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Case Report

Presentation of three cases followed up with a diagnosis of Felty syndrome

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Abstract

An effective treatment strategy for Felty syndrome (FS) has not been developed so far. In this article, three cases with FS, who responded to different treatment modalities, have been presented. Case 1 was a 52-year-old male patient who initially received methotrexate, and then, he was switched to granulocyte colony-stimulating factor (G-CSF) and cyclosporine treatment when his neutropenia was further deteriorated. The patient needed monthly doses of G-CSF for nearly 6 months, and his steroid dose was increased. Afterwards, his neutropenia improved with cyclosporine, methotrexate, and hydroxychloroquine combination treatment. Case 2 was a 78-year-old female patient who was started on leflunomide, hydroxychloroquine, and 60 mg methylprednisolone. Case 3 was a 69-year-old female patient who was first treated with 32 mg methylprednisolone, G-CSF, and then with cyclosporine. Neutropenia of both patients improved, and their health status normalized at 2 months. Different treatment strategies have been tried for the management of FS; disease-modifying anti-rheumatic drugs have been used successfully alone or in combination with G-CSF. As seen in the last case, it should be kept in mind that patients can present predominantly with symptoms of infection or hematologic disorders.

Key words: Felty syndrome, rheumatoid arthritis, neutropenia

Introduction

Felty syndrome (FS) is not a prevalent disease; however, in patients with rheumatoid arthritis (RA), it progresses with severe and life-threatening extra-articular symptoms (1). FS is characterized by a triad of RA, unexplained neutropenia, and splenomegaly (2). However, Bowman et al. (3) indicated that in the presence of RA and unexplained neutropenia without splenomegaly, a diagnosis of FS is also likely.

The number of controlled studies is inadequate, because FS is a rarely seen syndrome accompanied with RA. The positive effects of the drugs on leukopenia/granulocytopenia seen in FS that are used in the treatment of RA are based on experiences gained from small case series, and no effective treatment strategy for FS has been developed yet (4-8). In this paper, three cases with FS who responded to different treatment protocols have been presented.

Case Presentations

Case 1

A 52-year-old male patient. Eight years ago, the patient had had swellings on his hand and morning stiffness for 4-5 hours. He then consulted her family, who had given him 2000 mg/d sulfasalazine. This treatment had relieved his complaints within a few months, and he had maintained this therapy up to 1 year from that day on. Afterwards, he had only occasional joint pains. Physical examination and medical history findings were unremarkable. His test results were as follows: leukocyte (WBC): 1800/mm^3, neutrophil: 600/mm^3, RF: 148IU/mL, vitamin B12: 141 pg/mL, anti-CCP: 87 RU/m, and ANA and dsDNA: negative; erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values and biochemical test results were within normal limits. His bone marrow aspiration biopsy was not suggestive of myeloproliferative or lymphoproliferative disease. Abdominal ultrasonography (US) revealed splenomegaly (150 mm). These findings suggested a diagnosis of FS, and accordingly, methotrexate (MTX) (7.5 mg/w) and hydroxychloroquine (200 mg/d) were added to his therapy. His hematological parameters in the first month of the treatment were as follows: WBC: 800/mm^3, platelet: 121,000/mm^3, Hb: 10.9 g/dL, and innumerable neutrophils. Then, granulocyte colony-stimulating factor (G-CSF) was added to the therapy. Since the patient was unresponsive to this therapy, with a dramatic fall in his platelet counts down to thrombocytopenic levels (63,500/mm^3), MTX was discontinued and cyclosporine (200 mg/d) was initiated. From the first month of the treatment, steroid dose was tapered 2 mg per week. At the 6th month of therapy, detection of the following hematological pa-

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rameters (WBC: 2200/mm^3, neutrophil: 1400/mm^3) necessitated addition of MTX (5 mg/w) to the therapy, and its weekly dose was gradually increased to 12.5 mg. His daily steroid dose was tapered down to 4 mg, and he is currently receiving cyclosporine (150 mg/d), MTX (12.5 mg/w), hydroxychloroquine (200 mg/d), and methylprednisolone (4 mg/d). The most recent hematological parameters of the completely asymptomatic patient were as follows: WBC: 6100/mm^3 and neutrophil: 3100/mm^3 (Table 1).

Case 2

A 78-year-old female patient had complaints of swollen and painful fingers, restricted range of hand movements, and swollen feet for the last 3 years. She had suffered from morning stiffness until noon and tenderness on her first metacarpophalangeal joint of her left hand. Her biochemical parameters were within normal limits. Her hematological values were as follows: WBC: 4700/mm^3 and neutrophil: 800/mm^3. Her ESR and CRP values were within normal limits. ANA, dsDNA negativity, RF (85.6 IU/mL), and anti-CCP (>200 RU/mL) values were also recorded. Consultation was requested from the hematology clinic. No atypical cell was found in her differential blood count analysis, and methylprednisolone (64 mg/d) was initiated with an initial diagnosis of FS, based on the detection of splenomegaly. Bone marrow biopsy was planned in case of unresponsiveness to the therapy. Following this therapy, her neutrophil counts returned to normal. Leflunomide (20 mg/d) and hydroxychloroquine (200 mg) were added to her therapy. In the first month of the treatment, her hematological parameters were as follows: WBC: 4600/mm^3 and neutrophil: 1200/mm^3. She was complaint-free during the follow-up period, and her hematological parameters at the 6th month were as follows: WBC: 5900/mm^3 and neutrophils: 1800/mm^3 (Table 1).

Case 3

A 69-year-old female patient had complaints of fatigue after an episode of influenza-like syndrome that she had suffered 6 months ago. She was directed to the hematology upon detection of leukopenia, and splenomegaly. Her blood analysis had not revealed any atypical cells, and her bone marrow analysis had demonstrated interstitial mature plasmocytosis, normocellular bone marrow, and a decrease in the number of mature granulocytes. Her immunoelectrophoretic test results were within normal limits, and she was referred to the rheumatology clinic. Her medical history revealed swollen and painful hand joints and morning stiffness for 1 to 1.5 hours for the last 6 months. Her medical history was unremarkable, apart from hypertension. Her physical examination findings were within physiological limits. Her hematological parameters were as follows: WBC: 2280/mm^3, neutrophil: 91/mm^3. ESR: 70 mm/sec, and CRP: 38.6 mg/dL, which were compatible with anemia secondary to chronic disease. Other biochemical parameters were within normal reference ranges. Her abdominal US revealed splenomegaly (166 mm) and hepatosteatosis. ANA and ENA negativity was detected. Her RF (59 IU/mL) and anti-CCP (269 RU/mL) levels were also measured. With these findings suggestive of FS, the patient initially received methylprednisolone (32 mg/d), hydroxychloroquine (200 mg/d), and G-CSF. In the 3rd week of treatment, cyclosporine was added to the existing therapy. During control visits, her steroid dosage was tapered, and cyclosporine dose was increased to 200 mg/d. In the 6th month of the treatment, while she was still receiving cyclosporine (200 mg/d) and methylprednisolone (4 mg/d) therapy, her most recent hematological parameters were normal (Table 1).

Table 1. The characteristic features of the three cases

	Case 1	Case 2	Case 3
Age (years)	52	78	69
Sex	Male	Female	Female
Splenomegaly	(+)	(+)	(+)
ESH	N	N	70
CRP	N	N	38.6
CCP (RU/mL)	87	>200	269
RF (IU/mL)	148	85.6	59
ANA	(-)	(-)	(-)
*WBC (/mm^3)	1800	4700	2280
*Neutrophil (/mm^3)	600	800	91
*Hb (gr/dL)	14.1	13	10
*Hct (%)	40.7	38.6	29.8
*PLT (/mm^3)	177,000	219,000	215,000
**WBC (/mm3)	6100	5900	7300
**Neutrophil (/mm^3)	3100	1800	2900
Methylprednisolone	(+)	(+)	(+)
Methotrexate	(+)	(-)	(-)
Leflunomide	(-)	(+)	(-)
Cyclosporine	(-)	(-)	(+)
Hydroxychloroquine	(+)	(+)	(+)
G-CSF	(+)	(-)	(+)

* Pretreatment
**After the treatment

Discussion

Rheumatoid arthritis is a form of chronic inflammatory arthritis progressing with significant extra-articular findings. FS is characterized by a triad of RA, neutropenia, and splenomegaly, and its lifelong incidence in patients with RA is extremely low (<1%) (2). In very rarely seen cases, neutropenia can be encountered without any evidence of arthritis. The patients presented in this case report were referred to us with symptoms of arthritis. However, in Case 3, infection and malaise were dominant features, and she was initially sent to hematology polyclinics.

Recurrent bacterial infections are seen in FS, secondary to neutropenia. The mechanism of neutropenia has not been fully elucidated, and many hypotheses have been proposed. Both decreased granulopoiesis and increased degradation of granulocytes in peripheral blood and also cellular and humoral immunological mechanisms are thought to have a role in its pathogenesis (2, 4).

Treatment of neutropenia in FS consists of glucocorticoids, G-CSF, and mainly disease-modifying anti-rheumatic drugs (DMARDs). MTX is the safest and most effective drug, with easy tolerability in the treatment of neutropenia and arthritis (4). A limited number of case reports are available about leflunomide, sulfasalazine, and cyclosporine usage. Recently, a few case reports have been published about the use of a biological agent, rituximab, in the treatment of FS; however, the experience with its use is very limited (6, 7, 9). Splenectomy has demonstrated long-lasting favorable hematological responses in 80% of patients, which is a preferred alternative only in cases that are refractory to treatment (2). G-CSF is effective and easily tolerated in the treatment of neutropenia associated with FS. Besides, relatively faster

responses have been obtained with G-CSF (2, 8). However an effective treatment strategy for FS has not been developed so far.

As a conclusion, various treatment strategies have been tried in the treatment of FS. DMARDs can be used alone or together with G-CSF with successful results. As seen in Case 3, it must be kept in mind that occasionally, some patients with FS might present mainly with infectious and hematological symptoms.

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