POEMS Syndrome Demonstrating VEGF Decrease by Ticlopidine

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Abstract

POEMS syndrome is a syndrome that presents with polyneuropathy, organomegaly, endocrinopathy, M-proteins and skin changes. Elevated vascular endothelial growth factor (VEGF) has recently been reported in POEMS syndrome. We report a case of POEMS syndrome with high VEGF titers. Steroid, plasmapheresis and intravenous gamma-globulin had little effect. Various immunosuppressive agents were discontinued due to side effects. Although administration of aspirin did not decrease VEGF, ticlopidine decreased VEGF significantly. This case suggests that ticlopidine is a candidate for supportive therapy in POEMS syndrome and we should measure VEGF before and after the administration of ticlopidine in other cases.

Key words: POEMS syndrome, vascular endothelial growth factor, ticlopidine

Introduction

POEMS syndrome is a syndrome that presents with polyneuropathy, organomegaly, endocrinopathy, M-proteins and skin changes. Elevated vascular endothelial growth factor (VEGF) has recently been reported in POEMS syndrome and is considered closely related to its pathophysiology and activity.

Ma et al reported that VEGF was decreased by ticlopidine in experimental rats (1). Here we present a case of POEMS syndrome in which VEGF decreased after ticlopidine administration. An unknown chromosome abnormality was also detected in this patient.

Case Report

A 52-year-old man had a 5-year history of severe polyneuropathy. He was diagnosed as having chronic inflammatory demyelinating polyneuropathy by distal dominant polyneuropathy, loss of deep tendon reflexes, increased protein and normal cell counts in cerebrospinal fluid, and conduction block. Steroid, plasmapheresis and intravenous gamma-globulin had little effect. Various immunosuppressive agents were discontinued due to side effects. Then he was referred to our hospital. On initial examination, the patient presented with moderate ascites, bilateral pleural effusions, hypothyroidism, edema, organomegaly (swelling of the liver, kidneys and spleen) and dusky, bristled skin. Since all symptoms gradually worsened, he was admitted to our hospital. On examination, there were no deep tendon reflexes. He complained of severe pain in the distal limbs. He showed disturbance of all sensory perceptions and severe weakness of all limbs (MMT grade 2) as well as severe muscle atrophy over the whole body. There were no pathological reflexes. Platelet counts were 462,000/µl, creatinine was 2.2 mg/dl, BUN was 45 mg/dl, TSH was 5.02 µU/ml, fT3 was 1.2 pg/ml, fT4 was 0.6 ng/dl, interleukin-6 was 8.7 pg/ml and VEGF was over 2,000 pg/ml. All other cell counts, laboratory data, immunoglobulin, autoantibody tests and hormones were normal. M-proteins and Bence-Jones proteins were not detected at any point during these examinations. Bone marrow showed abnormal aggregation, polymorphism and polynucleus of plasma cells (Fig. 1). Chromosome test showed some abnormal cells with 45XY- t(12:18)(q24:q23). Ga and bone scintigraphies did not show any significant change.

Based on the clinical picture, high VEGF titers and plasma cell dyscrasia, he was diagnosed as having POEMS
syndrome. Steroid and intravenous gamma-globulin were still not effective. Aspirin (100 mg) was administered for anti-platelet therapy, but VEGF was not changed and his condition deteriorated. Aspirin was discontinued and ticlopidine (400 mg), which is reported to reduce VEGF in rats, was administered after an appropriate informed consent procedure. One month later, VEGF was reduced to 602 pg/ml. Neuropathy, thyroid function and other laboratory data did not change. Edema, ascites and pleural effusions were all ameliorated and the disease has remained clinically stable for several months.

Discussion

Scheinker’s autopsy case in 1938 was the first report of what is now called POEMS syndrome, Crow-Fukase syndrome, PEP syndrome or Takatsuki syndrome. Increased VEGF in POEMS syndrome was pointed out by Watanabe et al in 1996 (2). Preliminary data suggest that VEGF is an excellent candidate as a pathogenic factor in POEMS syndrome (3, 4). VEGF is detected in platelet cells by immunological staining using anti-VEGF antibody, and VEGF has been reported to be produced by plasma cells. VEGF induces a rapid and reversible increase in vascular permeability; it is a growth factor for endothelial cells and is considered important in angiogenesis. These functions may cause the development of ascites, pleural effusions, edema, organomegaly and neuropathy.

For control of platelet hyperactivity or hypercoagulation, anti-platelet therapy or anti-coagulation therapy is sometimes performed. However, there has not been any significant evidence supporting such therapy. Recently, Ma et al reported that VEGF was decreased by ticlopidine, but was not decreased by aspirin in experimental rats (1). They also demonstrated that ticlopidine affected the VEGF release from platelets, but not its levels within the platelets. Because ticlopidine inhibits ADP-induced platelet aggregation and the resulting α-granule release (5, 6), VEGF release from platelets is reduced. Otherwise, aspirin inhibits thromboxane synthesis by blocking cyclooxygenase but does not inhibit α-granule release and the resulting VEGF release. We first tried aspirin and then ticlopidine for POEMS syndrome. Although the administration of aspirin did not decrease VEGF, ticlopidine significantly decreased VEGF in the present case. This is the first case report indicating that ticlopidine reduced VEGF in a human with POEMS syndrome. This case suggests that ticlopidine is a candidate for supportive therapy in POEMS syndrome and that we should measure VEGF before and after the administration of ticlopidine in other cases.

The significance of this abnormal chromosome is unknown. There have not been any similar chromosome abnormalities in POEMS syndrome or any other diseases. It remains to be clarified whether or not this abnormality is related to POEMS syndrome.

References