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CASE REPORT

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Dramatic efficacy of cyclophosphamide pulsed therapy combined with double–filtration plasmapheresis for treating severe massive pulmonary hemorrhage associated with systemic lupus erythematosus

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Abstract Pulmonary hemorrhage (PH) is a rare but fatal complication of systemic lupus erythematosus (SLE). We report a patient with SLE and a massive PH who was treated with double-filtration plasmapheresis synchronized with cyclophosphamide pulsed therapy. The patient showed dramatic improvement immediately and was followed for 3 years without recurrence. Prompt treatment during the acute phase of PH with this short-term intensive combination therapy may offer the best chance of success. There are few reports of long-term followup, especially in Japan.

Key words Cyclophosphamide pulsed therapy · Double-filtration plasmapheresis (DFPP) · Plasma exchange · Pulmonary hemorrhage (PH) · Systemic lupus erythematosus (SLE)

Introduction

Massive pulmonary hemorrhage (PH) is a rare, often fatal complication of systemic lupus erythematosus (SLE). Among the autoimmune disorders, PH most frequently occurs in association with SLE and systemic vasculitis.[1–3] It is an uncommon complication, however, with frequency estimates ranging from less than 2.0% to 5.4% in cohorts of SLE patients. PH is frequently fatal, with reported mortality rates of 23%–92%.[4–12] Previous reports on PH in SLE patients have described survival rates of 50% or more,[7,8,11] the highest being 100%.[13]

Intravenous pulsed cyclophosphamide has been introduced as a treatment for severe SLE,[14–19] and there have been some reports that this treatment is efficacious. More recently, there have been a few reports that double-filtration plasmapheresis (DFPP) synchronized with intravenous cyclophosphamide pulsed therapy or cytotoxic therapy is efficacious in treating SLE with PH.[20–23]

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Case report

A 16-year-old female patient had been in good health until November 1998. She was admitted to our hospital in December 1998. Three weeks earlier, urinalysis abnormalities and immunological findings were discovered when she had a medical examination at another hospital because of a temperature higher than 38°C and polyarthralgia.

On admission, the physical findings were slight. She appeared anemic in the palpebral conjunctiva and had a facial skin rash. No heart murmurs or lung crackle sounds were found. The white blood cell count (WBC) was 4100/mm^3 (neutrophils 88%, lymphocytes 6%, monocytes 2%, eosinophils 4%), and platelets (23.6×10^4/mm^3) were in the normal range. Slight anemia was revealed [red blood cell count (RBC) 374×10^4/mm^3, hemoglobin 9.3 g/dl], but she did not complain of hemoptysis. The erythrocyte sedimentation rate (ESR) was markedly elevated to 135 mm/h, and the prothrombin time was in the normal range. Lupus anticoagulant and anticardiolipin β_2-GP1 antibodies were negative. The activated partial thromboplastin time was prolonged to 43.0 s (control 35.0 s). Serological and chemical findings were as follows: total protein 7.6 g/dl; albumin 2.8 g/dl; blood urea nitrogen (BUN) 16.5 mg/dl; creatinine 0.7 mg/dl; sodium 136 mEq/l; potassium 4.4 mEq/l; chlorine 103 mEq/l; glutamic oxaloacetic transaminase (GOT) 153 U/l; glutamate-pyruvate transaminase (GPT) 136 U/l; lactate dehydrogenase (LDH) 466 U/l; C-reactive protein 1.4 mg/dl, antinuclear antibody (ANA; fluorescent antibody assay) 5120× (homogeneous, speckled pattern); immune complex (IC)-C1q 29.6 μg/ml; anti-DNA antibody (radioimmunoassay, RIA) 300 IU/ml<; anti-ds-DNA-immunoglobulin G (IgG) antibody (enzyme-linked immunosorbent assay, ELISA) 1900 IU/ml. These factors were markedly elevated. The values of the complement

series, C3 (31 mg/dl), C4 (3 mg/dl>), and CH50 (9.8 U/ml) were markedly decreased. Other autoantibodies (anti-Sm, RNP, SS-A/Ro, SS-B/La; Ouchterlony method) were all negative. The p-ANCA (ELISA) and anti-GBM antibody (ELISA) were also negative. Urinary analysis abnormalities (proteinuria of 1.6 g/day, chance hematuria, and active columns) were also present. The chest roentgenogram showed no abnormalities in the lung field (Fig. 1).

Considering the physical and laboratory findings mentioned above, our patient fulfilled the American Rheumatic Association revised 1982 criteria for the diagnosis of SLE. She was immediately admitted for renal biopsy but failed to undergo the biopsy because her physical condition was objectively rather poor and her SLE activity was markedly elevated. As a result, on the second hospital day (December 18, 1998), steroid pulsed therapy with daily methylprednisolone (500 mg) was started at once and continued for 3 days. Immediately after the steroid pulse, bilateral alveolar-interstitial infiltrates in a pulmonary lower lobe appeared on the chest roentgenogram (Fig. 2). A computed tomography (CT) scan showed nonsegmental, frosted glass-like, faint absorption increases in bilateral pulmonary lower fields. At that time, hemoptysis and dyspnea were not present, and hemoglobin levels did not fall. As a result, it was difficult to distinguish between PH and more common pulmonary complications such as pneumonia.

We treated the patient with intravenous administration of broad-spectrum antibiotics. However, after that the

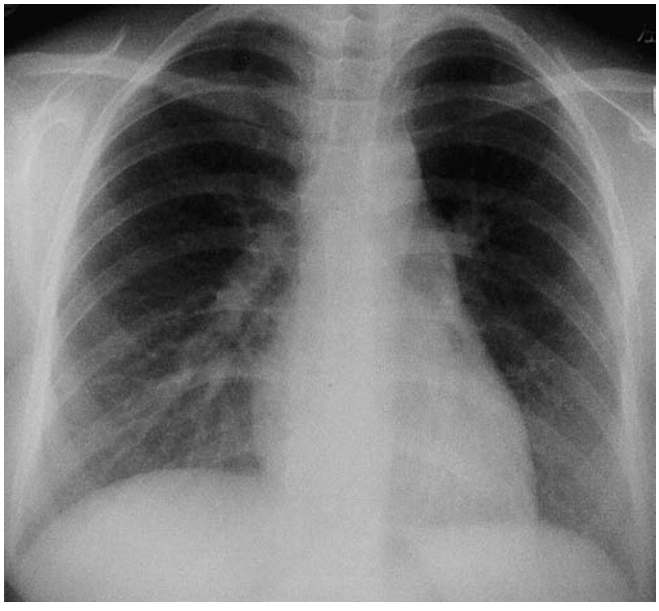

Fig. 1. Patient's chest roentgenogram on admission. No abnormalities appear in the lung field

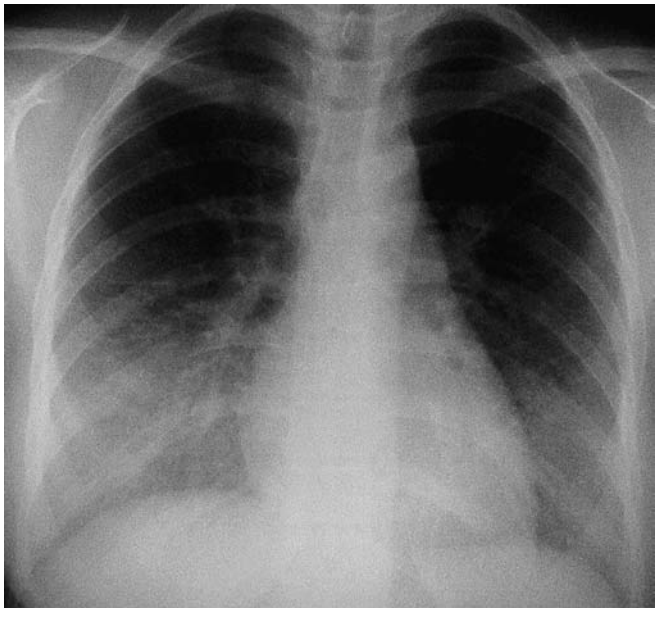

Fig. 2. Patient's chest roentgenogram after one course of pulsed steroid therapy. Alveolar interstitial infiltrates are present in the bilateral pulmonary lower lobe

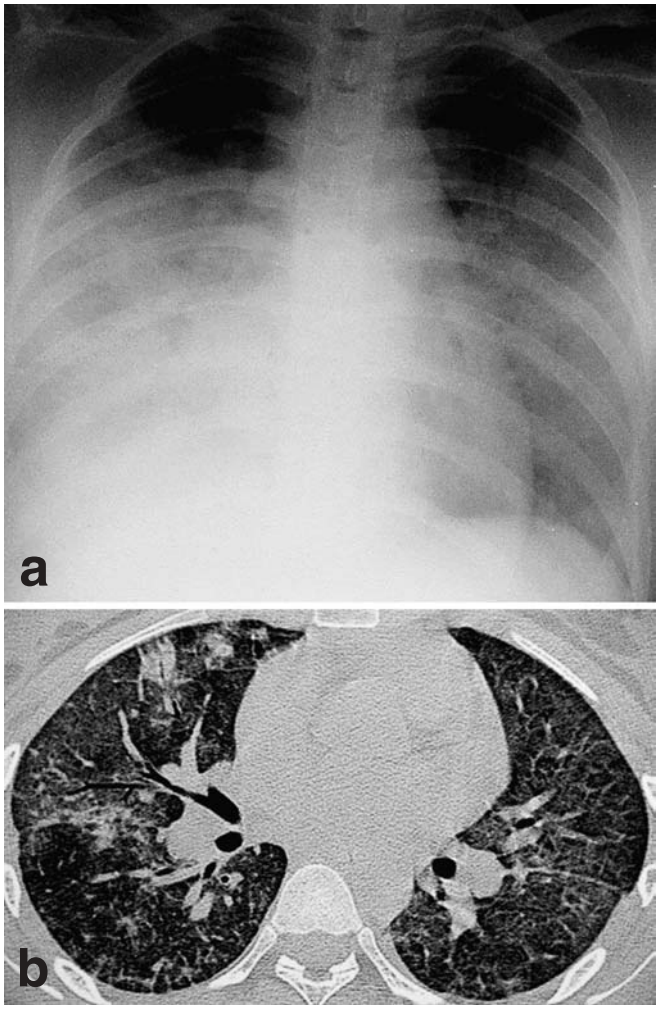

Fig. 3. **a** Patient's chest roentgenogram immediately after the second course of pulsed steroid therapy. Massive hemoptysis and respiratory deterioration have occurred. The roentgenogram reveals alveolar interstitial infiltrates in almost the entire bilateral pulmonary field. **b** Chest computed tomography (CT) image shows nonsegmental, frosted glass-like, faint absorption increases

hemoptysis gradually increased, and we diagnosed PH. We treated the patient with pulsed methylprednisolone (1000 mg) daily for 3 days beginning on the ninth hospital day (December 26, 1998). Despite this treatment, immediately after the second course of steroid pulse therapy the patient complained of hemoptysis and dyspnea. Massive hemoptysis and respiratory deterioration then suddenly occurred on the 12th hospital day (December 29, 1998). A chest roentgenogram revealed marked bilateral alveolar-interstitial infiltrates in all pulmonary fields (Fig. 3a). In addition, a CT scan showed further aggravation compared to her previous CT scan (Fig. 3b). Her hemoglobin level dropped from 7.5 to 5.8 g/dl. Blood gas analysis showed that the PO_2 was 66.0 mmHg and the PCO_2 45.0 mmHg. Bloody sputum and other cultures were negative.

Because her respiratory failure occurred so suddenly, tracheal intubation was performed immediately, and intensive institution of mechanical ventilatory assistance began with positive end-expiratory pressure (PEEP). The course of treatment and progress from admission to discharge is shown in Fig. 4. The CT scan shown in Fig. 4 (left, December 28) is the same as that in Fig. 3b. As shown in Fig. 4, the patient was treated with DFPP therapy after 3 h: 41 of plasma for 3 h using nafamostat mesilate as an anticoagulant and two hollow-fiber membrane devices; the first membrane was Plasma Flow OP05 (Asahi Medical, Tokyo, Japan), and the second membrane was Cascade Flow AC-1760 (Asahi). An albumin solution (5%) was used as the plasma-exchange replacement fluid. Immediately after DFPP, intravenous cyclophosphamide (500 mg) was administrated. DFPP was performed for a short time daily for four consecutive days. During these treatment sessions intravenous prednisolone (60 mg) was continuously administered. After this intensive treatment the patient's respiratory failure and chest roentgenogram dramatically and rapidly improved within as little as 6 days, and she was able to function without mechanical ventilatory assistance on the 18th hospital day (January 4, 1999) (Fig. 4).

At that time the laboratory indices of SLE activity were also markedly improved (Fig. 4). Anti-DNA (RIA) and anti-ds-DNA-IgG antibodies as well as IC(C1q), were markedly decreased from 300 IU/ml<, 1900 IU/ml, and 29.6 μg/ml, respectively, to 130×, 82 IU/ml, and 4.8 μg/ml, respectively. Complements C3, C4, and CH50 were elevated from 31 mg/dl, 3 mg/dl>, and 9.8 U/ml, respectively, to 59 mg/dl, 11 mg/dl, and 23.1 U/ml, respectively. Her chest

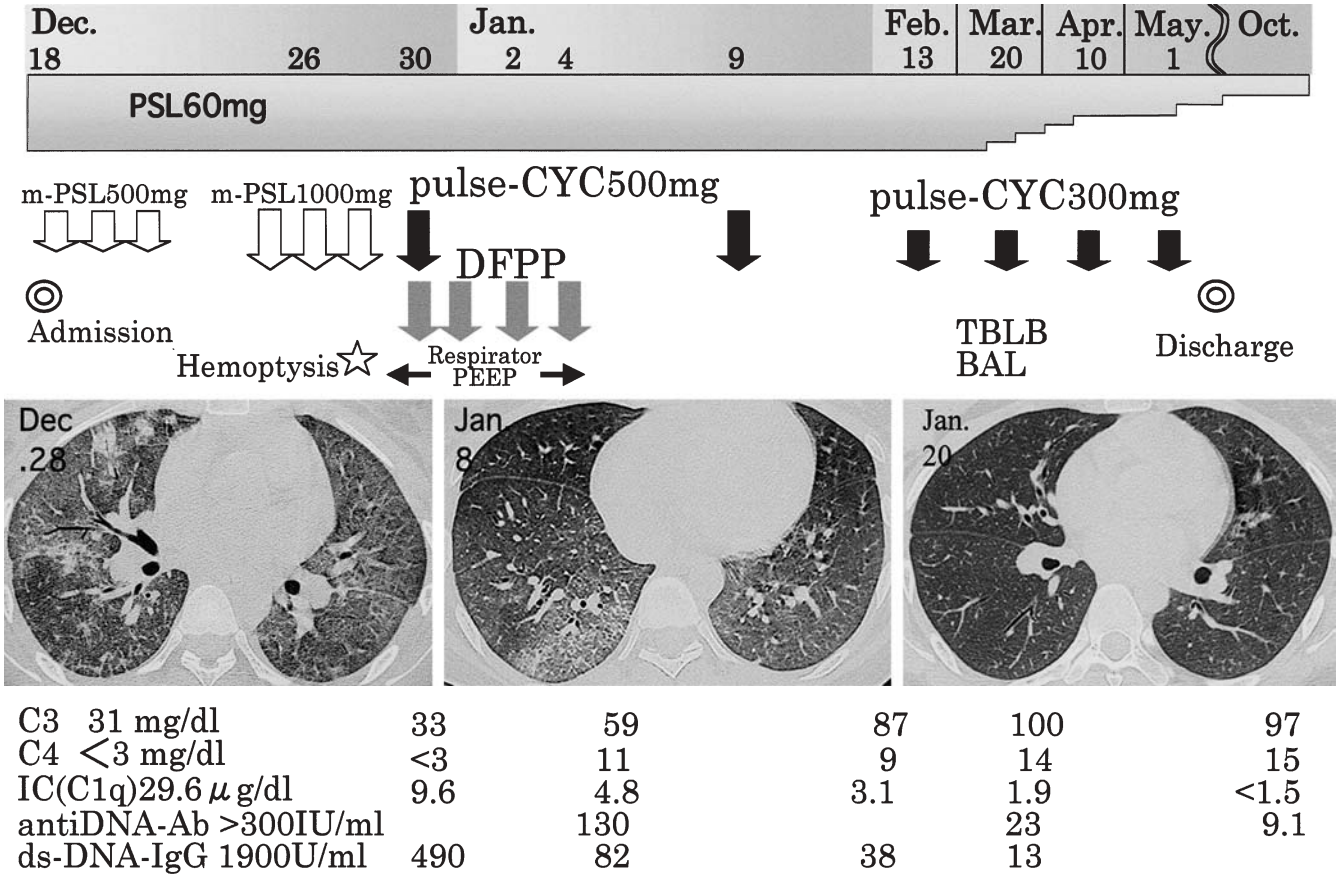

Fig. 4. Course of treatment and progress from admission to discharge. **Left** Chest CT scan (December 28) that is the same as that in Fig. 3b. **Center** CT scan obtained after four double-filtration plasmapheresis (DFPP) treatments and one course of intravenous pulsed cyclophosphamide (*CYC*) (500 mg) (January 8). **Right** CT scan obtained on January 20 after an additional pulse of cyclophosphamide (500 mg). Abnormal changes in the lung field have disappeared on this scan. *m-PSL*, pulsed methylprednisolone; *PEEP*, positive end-expiratory pressure; *TBLB*, transbronchial lung biopsy; *BAL*, bronchoalveolar lavage; *C3*, *C4*, complements 3 and 4; *IC*, immune complex; *Ab*, antibody; *IgG*, immunoglobulin G

CT scan is shown at center in Fig. 4. Compared to her pretreatment scan, it is markedly improved, but because alveolar hemorrhagic lung shadows remained in bilateral dorsal lung fields she was treated with intravenous cyclophosphamide (500 mg) on the 22nd hospital day (January 9, 1999). The CT scan obtained after the second round of cyclophosphamide pulsed therapy is shown in the left panel of Fig. 4 (January 20, 1999). The abnormal lung shadows are completely absent. The above-mentioned laboratory values, complement series, various antibodies, and IC, as an index of SLE activity, were also improved (Fig. 4).

Cyclophosphamide (300 mg) pulsed therapy was repeated four times once a month. Because hemosiderin-laden macrophages remained in her sputum specimens, bronchoscopy was performed. Bronchoalveolar lavage fluid (BALF) was collected, and lung tissue was obtained by transbronchial lung biopsy. On BALF and lung tissue specimens, cells appeared to be hemosiderin-laden macrophages (iron staining), but fresh red blood cells were not present. Lung tissue specimens were negative for anti-human IgG, IgA, IgM, C3, and C4 by immunofluorescence staining.

Based on these data we concluded that the presence of hemolysin-laden macrophages was the consequence of previous pulmonary hemorrhage and that no active hemorrhage or vasculitis was currently present. The presence of hemosiderin-laden macrophages in sputum after treatment does not always indicate active PH. Therefore, it is important to investigate thoroughly by bronchoscopy.

The patient had no relapse of PH and was discharged on oral daily prednisolone. After discharge, she was not treated with any immunosuppressive drugs. To date, the patient has been followed for approximately 3 years and she has not had a PH recurrence. During the last 12 months, she has been receiving 10 mg of oral prednisolone per day with gradual tapering.

Discussion

Massive PH is a rare and, until now, fatal complication of SLE. The frequency of PH ranges from less than 2.0% to 5.4% in cohorts of SLE patients.[4–12] It accounts for 1.5%–3.7% of hospital admissions due to SLE.[6,9] Death resulted from respiratory failure due to massive PH in most patients despite treatment with corticosteroids, including pulsed methylprednisolone or other immunosuppressants.

There are few reports on the effectiveness of methylprednisolone pulsed therapy for PH.[24,25] Takabayashi et al. emphasized the importance of bronchoscopy for early diagnosis of PH in SLE patients.[24] In most cases, however, the treatment efficacy of steroid pulsed therapy alone for PH associated with SLE has been transient or questionable.[7,23,26–28] Similarly, in our case, despite immediate administration of methylprednisolone pulsed therapy after admission, acute respiratory failure with massive hemoptysis due to PH appeared suddenly. Therefore, we concur that the efficacy of methylprednisolone pulsed therapy alone is questionable.

There have been a few reports that rapid initiation of DFPP has dramatic efficacy for severe, life-threatening SLE with PH.[29,30] However, the effect of plasma exchange (plasmapheresis) on the patient has been unclear until now. Many reports have suggested that its efficacy is transient.[20,21,31,32] For example, Klippel noted that the effects of plasmapheresis are transient and the patient rapidly returns to baseline status within days of stopping plasmapheresis; and until now plasmapheresis generally has been combined with administration of an immunosuppressive drug such as cyclophosphamide for repletion of circulating products of the immune system.[20] Jones determined that a sustained response to plasmapheresis in SLE patients was predominantly found in those treated concomitantly with daily oral cyclophosphamide, whereas plasmapheresis carried out without drug therapy generally provided only short-lived benefits.[32]

Recent reports indicate that PH is a survivable complication of SLE,[8,13] with some authors suggesting that the survival rate should be 100%.[13] In most of these cases, administration of cyclophosphamide as an immunosuppressive drug has been added to the treatment.[7,8,11,13] Intravenous pulsed cyclophosphamide has been introduced as a treatment for severe SLE,[14–19] and there have been some reports that this treatment is efficacious. More recently, cyclophosphamide pulsed therapy synchronized with plasmapheresis has been employed.[13,17,21,22,33] Dau et al. postulated that this approach is efficacious because autoreactive lymphocytes are stimulated by plasmapheresis to proliferate and remove feedback inhibitors of antibody production such as anti-idiotype antibodies or immune complexes. This allows increased entry of autoreactive lymphocytes into the cell cycle, where they can be more efficiently deleted by cyclophosphamide.[33]

Conclusions

We suggest that short-term, intermittent cyclophosphamide pulsed therapy synchronized with daily intensive plasmapheresis in conjunction with intensive respiratory care is the treatment of choice for acute-phase PH. It should be employed as early as possible. Previous reports on PH in SLE have described survival rates of 50% or more,[7,8,11] with the highest rate being a surprising 100%.[13] Patients have remained PH-free in these studies for 2–30 months.[8–11,13] However, in our literature search we found only a few documented cases of patients with PH associated with SLE who survived, as of March 2001 in Japan.[21,24,25,34,35] Few of these reports included long-term follow-up of patients with no PH recurrence.

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