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Case Study

A Long Course of Leukocytopenia and Splenomegaly with Extramedullary Hematopoiesis in the Absence of Clinically Manifested Rheumatoid Arthritis

Kazuo Muroi,[1)] Yasunaru Sakuma,[2)] Tohru Izumi,[3)] Kazuya Sato,[1)]
Akira Tanaka,[4)] and Keiya Ozawa[1)]

A 70-year-old female with a long history of progressive leukocytopenia and giant splenomegaly is described. She had no clinically manifested rheumatoid arthritis, although she complained of slight arthralgia in the digital joints, wrists and ankles at irregular intervals. Repeated bone marrow aspirations showed no cellular atypism, chromosomal abnormalities, or phenotypical abnormalities. Just before splenectomy, both anti-neutrophil antibody positivity and anti-cyclic citrullinated peptide antibody positivity were shown. Histology of the splenectomized spleen showed follicular hyperplasia with plasmacyte infiltration and extramedullary hematopoeisis. After splenectomy, leukocyte counts returned to normal with normal leukocyte differentials and anti-neutrophil antibodies disappeared. She was almost free of arthralgia one year after splenectomy, although the anti-cyclic citrullinated peptide antibody titers remained high. 〔*J Clin Exp Hematopathol 50(2) : 163-166, 2010*〕

Keywords: Felty's syndrome, splenomegaly, extramedullary hematopoiesis, anti-citrullinated protein antibody

INTRODUCTION

Felty's syndrome (FS), a triad of neutropenia, splenomegaly and rheumatoid arthritis (RA), occurs in less than 1% of patients with RA.[1,2] FS usually develops after a long course of RA and FS without concomitant RA is rare.[3,4] Palindromic rheumatism as a prodrome of FS has also been reported.[5] We report a patient who had severe neutropenia and a markedly enlarged spleen with extramedullary hematopoiesis in the absence of clinically manifested RA.

CASE REPORT

In December 1991, a 52-year-old woman first presented to the Outpatient Department of Respiratory Disease of Jichi Medical University Hospital because of continuing cough and fever. In February 1992, the patient was referred to the Outpatient Department of Hematology because of leukocytopenia. She had suffered from Basedow's disease at 17 years of age. No information on the treatment of her Basedow's disease was obtained. Physical examination revealed no abnormalities. Laboratory studies showed a leukocyte count of 2.5×10^9/L, a hemoglobin level of 12.6 g/dL, and a platelet count of 175×10^9/L. Leukocyte differentials were 9% bands, 21% segmented neutrophils, 5% eosinophils, 5% monocytes, and 60% lymphocytes. Serum IgG levels were slightly increased (2,320 mg/dL), but results of other laboratory studies, including serum transaminase and C-reactive protein (CRP) levels, were within normal ranges. An abdominal sonogram showed no hepatosplenomegaly or other abnormalities. Peripheral blood lymphocyte subsets were 78.3% $CD3^+$ cells, 53.6% $CD4^+$ cells, 24.6% $CD8^+$ cells, and 7.4% $CD56^+$ cells. The patient was suspected of having undetermined leukocytopenia. In September 1992, the patient first complained of slight arthralgia in the digital joints, wrists and ankles. The results of an RA test were positive, but CRP levels were negative (0.023 mg/dL ; normal, < 0.06 mg/dL). The patient's arthralgia spontaneously disappeared but later occasionally occurred. Bone marrow aspirate smears showed normal cellularity with no dysplastic features or increase in blasts. Chromosomal analysis of bone marrow cells showed 46, XX. In March 1997, the patient was admitted to our hospital because of an upper respiratory tract infection. Laboratory studies showed a leukocyte count of 1.7×10^9/L, a hemoglobin level of 10.9 g/dL, and a platelet count of 102 ×

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[1)]Division of Hematology, Department of Medicine, [2)]Department of Surgery, [4)]Department of Pathology, Jichi Medical University, Shimotsuke, Japan, and [3)]Department of Hematology, Tochigi Cancer Center, Utsunomiya, Japan
Address correspondence and reprint request to Kazuo Muroi, M.D., Division of Hematology, Department of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan.
E-mail : muroi-kz@jichi.ac.jp

10^9/L. Leukocyte differentials were 12% bands, 2% segmented neutrophils, 12% eosinophils, 2% basophils, 12% monocytes, and 60% lymphocytes. Bone marrow aspiration smears showed normal cellularity with no morphological abnormalities. In February 2006, the patient underwent an examination by a rheumatologist to clarify the etiology of arthralgia on an irregular base. Some of the patient's finger joints were slightly swollen, but X-rays showed no abnormalities in the fingers, wrists, ankles and toe joints. The results of an RA test were negative, the results of a rheumatoid arthritis particle agglutination (RAPA) test were ×40 (normal, < ×40), and CRP levels were 0.18 mg/dL. A diagnosis of RA was considered to be unlikely. In May 2006, the patient was admitted to our hospital because of high fever. Laboratory studies showed a leukocyte count of 1.4×10^9/L, a hemoglobin level of 12.3 g/dL, and a platelet count of 131×10^9/L. Bone marrow aspirate smears showed slight hypercellularity with no morphological abnormalities. Karyotypes of bone marrow cells were normal. Flow cytometric analysis of the cells did not reveal abnormal surface antigen expression in myeloid, lymphoid, and NK cells. An abdominal computed tomography (CT) scan showed an enlarged spleen (Fig. 1A). The fever declined with antibiotic treatment. Thereafter, leukocytopenia progressively deteriorated, and the spleen increased in size and was easily palpable under the left costal margin. In February 2008, an abdominal CT scan showed a markedly enlarged spleen (Fig. 1B). Serum soluble interleukin 2 receptor (sIL-2R) level was 1,660 U/mL (normal range, 124 to 466 U/mL). To rule out lymphoma in the spleen, positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG) was performed, and no abnormal accumulation of FDG was found in any organ. Bone marrow aspirate smears showed hypercellularity with slight maturation arrest in myeloid cells. Karyotypes of the cells were normal. Flow cytometric analysis of bone marrow cells and peripheral blood cells did not show abnormal surface antigen expression. A fine needle aspiration biopsy of the spleen showed normal structure with normal distribution of $CD10^+$, $CD20^+$, $CD21^+$, $CD3^+$, $CD5^+$, $CD138^+$, and bcl-2^+ cells. In April 2008, physical examinations by a rheumatologist showed slight swelling of some of her finger joints. A RAPA test was ×40 and CRP levels were 0.48 mg/dL. Complement levels of C3, C4 and CH50 were normal, and the immune complex value was 4.0 μg/mL (normal, < 3.0 μg/mL). The anti-cyclic citrullinated peptide antibody (anti-CCP antibody) levels were 890 U/mL (normal, < 4.5 U/mL). These results suggested that the patient was in an early stage of RA. Peripheral blood cells showed a leukocyte count of 0.6×10^9/L, a hemoglobin level of 10.0 g/dL, and a platelet count of 99×10^9/L. Leukocyte differentials were 12% bands, 6% segmented neutrophils, 20% monocytes, and 62% lymphocytes. To determine whether the patient's serum contained anti-neutrophil antibody, the patient's serum was reacted with paraformaldehyde-treated neutrophils from a healthy donor, then the mixture was incubated with fluorescein isothiocyanate-conjugated goat anti-human IgG, and stained cells were analyzed by flow cytometry. The results showed the existence of anti-neutrophil antibodies in serum. HLA allele analysis of peripheral blood mononuclear cells showed DRB1*0405 and DRB1*1502. To treat severe neutropenia and clarify the cause of splenomegaly, open splenectomy was successfully performed on July 3, 2008. The isolated spleen weight was 900 g. Histological examination of the spleen showed lymphoid follicular hyperplasia with plasmacyte infiltration and extramedullary hematopoiesis including myeloid cells, erythroblasts and megakaryocytes (Fig. 2). In August 2008, X-rays of the wrists showed hyperplastic synovial tissue and fluid retention. After splenectomy, peripheral blood cell counts returned to normal with normal leukocyte differentials and anti-neutrophil antibodies disappeared. In July 2009, the patient was well and almost free of arthralgia. Peripheral blood counts remained normal with normal leukocyte differentials. The RAPA test was negative (< ×40) and serum sIL-2R levels decreased to 651 U/mL. However, anti-CCP antibody titers were still high (1,770 U/mL).

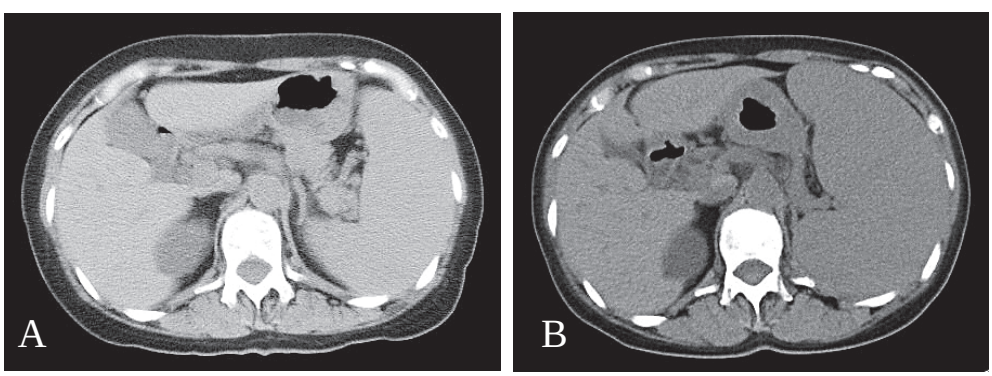

Fig. 1. Computed tomography of the abdomen. (***1A***) Enlarged spleen in May 2006. (***1B***) Markedly enlarged spleen in April 2008, just before splenectomy.

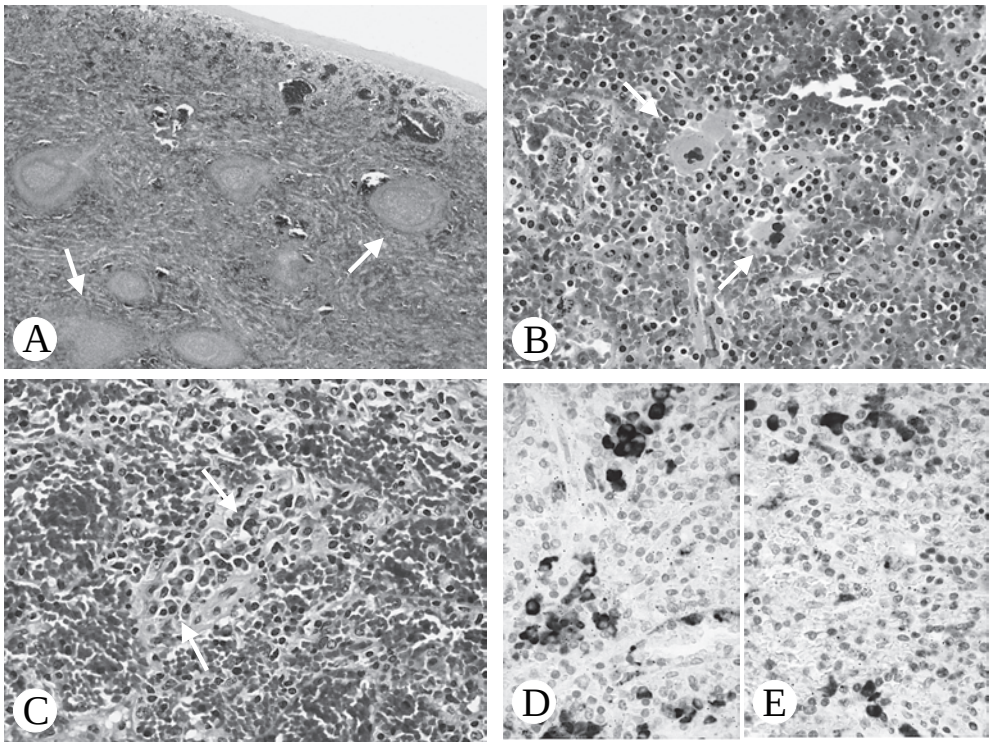

Fig. 2. Histological findings of the spleen. (***2A***) Follicular hyperplasia (*arrows*). hematoxylin-eosin (H&E) stain, ×40. (***2B***) Megakaryocytes (*arrows*). H&E stain, ×600. (***2C***) Proliferation of plasma cells (*arrows*). H&E staining, ×600. (***2D***) κ-light chain immunostaining of the plasma cells. counterstained with hematoxylin, ×600. (***2E***) λ-light chain immunostaining of the plasma cells. counterstained with hematoxylin, ×600. No light chain restrictions are shown.

DISCUSSION

A high percentage of HLA-DRB1*0401 has been shown among Caucasian patients with RA.[6] In Japan, the frequency of HLA-DRB1*0405, which was identified in the presently described patient, is significantly increased in RA patients with anti-CCP antibodies compared with the frequencies in healthy controls and RA patients without anti-CCP antibodies.[7] Although our patient had almost no typical symptoms or signs of RA before splenectomy, the existence of HLA-DRB1*0405 and the positivity of anti-CCP antibody specifically detected in the early onset of RA led to the diagnosis of RA. The diagnosis of FS in our patient seems to be appropriate because she had leukocyotpenia, splenomegaly, and RA.[1,2] The preceding leukocytopenia and splenomegaly before the manifestation of RA is not typical in FS, although there are several reports on such patients.[3,4,8]

Neutropenia is the most common and important feature of FS. Patients with FS develop bacterial infections, usually when neutrophil count is less than 0.5×10^9/L.[1,2] The pathogenesis of neutropenia in FS is unclear, but several mechanisms, including excessive margination of neutrophils, increased sequestration or peripheral destruction of cells, and impaired granulopoiesis, have been proposed.[1,2] In this setting, associations of anti-neutrophil antibodies and granulocyte-binding IgG with neutropenia in FS have been suggested.[9,10] Anti-neutrophil antibodies were detected in the serum of our patient before splenectomy and disappeared after splenectomy. Since splenectomy resulted in recovery of not neutrophils but lymphocytes, factors other than anti-neutrophil antibodies may have been involved in neutropenia and lymphocytopenia. Clonal proliferation of T-cell large granular lymphocytes (T-LGLs) associated with RA is called as Pesudo-Felty's syndrome,[11,12] although T-LGLs appear in RA at a variety of levels.[1,2] Since T-LGLs constitutively express Fas ligand and Fas is expressed on neutrophils at a high level, Fas-mediated apoptosis of neutrophils by T-LGLs in FS has been suggested.[13,14] In our patient, T-LGL proliferation was not observed during the entire clinical course. Therefore, the diagnosis of Pesudo-Felty's syndrome in our patient is not appropriate. Recently, Chavalitdhamrong *et al*. reported a case of Felty's syndrome with atypical features.[15] The patient showed neutropenia and splenomegaly in the absence of clinically manifested RA, although he had anti-CCP antibodies. Our patient is similar to this patient and previously reported patients.[3,4] The provisional diagnosis of

atypical Felty's syndrome for these patients including our patient could be made.

Splenomegaly is a common feature of FS, but it varies from being mild to severe in degrees.[1,2] Spleens in FS tend to show histological features of immune stimulation, including germinal center hyperplasia and prominent clusters of plasma cells within sinuses.[16] Our patient showed follicular hyperplasia with proliferation of reactive plasma cells and extramedullary hematopoiesis in the spleen. Extramedullary hematopoiesis in the spleen is observed in patients suffering from severe anemia of prolonged duration and appears to be a compensatory mechanism for disturbed medullary hematopoiesis. Hemoglobinopathies such as thalassemia and sickle cell disease and hematological malignancies such as leukemia and myelofibrosis are associated with extramedullary hematopoiesis.[17,18] As far as we know, there are no reports on extramedullary hematopoiesis in the spleen of FS. Several cytokines induce extramedullary hematopoiesis in the spleen of mice ; IL-12 suppresses hematopoiesis in the bone marrow but enhances hematopoiesis in the spleen and IL-13 induces extramedullary hematopoiesis and monocytosis.[19,20] In our patient, removal of the enlarged spleen led to normalization of peripheral blood cell counts and disappearance of anti-neutrophil antibody. These findings suggest that humoral factors produced by spleen cells caused abnormal peripheral blood cell counts and produced anti-neutrophil antibodies. Our patient had unique features of FS ; i.e., a long course of leukocytoepnia and splenomegaly with extramedullary hematopoiesis in the absence of clinically manifested RA. The anti-CCP antibody titers after splenectomy remained high. Therefore, the patient must be carefully followed up to detect symptoms and signs related to RA.

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REFERENCES

1 Rosenstein ED, Kramer N : Felty's and pseudo-Felty's syndromes. Semin Arthritis Rheum 21 : 129-142, 1991
2 Balint GP, Balint PV : Felty's syndrome. Best Pract Res Clin Rheumatol 18 : 631-645, 2004
3 Bradley JD, Pinals RS : Felty's syndrome presenting without arthritis. Clin Exp Rheumatol 1 : 257-259, 1983
4 Armstrong RD, Fernandes L, Gibson T, Kauffmann EA : Felty's syndrome presenting without arthritis. Br Med J 287 : 1620, 1983
5 Alvillar RE, O'Grady L, Robbins D : Coexistent Felty's syndrome and palindromic rheumatism. Ann Rheum Dis 50 : 953-955, 1991
6 Fries JF, Wolfe F, Apple R, Erlich H, Bugawan T, *et al.* : HLA-DRB1 genotype associations in 793 white patients from a rheumatoid arthritis inception cohort : frequency, severity, and treatment bias. Arthritis Rheum 46 : 2320-2329, 2002
7 Furuya T, Hakoda M, Ichikawa N, Higami K, Nanke Y, *et al.* : Differential association of HLA-DRB1 alleles in Japanese patients with early rheumatoid arthritis in relationship to autoantibodies to cyclic citrullinated peptide. Clin Exp Rheumatol 25 : 219-224, 2007
8 Raza K, Filer A : Predicting the development of RA in patients with early undifferentiated arthritis. Best Pract Res Clin Rheumatol 23 : 25-36, 2009
9 Capsoni F, Sarzi-Puttini P, Zanella A : Primary and secondary autoimmune neutropenia. Arthritis Res Ther 7 : 208-214, 2005
10 Fiechtner JJ, Miller DR, Starkebaum G : Reversal of neutropenia with methotrexate treatment in patients with Felty's syndrome. Correlation of response with neutrophil-reactive IgG. Arthritis Rheum 32 : 194-201, 1989
11 Toussirot E, Lafforgue P, Harle JR, Kaplanski S, Mannoni P, *et al.* : Pseudo Felty's syndrome. A polyclonal disease with a favorable prognosis. Report of two cases with Southern blot analysis of TCR. Clin Exp Rheumatol 11 : 591-595, 1993
12 Claudepierre P, Allanore Y, Larget-Piet B, Chevalier X : Pseudo-felty's syndrome. Report of a case with no symptoms for at least 15 years. Rev Rhum Engl Ed 63 : 56-58, 1996
13 Loughran TP Jr, Starkebaum G, Kidd P, Neiman P : Clonal proliferation of large granular lymphocytes in rheumatoid arthritis. Arthritis Rheum 31 : 31-36, 1988
14 Shah A, Diehl LF, St Clair EW : T cell large granular lymphocyte leukemia associated with rhumatoid arthritis and neutropenia. Clin Immunol 132 : 145-152, 2009
15 Chavalitdhamrong D, Molovic-Kokovic A, Iliev A : Felty's syndrome as an initial presentation of rheumatoid arthritis : a case report. Cases J 2 : 206, 2009
16 van Krieken JH, Breedveld FC, te Velde J : The spleen in Felty's syndrome : a histological, morphometrical, and immunohistochemical study. Eur J Haematol 40 : 58-64, 1988
17 Rivella S : Ineffective erythropoiesis and thalassemias. Curr Opin Hematol 16 : 187-194, 2009
18 O'Malley DP : Benign extramedullary myeloid proliferations. Mod Pathol 20 : 405-415, 2007
19 Tare NS, Bowen S, Warrier RR, Carvajal DM, Benjamin WR, *et al.* : Administration of recombinant interleukin-12 to mice suppresses hematopoiesis in the bone marrow but enhances hematopoiesis in the spleen. J Interferon Cytokine Res 15 : 377-383, 1995
20 Lai YH, Heslan JM, Poppema S, Elliott JF, Mosmann TR : Continuous administration of IL-13 to mice induces extramedullary hemopoiesis and monocytosis. J Immunol 156 : 3166-3173, 1996