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Case Report

A Case of Varicelliform Zoster in a Patient Treated with Etanercept for Ankylosing Spondylitis

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Tumor necrosis factor-α (TNF-α) inhibitors are increasingly used in treatment of inflammatory disorders because of their immunomodulatory efficacy. Increased risk of infection is an adverse effect of anti-TNF-α therapy. The incidence rate and severity of herpes zoster is significantly higher in patients on anti-TNF-α therapy than in the general population. The clinical presentation of varicella zoster virus infection is also often atypical in these patients. We experienced a patient who presented with a disseminated varicelliform rash while on etanercept therapy for ankylosing spondylitis. **(J Rheum Dis 2015;22:186-189)**

Key Words. Herpes zoster, TNFR-Fc fusion protein, Ankylosing spondylitis

INTRODUCTION

Tumor necrosis factor-α (TNF-α) inhibitors are immunomodulating agents which, since their development in the 1990s, are more increasingly used in the treatment of inflammatory disorders such as rheumatoid arthritis (RA), ankylosing spondylitis, and inflammatory bowel disease [1]. These biologic agents efficaciously reduce inflammatory activity by TNF-α blockade and thereby ameliorate symptoms and signs of inflammatory disorders. However, there is increasing evidence that patients on TNF-α inhibitors are at an increased risk of infections (particularly tuberculosis and intracellular bacterial, and viral infections) [1-3].

Varicella zoster virus (VZV) is a herpes-virus responsible for varicella (chicken pox) and herpes zoster (shingles). Varicella, the clinical syndrome associated with primary VZV infection, is a generalized febrile illness characterized by a pruritic evolving vesicular whole body rash. Herpes zoster occurs from local reactivation of latent VZV in dorsal-root ganglia: a localized painful vesicular rash appears in the involved dermatome. Immunosuppression is known to increase the risk of VZV reactivation, and also the morbidity and mortality associated with it [4].

Among patients on TNF-α inhibitors, an increased incidence of herpes zoster has been observed [2]. Also herpes zoster episodes tended to be more severe and more complicated than in the general population. A few cases which presented as disseminated zoster while on TNF-α inhibitors have been reported, however cases presenting with varicelliform eruptions are scarce [5].

We report a case of a 44-year-old man who presented with a disseminated varicelliform rash while on etanercept therapy for ankylosing spondylitis.

CASE REPORT

A 44-year-old man presented with blisters, pustules and scabs all over his scalp, face, neck and trunk. The skin lesions had first appeared as pruritic erythematous bumps on his forehead the day before. The next day, the lesions had spread to his face, trunk, and extremities. New lesions appeared as papules, while some older lesions had

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turned into vesicles, pustules, and scabs (Figure 1). Besides slight generalized pruritus, he complained about being febrile and having slight chills. He did not have any other symptoms.

He had been diagnosed with ankylosing spondylitis 6 years ago due to persistent right 1st metatarsal joint and ischial joint pain. His initial erythrocyte sediment rate (ESR) was elevated to 55 mm/h and C-reactive protein (CRP) was 1.22 mg/dL. Initial X-rays showed mild subchondral irregularity and sclerosis at both sacroiliac joints. He was negative for rheumatoid factor but positive for human leukocyte antigen-B27. Opthalmologic examination showed no evidence of uveitis. Initial treatment with nonsteroidal anti-inflammatory drugs and systemic steroids was not successful due to intolerability. After he was started on etanercept 2 years ago which he tolerated well, his disease activity was well controlled. His last ESR was 5 mm/h. Etanercept was given in subcutaneous doses of 25 mg once a week. He was not taking any other medications. His serologic tests were negative for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus. He did not recall a prior history of VZV infection nor his immunization history (including vaccination against VZV).

On examination, body temperature was 37.9°C. Blood pressure and pulse rate were 125/88 mmHg and 102 beats per minutes, respectively. His respiration appeared normal with a respiratory rate of 16 breaths per min. Besides the generalized skin lesions, no abnormal findings were detected. His range of motion was normal.

Complete blood counts were normal with white blood cell count of 4,800/μL (neutrophils 72%, lymphocytes 27%, and monocytes 1%), hemoglobin 17.3 g/dL, and platelet count 142,000/μL. His CRP level was minimally elevated to 2.03 mg/dL (reference range 0 to 0.5 mg/dL). Other laboratory test results, including renal- and liver-function tests, blood levels of electrolytes, and coagulation tests were normal. A tzanck smear was negative, however direct immunofluorescence assay (DFA) for VZV was positive. Serologic tests for anti-VZV antibody were initially negative for immunoglobulin (Ig) M but positive for IgG. Five days later, anti-VZV IgM seroconversion and a $>$4 fold rise of the anti-VZV IgG titer (2.73 index to 12.77 index) were confirmed.

The patient was immediately started on intravenous acyclovir at 10 mg/kg (750 mg) every 8 hours, and etanercept was discontinued. After initiation of antiviral treatment, no further lesions formed and his rash resolved into crusted scabs. He was treated with intravenous acyclovir for 7 days until all lesions were crusted, and discharged without other complications. Seven days after discharge, the patient was reexamined at the outpatient clinic and although some scars and hyperpigmentation remained, the skin lesions had improved

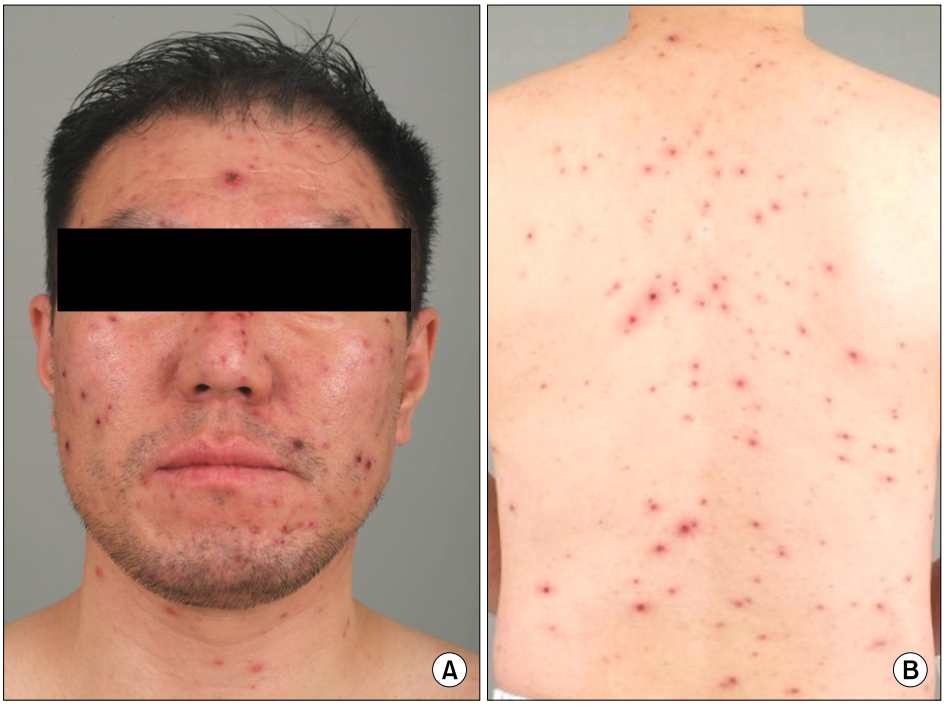

Figure 1. Erythematous papules, vesicles and scabs were diffusely scattered on (A) the face and neck, and (B) the trunk without a dermatomal distribution.

further. No other complications occurred.

DISCUSSION

VZV infection is a common disorder and causes substantial morbidity among elderly and immunocompromised patients. Patients with inflammatory disorders are also at an increased risk of VZV infection, which can be attributed to the immunomodulatory pathogenesis of the disorder itself and anti-inflammatory therapies [6,7].

The risk of VZV infection is most prominent among patients who receive anti-TNF therapies, which can be explained by the antiviral role of TNF-α in VZV infections: TNF-α is an important proinflammatory cytokine which acts in concert with interferons to inhibit the replication and spread of VZV [8,9]. TNF-α inhibitors, by blocking the antiviral action of TNF, therefore increase the incidence and severity of VZV infections, which has been observed in several studies [2,6,10]. In a large prospective cohort of 5,040 RA patients treated with TNF-α inhibitors, the incidence of herpes zoster was 10.1 events per 1,000 patient-years which was significantly higher compared to 5.6 events per 1,000 patient-years of the control population [2]. The incidence rate of severe zoster (multidermatomal and ophthalmic zoster) was also significantly higher in patients on anti-TNF therapy [2]. Among various anti-TNF therapeutics, etanercept seems to have a better safety profile than monoclonal anti-TNF-α antibodies regarding infectious complications [11, 12]. It is suggested that differences in pharmacokinetics of anti-TNF-α therapies attribute to this contrast by different mechanisms of action [12].

Herpes zoster in immunocompromised patients is likely to present with atypical or severer manifestations: for example, more severe local dermatomal disease, cutaneous dissemination, or visceral involvement [4]. Viremia in the course of zoster is known to occur in 10% to 40% of immunocompromised zoster patients and the incidence rate of varicelliform zoster is reported to be 2% to 5% in unselected patients with localized herpes zoster [13].

In severely immunocompromised hosts, VZV reactivation may present as a diffuse varicella-like rash: an unusual syndrome termed atypical generalized zoster, herpes zoster generalisatus, or varicelliform zoster [13-15]. This clinical entity of VZV infection, especially in the absence of dermatomal skin lesions, is clinically indistinguishable from varicella and has a high risk of visceral involvement by hematogenous dissemination and thereby a higher mortality rate [4,15].

We experienced a patient on etanercept who presented with a generalized rash consisting of blisters, pustules and scabs at the same time. The diffuse eruptions were clinically indistinguishable from varicella and could not be differentiated by medical history.

The etiologic virus was confirmed by VZV DFA and anti-VZV IgM seroconversion. The presence of anti-VZV IgG in initial serum confirmed the diagnosis of herpes zoster. Although varicelliform zoster is associated with a high rate of visceral involvement and complications, our patient was timely diagnosed and treated, and recovered uneventfully.

TNF-α inhibitors are more increasingly used as routine therapy for various inflammatory disorders. Because they are associated with an increased risk of certain infections and clinical manifestations maybe atypical, patients on anti-TNF therapy must be monitored more thoroughly.

SUMMARY

VZV reactivation in patients on TNF-α inhibitors are likely to show atypical presentations or more severe features. Herpes zoster with varicelliform eruptions in the absence of the typical dermatomal rash while on anti-TNF therapy have not been reported previously. We have experienced a case of atypical generalized zoster in a patient on etanercept for ankylosing spondylitis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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