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A Case of Pulmonary Hypertension Associated with Systemic Lupus Erythematosus without Anti-ribonucleoprotein Antibodies

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Summary. **We encountered a 32-year-old woman presenting with high-grade fever and swollen lymph nodes. Echocardiography showed a pericardial effusion and progressive pulmonary hypertension (PH). Although the criteria for systemic lupus erythematosus (SLE) were met, typical laboratory values and symptoms of SLE were not present. Anti-ribonucleaoprotein antibodies were negative. Computed tomography (CT) showed a dilatation of peripheral arteries and veins and a thickening of the interlobular septa. The patient was given anti-coagulants, but these were not effective. Steroids, however, improved her condition dramatically. The clinical course of this patient indicates the importance of steroid therapy for PH even when the patient does not show the typical clinical features of SLE.**

Key words — pulmonary hypertension, systemic lupus erythematosus, steroid therapy, anti-coagulation therapy.

INTRODUCTION

Pulmonary hypertension (PH) is frequently observed in patients with autoimmune diseases such as systemic sclerosis or mixed connective tissue diseases.[1]. PH is also observed in 5-10% of systemic lupus erythematosus (SLE) patients, for whom anti-ribonucleaoprotein (RNP) antibodies are usually positive.[2,3] We encountered a female SLE patient who showed PH without anti-RNP antibodies. Computed tomography (CT) showed dilation of peripheral arteries and veins and a thickening of the interlobular septa. Although her laboratory test results and symptoms were not typical for SLE, steroid therapy was very effective.

CASE REPORT

A 32-year-old woman developed a high-grade fever (39°C), cervical and left supraclavicular lymph node swelling, and erythema on the upper limbs and thighs in January 2003. The high-grade fever and lymph node swelling recurred in June 2003, and hematologic examination revealed anemia and the presence of positive anti-nuclear antibodies (homogeneous × 160, speckled × 160). The patient was admitted to our hospital in September of that year. Physical examination disclosed a rash on the superior

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Abbreviations–APTT, activated partial thromboplastin time, PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; RNP, ribonucleaoprotein; RVSP, ventricular systolic pressure; SLE, systemic lupus erythematosus.

palpebrae, linear erythema on the left forearm, telangiectasia on both palms, and swelling of the proximal interphalangeal joint of each middle finger. The right submandibular, and right and left cervical and subclavicular lymph nodes were swollen, distinct, elastic hard, and mobile. The swollen nodes were approximately 1 cm in diameter. The supraclavicular lymph nodes were swollen, indistinct, elastic hard, almost immobile, and formed masses. These nodes were approximately 1-1.5 cm in diameter.

Laboratory studies upon admission showed a hemoglobin level of 8.5 g/dl with a positive indirect Coombs test, platelet count of 19.1×10^4 /μl, and evidence of systemic inflammation including leukocytosis (9,300 cells/μl), accelerated erythrocyte sedimentation (146 mm/h), and an increase in C-reactive protein (4.16 mg/dl). However, the lymphocyte count was reduced to approximately 1,100 cells/μl. Partial thromboplastin time was normal at 14.8 sec, activated partial thromboplastin time (APTT) was slightly prolonged at 40.8 sec (normal 34.4 sec), fibrinogen was increased to 718 mg/dl, and the thrombin-antithrombin III complex was increased to 8.0 ng/ml. Urinalysis did not show any abnormalities. The concentrations of serum aspartate aminotransferase (83 U/l) and lactate dehydrogenase (1,040 U/l) were elevated, but serum alanine aminotransferase (17 U/l), alkaline phosphatase (400 U/l), creatine kinase (10 U/l), blood urea nitrogen (10.1 mg/dl), creatinine (0.47 mg/dl), and electrolyte levels were within normal limits. The total serum protein level was normal (7.9 g/dl), but the serum albumin level was decreased to 2.8 g/dl. Serum iron was slightly decreased (40μg/ml). Immunoglobulin G was elevated to 3,150 mg/dl, but levels of other immunoglobulins were normal (immunoglobulin A, 356 mg/dl; immunoglobulin M, 221 mg/dl). The C4 level was decreased to 8 mg/dl, but levels of other complements were normal (C3 119 mg/dl, CH50 35.4 U/ml). An anti-nuclear antibody was present (homogenous ×160, speckled ×160). Radioimmunoassay indicated that the anti-double strand deoxyribonucleic acid (DNA) antibody was slightly elevated to 7.3 IU/ml (normal, < 6.0 IU/ml), but enzyme-linked immunosorbent assay detected no other auto-antibodies. The myeloperoxidase antineutrophil cytoplasmic antibody titer was low (16 EU). A biologically false-positive reaction in a serologic test for syphilis (BFP-STS) was observed. Neither beta 2 gycoprotein-dependent anti-cardiolipin antibody (B2GPIαCL) nor lupus anticoagulant (LAC) was found. soluble interleukin-2 receptor (IL-2R) (2,230 U/ml), ferritin (14,285.3 ng/ml), and KL-6 (867 I U/ml) levels were elevated. Beta-D-glucan (19.6 mg/dl) was within normal values. Any infection of an Epstein-Bar(EB) virus, cytomegalovirus, Candida, or tubercle bacillus was ruled out. No fecal occult blood was found. Arterial blood gas analysis yielded the followings pH 7.45; PCO_2, 34.4 Torr and PO_2, 70.4 Torr. Malignant cells and hemophagocytic cells were not observed in bone marrow study.

Chest X-ray examination upon admission showed moderate cardiomegaly with a cardiothoracic ratio of

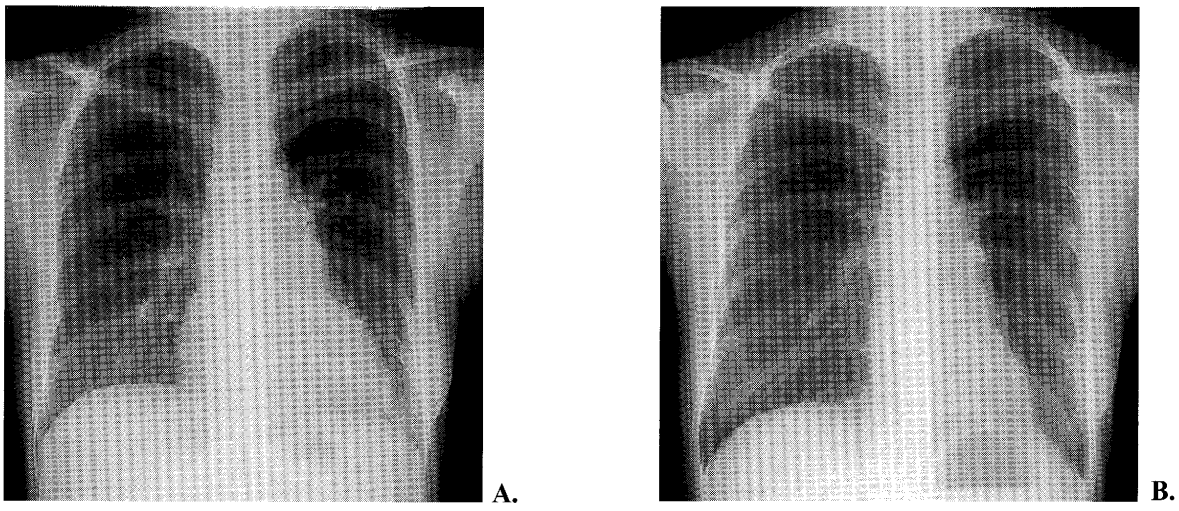
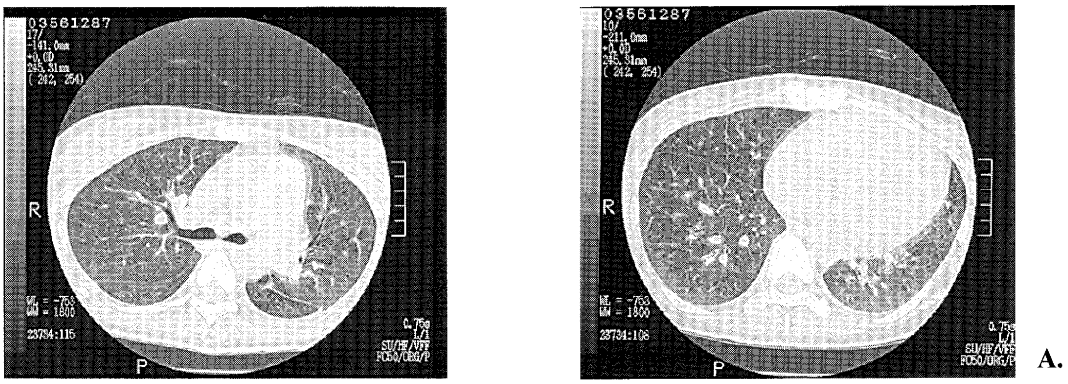


Fig. 1. Chest X-ray. Chest X-ray films obtained before and after treatment. **A.** Upon admission, moderate cardiomegaly, enlargement of the main pulmonary artery, and a reticulonodular shadow in both lower lung fields are seen. **B.** After treatment, the cardiomegaly, main pulmonary artery enlargement, and reticulonodular shadow have decreased.



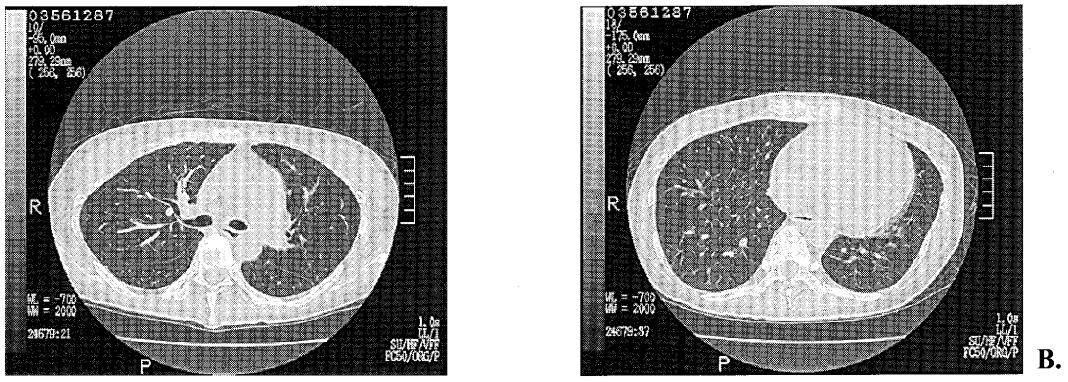


Fig. 2. Chest CT. CT scans obtained before and after treatment. **A**. Upon admission, a moderate dilatation of the pulmonary trunk and right ventricle, a remarkable dilatation of the peripheral pulmonary arteries and veins, and a thickening of interlobular septa are seen. **B**. After treatment, the dilatation of the pulmonary trunk, right ventricle, and peripheral pulmonary arteries and veins are reduced. The right hilar lymph node swelling has decreased.

56.8%, enlargement of the main pulmonary artery, and a reticulonodular shadow in both lower lung fields (Fig. 1A). High-resolution CT showed moderate dilatation of the pulmonary trunk and the right ventricle, ground-grass opacities, remarkable dilatation of the peripheral pulmonary arteries and veins, and thickening of the interlobular septa, especially in the right apex. There was no evidence of occlusion due to angiopathy or thrombi. Multiple swollen lymph nodes were observed at the right pulmonary hilum, exterior curve of the aortic arch, trachea, and axilla (Fig. 2A).

Echocardiography revealed a remarkable dilatation of the right ventricle, right atrium, and pulmonary artery and the presence of slight pericardial effusion. Second-degree tricuspid regurgitation was observed. The estimated right ventricular systolic pressure (RVSP) was very high (109 mmHg).

Lung perfusion scintiphotography showed large low-intensity areas in the left lung field (S6, S8, S9) and right lung field (S10). We therefore suspected a pulmonary embolism (Fig. 3A).

Examination of cervical lymph node biopsy specimens showed hyperproliferation of the lymph follicles and germinal center, expansion of the interfollicular spaces, and proliferation of epithelial cells and blood vessels. There were a few cells with mild atypia, but Southern blot analysis revealed no gene abnormalities. Thus, there were no signs of malignancy (Fig. 4).

According to our findings, the patient fulfilled the American College of Rheumatology (ACR) criteria for SLE: 1) seresitis (slight pericardial effusion), 2) hematologic disorder (lymphopenia), immunologic disorder (presence of anti-DNA antibodies and BEP-STS) and anti-nuclear antibodies [4, 5]. The presence of

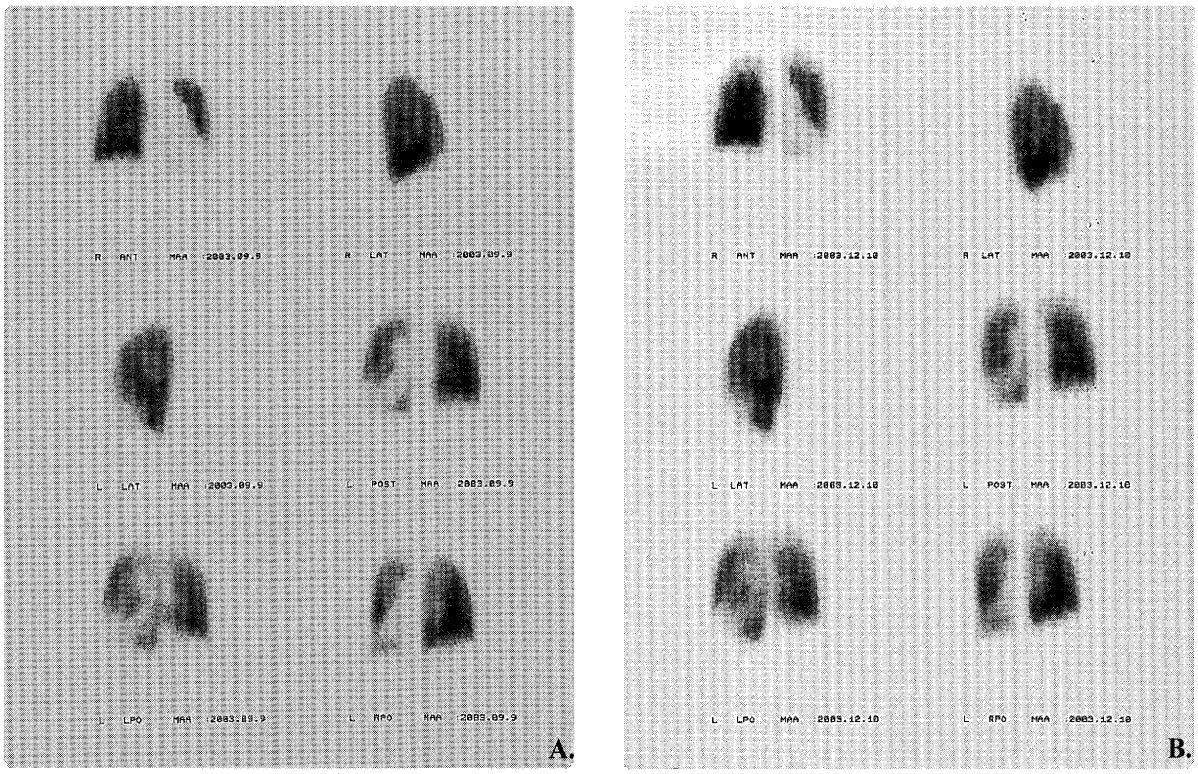


Fig. 3. Lung perfusion scintiphotograph. Lung perfusion scintiphotographs obtained before and after treatment. **A**. Upon admission, severe low-intensity areas in the left lung field (S6, S7, S9) and right lung field (S10) are seen. **B**. After treatment, the same low-intensity areas are present, but the area and degree of low-intensity are reduced.

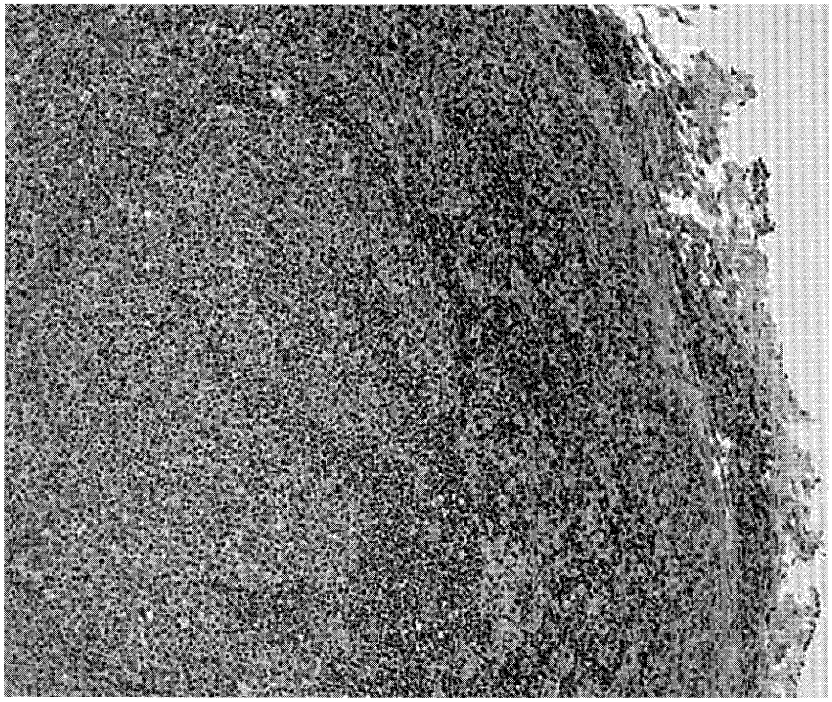


Fig. 4. Cervical lymph node biopsy. Hyperproliferation of the lymph follicles and germinal center, expansion of the interfollicular spaces, and the proliferation of epithelial cells and blood vessels are seen.

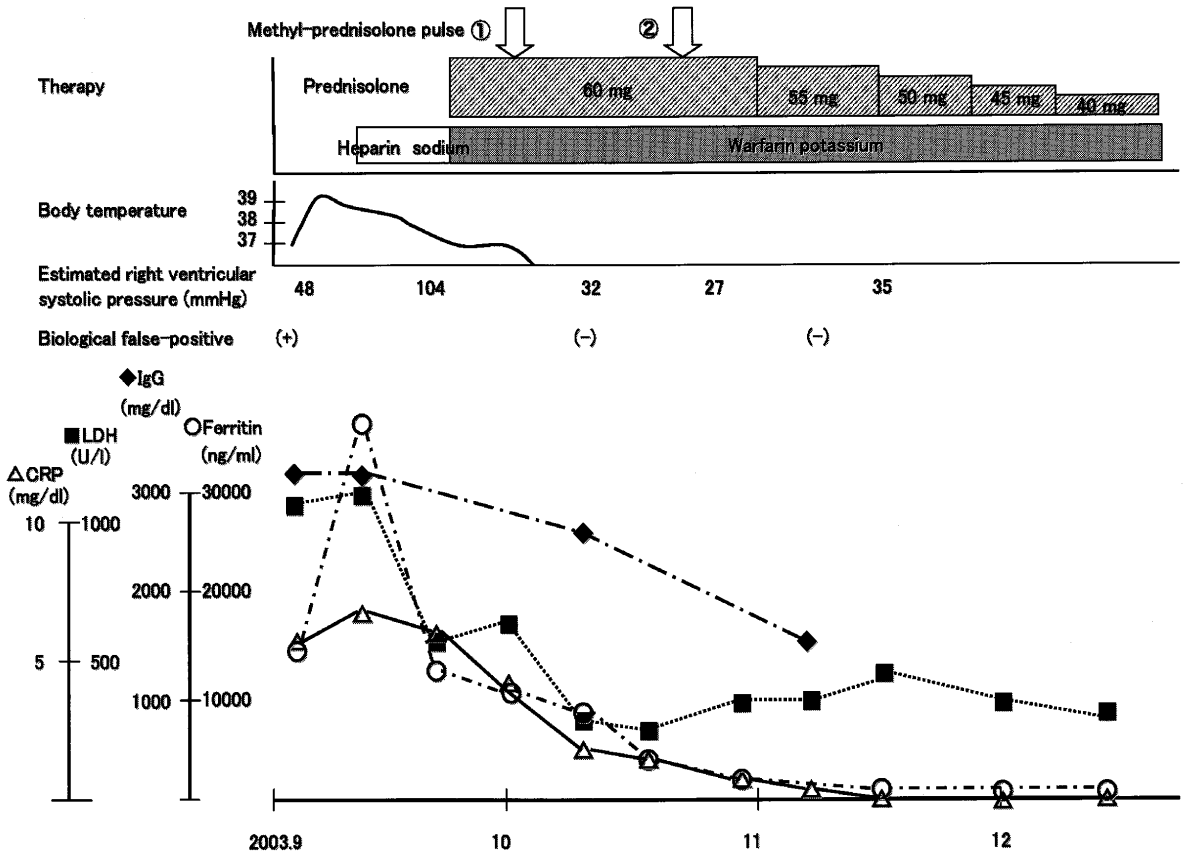


Fig. 5. Clinical course.

pericarditis, low complement levels, increased DNA binding, and fever merited a SLE Disease Activity Index score of 7 [6]. In addition, she suffered from progressive PH with CT abnormalities although there was no CT evidence of the pulmonary embolism suggested by the lung perfusion scintigraphy study. The patient was treated with anti-coagulation agents and oxygen therapy, but her estimated RVSP increased progressively, and the high-grade fever persisted. The patient was then given two cycles of methyl-prednisolone (m-PSL) pulse therapy (1 g/day, 3 days) followed by prednisolone (PSL) at 60 mg/day (Fig. 5). After two weeks, her symptoms disappeared, the lymph node swelling had diminished, and estimated RVSP had returned to normal. Laboratory test results had also improved (Fig. 5). Two months after treatment, the C-reactive protein was normal (0.05 mg/dl); hemoglobin was normal (13.2 g/dl); lactate dehydrogenase was slightly above normal but had decreased (370 U/l); ferritin had decreased to 66.5 ng/ml; and C4 had increased to 14 mg/dl. Blood gas levels had improved (pH 7.411, PCO_2 38.6 Torr, PO_2 132.3 Torr, under O_2 2 l/min incubation), so oxygen therapy was stopped. Chest X-ray findings after the pulse steroid therapy were almost normal (Fig. 1B). CT scans obtained after the treatment showed decreased vascular dilatation, reduced septal thickening, and reduced lymph node swelling (Fig. 2B). Lung perfusion scintigraphy showed an increased blood flow in the low-intensity areas (Fig. 3B). No signs of recurrence were observed, so the patient was discharged from our hospital three months after admission, and PSL was reduced to 40 mg/day.

DISCUSSION

Right heart failure is caused by many diseases, a principle one being PH. There are many types of PH, and the treatments are as various as the causes.

PH is defined clinically as a mean pulmonary arterial pressure greater than 25 mmHg at rest or 30 mmHg during exercise [7]. Histopathologically, PH comprises several types (revised clinical classification of pulmonary hypertension (Venice 2003)): pulmonary arterial hypertension; pulmonary hypertension with left heart disease; pulmonary hypertension associated with lung diseases and/or hypoxemia; pulmonary hypertension due to chronic thrombotic and/or embolic disease; and miscellaneous.

Collagen vascular disease is one of the most important causes of secondary PH. In cases of collagen vascular disease, the frequency of PH varies substantially. Scleroderma and mixed connective tissue disease are reportedly often complicated by PH. In contrast, rheumatoid arthritis, dermatomyositis, and polymyositis are rarely complicated by this disease [1]. PH is found in 5-10% of all patients with SLE [2].

Our patient presented with a high-grade fever and multiple swollen cervical and left supraclavicular lymph nodes. Laboratory tests upon admission yielded no signs of infection and-from a histopathological study of the cervical lymph nodes and slightly elevated sIL-2R-no malignancy was identified (Fig. 4), although the inflammatory reaction was severe. However, lymphopenia, prolonged APTT, a low C4 level, an elevated immunoglobulin G level, a high antinuclear antibody titer, BFP-STS, and a slightly elevated anti-DNA antibody level were observed. Echocardiography showed remarkable dilatation of the right ventricle, right atrium, and pulmonary arteries, and slight pericardial effusion. Estimated RVSP increased progressively (from 48 mmHg on September 8 in to 109 mmHg on September 25. All of these findings indicated remarkably progressive PH. The patient fulfilled the ACR criteria for SLE. The CT findings were not typical of PH, which is associated with an enlargement of the central pulmonary arteries without nodules in the lung fields [8]. Ground-grass opacities are reported in cases of SLE and other connective tissue diseases [3,9,10]. Thickening of the interlobular septa have also been reported[10,11]. Therefore, the CT findings could be due to SLE. differential diagnosis based on these CT findings include pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH). PVOD is a rare type of PH characterized by extensive and diffuse occlusion of pulmonary veins by fibrous tissue. Approximately 150 cases have been reported in the literature.[12] PCH is also a rare type of PH and is characterized by proliferating capillaries that invade the pulumonary interstitium and alveolar septae and occlude the pulmonary vasculature; approximately 40 cases have been to reported to date [13].

PVOD and PCH are similar diseases as pulmonary postcapillary vasculopathies, and very difficult to distinguish from each other [14]. Antemortem diagnoses of PVOD or PCH are rare; most reported cases were diagnosed histologically at autopsy [14,15]. Microscopically, PVOD is characterized by patchy vaenous sclaerosis with associated fibrotic thickening of intearlobular septa[16], and PCH is characterized by the proliferation of small uniform capillaries within the pulmonary interstitium and alveolar septa. The most important diagnostic feature of PCH is, at least, a double row of capillaries along the alveolar walls [14]. It is difficult to distinguish between specific PVOD or PCH symptoms and common PH symptoms such as progressive dyspnea, cough, and fatigue. A lung biopsy is necessary to diagnose PVOD or PCH, but patient's condition worsened progressively, so we were unable to perform such a procedure. SLE is rarely complicated by PVOD [17] or PCH[15].

The prolonged APTT and the BFP-STS in our patient suggested the presence of an anti-phospholipid antibody and supported the diagnosis of SLE; however, neither β 2GPI αCL nor LAC was detected and no thrombosis was not apparent. The elevation of CRP, serum ferritin and sIL-2R suggested macrophage activation [18]. Aoki et al. reported a patient with SLE who developed hemophagocytic syndrome (HPS) and showed high serum CRP, ferritin, and sIL-2R [18]. Matsuno et al. also reported a patient with SLE who developed HPS and showed high serum CRP and ferritin levels [19], but hemophagocytosis was not observed in our patient. Recently, it was reported that the serum ferritin level can be used as a marker of disease activity in patients with SLE [20,21]. Bayan et al. reported that, in 72 SLE patients, there was a significant difference in ferritin levels before and after treatment [20]. Ferritin levels in patients with SLE were positively correlated with the SLE disease activity index (SLEDAI). Hesselink et al. reported that in 10 SLE patients, the correlation between SLEDAI and ferritin was positive in seven patients [21]. It is possible that the high serum ferritin level in our patient was due to high SLE disease activity.

In conclusion, steroid therapy was very effective for PH in our female SLE patient without anti-RNP antibodies. Steroid therapy should be considered for PH in patients with SLE even laboratory data and symptoms are not typical for SLE.

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