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CASE REPORT

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A case of systemic sclerosis complicated by autoimmune hemolytic anemia

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Abstract We encountered a 65-year-old Japanese woman with systemic sclerosis (SSc) of the diffuse cutaneous type complicated by autoimmune hemolytic anemia (AIHA), whose chief complaints were shortness of breath and palpitation. Since the complication of AIHA with SSc is known to be rare (less than 20 cases in the literature), we reported this case for further study of the association of SSc with AIHA by accumulating data from similar cases.

Key words Autoimmune hemolytic anemia (AIHA) · Hypocomplementemia · Scleroderma · Systemic sclerosis (SSc)

Introduction

We experienced a case of systemic sclerosis (SSc or scleroderma) associated with autoimmune hemolytic anemia (AIHA). Because less than 20 cases of SSc with AIHA have been reported so far,[1–16] such a complication is thought to be relatively rare. Since the accumulation of data from similar cases is believed to be important, we herein report the clinical features of this case along with a review of some past literature.

Case report

A 65-year-old Japanese woman without any particular past history was admitted to the hospital on May 14, 2004 due to shortness of breath and palpitation that had started in the autumn of 2003 and had worsened in January 2004. The chest X-ray and computed tomography (Fig. 1) showed congestive heart failure (including cardiomegaly and pulmonary congestion) and interstitial pneumonitis (IP) with possible lung fibrosis. The laboratory data (Table 1) showed severe anemia with erythroid hyperplasia (without increase in megaloblasts), elevation of lactate dehydrogenase and indirect bilirubin, decrease of haptoglobin, and positive direct and indirect Coombs test (anti-IgG was 3+ and anti-complement was weakly positive in the direct Coombs test); these results indicated AIHA. Elevated IgM levels and hypocomplementemia were also observed. The cold hemagglutinin test and Donath–Landsteiner antibody test were negative. The levels of vitamin B12 and folic acid were normal. She had not had any drug which could cause AIHA. There was no sign of renal involvement.

She had been experiencing Raynaud's phenomenon approximately since the beginning of dyspnea and palpitation, and exhibited sausage-like swelling of the fingers and generalized skin sclerosis (with difficulty in pinching even large folds of skin) along with pigmentation over her hands (with mild phalangeal contracture), forearms, chest, and face (Fig. 2). Combining the above-mentioned findings with the positive test for anti-Scl-70 antibody and the presence of IP, she was diagnosed as having SSc (diffuse cutaneous type[17]) complicated by AIHA. Because her skin changes were visible, skin biopsy was not attempted. She had no sicca symptoms and no family history of collagen vascular diseases.

Other findings included normal blood pressure; sinus tachycardia of 100 beats/min; hyperdynamic cardiac state with no evidence of coronary heart disease or pulmonary hypertension by electrocardiogram, echocardiography, coronary angiography, and right cardiac catheterization; mild hyperventilation with respiratory alkalosis (pH 7.486, pCO_2: 30.8 mmHg, pO_2: 83.2 mmHg) by blood gas analysis; reduced vital capacity (%VC: 42.9%) by spirometry; mild splenomegaly by abdominal ultrasonography and computed tomography; and no occult blood in stools. Severe disturbance of esophageal peristalsis, mild hiatal hernia of the esophagus, and mild esophagitis were observed by

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Table 1. Laboratory findings on admission

ESR	143 mm/h	Total bilirubin	3.1 mg/dl	ANA	5120× (speckled)
Peripheral blood		Indirect bilirubin	2.3 mg/dl	Rheumatoid factor	15 IU/ml
White blood cells	5600/μl	AST	33 IU/l	Anti-DNA Ab	0 IU/ml
Stab leukocytes	12%	ALT	14 IU/l	Anti-RNP Ab	1×
Segmented leukocytes	73%	LDH	808 IU/l	Anti-Sm Ab	(–)
Eosinophils	0%	γ-GTP	8 IU/l	Anti-SS-A Ab	4×
Basophils	0%	ChE	5393 IU/l	Anti-Scl-70 Ab	16×
Monocytes	5%	ALP	180 IU/l	Anti-centromere Ab	(–)
Lymphocytes	10%	CPK	54 IU/l	Anti-cardiolipin Ab	<8 U/ml
Erythrocytes	1%	BUN	14.1 mg/dl	PR3-ANCA	<1.0 U/ml
Red blood cells	189×10^4/μl	Creatinine	0.8 mg/dl	MPO-ANCA	0.5 U/ml
Hemoglobin	7.5 g/dl	CRP	1.0 mg/dl	APTT	41.3 s
Hematocrit	22.0%	Total protein	7.3 g/dl	Lupus anticoagulant	1.35 [0.00–1.29]
MCV	116 fl	Albumin	53.9% (3.93 g/dl)	Direct Coombs	(+)
MCH	39.7 pg	α_1-Globulin	3.6%	Indirect Coombs	(+)
MCHC	34.1%	α_2-Globulin	8.0%	Donath-Landsteiner Ab	(–)
Platelets	22.1×10^4/μl	β-Globulin	8.4%	Cold hemagglutinin test	8× (–)
Reticulocytes	109‰	γ-Globulin	26.1% (1.91 g/dl)	Haptoglobin	<3 mg/dl
Bone marrow		IgG	1453 mg/dl	Fe	118 μg/dl
NCC	56.5×10^4/μl	IgA	233 mg/dl	Ferritin	313 ng/ml
Megakaryocytes	222/μl	IgM	402 mg/dl	Vitamin B12	594 pg/ml
M/E	0.71	C3	87 mg/dl	Folic acid	4.6 ng/ml
Megaloblasts	(–)	C4	<3 mg/dl	Erythropoietin	150.0 mU/ml [8.0–30.0]
Urinalysis	Normal	CH50	<10 U/ml	Free T4	0.8 ng/dl
Urine hemosiderin	Not done	KL-6	1030 U/ml [0–500]	Free T3	2.6 pg/ml
Stool occult blood	(–)	BNP	42.2 pg/ml [0.0–18.4]	TSH	4.43 μIU/ml

The values in square brackets are the reference range
ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; NCC, nucleated cell count; M/E, myeloid/erythroid ratio; AST, asparate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyl transpeptidase; ChE, choline esterase; ALP, alkaline phosphatase; CPK, creatine phosphokinase; BUN, blood urea nitrogen; CRP, C-reactive protein; BNP, brain natriuretic peptide; ANA, antinuclear antibody; Ab, antibody (or antibodies); PR3, proteinase-3; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; APTT, activated partial thromboplastin time; TSH, thyroid-stimulating hormone

esophageal barium examination and gastroscopy in August 2004. Neither dilatation nor stenosis of the esophagus was observed. Colonoscopy performed in September 2004 revealed only a small Is polyp in the descending colon. Collectively, no sign of any lymphoproliferative disorder was found.

On May 24, 2004, prednisolone (PSL; 60 mg/day) was started for treating AIHA, after which the anemia improved gradually with normalization of the number of reticulocytes and the haptoglobin level. The complement level slowly increased although it remained below the normal level (C3: 113 mg/dl; C4: 3 mg/dl; CH50: 27.6 U/ml; in July 2005). The Coombs test continued to remain positive. The skin sclerosis reduced and pinching was possible with only a little difficulty. The interstitial change in her lungs did not show remarkable improvement. Steroid-induced diabetes mellitus, hypertension, hyperlipidemia, osteoporosis, and compression fracture of the spines occurred during the course and were treated. The dose of PSL was gradually reduced; it has been less than 10 mg/day since July 2005.

Discussion

We experienced a rare case of SSc complicated by AIHA. As the cause of the anemia accompanying SSc, malabsorption from intestines (for example, iron-deficiency anemia), renal insufficiency, and microangiopathic hemolysis are relatively known. However, less than 20 cases of SSc with AIHA have been reported (Table 2).[1–16] The possibility of an overlap with systemic lupus erythematosus (SLE) should always be considered in such cases of SSc complicated by AIHA. Although the hematological disorder (AIHA and lymphopenia) and the weakly positive anti-RNP antibody and lupus anticoagulant in this case were suggestive of SLE, she had not been diagnosed as having SLE because of the lack of other characteristic symptoms and findings. However, there is a possibility that SLE could show up in the future.

In most of the reported cases of SSc associated with AIHA (14 out of 16 cases), SSc preceded AIHA. In the present case, it is difficult to determine which of the disorders occurred first, mainly because the onset of SSc was unclear. If Raynaud's phenomenon appeared when the patient started to develop SSc and if the anemia caused or enhanced the dyspnea and palpitation, SSc could have

Table 2. Reported cases of SSc complicated by AIHA

First author, year[Ref.]	Nation	Age (years)/sex	Type of SSc	Preceding disorder[a]	Antierythrocyte autoantibodies[b]	Therapy for AIHA	Other profiles
Fundenberg, 1955[1]	USA	34/M	L[c]	S (7 years)	C/W	CS (400 mg/day cortisone), effective	
Chaves, 1970[2]	Portugal	26/M	D	S (9 months)	C/W	NA	IgM↑, ANA (–)
Rosenthal, 1971[3]	USA	65/M	NA (L?)	S (10 years)	W	Azathioprine, effective (CS not used)	
Ivey, 1971[4]	USA	60/F	L	S (23 years)	C/W	CS (40 mg/day PSL), effective	Thrombocytopenia (autoimmune suspected)
Loft, 1973[5]	Denmark	71/F	L[c]	S ≒ A	W	CS (200 mg/day PSL), effective	Ham's and Crosby's test (+), ANA (–)
Krylov, 1975[6]	Russia	38/F	D	A (5 years)	NA	Initially responded to CS but splenectomy required	
Sumithran, 1976[7]	Malaysia	24/F	L	A (4 years)	C	CS (60 mg/day PSL), effective	IgM↑, ANA (–)
Cayla, 1976[8]	France	32/M	D	S (1 year)	W	Initially responded to CS but splenectomy required	ANA (–)
Cordova, 1981[9]	Mexico	54/F	NA (D?)	S (6 years)	NA	Recovered spontaneously after blood transfusion	Thrombocytopenia, IgA deficiency, ANA (–)
Jones, 1987[10]	Canada	66/F	L	S (11 years)	NA	CS (40 mg/day PSL), effective	CREST syndrome, deficiency of IgA and C4
Pettersson, 1988[11]	Finland	27/M	L	S (11 years)	W	mPSL pulse ineffective, plasmapheresis required	Autoimmune thrombocytopenia
Jordana, 1990[12]	Spain	59/F	L	S (20 years)	W	CS (0.5 mg/kg per day mPSL), effective	CREST syndrome, ANA (–)
Lugassy, 1993[13]	Israel	45/F	D	S (2 years)	C	Resistant to CS but responded to danazol	IgM↑
Kamada, 2000[14]	Japan	55/F	D	S (11 months)	NA	Resistant to CS but responded to cyclosporin	Thrombocytopenia ANA (–)
Andrews, 2002[15]	UK	41/F	L	S (6 years)	NA	Resistant to CS and splenectomy required	Overlapped with dermatomyositis
Oshima, 2004[16]	Japan	60/F	NA (D?)	S (7 years)	C	CS (60 mg/day mPSL), effective	Low-titer CAD, IgM↓, aScl-70 Ab (+)
Present case	Japan	65/F	D	S	W	CS (60 mg/day mPSL), effective	IgM↑

SSc, systemic sclerosis; AIHA, autoimmune hemolytic anemia; L, limited cutaneous type; D, diffuse cutaneous type; NA, not available; CS, corticosteroid; PSL, prednisolone; mPSL, methylprednisolone; ANA, antinuclear antibody; Ab, antibody; CAD, cold agglutinin disease

[a] S, systemic sclerosis (SSc); A, autoimmune hemolytic anemia (AIHA). The period in parentheses is the interval between the two disorders, assuming that the onset of SSc is defined as the earliest appearance of polyarthralgia, Raynaud's phenomenon, or skin sclerosis

[b] Type of antierythrocyte autoantibodies. C, cold antibody; W, warm antibody

[c] Linear sclerodermatous plaques were present on the trunk

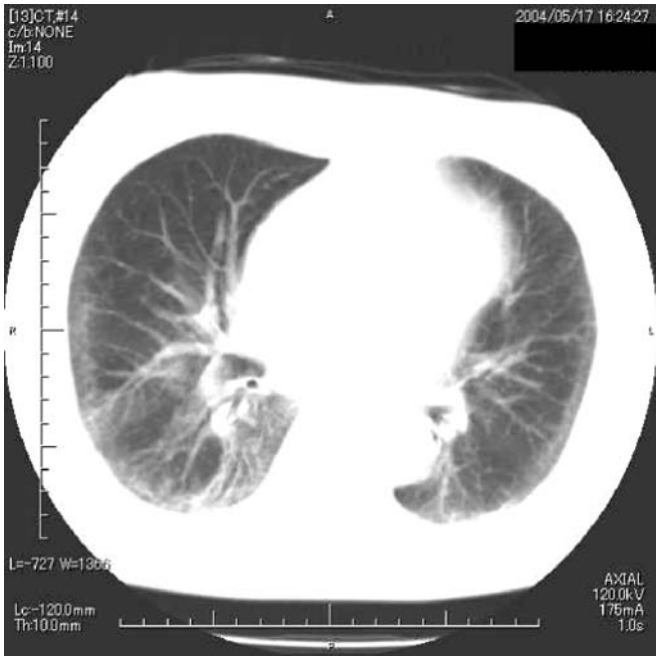

Fig. 1. Congestive heart failure and interstitial pneumonitis were seen on chest computed tomography on admission

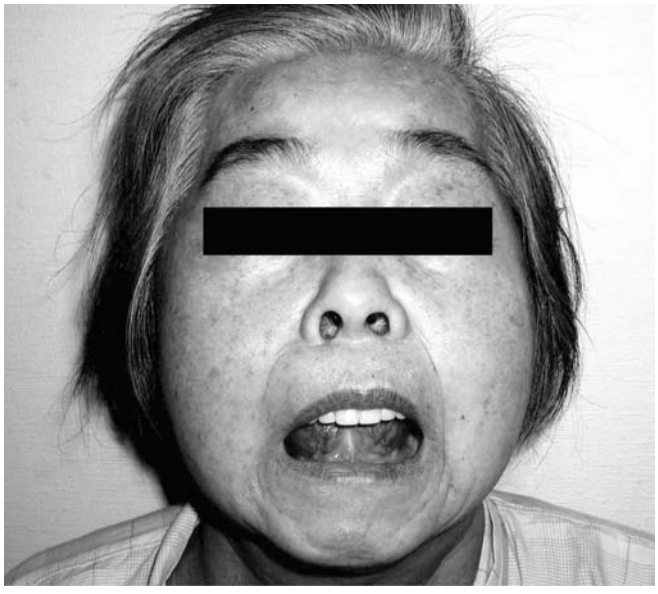

Fig. 2. There was a lack of cutaneous wrinkles, particularly on the forehead, and contraction of the lingual frenulum

started almost simultaneously with AIHA or could have preceded AIHA by a short period. However, from the generalized extension of skin sclerosis and the presence of lung change with the remarkable reduction of vital capacity, we speculate that SSc might have started even earlier.

In this case, SSc was of the diffuse cutaneous type. However, among the cases of SSc complicated by AIHA, a considerable number of cases of the limited cutaneous type have been reported.[1,4,5,7,10–12,15] In addition, there have been several cases with cold agglutinin,[1,2,4,7,13,16] thrombocytopenia (including autoimmune thrombocytopenia),[4,9,11,14] or IgA deficiency;[9,10] none of these conditions were observed in this case. All three reported cases with elevated serum IgM levels had cold agglutinin,[2,7,13] but the present case did not have cold agglutinin despite the elevated serum IgM level. Notably for SSc, as many as 7 cases[2,5,7–9,12,14] out of the 16 past cases were negative for antinuclear antibody (ANA), although the present case was ANA-positive. The age of onset of SSc among the reported cases (16–71 years, median age: 41.7 years including the present case) was not different from that of the SSc cases in general. Autoimmune hemolytic anemia occurred at 24–71 years of age (median age: 47.4 years), including the present case; the age of onset of secondary AIHA was difficult to evaluate since it would largely depend on the primary diseases. The ratio of males to females (5:12, including the present case) was slightly higher than that reported for SSc overall. In some of the reported cases,[11,13–15] AIHA was resistant to corticosteroid (CS) therapy and required other treatments. However, most of the other cases including the present case exhibited a good response to CS therapy against AIHA, at least initially.

Thus, it was possible to highlight some tendencies in the clinical features among the cases of SSc complicated by AIHA when compared with SSc in general, for example, the infrequency of the positive test for ANA and the slight increase in the male-to-female ratio. However, these were not applicable to the present case. Further accumulation of data from similar cases is required for a more significant evaluation for this association.

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