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CASE REPORT

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Successful treatment of pure red cell aplasia and autoimmune cytopenia with cyclosporine and prednisolone in a patient with Sjögren's syndrome

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Abstract A 68-year-old woman was admitted to our hospital with xerophthalmia, xerostomia, leukopenia, and thrombocytopenia. She was diagnosed to have Sjögren's syndrome and autoimmune cytopenia. After 11 months, she was readmitted with severe anemia and reticulocytopenia. Mild hemolysis was seen, and bone marrow aspirate showed markedly decreased erythropoiesis. An association of pure red cell aplasia (PRCA) and autoimmune hemolytic anemia was diagnosed. After treatment with cyclosporine and prednisolone, her anemia dramatically improved. We discuss the mechanism of PRCA associated with Sjögren's syndrome.

Key words Autoimmune hemolytic anemia (AIHA) · Leukopenia · Pure red cell aplasia (PRCA) · Sjögren's syndrome (SS) · Thrombocytopenia

Introduction

Pure red cell aplasia (PRCA) is characterized by erythropoietic hypoplasia occurring in the absence of abnormalities in the leukopoietic or thrombocytopoietic systems.[1] The marrow is normally cellular, but devoid of any erythroblasts. Irrespective of congenital or acute acquired PRCA caused by drugs or infections, PRCA has often been associated with benign thymoma and a wide variety of immunological abnormalities, including systemic lupus erythematosus[2,3] and rheumatoid arthritis.[4] Immunosuppressive therapies, including adrenal steroids, cytotoxic agents, cyclosporine, antithymocyte globulin, or a splenectomy, have all been reported to improve this condition. We describe a patient with Sjögren's syndrome (SS) which was complicated with PRCA and autoimmune cytopenia. Severe anemia was successfully treated with cyclosporine and prednisolone.

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Case report

A 68-year-old woman was admitted to our hospital suffering from xerophthalmia, xerostomia, leukopenia, and thrombocytopenia on January 27, 2000. A physical examination showed struma. She had no skin lesions, joint swelling, or any neurological abnormality. Laboratory findings revealed normal urinalysis data, hemoglobin 13.6 g/dl, white blood cells 2.36×10^9/l (35% neutrophils, 5% eosinophils, 0% basophils, 4% monocytes, 56% lymphocytes), and platelets 88×10^9/l (Table 1). Antinuclear antibody, anti-SS-A antibody, antithyroglobulin antibody, and anticardiolipin antibody were positive. The findings of both a Schirmer test (right 0 mm, left 2 mm) and a Saxon test (0.7 g) were positive. Sialography revealed abnormal pooling with an apple-tree-like pattern. A biopsy of the minor salivary gland in the lip revealed moderate lymphocytic infiltration around the ducts, which was associated with focal atrophy of the acini (Fig. 1). Thymoma was not seen on computed tomography. Bone marrow aspirate showed a decrease in mature neutrophils, while the number of erythroblasts was within the normal range (erythroblasts 41.0%). The patient was diagnosed as having SS and Hashimoto's thyroiditis. Neutropenia and thrombocytopenia were also considered to have been induced by autoimmune mechanisms. She was initially treated with a low dose of aspirin and a replacement of thyroid hormone.

On December 18, 2000, she was readmitted to our hospital owing to fatigue and palpitations. The laboratory data on the second admission are shown in Table 1. Her hemoglobin level had decreased (5.6 g/dl), and her reticulocyte

Table 1. Laboratory findings

	1st admission	2nd admission
Hematology		
WBC (/μl)	2360	1320
St (%)	10	13
Seg (%)	25	32
Eo (%)	5	0
Ba (%)	0	0
Mo (%)	4	9
Ly (%)	56	46
RBC ($\times 10^4$/μl)	475	128
Hb (g/dl)	13.6	5.6
Ht (%)	41.1	12.8
Retic (%)	0.5	0
Plt ($\times 10^4$/μl)	8.8	5.8
Haptoglobin (mg/dl)	<10	<10
Coagulation		
PT (%)	105.7	98.8
APTT (s)	49.3	57.5
Serum chemistry		
T. Bil (mg/dl)	0.86	1.29
D. Bil (mg/dl)	0.25	0.4
AST (IU/l)	24	26
ALT (IU/l)	15	12
LDH (IU/l)	375	626
BUN (mg/dl)	12	13.4
Cr (mg/dl)	0.4	0.7
Fe (mg/dl)		278
Ferritin (μg/dl)		429.4
CRP (mg/dl)	0.26	<0.28
Immunology		
C3 (mg/dl)	33	52
C4 (mg/dl)	6	3
ANA ×	640	160
Anti-dsDNA Ab	(−)	(−)
Anti-RNP Ab	(−)	
Anti-Sm Ab	(−)	
Anti-SS-A Ab	4	
Anti-SS-B Ab	(−)	
Anti-Scl-70 Ab	(−)	
Anti-centromere Ab	172	
Anti-clβ2GPI Ab (U/ml)	<1.2	2.3
Anti-CL Ab IgG	<8	
Anti-CL Ab IgM	5.1	
Lupus anticoagulant (U/ml)	1.8	
Direct Commbs (U/ml)	(2+)	(2+)
Anti-thyroglobulin Ab	6.6	
Anti-TPO Ab	>30	
PA IgG (ng/10^7cells)	243.3	1475.5
Anti-neutrophil Ab		(−)
Anti HPV B19 Ab IgG		(+)
IgM		(−)
HPV B19 DNA-PCR		(−)
Others		
fT3 (pg/ml)	3.9	2.7
fT4 (ng/ml)	0.5	0.76
TSH (μIU/ml)	2.91	1.85

RBC, red blood cells; Hb, hemoglobin; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; BUN, blood urea nitrogen; CRP, C-reactive protein; ANA, antinuclear antibody; PA IgG, platelet associated IgG; HPV, human parvovirus; TSH, thyroid-stimulating hormone

count was 0%. Both leukopenia and thrombocytopenia were unchanged. The levels of lactate dehydrogenase and indirect bilirubin were elevated. The finding of a direct Coombs test was positive, and the haptoglobin level was

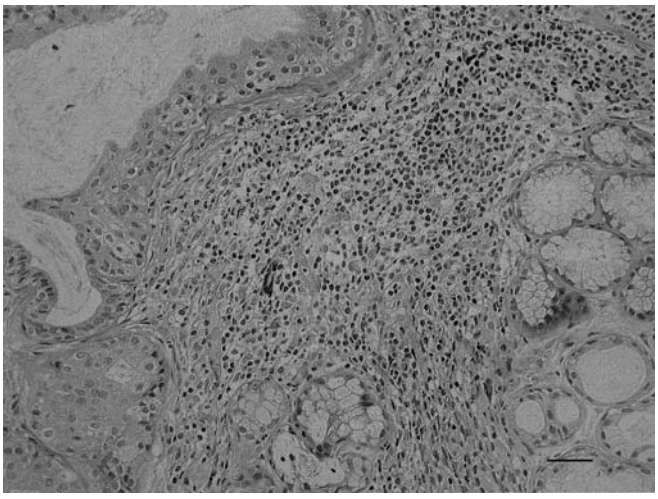

Fig. 1. A biopsy of the minor salivary gland in the lip showing moderate lymphocytic infiltration around the ducts associated with focal atrophy of the acini (hematoxylin–eosin ×200). *Bar* 50 μm

<10 mg/dl. Hypocomplementemia was observed. Platelet-associated IgG was positive. Antihuman parvovirus B19 IgM antibody and human parvovirus B19 DNA were negative. The erythropoiesis in her bone marrow had markedly decreased (erythroblasts 2.0%), and mature neutrophils had also decreased, but no dysplastic change was seen (Fig. 2A). Expressions of CD55 (decoy accelerating factor) and CD59 (membrane inhibitor of reactive lysis) on erythrocytes were normal. A complication of PRCA and autoimmune cytopenia was therefore diagnosed, and the patient was treated with cyclosporine and prednisolone. Two weeks after the initiation of the treatment, her reticulocyte count increased to 5% and her hemoglobin level gradually increased. The levels of lactate dehydrogenase, haptoglobin, and direct Coombs test were ameliorated, and her hemoglobin level reached 13.6 g/dl after 2 months. Her white blood cell and platelet levels also returned to normal ranges (Fig. 3). A bone marrow aspirate showed a restoration of erythropoiesis (Fig. 2B; erythroblasts 37.2%). After the cessation of cyclosporine and a decrease in the dose of prednisolone, the patient's white blood cell count gradually decreased, but her red blood cell and platelet counts remained within the normal ranges.

Discussion

SS is characterized by lymphocyte infiltration into the salivary and lachrymal glands. It is usually associated with polyclonal hypergammaglobulinemia, and is often accompanied by the appearance of various autoantibodies.[1] In SS patients, leukopenia is reported to be present in 20% of all patients. The leukopenia is considered to be caused by destruction as a result of antileukocyte antibody, splenic consumption, or abnormal bone marrow maturation.[1,5,6] Thrombocytopenia is occasionally seen, and its mechanism is considered to be similar to that of leukopenia.[1,7,8] Associ-

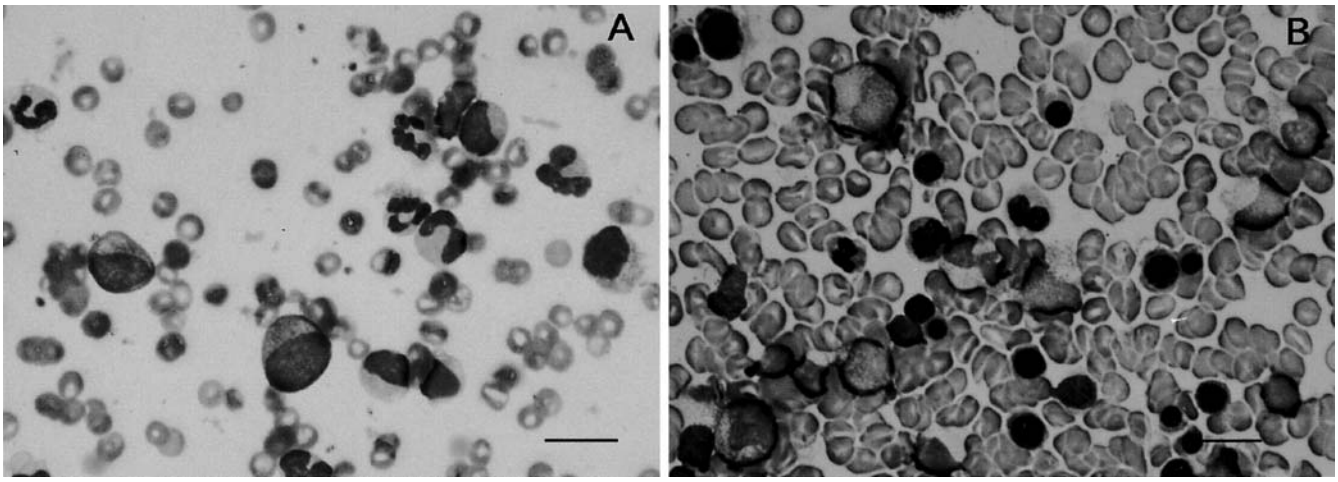

Fig. 2. Bone marrow aspiration performed (**A**) before and (**B**) after treatment with cyclosporine and prednisolone (May–Giemsa, ×400). *Bar* 25 μm

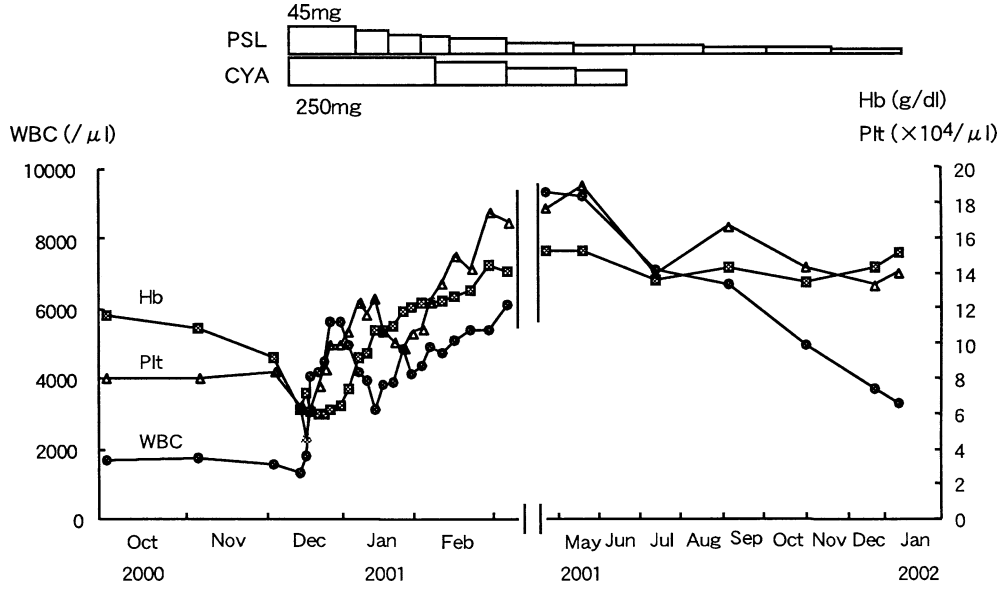

Fig. 3. Clinical course of the patient. *PSL*, prednisolone; *CYA*, cyclosporine

ated anemia is reported in almost 25% of SS patients. This is caused by chronic inflammation, iron deficiency, and autoimmune mechanisms often associated with positive findings for Coombs tests.[1,6] Although our case showed a positive finding for the direct Coombs test, the patient's hemoglobin level was lower than we expected according to her laboratory data. As both the reticulocyte count and the number of erythroblasts in her bone marrow were found to be extremely low, an association of PRCA was considered.

Although PRCA is a erythropoietic disorder of unknown etiology, autoimmune mechanisms are widely accepted.[9] Normal erythroid colony formation was reported to decrease significantly when erythroid progenitor cells were incubated with the patient's serum,[10] or lymphocytes.[11] In our case, the patient had various autoimmune diseases, including SS, Hashimoto's thyroiditis, and autoimmune hemolytic anemia (AIHA). The combination of AIHA and PRCA has rarely been reported.[12,13] Ziedman et al.[12] reported that a patient's serum had suppressed normal erythroid colony growth, which was considered to be a warm autoantibody-mediated mechanism. On the other hand, Tohda et al.[13] reported that the patient's serum did not suppress normal colony formation, while the patient's mononuclear cells did suppressed it.

SS associated with PRCA has only been reported in three cases. Giordano et al.[14] reported the case of a 40-year-old woman with SS associated with PRCA. The patient was diagnosed to have PRCA 8 years after the diagnosis of SS. She was successfully treated with danazol and 6-methylprednisolone. Ramakrishna et al.[15] reported the case of a 36-year-old woman with SS whose direct Coomb's test was positive. Treatments with prednisolone, antithymocyte globulin, cyclosporine, vincristine, and danazole were not effective, but therapy with azathioprine was encouraging.

Ergas et al.[16] reported the case of an SS patient which was complicated with PRCA and large granular lymphocyte leukemia. In the first two cases, PRCA was induced by autoantibody-mediated mechanisms, and in the last case, it was induced by a T-cell-mediated mechanism.

Cases of PRCA developing in association with various drug therapies have been reported.[9] In our case, the patient was given an antithrombotic therapy with aspirin. This is one of more than 30 drugs reported to be associated with PRCA, but the frequency of aspirin-induced PRCA is extremely low. Although we stopped the therapy with aspirin and started immunosuppressive therapy immediately, aspirin was an unlikely cause of PRCA because the patient had taken it for 11 months.

Corticosteroids or cytotoxic drugs have commonly been used for the treatment of PRCA. Corticosteroids and cytotoxic drugs have been reported to produce remissions in 18 of 32 cases (56%), but more than half of all patients relapse.[17] Recent studies have shown that cyclosporine, which suppresses the production of interleukin-2 of T cells, is more effective than corticosteroids and cytotoxic drugs.[18] A total of 31 of 38 Japanese PRCA patients (82%) have been reported to respond to cyclosporine. In the present case, we used prednisolone for the treatment of autoimmune cytopenia, and cyclosporine for PRCA. A rapid recovery of leukopenia and thrombocytopenia was observed, followed by a gradual restoration of erythropoiesis.

In aplastic anemia, patients with HLA-DR2, DRB1*1501 have shown a higher response rate to cyclosporine therapy have than those with DRB1*1502. On the other hand, patients with DRB1*1502 who responded well to cyclosporine therapy have demonstrated a sustained remission even after the treatment was concluded.[19] Whether the pathophysiology of PRCA is similar to that of aplastic anemia is still not certain, but the patient described here possessed DRB1*1502 and has demonstrated stable erythropoiesis even after the cessation of cyclosporine therapy.

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