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Case Report

Very elderly-onset systemic lupus erythematosus presented with mixed-type autoimmune hemolytic anemia

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ABSTRACT

An 86-year-old Japanese woman presented with severe anemia and was diagnosed as mixed-type autoimmune hemolytic anemia (AIHA). Subsequently, although she did not show typical manifestations of systemic lupus erythematosus (SLE), she was diagnosed as SLE complicated with Sjögren's syndrome and Greaves' disease. While AIHA occurs in 5-10% of SLE patients and SLE is the most common underlying condition of mixed-type AIHA, complication of mixed-type AIHA among SLE patients has not been studied yet. SLE mainly affects women of child-bearing age and is seldom diagnosed in elderlies and the present case is the oldest SLE patient presented with mixed type-AIHA reported so far in the literature, indicating that mixed-type AIHA may complicate in elderly SLE patients and thorough evaluation of the possibility of the complication is justified. She also exemplifies the notion that elderly SLE patients often present with manifestations different from those in younger patients.

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INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a rare autoimmune disorder, in which autoantibodies that react with antigens on the red blood cells (RBCs) lead to premature peripheral destruction of RBCs. There are three serological subtypes of AIHA: warm-type AIHA, cold agglutinin disease (CAD), and paroxysmal cold hemoglobinuria, however, some patients have both warm- and cold-type autoantibodies and are referred to as mixed-type AIHA.^{1,2,3}

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disorder which can affect virtually every organ. SLE patients may develop various hematological complications and AIHA occurs in 5-10% of SLE patients,⁴ however, complication of mixed-type AIHA in SLE patients has not been specifically studied so far. As mixed-type AIHA may differ from warm-type AIHA in the clinical characteristics and response to therapy, it is important to consider the possibility of mixed-type AIHA in the management of AIHA patients.¹ On the other hand, SLE mainly affects women of child-bearing age and only 10-20% of the patients are diagnosed beyond the age of 50 years old.^{5,6,7} It is very rare that SLE is diagnosed in individuals aged beyond 70 years.

We herein report the case of SLE who presented with mixed-type AIHA at a very advanced age.

CASE REPORT

An 86-year-old Japanese woman was admitted to our hospital due to severe anemia. Two weeks prior to the admission, she started to feel shortness of breath while walking. The symptom gradually worsened and she visited her primary care doctor on the day of the admission. Anemia with a hemoglobin (Hb) value of 5.6 g/dL was noted and she was referred to our hospital and admitted. She had been treated for chronic heart failure, angina pectoris, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, and gastric ulcer. She had a brother who had systemic sclerosis.

On admission, she was anemic and small dark-brown pigmentations were seen on the face and mildly edematous lower legs. The thyroid and salivary glands were not enlarged. There was no palpable superficial lymph node. The chest and abdomen were normal and neurological examination did not reveal any abnormal findings.

The patient's laboratory data were follows: white blood cell count $4.5 \times 10^9/L$, RBC count $0.94 \times 10^{12}/L$ with 8.4% reticulocytes, Hb 4.1 g/dL, hematocrit 12.2%, platelets $165 \times 10^9/L$, and erythrocyte sedimentation rate above 100 mm/hr. The coagulation tests were normal. The blood chemistry showed that the total bilirubin was 3.4 mg/dL, the direct bilirubin 1.6 mg/dL, the aspartate aminotransferase 30 U/L, the alanine aminotransferase 12 U/L, the lactate

dehydrogenase (LDH) 473 U/L, and the creatinine 0.71mg/dL. The results of the urinalysis were unremarkable.

The haptoglobin level was below the level of detection. The direct and indirect Coombs' tests were both positive and monospecific antibodies revealed that the RBCs were coated with immunoglobulin (Ig) G and fragments of the third component of complement (C3). The IgG level was 1,510 mg/dL, IgA 268 mg /dL, IgM 140 mg/dL, C3 36 mg/dL (reference range, 65-135), the fourth component of complement (C4) 2 mg/dL (reference range 13-35), and the 50% hemolytic complement activity (CH50) was below 10 U/mL (reference range 30-50).

The antinuclear antibody was positive with a ratio of 1:160 with speckled and homogenous patterns. The anti-double stranded (ds) DNA antibody (RIA) was positive at 7 IU/mL (reference range, 0-6). The anti-smith, anti-RNP, anti-cardiolipin, anti-aminoacyl-tRNA synthetase (ARS), anti-Jo-1, anti-centromere, anti-Scl-70, and anti-cardiopipin- 2 glycoprotein antibodies were all negative. The anti-SS-A/Ro antibody titer was 744 U/mL (reference range, <10) and anti-SS-B/La 2.8 U/mL (reference range, <10). The hepatitis B surface (HBs) antigen, anti-HBs, anti-hepatitis C virus, and anti-human immunodeficiency virus antibodies were negative. The anti-*Mycoplasma pneumoniae* antibody (PA) was not detected one week after the admission.

The serum free thyroxine (T4) level was 4.20 ng/dL (reference range, 1.00-1.64), free triiodothyronine (T3) 6.0 pg/mL (reference range, 2.3-4.3), and thyrotropin (TSH) below 0.01 mIU/mL (reference range, 0.45-4.95). The anti-thyroid peroxidase (TPO) antibody titer was 26 IU/mL (reference range, <16), thyroid stimulating antibody (TSAb) 114 % (reference range, <120.0), TSH receptor antibody (TRAb) titer 31.4 IU/L (reference range, <2.0). The anti-thyroglobulin antibody was negative.

The bone marrow was hypercellular with a marked hyperplasia of erythroid precursor cells compatible with compensatory bone marrow response to hemolysis (Figure. 1). There was no increase of immature cells or evidence of lymphoproliferative diseases. The flow cytometry did not detect abnormal cell or clonal B-cell population.

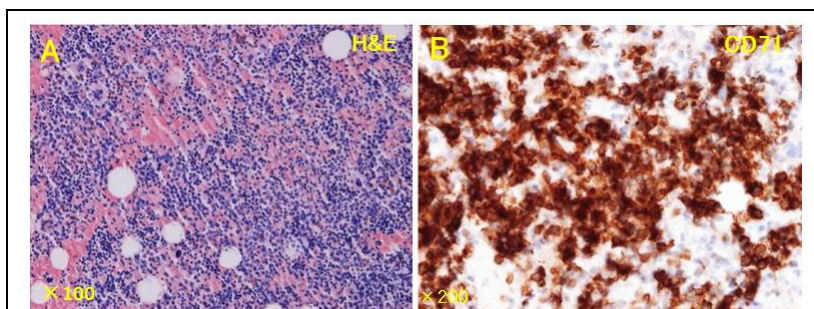


Figure 1. Bone marrow findings on admission. (A) The clot section of the bone marrow aspirate shows a hypercellular bone marrow with markedly increased erythroblasts (Hematoxylin and eosin stain, x100). (B) Immunostaining with anti-CD71-antibody confirms the increase of erythroid cells (x200).

As RBC agglutination was observed but the cold agglutinin titer was 1:32 (reference range, <1:40), the thermal amplitude of the cold agglutinin was studied by incubating O type RBCs and the serum of the patient serially

diluted in normal saline at room temperature, 4, 30, and 37 °C (Table 1). The results showed that the patient's serum contained cold agglutinins which were active at 30 °C and judged to have wide thermal amplitude and mixed-type AIHA was diagnosed.

The whole body computed tomography scan, upper gastrointestinal endoscopy, and capsule endoscopy did not detect any findings suggestive of neoplasms.

Biopsy of the salivary gland of the lip was performed, which revealed chronic sialadenitis and Sjögren's syndrome was diagnosed. On the other hand, skin biopsy of the pigmentation on the thigh revealed perivascular dermatitis without deposition of immunoglobulins, C3, or immune complex.

Oral prednisolone (PSL) was started at 0.5 mg/kg/day and prompt improvement of the hemolysis, indicated by the decrease in the serum bilirubin and LDH levels to the reference ranges in two weeks, was noted. The reticulocyte count also decreased to the reference range three weeks later, however, the direct Coombs' test remained positive. Currently she is stable on outpatient basis with maintenance dose PSL and 100mg mizoribine eleven months after the presentation. She is also taking thiamazol for Graves' disease.

Table 1. Thermal amplitude of the cold agglutinin

Dilution	x1	x2	x4	x8	x16	x32	x64
4°C	4+	4+	3+	2+	1+	1+	weak
RT	2+	1+	weak	weak	0	0	0
30°C	2+	1+	weak	weak	0	0	0
37°C	weak	weak	0	0	0	0	0

The patient serum was serially diluted in normal saline and incubated with O type RBCs at room temperature, 4, 30, and 37 °C for 45 minutes and agglutination was determined. RT, room temperature.

DISCUSSION

While the majority of AIHA is warm-type AIHA which comprises about 75% of all AIHA cases, 6-8% of AIHA patients simultaneously develop both warm- and cold-type autoantibodies and these patients are referred to as mixed-type AIHA.^{1,2,3} 40-50% of mixed-type AIHA occurs secondary to underlying conditions, of which SLE is the most frequently associated disorder.^{1,8} Lymphoproliferative disorders and, less often, other neoplasms may cause secondary AIHA of both warm- and cold-type.^{9,10} In the present case, the radiological and endoscopic studies did not detect any findings suggestive of neoplasms. The laboratory and bone marrow studies did not suggest hematological or lymphoproliferative disorders, either. Infections, especially *Mycoplasma pneumoniae* infection, may be occasionally associated with CAD,^{9,10} however, we did not find any symptoms or laboratory findings which suggested infections complications in the present case. Thus, we consider that mixed-type AIHA diagnosed in the present case was secondary to SLE. On the other hand, AIHA complicates 5-10% of SLE patients⁴ and about two thirds of AIHA occurs at the onset of SLE as a presenting symptom of SLE.^{11,12} However, in most of the reports of AIHA in SLE patients,

diagnosis of AIHA was made based solely on the positive Coombs' test and, therefore, the frequency and clinical relevance of mixed-type AIHA in SLE patients have never been reported.^{11,12,13}

SLE mainly affects women of child-bearing age with mean age of disease presentation or diagnosis around thirty years of age.¹⁴ While the definition of elderly-onset SLE varies among studies,^{14,15,16,17,18} onset after age 50-65 years appears to be a widely accepted definition.^{5,6} The incidence of SLE decreases beyond this age point, 10-20% of SLE patients having disease onset beyond the age of 50 years,^{5,6,7} and only 0.5% of the patients develop SLE after 70 years of age.¹⁴ The present case presented with and was diagnosed as SLE at the age of 86 years old and, as only four cases of SLE diagnosed above 90 years of age have been reported in the literature^{17,19} and the oldest age at diagnosis of SLE in 1,000 and 342 patients was 82 and 78 years, respectively,^{14,20} she may be one of the rare SLE patients diagnosed at a very advanced age.

At presentation, we did not consider that the patient had SLE because she did not present typical manifestation of SLE except AIHA. Elderly-onset SLE patients tend to present with considerably different clinical manifestations from those of younger patients. Elderly SLE patients are frequently complicated with serositis, pulmonary diseases, and Sjögren's syndrome but less frequently with skin changes, photosensitivity, arthritis, nephropathy, and neuropsychiatric symptoms than younger patients.^{5,6,7} As for the immunological tests, elderly patients have a high frequency of rheumatoid factor, anti-SS-A/Ro and anti-SS-B/La antibodies and low frequency of anti-RNP, anti-dsDNA, and anti-Smith antibodies and hypocomplementemia.^{5,6,7} In addition to the low prevalence and these atypical presentations, elderly SLE patients tend to have insidious onset and non-specific manifestation.^{5,6,7,16} These characteristics may result in the delay or even failure to make diagnosis of elderly-onset SLE unless SLE is suspected.

Although the number of the patients is limited, 15-20% of elderly-onset SLE patients are complicated with AIHA.^{15,19} However, as it can be easily assumed, complication of mixed-type AIHA in elderly SLE patients has never been studied. Nonetheless, the present case clearly indicates that it is important to consider the possibility of mixed-type AIHA in SLE patients even when the patient has a very advanced age. Because it is reported that mixed-type AIHA often require prolonged corticosteroid therapy for disease control despite favorable initial response,¹ considering the adverse effects of long-term corticosteroid therapy especially in the elderly, attempts to study the possibility of mixed-type AIHA is warranted in elderly patients with AIHA. For the present case, mizoribine was started with an aim to reduce the corticosteroid dose.

In summary, we presented a very elderly SLE patient who presented with mixed-type AIHA. This case is another example of very elderly-onset SLE who indicates that elderly SLE patients often do not present with typical clinical manifestations and that possibility of mixed-type AIHA should be considered and sought even in very elderly SLE patients with AIHA.

CONFLICT OF INTEREST STATEMENT

No conflict of interest was declared among authors.

REFERENCES

1. Shulman IA, Branch DR, Nelson JM, Thompson JC, Saxena S, Petz LD. Autoimmune hemolytic anemia with both cold and warm autoantibodies. *JAMA* 1985;**253**:1746-8.
2. Sokol RJ, Hewitt S, Stamps BK. Autoimmune haemolysis: an 18-year study of 856 cases referred to a regional transfusion centre. *Br Med J* 1981;**282**:2023-7.
3. Barcellini W, Fattizzo B, Zaninoni A, Radice T, Nichele I, Di Bona E, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. *Blood* 2014;**124**:2930-6.
4. Kao AH, Manzi S, Ramsey-Goldman R. Review of ACR hematologic criteria in systemic lupus erythematosus. *Lupus* 2004;**13**:865-8.
5. Lazaro D. Elderly-onset systemic lupus erythematosus. Prevalence, clinical course and treatment. *Drugs Aging* 2007;**24**:701-15.
6. Rovenský J, Tuchynová A. Systemic lupus erythematosus in the elderly. *Autoimmun Rev* 2008;**7**:235-9.
7. Arnaud L, Mathian A, Boddaert J, Amoura Z. Late-onset systemic lupus erythematosus. Epidemiology, diagnosis and treatment. *Drugs Aging* 2012;**29**:181-9.
8. Sokol RJ, Hewitt S, Stamps BK. Autoimmune haemolysis: mixed warm and cold antibody type. *Acta Haematol* 1983;**69**:266-74.
9. Packman CH. Hemolytic anemia due to warm autoantibodies. *Blood Rev* 2008;**22**:17-31.
10. Berentsen S, Tjonnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. *Blood Rev* 2012;**26**:107-115.
11. Kokori SIG, Ionnidis JPA, Voulgarelis M, Tzioufas AG, Moutsopoulos HM. Autoimmune hemolytic anemia in patients with systemic lupus erythematosus. *Am J Med* 2000;**108**:198-204.
12. Gomard-Mennesson E, Ruivard M, Koenig M, Woods A, Magy N, Ninet J, et al. Treatment of isolated immune hemolytic anaemia associated with systemic lupus erythematosus: 26 cases. *Lupus* 2006;**15**:223-31.
13. Sultan SM, Begum S, Isenberg DA. Prevalence, patterns of disease and outcome in patients with systemic lupus erythematosus who develop severe haematological problems. *Rheumatology* 2003;**42**:230-4.
14. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. *Medicine* 1993;**72**:113-24.
15. Pu SJ, Luo SF, Wu YJJ, Cheng HS, Ho HH. The clinical features and prognosis of lupus with disease onset at age 65 and older. *Lupus* 2000;**9**:96-100.
16. Chen T-L, Wong C-H, Lee C-S, Loo J-H, Lin M. Systemic lupus erythematosus in the elderly. *Int J Gerontol* 2009;**3**:108-13.
17. Cinar E, Atmis V, Cengiz ÖK, Aras S, Varli. A rare case of systemic lupus erythematosus in an elderly man. *J Am Geriatr Soc* 2015;**63**:1709-10.
18. Tomic-Lucic A, Petrovic R, Radak-Perovic M, Milovanovic D, Milovanovic J, Zivanovic S, et al. Late-onset systemic lupus erythematosus: clinical features, course, and prognosis. *Clin Rheumatol* 2013;**32**:1053-8.
19. Chen F, Zhang L, Wang G, Lin B, Wang L. A case of very late-onset systemic lupus erythematosus and updated pooled analysis of late-onset cases in the literature. *Rheumatol Int* 2012;**32**:2993-7.
20. Achour A, Mankai A, Thabet Y, Sakly W, Braham F, Kechrid C, et al. Systemic lupus erythematosus in the elderly. *Rheumatology* 2012;**32**:1225-9.