Case Report

Salazosulfapyridine-Induced Remission of Felty's Syndrome Along with Significant Reduction in Neutrophil-Bound Immunoglobulin G

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ABSTRACT. Felty's syndrome is characterized by neutropenia, splenomegaly, and leg ulcers in patients with rheumatoid arthritis. The pathogenesis of the neutropenia is an immune-mediated process that involves immune complexes, antineutrophil antibodies, and abnormal white cell kinetics. We prescribed salazosulfapyridine to a 65-year-old woman with this syndrome. The neutropenia improved along with a reduction in neutrophil-bound IgG, demonstrated by flow cytometric analysis. Salazosulfapyridine may be of benefit for the treatment of Felty's syndrome, and flow cytometry can be used to monitor disease activity and therapeutic efficacy. (J Rheumatol 2003;30:404–6)

Key Indexing Terms:
FELTY'S SYNDROME SALAZOSULFAPYRIDINE

Felty's syndrome is characterized by the triad of rheumatoid arthritis (RA), splenomegaly, and neutropenia[1]. This syndrome is a rare complication that occurs in less than 1% of patients with RA. As recurrent and sometimes fatal opportunistic infections may develop as a consequence of severe neutropenia, efficacious treatment with minimal adverse effects is highly desirable. A variety of treatment approaches have been tried for Felty's syndrome including splenectomy, corticosteroids, gold, methotrexate (MTX), and recombinant granulocyte colony stimulating factors (G-CSF)[2-5]. However, an effective treatment strategy has yet to be developed and reliable methods for monitoring disease activity and treatment do not exist.

We describe a patient with Felty's syndrome with profound neutropenia that was successfully treated with salazosulfapyridine. A significant decrease in neutrophil-bound IgG was confirmed by fluorescence-activated cell sorting (FACS).

CASE REPORT

A 65-year-old woman, who had been diagnosed with RA several years previously, was referred to our hospital in September 2000 for evaluation of severe neutropenia. She had mild arthritis in both hands, elbows, and knees and had been treated only intermittently with nonsteroidal antiinflammatory drugs. Her peripheral white blood cell (WBC) count was 3100/ml in 1996, 2800/ml in 1997, 1500/ml in 1998, and in 1999, it was 1100/ml. Fortunately, she had not developed any serious infection during this period.

On admission, she complained of morning stiffness. Physical examination showed swollen metacarpal and right knee joints, several of which were tender. Complete blood cell count revealed a WBC count of 800/ml (neutrophils 8%, lymphocytes 86%, and monocytes 6%); platelet count 117,000/ml; and hemoglobin concentration 10 g/dl. Antinuclear antibody was positive at 1:160 dilution (homogeneous and speckled pattern), rheumatoid factor (RF) was 1160 IU/ml, serum IgG concentration was 3210 mg/dl, and serum C-reactive protein concentration was 0.7 mg/dl. Eosinophil sedimentation rate (ESR) was 109 mm/h. Bone marrow aspiration showed normal appearance of granulopoiesis. Roentgenograms of both hands showed multiple bone erosions despite a relatively quiescent clinical course. Abdominal ultrasonography and computed tomography revealed splenomegaly (8 × 6 cm) and mild hepatomegaly. She had no history of skin ulcers.

Oral administration of salazosulfapyridine (1 g/day) was started. Thereafter, the neutrophil count and total WBC count gradually increased, while the platelet count remained stable. After 6 months, the WBC count reached 3100/ml (neutrophils 72%) and the RF concentration decreased from 1160 to 150 IU/ml (Figure 1). ESR decreased only slightly to 98 mm/h. After 1.5 years on the same treatment regimen, her WBC count is constant at about 3000/ml.

We analyzed the patients's neutrophil-bound IgG by FACS (Ortho Clinica Diagnostics, Tokyo, Japan). Phycoerythrin-conjugated monoclonal antibody recognizing human CD11b was used to verify neutrophils, and biotinylated anti-human IgG antibody and avidin-conjugated fluorescein isothiocyanate (FITC) were used to detect IgG bound to the surface of neutrophils. Before treatment, most neutrophils (84.3%) were IgG positive, while after treatment, only 15% of neutrophils contained IgG, despite an increase in their absolute number (Figure 2).

Platelet-associated IgG was also measured before and after treatment and decreased from 968.6 ng/10^7 cells to 123.2 ng/10^7 cells (SRL, Tokyo, Japan), although the platelet count did not change during treatment.

DISCUSSION

Both cell-mediated and humoral immune mechanisms have

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Submitted April 2, 2002; revision accepted July 29, 2002.

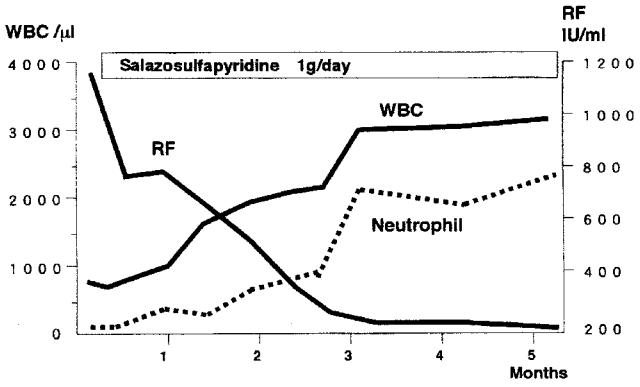

Figure 1. Clinical course of a 65-year-old woman with Felty's syndrome. The white blood cell (WBC) count and the absolute neutrophil count increased with salazosulfapyridine therapy, while the rheumatoid factor concentration decreased reciprocally.

been implicated in the pathogenesis of Felty's syndrome. Several studies have found immune complexes or antibodies that react with neutrophils[2,6-8]. Neutrophil-bound IgG in this syndrome has been measured by the inhibition of anti-IgG-induced lysis of IgG-coated sheep erythrocytes[6], the sensitive antiglobulin inhibition assay[7], and enzyme-linked immunosorbent assay (ELISA)[2]. A high prevalence of neutrophil-specific antinuclear factors has been reported among patients with this syndrome[8]. Recently, a novel nuclear target of an autoantibody highly specific for this syndrome has been reported[9]. The pathogenetic role of these antinuclear antibodies is still unclear, but they suggest that the existence of an immunological basis for Felty's syndrome is distinct from that of typical RA.

We monitored the change in neutrophil-bound IgG before and after the salazosulfapyridine therapy by double-stained FACS, and found that the percentage of IgG-bearing neutrophils decreased significantly. This change correlated with the steady increase in the absolute neutrophil count. Our findings suggest that FACS analysis can be used to monitor disease activity in Felty's syndrome and track therapeutic efficacy. FACS may also prove useful in the diagnosis and management of other forms of autoimmune neutropenia.

Many strategies for treating Felty's syndrome have been reported. Initially, splenectomy was the only option. As most patients remain vulnerable to severe opportunistic infections after this treatment, it is not advocated currently. Corticosteroids have also been widely tried. However, results have been equivocal, as corticosteroids cause immunosuppression, although the neutrophil count may increase transiently.

Based on treatments for RA, a variety of agents have been tried with variable efficacy and toxicity, including D-penicillamine, parenteral gold, lithium carbonate, cyclosporine A, cyclophosphamide, MTX[2,3], and leflunomide[4]. Only low dose MTX has been shown to have a therapeutic effect in a large scale trial[3]. Temporary use of G-CSF has been proved to be useful during severe infection[5], although it does not target the underlying immunologic abnormalities. There are only a few cases describing salazosulfapyridine use for Felty's syndrome in the literature. Two out of 4 patients showed further decrease in WBC counts: 2400/ml and 3000/ml, respectively[10,11]. Whether these changes can be regarded as adverse effects for Felty's syndrome requires further discussion.

Salazosulfapyridine is a commonly used antirheumatic drug in early RA. Because of its lower toxicity, it is better tolerated than gold, D-penicillamine, hydroxychloroquine, and MTX. More recently, salazosulfapyridine was compared with MTX, and the antirheumatic effects of the 2 drugs were similar[12]. In addition to the several antiinflammatory effects of salazosulfapyridine, it has direct immunosuppressive effects. Salazosulfapyridine inhibits B cell activation and hyperreac-

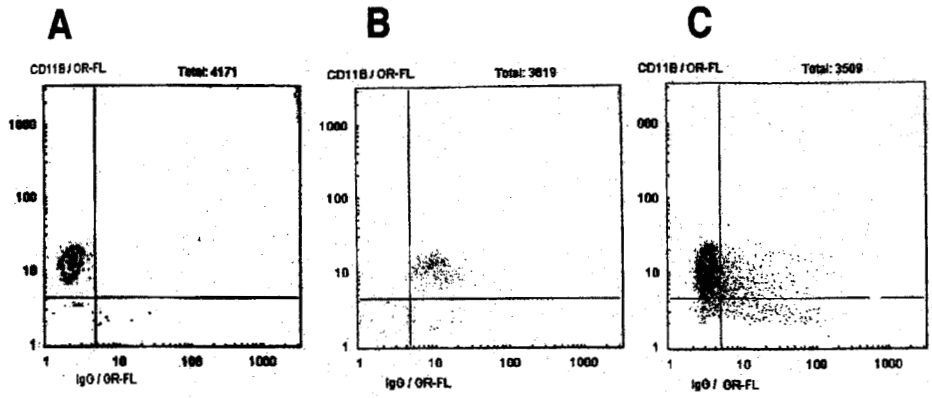

Figure 2. Flow cytometric analysis of CD11b (stained with phycoerythrin, y axis) and surface IgG (stained with avidin-conjugated fluorescein isothiocyanate, x axis) in peripheral blood neutrophils. The percentage of IgG positive neutrophils was 84.3% (panel B) compared with 1.86% in the control (panel A). After salazosulfapyridine therapy, the absolute number of neutrophils increased, and the percentage of IgG positive neutrophils decreased to 15% (panel C). Fluorescence intensity is shown on a logarithmic scale on both the x and y axes. Gates are set with the isotype-matched control antibody.

tivity in RA and also restores normal responses of lymphocytes to various stimuli *ex vivo*[13,14]. Recently, it was shown that salazosulfapyridine enhances adenosine release at an inflamed site in the same fashion as MTX[15].

These pharmacologic features seem to justify a therapeutic trial of this drug in patients with Felty's syndrome because it is characterized by hyper-autoimmunity in patients with RA. We selected low dose salazosulfapyridine as the initial treatment for our patient and found it increased the neutrophil count. Also, it clearly showed immunomodulatory effects because it suppressed at least several autoantibodies, including antineutrophil and antiplatelet antibodies, and RF.

Low dose MTX is the most widely prescribed treatment for RA, and it is the anchor drug in several different combination therapies. However, MTX has side effects, such as hepatotoxicity, acute interstitial pneumonitis, gastrointestinal intolerance, and hematopoietic suppression. When patients cannot tolerate MTX, low dose salazosulfapyridine is a reasonable alternative for treatment of Felty's syndrome.

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