspected because of the abrupt onset of hemoptysis, rapid progression of anemia, and diffuse alveolar infiltrates seen on chest X-ray and CT. A diagnostic evaluation indicated negative sputum and blood culture, negative anti-GBM antibody, and negative anti-neutrophil cytoplasmic antibodies. Therefore infections or other autoimmune disorders including Goodpasture's syndrome and ANCA-related vasculitis were excluded as the etiology of the pulmonary hemorrhage in this case. We concluded that pulmonary hemorrhage had occurred as a complication of SLE.

It is generally believed that high-dose corticosteroids and cytotoxic agents should be started as soon as a diagnosis of pulmonary hemorrhage is established.[1,6] However, in our case, alveolar hemorrhage occurred after steroid pulse therapy. Thus, plasmapheresis was initiated, resulting in a prompt resolution of the symptoms and clearing of chest-infiltrating shadows.

The pathogenesis of alveolar hemorrahge in SLE is presumed to be immune complex (IC)-mediated, since granular immune deposits and complements have been detected in alveolar septae and blood vessel walls by electron microscopy or immunofluorescence techniques.[7,8] Several authors have recommended the use of high-dose steroids and cytotoxic agents to treat alveolar hemorrahge to reduce the IC or autoantibodies.[9,10] The most recent series of reports indicated a 75% survival rate in five patients who received cyclophosphamide in addition to steroid therapy.[5] However, it has also been reported that high-dose steroids and cyclophosphamide have been of only limited value, and still result in 83%–90% mortality.[2,4]

The other treatment intervention used for alveolar hemorrhage is plasmapheresis. Considering the possible pathogenic role of the IC, plasmapheresis should successfully reverse alveolar hemorrhage by removing the IC or autoantibodies rapidly. It has been shown that treatment with plasmapheresis plus a standard regimen of steroids and cyclophosphamide did not improve the clinical outcome of patients with lupus nephritis as compared with the standard regimen alone.[11] However, in SLE patients with alveolar hemorrhage, the prompt initiation of plasmapheresis may improve the catastrophic clinical consequences of alveolar hemorrhage without waiting for the effects of steroids and immunosuppressive therapy to modulate the disease activity of SLE. In our case, plasmapheresis resulted in the rapid removal of anti-dsDNA antibodies, normalization of hypocomplementemia, and clearing of the alveolar hemorrhage which had occurred in spite of steroid pulse therapy. Therefore, it is suggested that plasmapheresis in addition to a high-dose steroid is more effective for this serious pulmonary complication than steroid therapy alone.

Because alveolar hemorrhage is an infrequent complication of SLE, no randomized trials addressing the efficacy of plasmapheresis are available. However, it has been suggested that the addition of plasmapheresis to steroid therapy improves the chances of a favorable outcome compared with the results of immunosuppressive therapies.[12,13]

Although the therapeutic benefit of plasmapheresis in SLE was believed to be the rapid removal of immunoglobulins, a number of instances of increased antibody synthesis in response to the rapid removal of immunoglobulins have been reported.[14] Thus, immunosuppressive therapy should follow plasmapheresis to improve its efficacy.

In summary, the dramatic improvement in the alveolar hemorrhage observed in our patient leads us to conclude that the rapid initiation of plasmapheresis should always be considered in alveolar hemorrhage associated with SLE if it is not responsive to conventional immunosuppressive treatments.

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