Hemophagocytic Syndrome in a Patient with Rheumatoid Arthritis

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A 63-year-old female, who had been diagnosed with rheumatoid arthritis (RA) 3 years previously, was admitted due to progressive pancytopenia, lymphadenopathy, fever, and weight loss. The physical and laboratory findings fulfilled all of the American Rheumatism Association (ARA) revised criteria for RA. Her bone marrow aspirate revealed a decreased nuclear cell count ($1.8 \times 10^4/\mu l$) and megakaryocyte count ($0/\mu l$), and macrophages phagocytizing blood cells (4%), indicating the presence of hemophagocytic syndrome. The serological tests for several viruses revealed no obvious viral etiology. However, a slight Epstein-Barr virus (EBV) reactivation could not be excluded. Administration of 40 mg prednisolone daily improved her abnormal hematological findings and immunological laboratory parameters. This is a case of RA accompanied by hemophagocytic syndrome, which has not been reported previously as a complication of RA.

Case Report

A 63-year-old woman, who had been previously diagnosed with rheumatoid arthritis (RA) in 1989, was referred to our department by her family doctor in June 1992 for progressive anemia and thrombocytopenia. In March 1991 her hemoglobin was 10.2 g/dl, dropping to 8.0 g/dl by February 1992. Her platelet count was 15.5x10^4/\mu l in March 1992, rapidly decreasing to 5.7x10^4/\mu l in May 1992. She had a poor appetite, lost 17 kg over 4 months, and had a fever for a week.

Physical examination revealed a malar rash on her face, anemic conjunctiva, multiple lymphadenopathy less than 2 cm in diameter, petechiae and ecchymoses on the trunk and limbs, and a subcutaneous nodule on the extensor surface of her left forearm. There were typical rheumatoid deformities in her hands. Her liver and spleen were not palpable and an abdominal sonogram showed that they were normal size. She had a continuous fever between 37.5–38.5°C.

Laboratory parameters included a red blood cell count of $1.9 \times 10^5/\mu l$, hemoglobin level 5.8 g/dl, white blood cell (WBC) count 2,400/\mu l with 51% neutrophils, 23% lymphocytes and 16% monocytes, a platelet count of $5.6 \times 10^4/\mu l$, and 2.0% reticulocytes. Serum chemistry, including serum bilirubin, was within normal ranges except for GOT (AST) of 58 IU/L and LDH of 545 IU/L (normal 8–35 and 184–460 IU/L, respectively). Her serum ferritin was 1,700 ng/ml (normal 8–74 ng/ml), serum iron 94 μg/dl (normal 48–154 μg/dl), and total iron binding capacity (TIBC) 172 μg/dl (normal 246–396 μg/dl), although she had been administered iron intravenously by her family doctor. Bone marrow aspirate revealed a decreased nuclear cell count ($1.8 \times 10^4/\mu l$) and megakaryocyte count (0/\mu l), and an increased level of macrophages (4%). The macrophages had a low nuclear/cytoplasmic ratio, mature nuclear chromatin pattern, and abundant cytoplasm including multiple vacuoles. They showed phagocytosis of blood cells including erythroblasts, myeloid cells, and platelets (Fig. 1).

Immunological examinations revealed positive LE cells, high titers of RAHA (1:2,560) and antinuclear antibody (ANA) [1:320], and elevated double stranded DNA (dsDNA) antibody (52 U/ml; normal <10 U/ml). It was also demonstrated that the levels of complements were decreased: <12.0 U/ml CH50, 17 mg/dl C3, and <3 mg/dl C4 (normal 30.0–40.0 U/ml, 60–116 mg/dl, and 15–44 mg/dl, respectively). The concentration of the immune complexes as measured by anti-C1q was increased to 83.4 μg/ml (normal <34.5 μg/ml). Assays for extractable nuclear antigens (ENA) antibody, nuclear ribonucleo-protein (RNP) antibody, Sm antibody, SS-A/Ro antibody, and SS-B/La antibody, and both direct and indirect Coombs’ tests were negative. The titers of antibodies to the Epstein-Barr (EB) virus as measured by immunofluorescence assay (IF) were as fol-
The titer of viral capsid antigens (VCA)-IgG, VCA-IgM, VCA-IgA, early antigens (EA)-DR-IgG, and EA-DR-IgA were 1:1,280, 1:640, <1:10, <1:10, and <1:10, respectively. To avoid the influence of non-specific binding due to autoantibodies in the serum, EA-IgM and EBV-nuclear antigens (EBNA)-IgG were also measured by enzyme-immunoassay (EIA) using recombinant EB viral antigen and proved to be positive (O.D. 3.0 and 12.2, respectively). The titers of antibodies to herpes simplex virus type 1 (HSV-1), varicella zoster virus (VZV), cytomegalovirus (CMV), and mycoplasma were as follows: HSV-1-IgG, 1:320, HSV-1-IgM, <1:20, VZV-IgG, <1:10, VZV-IgM, <1:10, CMV-IgG, 1:160, CMV-IgM, <1:10, and mycoplasma, <1:4.

Flow cytometric analysis of her peripheral blood mononuclear cells (PBMC) before therapy revealed that the fluorescence intensity of CD4+ cells was weaker than the control level, although her CD4/CD8 ratio was within the normal range. On the other hand, the fluorescence intensities of CD3, CD8, and HLA-DR were all normal (Fig. 2A–D).

Biopsies of an inguinal lymph node and skin from her cheek were performed. Histologically, the lymph node revealed follicular hyperplasia while hemophagocytosis was not seen. Her epidermis was atrophic with liquefaction degeneration at the basal layer and perivascular infiltration of inflammatory cells in the upper dermis, which was compatible with systemic lupus erythematosus (SLE). Radiographic examination of her hands demonstrated joint space narrowing in the proximal interphalangeal joints and metacarpophalangeal joints, and destruction of the carpus. We diagnosed her condition as hemophagocytic syndrome (HS) associated with RA and accompanied by SLE-like symptoms, and began to administer 40

Fig. 1. Bone marrow macrophages phagocytizing blood cells including erythroblasts, myeloid cells, and platelets (×1,000).

Fig. 2. Surface markers of peripheral blood mononuclear cells from the patient before (A–D) and after (E–H) prednisolone treatment. Cells were stained with the fluorescein-conjugated monoclonal antibodies OKT3 (A, E), OKT4 (B, F), OKT8 (C, G), and OKIa (D, H), and analyzed using a flow cytometer (SRL Co. Ltd., Tokyo, Japan). The percentages of positive cells were: (A) 69.3, (B) 35.5, (C) 21.9, (D) 32.3, (E) 71.3, (F) 48.0, (G) 20.0, and (H) 47.1. Similar results were obtained when the monoclonal antibodies Leu4, Leu3a, and Leu2a were used in place of OKT3, OKT4, and OKT8, respectively.
Hemophagocytic Syndrome in RA

![Diagram showing changes in Hb, WBC, and Pt counts over time with arrows indicating blood transfusions.](image)

- Hemoglobin (Hb) •
- White blood cell (WBC) ○
- Platelet (Pit) ▲

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Fig. 3. Response of peripheral blood data to prednisolone (PSL) therapy. Changes in the white blood cell (WBC) count (○), hemoglobin (Hb) (●), and platelet (Pit) count (▲) are shown. Arrows show the blood transfusions (↓, concentrated red cells; ↓, platelet concentrate). The levels of antinuclear antibody (ANA) and CH50 are also shown.

mg prednisolone daily. Her fever subsided rapidly and the malar rash on her cheek was gradually diminished after the administration of corticosteroids. Her hematological abnormalities gradually improved and by day 14 of corticosteroid therapy the following hematological findings were recorded: hemoglobin 7.6 g/dl; WBC count 5,500/µl; and platelet count 11.0×10⁴/µl. The fluorescence intensity of the CD4 antigen was restored after therapy (Fig. 2E-H). The hematological parameters almost returned to normal after 6 weeks of therapy: WBC count 6,700/µl; hemoglobin 10.4 g/dl; and platelet count 23.1×10⁴/µl. The dosage of prednisolone has been reduced slowly to 20 mg daily. In August 1993 the titers of antibodies to EBV as measured by IF were as follows: the titers of VCA-IgG, VCA-IgM, VCA-IgA, EA-DRIgG, EA-DRIgA, and EBNA were 1:640, 1:10, <1:10, 1:20, <1:10, and <1:10, respectively. Her clinical course is further outlined in Fig. 3.

**Discussion**

The present patient had been diagnosed with RA and treated for 3 years. She met all of the revised criteria for RA of the American College of Rheumatology (1), and the destructive changes demonstrated in the hand roentgenogram supported the diagnosis of RA.

It is well known that connective tissue diseases are frequently complicated by hematologic abnormalities (2). Approximately 60% of RA patients have anemia known as “chronic disease anemia,” and its severity is usually mild to moderate. Pancytopenia caused by drugs such as gold, p-penicillamine, and NSAIDs is also seen in some patients. Although Felty’s syndrome can cause severe pancytopenia, splenomegaly, which is characteristic of Felty’s syndrome, was not found in this patient.

The patient met three of the revised criteria for SLE (3): malar rash, immunologic abnormalities with the presence of dsDNA antibody, and positive ANA. Her serum complement levels were decreased and elevated levels of immune complexes were noted. Although “hematologic abnormalities” is one of the criteria for SLE, her hematologic abnormalities did not include hemolytic anemia, lymphopenia, or thrombocytopenia due to the autoimmune mechanism (4). The present patient showed normal levels of GOT, LDH, and bilirubin, and reduced levels of reticulocyte (0.3 to 0.6%), except on the day of admission when the levels were all slightly elevated. Hemolytic anemia was thought to have little or no contribution to the development of severe anemia. Furthermore, a reduced level of megakaryocytes was found in her bone marrow, suggesting that autoimmune mechanisms, such as idiopathic thrombocytopenic purpura, were unlikely.

Several studies have found an increase or a decrease in the percentage of CD4⁺ T cells in patients with autoimmune diseases. A case of hemophagocytic syndrome with a marked
decrease in the percentage of CD4 cells was reported by Arya and colleagues (5). They discussed the relation between the immunological abnormality and the hemophagocytosis in their patient. However, a specific decrease in the fluorescence intensity of the CD4 antigen combined with a normal number of CD4+ T cells has not been reported and suggests changes in the cell surface membrane. Similar changes were probably present in other immunological cells, and these changes could affect the interaction between macrophages and blood cells. Moreover, cytokines secreted by these "abnormal" T cells could have some influence on macrophages, resulting in the malfunction of macrophages and hemophagocytosis.

Since 19 cases of virus-associated hemophagocytic syndrome were reported by Risdall et al in 1979 (6), several reports have been made on other infectious diseases or malignant neoplasms that cause phagocytic marrow histiocytoses, including tuberculosis (7), mycoplasma (8), fungi (9), malignant lymphoma (10), leukemia (11), and gastric carcinoma (12).

Recently, hemophagocytic syndrome associated with SLE has been reported in Hong Kong as acute lupus hemophagocytic syndrome [ALHS] (13). ALHS was described as SLE with febrile illness, fulminant pancytopenia and bone marrow proliferation of reactive histiocytes which phagocytize hematopoietic cells. The present case has some of the characteristics of ALHS but the patient met only three criteria for SLE and the immediate improvement in immunological abnormalities such as the high titer of ANA, presence of ds-DNA antibody and immune complexes, low levels of complements, and malar rash was inconsistent with definite SLE. Therefore, the present patient was diagnosed as having RA accompanied by hemophagocytic syndrome with "SLE-like" symptoms.

The patient showed high titer of VCA-IgG and VCA-IgM by IF and positive EA-IgM together with EBNA-IgG by EIA using recombinant EB antigens. Frequent elevations in anti-VCA and anti-EA titers have been observed in RA patients, leading to the hypothesis that EBV reactivation may contribute to the clinical outcome of RA patients (14–16). This hypothesis is still under debate (17–19). In the present patient, elevated levels of anti-VCA-IgG (IF), anti-VCA-IgM (IF) and anti-EA-IgM (EIA) suggested a slight degree of EBV reactivation despite the absence of anti-EA-IgG (IF). Several recent observations have demonstrated that RA patients appear to be deficient in their ability to regulate EBV infection (20–22) and that B cells in the blood of patients with RA are frequently infected by EB viruses (23). It has been reported that EBV is involved in the production of autoantibodies in SLE (24).

The exact mechanism by which HS and "SLE-like" symptoms developed in the present patient has remained unclear. One possible explanation is that the patient’s “SLE-like” symptoms and concomitant HS was induced by the reactivation of EBV; a state which has been popularly reported in RA patients. Another explanation is that underlying immunological abnormalities in RA are directly related to the development of HS and "SLE-like" symptoms, since successful therapeutic intervention of both HS and "SLE-like" symptoms by steroid was not inevitably associated with the alteration of the EBV reactivated state. We cannot determine whether the EBV reactivation is related to her “SLE-like” symptoms and HS, or it developed by chance as one of the typical immunological abnormalities in RA patients. There have been no previous reports on HS as a complication of RA.

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References

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