CASE REPORT

Autoimmune Neutropenia Associated with Multiple Sclerosis


Abstract

A 53-year-old Japanese man with multiple sclerosis developed autoimmune neutropenia. The neutrophil count was consistently less than 0.2×10^9/l, irrespective of the disease activity of multiple sclerosis or the administration of immunosuppressive agents or granulocyte colony-stimulating factor. After high-dose γ-globulin therapy was started, temporary increases in the neutrophil count were observed. Despite a wide spectrum of clinical manifestations in multiple sclerosis, autoimmune neutropenia has never been reported previously. (Internal Medicine 42: 102-104, 2003)

Key words: autoimmune neutropenia, multiple sclerosis, neutrophil antibody, cyclosporine

Introduction

Autoimmune neutropenia (AIN) is a disorder caused by increased peripheral destruction of neutrophils as a result of antibodies in the patient's blood that are directed against their own neutrophils (1, 2). Acquired AIN has been associated with various disorders, including collagen vascular diseases (rheumatoid arthritis and Felty’s syndrome, Sjögren’s syndrome, and systemic lupus erythematosus), immune cytopenias (idiopathic thrombocytopenic purpura and Evans’ syndrome) and lymphoproliferative disorders (large granular lymphocyte leukemia, malignant lymphoma) (3–7). Here, we report a case of multiple sclerosis (MS) complicated by AIN. We are not aware of any similar clinical condition described in the literature.

Case Report

A 53-year-old Japanese man was admitted to our hospital in April 1993, presenting with fever, muscular weakness in the lower extremities and dysuria. One year before admission, he was accidentally found to have neutropenia (0.2×10^9/l) of undetermined cause. On physical examination, muscle power of the quadriceps femoris was markedly reduced. Neurophysiologic function studies revealed a prolonged latency from stimulus to the visual evoked response, suggesting a demyelinating pattern. The neurological disturbances lasted for several days, but they spontaneously improved in the next three weeks with a little residual deficit upon recovery. He was observed without medication.

After three months, high fever, paraparesis and left visual blurring with a small central scotoma developed. Atrophy of an optic nerve was detected in bilateral ocular fundi. A T2-weighted magnetic resonance image of the brain showed scattered foci of hyperintensity involving the periventricular white matter bilaterally. A study of the cerebrospinal fluid revealed an elevated concentration of IgG (8.2 mg/dl) with oligoclonal bands; the level of myelin-associated proteins was within the normal range. Serum tests for antinuclear antibodies, anti-double-stranded DNA antibodies, anti-Sm antibodies, anti-U1-RNP antibodies, antineutrophil cytoplasmic antibodies and immune-complexes were negative. A diagnosis of MS was made (8). High-dose methylprednisolone therapy (10 mg/kg/d for 3 days) was started and the neurologic disturbances gradually subsided. He received three additional courses of the methylprednisolone treatment. A third neurological attack occurred in January 1996, when he developed visual acuity disturbance, incoordination, retention of urine and gait disturbance. He was successfully treated with lymphocytapheresis. Oral cyclosporine was started at a dose of 200 mg per day, and thereafter he has remained in remission.

During the entire disease course he had sustained neutropenia, ranging from 0.05 to 0.2×10^9/l (white cells, 1.1–5.7×10^9/l; monocytes, 5–15%; lymphocytes, 72–89%). His hemoglobin concentrations and platelet counts were within normal limits, and there were neither circulating myeloid precursors, erythroblasts nor granular lymphocytes. Bone
marrow films repeatedly revealed normocellular marrow with a reduced number of segmented forms with no morphologic abnormalities. There was no evidence of hemophagocytosis. Cytogenetic analyses of bone marrow cells showed a normal karyotype (46, XY). The neutrophil-specific alloantigen of this patient was NA 1/2, and an indirect granulocyte immunofluorescence test revealed the presence of pan-Fcγ-receptor IIIb (FcyRIIIb: CD16)-specific antibodies in the serum. A diagnosis of secondary AIN was made. The neutropenia did not respond to high-dose methylprednisolone therapy, lymphocytapheresis, oral cyclosporine treatment nor an administration of granulocyte colony-stimulating factor (2 μg/kg once weekly subcutaneously) (Fig. 1). However, a high-dose γ-globulin therapy (400 mg/kg daily intravenously for 4 days) resulted in a transient increase in neutrophil counts up to 3.7×10^9/l.

Discussion

He has not suffered from severe infections despite the long-standing and profound neutropenia. This could be partly associated with the administration of granulocyte colony-stimulating factor which actively enhances neutrophil functions (9). However, it has also been known that patients with acquired AIN are often asymptomatic concerning infections and neutropenia is detected mostly by chance (2). In addition to the demonstration of autoantibodies directed against the neutrophil-specific antigen FcγRIIIb, an absence of recurrent infections is consistent with the clinical diagnosis of acquired AIN. MS is a demyelinating disease of the central nervous system (CNS) (10). Several reports have described the presence of autoantibodies recognizing myelin basic protein, myelin proteolipid protein, myelin-associated glycoprotein, myelin-oligodendrocyte glycoprotein and other CNS antigens (11–13). In the present case the repeated neurological exacerbations responded to immunosuppressive therapies including high-dose methylprednisolone therapy, lymphocytapheresis and oral cyclosporine treatment, while the neutropenia remained unchanged. Nevertheless, the neutrophil count increased in response to the intravenous γ-globulin therapy. The efficacy of intravenous γ-globulin therapy has been described in patients with both MS (14) and AIN (15). The transitory neutrophil recovery may suggest that the mechanisms of action of intravenous γ-globulin could mainly include blockade of reticuloendothelial system Fc receptors and interference in the binding of autoantibodies to target neutrophils.

Because of the almost simultaneous manifestation of MS and AIN, the association of these two disorders does not seem to be coincidental. Although it is unclear whether the antibodies recognizing neutrophil antigens and CNS antigens had cross-reactivities, we speculate that the immunogenetic abnormalities underlying the pathology of MS might be closely associated with the development of AIN. Our experience suggests that AIN can occur as a hematologic presentation of MS.

References

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