Angioedema of the Periorbital Region that Developed during Treatment with Etanercept in a Case of Refractory Adult-Onset Still’s Disease

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Abstract

A 78-year-old Japanese man with adult-onset Still’s disease that was refractory to conventional treatment, such as prednisolone (PSL) concomitant with methotrexate (MTX). Etanercept (50 mg/week) was added to PSL (12.5 mg/day) and MTX (12 mg/week). His manifestation improved dramatically, nonetheless massive edema of the periorbital region developed by the fourth injection, which kept his palpebral fissure completely closed. There was also a marked injection site reaction to etanercept. A diagnosis of angioedema due to etanercept was thus made, and the drug was discontinued. His angioedema began to ameliorate soon after antihistamines were introduced without any critical involvement, such as laryngeal obstruction.

Key words: adult-onset Still’s disease (AOSD), adverse event, angioedema, etanercept, hypersensitivity

Introduction

Adult-onset Still’s disease (AOSD) is an autonomous systemic inflammation, which is characterized by high-grade fever concomitant with evanescent salmon pink rash, arthritis, sore throat, myalgia, lymphadenopathy, splenomegaly, neutrophilic leukocytosis and liver dysfunction (1). More than a moderate dosage of prednisolone (PSL) is often necessary as the initial therapy to improve the manifestations (2). However, not all patients achieve remission with corticosteroid monotherapy, and an additional immunosuppressant, such as methotrexate (MTX), cyclosporine and tacrolimus, may be necessary for disease remission or reducing the PSL dosage (3-5). Furthermore, over the past decade, anti-proinflammatory cytokine agent (biologics), such as infliximab, etanercept, tocilizumab, and anakinra, has proven the therapeutic efficacy in AOSD patients refractory to the conventional treatments (6-11).

This report describes a patient with AOSD refractory to the conventional treatment in whom angioedema of the periorbital region and a marked injection site reaction due to etanercept developed by the fourth injection of etanercept (50 mg, once a week). Etanercept is a recombinant tumor necrosis factor (TNF)-α receptor fused with the Fc domain of human immunoglobulin G (IgG)1, and can inhibit TNF-α activity with demonstrated therapeutic effectiveness in refractory rheumatic diseases such as rheumatoid arthritis (RA) (12). Angioedema triggered by etanercept is an extremely rare adverse event (13), and was demonstrated only in an RA patient, in whom angioedema had developed due to treatment with etanercept (13). Furthermore, no AOSD patients with angioedema caused by adverse events have so far been described in the literature. Nonetheless, the possibility of angioedema should be paid attention to because it can develop into a critical condition, such as laryngeal obstruction.

Case Report

A 78-year-old Japanese man was admitted in April 2012 because of a 1-week history of massive edema of the periorbital region and a marked injection site reaction due to etanercept.
nosis of AOSD was made and treatment with prednisolone (PSL) was started for the purpose of reducing the dosage of PSL. The patient was readmitted in June 2009, and MTX (10 mg/week) was introduced in April 2012, concomitantly with PSL (12.5 mg/day) and MTX (12 mg/week). Severe bacterial pneumonia occurred the next month, and tocilizumab was introduced to reduce the dosage of PSL, nonetheless his corticosteroid dependency was not resolved. Treatment with PSL (10 mg/day) and MTX (10 mg/week) in August 2011 induced AOSD manifestations, such as a high fever spike, erythema, myalgia and episceritis, and therefore his illness was thought to have shown a refractory polycyclic systemic pattern. Tocilizumab (8 mg/kg, once a month) was added for the purpose of reducing the dosage of PSL. Thereafter, PSL dose was gradually tapered to 5 mg/day by March 2011. However, episceritis, erythema of the lower limbs and general malaise recurred, and the dosage of PSL thus had to be increased to 15 mg/day in June 2011. In addition, steroid induced diabetes mellitus was triggered, and therefore had to be increased to 15 mg/day in June 2011. In addition, reaction of the previous etanercept injection site on the left lower abdomen was detected, showing erythema (5 cm in diameter) accompanied by tenderness and subcutaneous induration. The chest and abdomen were intact except for a surgical scar on the abdomen. No abnormal findings, such as sore throat, goiter, superficial lymph-node swelling, arthralgia, myalgia, or edema of the extremities were observed. In addition, no abnormalities within the eyeballs, such as episcleritis, were detected by an ophthalmologist.

Laboratory findings were; white blood cell count 8,600/μL (neutrophil 71.4%, monocyte 9.9%, lymphocyte 15.1%, eosinophil 0.6%, basophil 3.0%), hemoglobin 11.1 g/dL, platelet count 14.2×10^4/μL, total protein 7.0 g/dL, total bilirubin 1.1 mg/dL, aspartate aminotransferase (AST) 16 IU/L, alanine aminotransferase (ALT) 18 IU/L, alkaline phosphatase (ALP) 190 IU/L, gamma-glutamyl transpeptidase (γ-GTP) 45 IU/L, lactate dehydrogenase (LDH) 208 IU/L, creatine phosphokinase (CPK) 29 IU/L, amylase 37 IU/L, blood urea nitrogen (BUN) 15 mg/dL, creatinine 0.81 mg/dL, alanine aminotransferase (ALT) 18 IU/L, alkaline phosphatase (ALP) 190 IU/L, gamma-glutamyl transpeptidase (γ-GTP) 45 IU/L, lactate dehydrogenase (LDH) 208 IU/L, creatine phosphokinase (CPK) 29 IU/L, amylase 37 IU/L, blood urea nitrogen (BUN) 15 mg/dL, creatinine 0.81
mg/dL, and casual blood glucose 154 mg/dL. The serum electrolytes were intact. The serological findings were; CRP 18.2 mg/dL (normal range <0.2), IgG 1,208 mg/dL, IgA 350 mg/dL, IgM 56 mg/dL, IgE 46.1 IU/mL (normal range <172), complement factor 3 (C3) 140 mg/dL, C4 38 mg/L, rheumatoid factor (RF) 2 IU/mL (normal range <19). Anti-nuclear antibodies (ANA) were low titer (1 : 40), and anti-deoxyribonucleic acid (DNA) antibodies, myeloperoxidase antineutrophil cytoplasmic antibodies (MPO ANCA), and proteinase 3 antineutrophil cytoplasmic antibodies (PR-3 ANCA) were negative. Hepatitis B viral surface antigen (HBsAg) and serology against hepatitis C virus (HCV) and cytomegalovirus (CMV) were negative. The serum β-D-glucan level was not elevated, and Cryptococcus antigen was negative. Blood cultures were negative. Chest X-ray and electrocardiogram were unremarkable except for a complete right bundle branch block. An orbital computed tomographic (CT) scan demonstrated the presence of subcutaneous edema in the periorbital regions (the right-side was dominant) (Fig. 1).

Hypersensitivity against etanercept was therefore diagnosed, based on the intensive injection site reaction of etanercept. Etanercept was terminated, based on the assumption that etanercept might have caused angioedema of the periorbital region. MTX was also discontinued because the other inflammatory illness, such as sepsis could not be fully excluded on day 1 of the admission. The H1 antihistaminic agent (5 mg of d-chlorpheniramine maleate) was added intravenously for the angioedema due to etanercept. His massive edema of the periorbital region began to resolve, and he could open the right palpebral fissure two hours after the injection (Fig. 2). In addition, oral antihistamine (fexofenadine hydrochloride, 60 mg twice a day) was initiated. The edema of the periorbital region was resolved completely on day 2 of the admission. The low-grade fever also ameliorated, and the serum CRP level decreased from 18.2 mg/dL to 6.3 mg/dL on day 5 of the admission (Fig. 3). He was finally discharged on day 6 of the admission.

**Discussion**

Angioedema is defined as a well-demarcated localized edema involving the deeper layers of the skin and subcutaneous tissue. The mechanism is divided into IgE-dependent, bradykinin-mediated, complement-mediated, and nonimmunological (such as alterations of arachidonic acid metabolism due to aspirin administration) processes. The etiology includes the inhalation of pollens, animal dust, the ingestion of food and fruits, physical stimuli, mechanical irritation, and drug intake. The same process can be triggered in the upper respiratory and gastrointestinal tract, and severe angioedema at the upper respiratory may be life-threatening due to laryngeal obstruction (14). Fortunately, the current case had no apparent involvement of the respiratory and gastrointestinal tract except for the periorbital region. The concomitant administration of PSL and MTX may have pre-
vented the systemic spreading of the angioedema in the current case. In addition, a diagnosis of hereditary angioedema was not suggested because of the lack of its typical features, such as possessing a family history of angioedema, a decreased serum C4 level and recurrent attacks of gastrointestinal and laryngeal edema (14).

TNF-α blockers such as etanercept can suppress Th1 responses of the inflammatory process. Therefore, Th1 dominant rheumatic diseases such as RA can be improved and achieved to remission by treatment with TNF-α blockers. In addition, TNF-α blockers may augment Th2 responses because the balance between Th1 and Th2 is competitive (15, 16). CD4+ cells that differentiate into Th2 cells secrete interleukin (IL)-4 and IL-13, which act on B cells to stimulate production of antibodies, such as IgE that bind to mast cells. Activated mast cells secrete mediators, such as histamine, which can trigger allergic reactions including urticaria and angioedema (17). Histamine may thus have played an essential role in the angioedema through mast cell activation via the Th2 response in the current case, because treatment with an antihistaminic agent dramatically improved his periorbital edema.

In addition, AOSD itself may possess allergic properties according to the findings that the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) had to be stopped due to their severe hepatic toxicity in 4 of 18 patients with AOSD, which is a relatively high incidence (2). Furthermore, treatment with sulfasalazine has also been reported to be associated with increased drug toxicity in AOSD patients, and that drug should therefore be avoided (1). These findings suggest that more attention concerning drug allergy has to be given for patients with AOSD than for those with other rheumatic diseases.

The authors state that they have no Conflict of Interest (COI).

References


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