Diurnal Fluctuation of Edema Synchronized with Plasma VEGF Concentration in a Patient with POEMS Syndrome

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Abstract

A case of POEMS syndrome in a 49-year-old Japanese woman is reported. The patient exhibited prominent edema in her legs at night, but her edema usually improved by the following morning. The plasma concentrations of VEGF in the patient showed diurnal fluctuations; plasma VEGF levels peaked at night and decreased in the daytime. Immunocytochemical study demonstrated the expression of VEGF in IgA- and λ-positive plasma cells in bone marrow. The results indicate that VEGF was produced at least by plasma cells and that VEGF production was regulated by circadian rhythm in synchronization with the development of edema. (Internal Medicine 41: 1196–1198, 2002)

Key words: IgA(λ), adrenal cortex dysfunction, circadian rhythm

Introduction

POEMS syndrome is a rare multisystemic disorder usually associated with plasma cell dyscrasia and characterized by the combination of polynuropathy, organomegaly, endocrinopathy, presence of M protein and skin changes. Vascular endothelial growth factor (VEGF) is a potent, multifunctional cytokine that induces angiogenesis and microvascular hyperpermeability (1, 2). It has recently been reported that plasma VEGF levels are significantly elevated in patients with POEMS syndrome, corresponding to the clinical manifestations of POEMS syndrome (3–5). We herein report a patient with POEMS syndrome whose edema was prominent at night.

Case Report

A 49-year-old Japanese woman with no family history was healthy until the age of 47 years, when she noticed edema of the face and feet. She was diagnosed as having Hashimoto’s disease and was treated with Levothyroxine (150 μg/day). From the age of 48, she suffered from progressive numbness in her hands and feet. On July 28, 1998, she was referred to Tokushima University Hospital. Her height was 152 cm and weight was 48 kg. Physical examination on admission revealed skin hyperpigmentation, soft struma and edema of her whole body. Her edema was prominent at night but improved by the following morning. Neurologic examination showed moderate muscle wasting and weakness in distal limbs. Deep tendon reflexes were diminished in all four limbs. Superficial and deep sensation was markedly disturbed in distal limbs. The results of laboratory examinations, including those of peripheral blood cell counts and routine blood chemistry including BUN (12 mg/dl) and creatinin e (0.53 mg/dl), were normal. A serum proteinogram revealed M-protein and serum immunoelectrophoresis detected IgA(λ) M-protein. Thyroid function was normalized by compensation therapy. Anti-thyroglobulin antibody and anti-microsome antibody were positive: 1:25,600 and 1:200, respectively. Serum levels of cytokines, including interleukin (IL)-1β, IL2, IL-6, IL8, tumor necrosis factor-α, and interferon-γ, were almost normal. Pituitary function was examined by combined intravenous administration of four hypothalamic releasing hormones (CRH, 100 μg; GRH, 100 μg; TRH, 500 μg; LHRH 100 μg). As shown in Fig. 1A, plasma ACTH concentration was elevated, and ACTH showed hyperreaction to CRH administration, but serum cortisol did not respond to CRH, indicating mild adrenal cortex dysfunction. The responses of PRL, TSH, GH, LH and FSH were normal (data not shown). In cerebrospinal fluid, protein was increased to 107 mg/dl, but the cell count was normal (3/3). Bone lesion was not detected by X-ray films nor by 99mTc bone scintigram. Chest CT and a cardiac echogram showed right pleural effusion and pericardial effusion. Abdominal CT revealed mild hepatosplenomegaly and paraaortic lymphadenopathy. The results of bone marrow examination demonstrated an increased plasma cell count (4%, NCC 45×10⁹/μl) with immature appearance of cells. Immunocytochemical study demonstrated IgA expression in λ-positive plasma cells, indicating monoclonal proliferation. The bone marrow lymphocyte infiltration was significant (30% of the bone marrow population). The patient exhibited prominent edema in her legs at night, but her edema usually improved by the following morning. The plasma concentrations of VEGF in the patient showed diurnal fluctuations; plasma VEGF levels peaked at night and decreased in the daytime. Immunocytochemical study demonstrated the expression of VEGF in IgA- and λ-positive plasma cells in bone marrow. The results indicate that VEGF was produced at least by plasma cells and that VEGF production was regulated by circadian rhythm in synchronization with the development of edema.
Edema and VEGF Levels in a POEMS Patient

Figure 1. A) Pituitary function was examined by combined administration of hypothalamic releasing hormones. Plasma ACTH concentrations were elevated, and ACTH hyperreacted to CRH, but serum cortisol concentrations did not respond, indicating mild adrenal cortex dysfunction. B) Plasma concentrations of VEGF were higher at night than in the daytime, when the patient’s edema was improved. C) Double immunofluorescent microscopy of bone marrow cells with anti-IgA and anti-VEGF antibodies. Signals of IgA and VEGF were visualized by FITC (left panel) and TRITC (middle panel), respectively. VEGF signals were detected in some IgA-positive plasma cells (right panel).

Discussion

The patient showed typical symptoms of POEMS syndrome. The results of endocrinological examination revealed hypothyroidism and adrenal insufficiency. Adrenal insufficiency was subclinical and was disclosed only after the administration of hypothalamic releasing hormone. It is thought that adrenal dysfunction induced hypersecretion of ACTH and MSH, leading to hyperpigmentation as in Addison’s disease. Adrenal dysfunction is reportedly very rare in POEMS syndrome (6), but diffuse hyperpigmentation is a major clinical manifestation observed in 91% of patients with POEMS syndrome (6). These findings suggest that subclinical adrenal insufficiency may be more frequent if further examination is performed.

In our patient, M-protein consisted of λ chain of IgA and bone marrow puncture demonstrated that the count of immature plasma cells was increased and that some of them were immunopositive to the IgA λ chain. It is notable that edema, one of most frequent symptoms of this syndrome (6), exhibited diurnal fluctuation; the patient’s edema was usually prominent at night and improved by the following morning. Since plasma VEGF levels are significantly increased in patients with POEMS syndrome (5, 7, 8), we examined the cytokine levels and found that the fluctuation in edema corresponded to changes in plasma VEGF concentrations. VEGF potentially induces edema by increasing micro vascular permeability (1, 2). Considering these facts, it seems that the fluctuation in edema depended on the diurnal rhythmicity of VEGF production. To our knowledge, these phenomena have not been recognized. We aimed to identify the source of VEGF production, and VEGF expression was detected in IgA- and λ-positive plasma cells. This findings does not agree with previous reports showing that VEGF was highly concentrated in platelets in patients with POEMS syndrome (9). However, we recently reported that VEGF was overexpressed in solitary plasmacytomas from pa-
tients with polyneuropathy (10). The results in the present study as well as our previous observation suggest that plasma cells produce VEGF and that the production of VEGF was regulated by circadian rhythm in the present patient. Diurnal rhythms are also observed in serum concentrations of several inflammatory cytokines such as tumor necrosis factor alpha, interferon gamma, interleukin 1 and interleukin 12 (11–14). The rhythms of these cytokines peak at midnight and are inversely related to the rhythm of plasma cortisol. Although a diurnal rhythm of VEGF has not been reported, the fact that plasma VEGF levels were decreased after corticosteroid administration indicates a similar physiological regulation of VEGF production to those of the above-mentioned cytokines.

References