Mod Rheumatol (2006) 16:267–268
DOI 10.1007/s10165-006-0483-5

LETTER

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Early morning neutropenia in a patient with systemic lupus erythematosus

Received: March 10, 2006 / Accepted: April 3, 2006

Key words Early morning neutropenia · Systemic lupus erythematosus (SLE)

Hematological abnormalities are common in systemic lupus erythematosus (SLE) and often are major manifestations of the disease. However, neutropenia occurs infrequently in patients with SLE and can have many causes including drug reaction, severe infection, and destruction mediated by anti-granulocyte antibodies.[1] We encountered a patient with SLE whose neutrophil counts were extremely low in the early morning and increased in the late morning.

The 35-year-old woman, with a 3-year history of SLE, was admitted because of fever and skin rash on the trunk. She had developed a high fever, arthritis, and proteinuria with a high titer of antinuclear antibody and anti-double-stranded DNA (ds-DNA) antibody at the age of 32. Renal biopsy showed diffuse basement membrane thickening associated with subepithelial immune deposits consistent with membranous lupus nephritis. Upon diagnosis of SLE, she had started on corticosteroid therapy. The treatment had improved her clinical manifestations and laboratory abnormalities, such as fever, arthritis, proteinuria, and the high levels of anti-ds-DNA antibodies, and her general condition had been stabilized with prednisolone at a dose of 15 mg every morning. She had shown mild leukocytopenia and lymphocytopenia at the onset of SLE; however, she had not presented any hematological abnormalities including leukocytopenia and neutropenia.

During the most recent several months, however, she had experienced hand pain with Raynaud's phenomenon; thus she had been receiving stellate block at a pain clinic. She had started taking Zonisamide, an anticonvulsant, for the pain; 4 days later she had developed a high fever and skin rashes, had stopped taking it, and presented at our outpatient clinic. She was in mild distress and showed neck lymphadenopathy, erythema on the trunk, mild leukocytopenia (1800/μl), and neutropenia (1100/μl; band cells, 560/μl). No other hematological, liver function, or urinary abnormalities, renal dysfunction, or inflammatory signs were identified. She was admitted to our hospital the next day.

On admission, she was afebrile and seemed in better condition than when seen at the outpatient clinic. Physical examination did not reveal any abnormalities of the cardiovascular or respiratory system, marked hepatosplenomegaly, or neurological abnormalities. Her lymphadenopathy and erythema were improved. The next morning, the peripheral neutrophil count was decreased, to 280/μl (band cells, 45/μl; total leukocytes, 1800/μl); a blood sample obtained later the same day, however, showed that the neutrophil count had risen to 1400/μl (band cells, not detected; total leukocytes, 2200/μl). On the 3rd and 6th hospital days severe neutropenia, i.e., 360/μl (band cells, 70/μl; total leukocytes, 1400/μl) and 260/μl (band cells, 130/μl; total leukocytes, 1400/μl), respectively, was found again, but in the second blood samples obtained on the same days the neutrophil counts were again increased, to 1060/μl (band cells, not detected; total leukocytes, 2500/μl) and 2580/μl (band cells, not detected; total leukocytes, 3400/μl), respectively. During the hospitalization, her general condition markedly improved and we identified no remarkably abnormal laboratory findings for cytomegalovirus pp65 antigen assay, anti-human herpesvirus-6 IgM antibody, Epstein–Barr virus-associated antibodies, anti-histone antibody, anti-ds-DNA antibody, or anti-granulocyte antibody. However, a lymphocyte-stimulating test was positive only for Zonisamide, indicating that her symptoms including fever and skin rashes were evoked by allergic reactions for Zonisamide, rather than flare-up of SLE or viral infection.

The severe neutropenia was identified only for the blood samples obtained at around 06:00 h, not in the second samples, taken at around 10:00 h, on the same days. (In our hospital, blood is usually sampled from in-patients at 06:00–06:30, before breakfast). Thus, as we suspected diurnal

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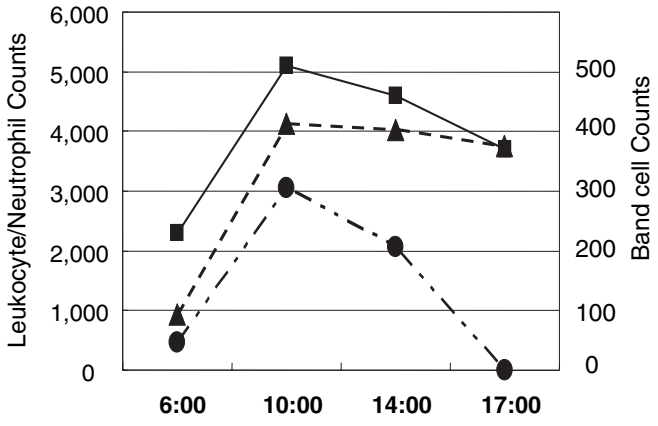

Fig. 1. Diurnal changes in the counts of leukocytes, neutrophilic granulocytes, and band cells in blood samples from the patient. *Squares*, leukocyte counts/μl; *triangles*, neutrophil counts/μl; *circles*, band cell counts/μl

changes in the counts of total leukocytes and neutrophilic granulocytes, we measured the number of peripheral blood cells at 06:00, 10:00, 14:00, and 17:00 h on the 8th hospital day. The drug prednisolone was given at 15 mg just after breakfast at 08:00 h. The neutrophil count was lowest at 06:00 and increased at 10:00 h (Fig. 1). As her clinical manifestations had resolved, she was discharged. At a follow-up visit 2 weeks later, she did not complain of any symptoms and the neutrophil count for blood sampled at around 10:00 h was 1780/μl (band cells, 175/μl; total leukocytes, 3500/μl) without the morning dose of prednisolone, indicating that the neutropenia had spontaneously improved. Based on the clinical course, the only change of her medication being Zonisamide, and the laboratory findings, we suppose the neutropenia could have been caused by Zonisamide.

The effects of corticosteroid on granulocyte kinetics are well known. Following corticosteroid administration, the granulocyte counts in peripheral blood samples increase, the peaks occurring 4–6 h after administration. This phenomenon is caused by both increased mobilization of granulocytes from the bone marrow reserve pool into the blood and reduced egress from the circulation.[2,3] Thus, the medication with prednisolone after breakfast mobilized granulocytes into the circulation and increased the neutrophil counts in the peripheral blood. Further, we speculate that the dose of prednisolone, 15 mg every morning, was not sufficient to last the whole day under the stressful condition, in our case the allergic reactions, which might unmask the drug-induced neutropenia in the early morning. Severe neutropenia, as in our case, might be masked in outpatient clinics because the blood is usually taken after the morning dose of corticosteroid is given. Thus, this type of neutropenia, early morning neutropenia, is thought to occur more frequently in patients with SLE.

Neutropenia in patients with SLE is sometimes life threatening. In this case, however, even though severe neutropenia developed, our patient did not present any clinical manifestations, such as sore throat or fever. The resampling of the blood revealed these unusual diurnal changes in leukocyte and neutrophil counts. Her clinical condition improved under close clinical observation without overzealous examinations or treatments. However, it remains to be determined whether this type of neutropenia might increase the risk of life-threatening infection in patients with SLE; thus further clinical observation is necessary. Our experience in this case indicates that the diurnal changes in leukocyte and neutrophil counts should be considered in the differential diagnosis of neutropenia in patients treated with corticosteroid.

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