Single Case

Psoriasiform Dermatitis Developing during Treatment of Juvenile Idiopathic Arthritis with Tocilizumab

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Keywords

Adverse event · Biologic · Interleukin 6 · Psoriasis · Tocilizumab

Abstract

We present a case of psoriasiform dermatitis developing during the treatment of juvenile idiopathic arthritis with tocilizumab (TCZ). The keratotic erythema with central healing showed a periodicity of growing worse 1 week after TCZ infusion, and then disappeared within 3 weeks. Skin biopsy showed parakeratosis, microabscess, rete ridge elongation, and abundant lymphocytes as well as a few neutrophil infiltrate in the upper dermis. TCZ is a humanized monoclonal antibody against interleukin 6 (IL-6) receptor. IL-6 plays a critical role in the differentiation from naïve T cells into Th17 cells in cooperation with transforming growth factor- β . IL-6 may be important in psoriasis pathogenesis, and therefore this phenomenon may be the adverse effect. The mechanism of TCZ-associated psoriasiform dermatitis is unclear. The serum IL-6 level seems to be elevated transitorily after TCZ administration, probably due to the competitive inhibition of IL-6 receptor alpha to IL-6. Excess free IL-6 may effect on other IL-6 family receptors. Since TCZ does not alter serum IL-17F level, another cytokine may be involved in the

psoriasis formation in our case. Psoriasiform dermatitis during the use of TCZ may be due to relative cytokine balance disturbance.

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Introduction

Tocilizumab (TCZ) is a humanized monoclonal antibody against interleukin 6 (IL-6) receptor utilized for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, Castleman disease, adult-onset Still disease, and other inflammatory diseases. Frequent adverse events with the use of TCZ are infections as well as elevation of liver enzyme and lipid levels. We here report a case of psoriasiform dermatitis developing during treatment for juvenile idiopathic arthritis with TCZ.

Case Presentation

A 26-year-old woman who had had juvenile idiopathic arthritis for 13 years and who had been administered TCZ for 11 years consulted our department. She was originally treated with 8 mg/kg TCZ every 4 weeks. Fifteen months before, the interval was extended to 6 weeks because of the disappearance of joint pain. The keratotic erythema with central healing appeared on the right buttock 12 months before (Fig. 1a), and a relapse of joint pain appeared 8 months before. The skin eruption showed a periodicity of growing worse 1 week after TCZ infusion and then disappeared within 3 weeks. Fungus was undetected by microscopic inspection and tissue culture revealed no bacterial or fungal growth. Skin biopsy showed parakeratosis, microabscess, rete ridge elongation, and abundant lymphocytes as well as a few neutrophil infiltrates in the upper dermis (Fig. 1b, c). Grocott staining was negative in the same specimen. Topical corticosteroid was effective, but the erythema recurred every time after TCZ administration. Pain, swelling, and tenderness of juvenile idiopathic arthritis were completely controlled. C-reactive protein was negative, anticyclic citrullinated peptide antibody was 14.5 U/mL (normal <4.5 U/mL), rheumatoid factor was 209 IU/mL (normal 0–10 IU/mL), and IL-6 was 22.20 pg/mL (normal <4 pg/mL). Due to the exacerbation of joint pain, the injection interval was shortened to 4 weeks, and the joint pain as well as the psoriasiform dermatitis improved.

Discussion

The mechanism of TCZ-associated psoriasiform dermatitis remains unclear. IL-6 plays a critical role in the differentiation from naïve T cells into Th17 cells in cooperation with transforming growth factor- β [1]. In psoriasis patients, the IL-6 level is high in psoriatic plaque and serum [2]. IL-6 may be important in psoriasis pathogenesis; however, an attempt of treatment with TCZ in psoriasis or psoriatic arthritis has clinically failed [3]. There is a report of exacerbation of rheumatoid arthritis and the appearance of skin eruption after the start of TCZ [4]. Arthritis and rash improved by shortening the injection interval. In our case, TCZ was administered for a long time, but joint pain and rash appeared after extending the administration period. Relief in joint pain and skin rash was observed after shortening the interval to the original.

IL-6 is one of the IL-6 cytokine family members, including IL-6, IL-11, IL-27, IL-35, IL-39, oncostatin M, leukemia inhibitory factor, ciliary neurotrophic factor, cardiotrophin 1, and cardiotrophin-like cytokine factor 1. The receptors for each cytokine are similar in structure, and gp130, as a signal transducer, is a common subunit [5]. The serum IL-6 level seems to be elevated transitorily after TCZ administration [6], probably due to the competitive inhibition of IL-6 receptor alpha to IL-6. Excess free IL-6 may effect on other IL-6 family receptors. Since TCZ does not alter serum IL-17F levels [6], another cytokine may be involved in the psoriasis formation in TCZ cases.

In some cases, psoriasis-like eruption occurs during the use of TNF- α inhibitors: paradoxical psoriatic reaction. One of the reasons for this reaction is that plasmacytoid dendritic cells increase IFN- α production when TNF- α signaling is inhibited [7]. IFN- α is increased in the region of paradoxical psoriasis. This process may cause the paradoxical psoriatic reaction. On the other hand, the cause of psoriasiform dermatitis with the use of TCZ is also unknown. When the amount of TCZ is insufficient and IL-6 receptors are not completely blocked, temporarily increased IL-6 may bind to the remaining IL-6 receptor or other IL-6 cytokine family receptors and cause inflammation. After IL-6 has been consumed and becomes low level relative to residual IL-6 receptor, psoriasiform dermatitis may be relieved. The disappearance of the eruption by shortening the interval seems to be reasonable because the receptors may be neutralized by the saturated substantial antibodies. Paradoxical psoriasis caused by TNF- α inhibitors is the result of drug action, whereas psoriasiform dermatitis during the use of TCZ is caused by a relatively insufficient effect, therefore shortening the interval may improve the rash. Psoriasiform dermatitis with the use of TCZ may be due to relative cytokine balance disturbance.

Statement of Ethics

The authors have no ethical conflicts to disclose. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient gave written informed consent to publish her case including images.

Disclosure Statement

The authors declare that no competing interests exist.

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Author Contributions

Y. Matsushima, M. Kondo, K. Mizutani, Y. Nakai, K. Habe, and H. Wakabayashi took care of the patient. A. Hayashi and Y. Kozuka performed immunological staining. Y. Matsushima, Y. Yamaguchi, and K. Yamanaka wrote the manuscript.

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Fig. 1. **a** Keratotic erythema with central healing on the right buttock. **b** The histopathological findings were psoriasis-like dermatitis with elongated rete ridge, spongiosis, parakeratosis, and perivascular infiltrate of lymphocytes and a few neutrophils in the upper dermis (hematoxylin-eosin, original magnification $\times 100$). **c** A microabscess in parakeratotic scale was also detected (hematoxylin-eosin, original magnification $\times 200$).