

[CASE REPORT]

Pure White Cell Aplasia Complicated by Systemic Sclerosis with Accompanying Scleroderma Renal Crisis

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Abstract:

Pure white cell aplasia (PWCA) is a rare neutropenic disorder caused by absence of neutrophil-lineage cells. A 49-year-old man was diagnosed with scleroderma renal crisis 2 months prior to admission to Ohta-Nishinouchi Hospital after experiencing a fever and abdominal pain. Blood tests revealed severe neutropenia, and bone marrow aspirate showed the absence of neutrophil-lineage cells. He was diagnosed with PWCA. Steroids alone were not effective, but adding cyclosporine A and high-dose immunoglobulin recovered his neutropenia and improved his condition. Cyclosporine A and high-dose immunoglobulin are thus considered effective for treating PWCA in autoimmune diseases.

Key words: pure white cell aplasia, systemic sclerosis, scleroderma renal crisis, cyclosporine A, high dose intravenous immunoglobulin

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Introduction

Systemic sclerosis (SSc) is an immune-mediated rheumatic disease characterized by fibrosis of the skin and internal organs, as well as vasculopathy (1). Organ-based manifestations have been observed in some patients with SSc. These include lung fibrosis, pulmonary arterial hypertension, gastrointestinal complications, and scleroderma renal crisis (SRC) with accelerated-phase hypertension and thrombotic microangiopathy (1, 2). The exact cause of SSc remains elusive. The pathogenesis is dominated by vascular changes as well as fibrosis of the skin and visceral organ changes that result in irreversible scarring and organ failure (3). Although no disease-modifying drugs for SSc exist, early screening and management of patients appear to improve mortality (1).

Pure white cell aplasia (PWCA) is a rare disease characterized by complete disappearance of granulocytopoietic tissue from the bone marrow but normal erythropoiesis and megakaryocytopoiesis. The number of neutrophils in the peripheral blood is very low, although the numbers of red blood cells and platelets are usually normal (4). Clinically,

patients with PWCA suffer from recurrent infections. Previously, thymoma and thymic carcinoma (5-7) as well as drug-induced (8-12) and autoimmune diseases (13-15) were reported in PWCA patients. The immunologic mechanisms have been demonstrated in some PWCA cases where an inhibiting antibody was found (15). However, the precise mechanisms underlying PWCA are yet to be revealed due to the rarity of this disease.

We herein report a patient diagnosed with diffuse cutaneous SSc based on widespread skin sclerosis, including the proximal limbs, and positive serum anti-Scl-70 antibody who was complicated with SRC. After SSc improved with the exception of renal dysfunction due to SRC, the white cell count suddenly decreased, and he was diagnosed with PWCA based on a bone marrow examination. He was then given several immunosuppressive agents.

Case Report

A 49-year-old man presented to our hospital due to chest pain. He was diagnosed with SSc one year before this admission because of interstitial pneumonia, widespread skin

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Table 1. Laboratory Findings on the Second Admission*.

WBC (μL)	700	BUN (mg/dL)	48	ANA (fold)	320
Neutrophils (%)	0	Creatinine (mg/dL)	9.85	Homogenous	
Eosinophils (%)	2.0	Na (mEq/L)	139	Cytoplasmic	
Monocytes (%)	2.9	K (mEq/L)	4.0	Anti-Scl-70 antibody (fold)	8
Lymphocytes (%)	89.0	Cl (mEq/L)	102	Anti-centromere antibody (fold)	ND
RBC ($10^6/\mu\text{L}$)	3.85	CK (U/L)	67	Anti-RNA polymerase 3 antibody (fold)	ND
Hb (g/dL)	11.4	Ferritin (ng/mL)	455.8	β -D glucan (pg/mL)	26.2
Hct (%)	34.1	CRP (mg/dL)	38.3	Procalcitonin (IU/mL)	>100
PLT ($10^3/\mu\text{L}$)	353	IgG (mg/dL)	1,027	Prothrombin time (%)	64.4
TP (g/dL)	6.1	IgA (mg/dL)	145	APTT (s)	39
Alb (g/dL)	2.6	IgM (mg/dL)	76	Fibrinogen (mg/dL)	727
TB (mg/dL)	0.36	CH50 (U/mL)	49.2	FDP ($\mu\text{g}/\text{mL}$)	7.5
AST (U/L)	16	C3 (mg/dL)	103	D dimer ($\mu\text{g}/\text{mL}$)	2.3
ALT (U/L)	49	C4 (mg/dL)	33		
LD (U/L)	220				
ALP (U/L)	282				
γ -GTP (U/L)	44				

*WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, PLT: platelet, TP: total protein, Alb: albumin, TB: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactic dehydrogenase, ALP: alkaline phosphatase, γ -GTP: γ -glutamyl transpeptidase, BUN: blood urea nitrogen, Na: sodium, K: potassium, CK: creatine kinase, Cl: chloride, CRP: C-reactive protein, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, CH50: 50% hemolytic complement activity, C3: third component of complement, C4: fourth component of complement, ANA: antinuclear antibody, APTT: activated partial thromboplastin time, FDP: fibrinogen-fibrin degradation product

sclerosis including the forearms and fingers, and positive anti-Scl-70 antibody. He had been treated previously with 10-15 mg prednisolone at another hospital.

At the first admission, he was slightly agitated, had an axillary temperature of 37.0°C , blood pressure of 242/137 mmHg, and a heart rate of 137 beats per minute with an oxygen saturation of 95% on room air. Severe skin thickening was observed on his face, anterior chest, and upper extremities. Cyanosis was observed on the fingers, but no skin ulcerations were observed. His laboratory findings were as follows: white blood cell (WBC) count, $16,900/\mu\text{L}$ (neutrophils, 89.4%; eosinophils, 0.1%; basophils, 0.1%; monocytes, 2.5%; and lymphocytes, 7.9%); hemoglobin, 8.7 g/dL; platelet count, $57 \times 10^3/\mu\text{L}$; total bilirubin, 2.37 mg/dL; lactate dehydrogenase, 1,495 U/L; blood urea nitrogen, 97.7 mg/dL; creatinine, 6.66 mg/dL; C-reactive protein (CRP), 3.12 mg/dL; plasma renin activity, over 20 ng/mL/h; and haptoglobin, undetectable. The patient underwent cardiac catheterization, which revealed no stenosis in the coronary arteries. Subsequently, he was diagnosed with SRC based on elevation of serum creatinine, malignant hypertension, hyperreninemia, and microangiopathic hemolytic anemia.

He was immediately administered nicardipine, nitroglycerin, captopril, and irbesartan, and a quick drop in blood pressure was observed. However, he developed renal failure and had to undergo hemodialysis three times per week. He was also administered 10 mg vonoprazan to prevent peptic ulcers on admission and beraprost for peripheral circulatory disturbances after 40 days of hospitalization. The patient was finally discharged 54 days after admission. His condition was good at two weeks after hospital discharge. His

follow-up laboratory findings were as follows: WBC count, $9,100/\mu\text{L}$ (neutrophils, 65.8%; eosinophils, 3.9%; basophils, 1.4%; monocytes, 4.6%; and lymphocytes, 24.3%); hemoglobin, 14.6 g/dL; and platelet count, $449 \times 10^3/\mu\text{L}$.

About one month after the discharge, he was readmitted to the emergency room of our hospital because of abdominal pain, diarrhea, and a high-grade fever. At the second admission, he exhibited a normal level of consciousness, had an axillary temperature of 39.0°C , blood pressures of 99/65 mmHg, and a heart rate of 125 beats per minute with an oxygen saturation of 95% on room air. Chest auscultation revealed fine crackles bilaterally. His abdomen was soft and flat, but tender with guarding to the epigastrium. The extremities were cold, and periungual erythema was observed. There were no digital ulcers. His laboratory findings were as follows: WBC count, $700/\mu\text{L}$ (neutrophils=0%, eosinophils=2%, monocytes=2.9%, and lymphocytes=89%), hemoglobin=11.4 g/dL, platelet count= $353 \times 10^3/\mu\text{L}$, CRP=38.3 mg/dL, and procalcitonin=>100 IU/mL (Table 1). Two sets of blood cultures were negative, and stool culture showed normal flora.

Chest X-ray showed enlargement of the heart shadow and interstitial shadows in the lower lung fields. Computed tomography (CT) showed interstitial shadows on the dorsal side of the lower lungs and edema in widened areas of the small intestine (Fig. 1); however, thymoma was not detected on CT images.

After admission, hemodialysis was continued 3 times per week, and he was administered 150 $\mu\text{g}/\text{day}$ of filgrastim - a human granulocyte colony-stimulating factor - for neutropenia. Medications were discontinued because drug-induced

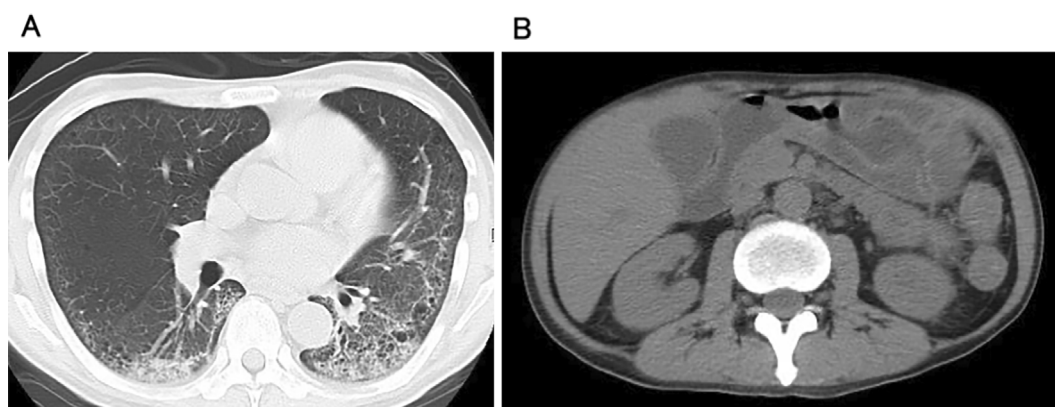


Figure 1. Computed tomography (CT) at the second admission shows interstitial shadows in the dorsal aspect of both lower lung fields (A) and edematous small intestines (B).

Table 2. Examination of Bone Marrow Aspirate.

	8th hospital day	43rd hospital day
Nuclear cell count (μL)	2.3×10^4	39.5×10^4
Megakaryocyte count (μL)	44	138
Myeloid series total (%)	6.0	78.0
Myeloblasts (%)	3.2	0.8
Promyelocytes (%)	0	1.2
Myelocytes (%)	0	18.2
Metamyelocytes (%)	0	15.2
Band form (%)	0	12.8
Segmented form (%)	0	26.4
Eosinophils (%)	0	1.2
Basophils (%)	2.8	2.2
Erythroid series, total (%)	22.8	18.2
Proerythroblasts (%)	22.4	0.2
Orthochromatic (%)	0.2	2.2
Mitotic figures (%)	0.2	15.8
Monocytes (%)	12.2	1.0
Lymphocytes (%)	38.4	2.4
Plasma cells (%)	18.8	0.4
Macrophages (%)	1.8	0
Myeloid/Erythroid	0.26	4.29

neutropenia was also considered.

His symptoms and CT findings suggested intestinal infection; therefore, meropenem and micafungin were administered. His abdominal pain and high-grade fever improved after a few days; however, the neutropenia persisted. Initially, we believed that his neutropenia was drug-induced; therefore, nicardipine, captopril, irbesartan, and beraprost were discontinued; vonoprazan was changed to rabeprazole; and filgrastim was initiated. However, because the neutrophil count did not improve at all after a week, we administered nicardipine, captopril, irbesartan, and beraprost again. An examination of bone marrow smears on day 8 of hospitalization showed slightly hypocellular marrow and the complete disappearance of neutrophil-lineage cells, but erythropoiesis and megakaryocytopoiesis remained normal (Table 2, Fig. 2). A diagnosis of PWCA was made based on these bone marrow examination findings. In addition, the SSc was

considered to be associated with PWCA in this patient. Therefore, he was administered 500 mg/day of methylprednisolone for 3 days intravenously commencing on day 15 of hospitalization, followed by 30 mg/day of prednisolone orally. Furthermore, 100 mg/day of cyclosporine A (CyA) was added, as was vancomycin, since *Enterococcus faecium* was detected from blood culture on hospital day 20. Since neutropenia persisted despite these treatments, high-dose (20 g) intravenous immunoglobulin (IVIg) was administered on hospital days 29, 31, and 33. Abdominal pain and a fever were intermittently observed.

However, the number of WBCs suddenly increased to $5,500/\mu\text{L}$ (neutrophils=66.2%, eosinophils=0.2%, basophils=0.7%, monocytes=6.1%, and lymphocytes=26.8%) on hospital day 37, although the number of neutrophils remained constant. Administration of filgrastim was stopped, and the dosage of prednisolone was gradually reduced. An examination of aspirated bone marrow smears on hospital day 43 showed hypercellular bone marrow and recovering neutrophil-lineage cells (Table 2, Fig. 2). After his neutrophil count recovered, his infectious state gradually improved. He was discharged on hospital day 107 after rehabilitation (Fig. 3).

Discussion

Although PWCA is a rare disease involving neutropenia, several cases have been reported with various primary diseases of PWCA. Autoimmune diseases are thought to be key basal disorders of PWCA. In previous reports, cases of PWCA were reported as associated with primary biliary cirrhosis (13), autoimmune hepatitis (14), and necrotizing myositis (15). We found no reports that described cases of PWCA complicated by SSc on a search of PubMed; therefore, this report is thought to be the first to describe a case of PWCA complicated by SSc.

In the present case, differential diagnoses of drug-induced neutropenia or drug-induced PWCA had to be considered, as about three months before developing PWCA, the patient was diagnosed with SRC and was continuously administered

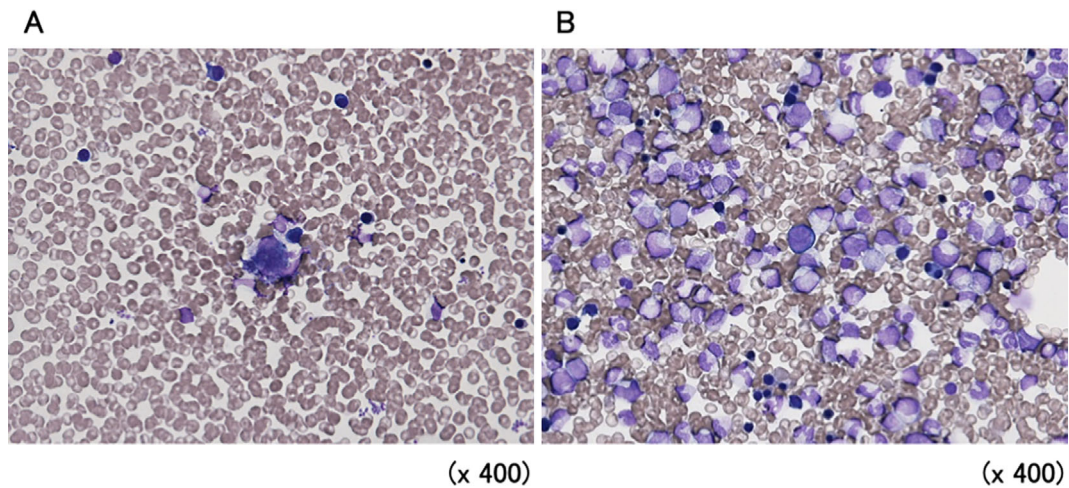


Figure 2. (A) The images of bone marrow smear on the eighth hospital day of the second admission show no differentiated cells of myeloid lineage after promyelocytes. (B) The images of bone marrow smear on the 43rd hospital day of the second admission show hypercellular bone marrow and recovering myeloid lineage cells.

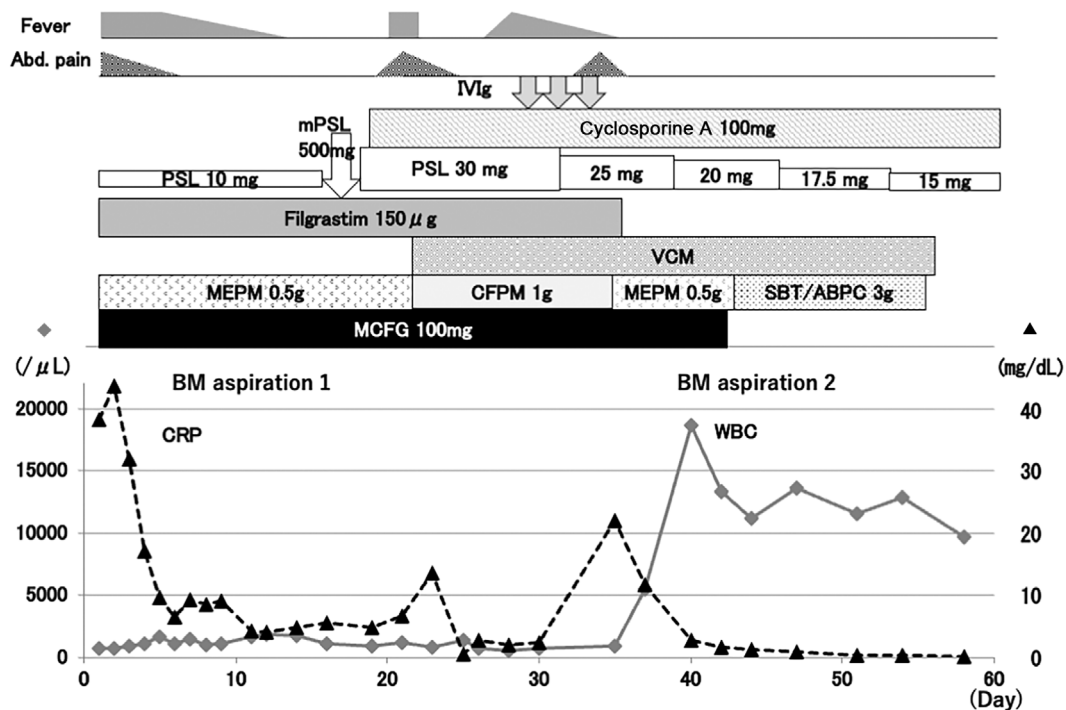


Figure 3. Clinical course of the second admission. BM: bone marrow, CFPM: cefepime, CRP: C-reactive protein, IVIg: intravenous gamma-globulin, MEPM: meropenem, mPSL: methyl prednisolone, PSL: prednisolone, SBT/ABPC: sulbactam/ampicillin, VCM: vancomycin, WBC: white blood cell

nicardipine, captopril, irbesartan, beraprost, and vonoprazan. At the time of neutropenia, the medications used since the onset of SRC were promptly discontinued or changed, but the neutrophil count did not improve. Therefore, the discontinued drugs were readministered one week later, and the neutrophil count eventually improved under immunosuppressive therapy on hospital day 37. Drug-induced neutropenia has been reported with many drugs, including antihyperten-

sive agents and proton pump inhibitors. However, drug-induced neutropenia was able to be ruled out in this case, as the neutrophil count eventually recovered even after continued medication. While the possibility of drug-induced PWCA could not be completely ruled out, a PubMed search revealed that the drugs commonly reported for drug-induced PWCA are chlorpropamide (8), ibuprofen (9), imipenem-cilastatin (10), mesalazine (11), and amodiaquine (12). No

PWCA-inducing drugs or drugs of the same type were used in the present case. Although we cannot completely deny the possibility that drugs other than those reported may cause drug-induced PWCA, we believe that the PWCA in the present case was more likely secondary to SSc, an autoimmune disease, rather than drug-induced.

Furthermore, the pathogenesis of PWCA has not been elucidated. PWCA was first described by Levitt et al. (16). Immunological mechanisms underlying granulocytopenia have been described in patients with PWCA, including lymphocytes or serum-mediated inhibitors of granulocyte colony formation in the bone marrow (4, 9, 16). Cases of PWCA complicated with thymoma or thymic cancer (5-7) have been reported. The thymus is a critical organ for the maturation of T lymphocytes, which are associated with the development of autoantibodies against granulopoietic cells. Therefore, the existence of inhibiting autoantibodies against maturing neutrophils is a plausible explanation for the pathogenesis of PWCA; however, measuring inhibiting antibodies is uncommon. Marinone et al. (4) described in their report the possible pathological mechanisms of nonthymoma-related PWCA. One was the antibody-mediated autoimmune inhibition of granulopoiesis, the other was a cellular inhibitory mechanism of T lymphocytes without inhibitory serum activity. This patient was diagnosed with SSc before developing PWCA, and anti-Scl-70 antibody was detected at the time of the diagnosis. SSc is an autoimmune disease, and in the present case, the patient had developed SRC about three months before the onset of PWCA, which might have activated the autoimmune response. Therefore, in the present case, an autoimmune mechanism was believed to be the cause of PWCA, specifically a humoral inhibitory mechanism, which mediated autoantibodies inhibiting the proliferation of granulocyte precursor cells and/or a cellular inhibitory mechanism, which mediated auto-reactive T cells. However, we were unable to measure inhibiting antibodies against granulopoietic cells in the present patient.

Although treatments for PWCA have not been established, given the rarity of the disease, most patients with PWCA associated with autoimmunity are given immunosuppressive agents in order to increase the granulocyte number. Corticosteroid, cyclophosphamide, azathioprine, and CyA were administered to patients with PWCA in previous reports. In addition, plasmapheresis and high doses of IVIg were also reported to be effective (4). There were some difficulties in treating PWCA in our patient. He was administered antibiotics and anti-fungal agents because he was complicated with severe infection. We initially considered that his granulopenia was drug-induced; therefore, he was administered filgrastim in order to increase his WBC count. Because he was diagnosed with PWCA after the bone marrow examination, he was administered methylprednisolone pulse therapy, followed by a moderate amount of prednisolone; however, his WBC count did not improve. We were unable to administer cyclophosphamide because we were

concerned about a further drop in the WBC count secondary to a decreased bone marrow function. He was then administered CyA and high-dose IVIg. It was difficult to determine whether high-dose IVIg or CyA was more effective for PWCA; however, it was suggested that high-dose IVIg triggered the elevation of granulocytes, and CyA was involved in its persistence. Both treatments were given in the context of severe infections. Great care must be taken to control the infection in such cases.

Furthermore, the present patient developed PWCA two months after the onset of SRC. Vasculopathy with endothelial cell activation and decreased renal perfusion is thought to contribute to the development of SRC, but the precise triggers and pathogenesis of SRC remain unclear. In SRC, vascular damage due to ischemia is thought to be more involved in the pathogenesis than activation of the immune system, but autoimmune mechanisms are also thought to be involved in endothelial cell activation and vascular damage. In addition, the activation of immune cells might occur after development of SRC (17). Although there have been no reports concerning PWCA complicated with SRC, the development of PWCA after SRC in the present patient might be pathophysiologically relevant.

In conclusion, we encountered a patient with PWCA complicated by SSc accompanied by SRC. Although the presence of autoimmune diseases as the underlying disorder of PWCA has been reported, this report is thought to be the first to describe a case of SSc complicated with PWCA. Since PWCA developed after SRC, the exacerbation of SSc might be associated with the development of PWCA. In our case, IVIg and CyA may have been effective in treating agranulocytosis caused by PWCA, although the patient was difficult to treat and had a severe infection. The details concerning the pathogenesis of PWCA remain unclear; therefore, further cases need to be accumulated.

The authors state that they have no Conflict of Interest (COI).

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