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Case Series

Two Cases of Cutaneous Adverse Effects Induced by Tumor Necrosis Factor-Alpha Inhibitors

Ena Masukawa[a, b] Yoshiaki Matsushima[b] Koji Habe[b]
Keiichi Yamanaka[b]

[a]Department of Dermatology, Yokkaichi Municipal Hospital, Yokkaichi, Japan;
[b]Department of Dermatology, Graduate School of Medicine, Mie University, Tsu, Japan

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Abstract
Here, we report two cases of cutaneous adverse effects possibly induced by the use of tumor necrosis factor-alpha (TNF-α) inhibitors. The first case presented alopecia areata (AA) and atopic dermatitis (AD) that developed during the treatment of ulcerative colitis using infliximab; the other case presented urticaria and AD that developed during the treatment of rheumatoid arthritis using etanercept. AA, AD, and urticaria are relatively common skin diseases; however, they are not well known as adverse effects of TNF-α inhibitors. Although immunological studies were not performed, the clinical courses suggested that these skin disorders might have developed as a result of an immune four-way imbalance in T helper 1 (Th1), Th2, Th17, and regulatory T cells by the administration of TNF-α inhibitors.

Keiichi Yamanaka
Department of Dermatology
Graduate School of Medicine, Mie University
2-174 Edobashi, Tsu, Mie 514-8507 (Japan)
yamake@clin.medic.mie-u.ac.jp

Introduction

T helper 1 (Th1) and Th2 cells affect each other exclusively, and their normal levels help maintain an immunological balance in homeostasis. The Th1/Th2 axis is disrupted in various autoimmune and allergic diseases including rheumatoid arthritis (RA), Crohn disease, urticaria, and atopic dermatitis (AD). Besides Th1 and Th2, Th17 cells are involved in the pathogenesis of psoriasis, RA, and inflammatory bowel disease. An additional lymphocyte is the regulatory T cell (Treg), which suppresses excessive immunological burden. Th1, Th2, Th17, and Tregs comprise an immunological four-way axis balance that affects each other; an imbalance of the four-way axis induces the onset of autoimmune diseases. Tumor necrosis factor-alpha (TNF-α) is an inflammatory cytokine mainly produced by macrophages and lymphocytes and plays a critical role in the development of various inflammatory diseases. At present, anti-TNF-α monoclonal antibody and soluble TNF-α/lymphotoxin-alpha receptor have been used to treat several diseases. However, infections, elevation of liver enzyme levels, interstitial pneumonia, and blood disorders are well-known adverse events of using these anti-inflammatory drugs. These drugs block the abnormal immune cells in autoimmune diseases; yet, they may cause other four-way axis imbalances and unexpected adverse effects. Here, we report the cutaneous adverse effects possibly induced by the administration of TNF-α inhibitors.

Case Presentation

Case 1

A 31-year-old woman with ulcerative colitis (UC) under treatment using infliximab was referred to our department owing to continuous hair loss and skin eruption. She had no other previous medical history and showed no signs of alopecia areata (AA) or AD. Her UC was reported to have remained in remission for several years. Two years before her first visit to our department, the patient developed hair loss, which started to worsen. Hair loss spots (2 cm in diameter) were scattered on the temporal and occipital regions of the head (Fig. 1a). In addition, skin eruptions present on her ears had worsened in the past 5 months before the first visit. Exudative erythema and crusts were found in both ears (Fig. 1b). The measured C-reactive protein (CRP) was within the normal range and the eosinophil count was 131 cells/μL (normal: 70–450 cells/μL). The hair loss and erythema were considered to be typical symptoms of AA and AD. Since the observed AA and AD were considered cutaneous adverse effects caused by infliximab, it was switched to vedolizumab, an anti-α4β7 integrin antibody. Both AA and AD symptoms improved promptly without the need for any specific medication (Fig. 1c, d).

Case 2

A 28-year-old woman afflicted by RA for 1 year, who underwent treatment using etanercept for 3 months, was referred to our department. She had no medical history and showed no signs of urticaria or AD. At her first visit to the orthopedics department, the level of rheumatoid factor (RF) measured was 150.0 IU/mL (normal: ≤15 IU/mL) and the level of anti-cyclic citrullinated peptide antibody was 119 IU/mL (normal: <4.5 IU/mL). The patient was treated with the nonsteroidal anti-inflammatory drugs methotrexate and salazosulfapyridine; however, her joint pain worsened and the following test results were obtained: CRP 2.03 mg/dL (normal: ≤0.30 mg/dL), RF 188.0 IU/mL, and matrix metalloprotease-3

174.8 ng/mL (normal: 17.3–59.7 ng/mL). After commencing treatment with etanercept, her joint pain resolved and CRP was negative. The measured RF level was 138.0 IU/mL and the matrix metalloprotease-3 level was 171.3 ng/mL. Approximately 1 month before her first visit to our department, she felt an itching sensation over the whole body that worsened progressively; therefore, she consulted our department. Wheals were observed on her whole body (Fig. 2a) that recurred over time. The eosinophil count was 88 cells/μL (normal: 70–450 cells/μL). The wheals and clinical course were considered typical of urticaria. The observed urticaria was considered to be associated with etanercept treatment. Etanercept was very effective in treating the patient's RA. Since urticaria was mild, the administration of etanercept was continued. The patient was administered an antihistamine, which partially ameliorated the symptoms of urticaria. However, the itching sensation on the whole body remained and she visited our department again. Erythema with scales was observed on the back (Fig. 2b), which was typical of AD. We considered that it was possibly associated with etanercept treatment. Topical corticosteroid was partially effective for AD; therefore, etanercept treatment was continued.

Discussion

TNF-α is a major cytokine involved in the pathogenesis of various diseases, including bowel diseases such as Crohn disease and UC, psoriasis, Behçet's disease, ankylosing spine, and RA. Infliximab is an anti-TNF-α monoclonal antibody and etanercept is a fully humanized soluble TNF-α/lymphotoxin-alpha receptor. Here, we report two cases of cutaneous adverse effects possibly induced by TNF-α inhibitors: a case of AA and AD that developed during the treatment of UC using infliximab, and another case of urticaria and AD that developed during the treatment of RA using etanercept. Proliferation of inflammatory cells and activation of T cells are involved in the development and pathogenesis of inflammatory and allergic diseases. The CD4+ T cells include Th1 cells, Th2 cells, Th17 cells, and Tregs, which exclusively affect each other in maintaining balance in homeostasis [1]; a four-way axis imbalance occurs at the onset of autoimmune disease [2]. Th1 cell-related diseases include RA and Crohn disease [3, 4]. AD is a Th2 cytokine-related disease and is characterized by an increase in Th2 cytokines such as interleukin 4 (IL-4), IL-5, IL-9, IL-13, and IL-31 [5]. Th17 cells have been implicated in the pathogenesis of common autoimmune diseases such as psoriasis, RA, and inflammatory bowel disease [6].

IL-17 and Th17 cells are critical inducers of AA [7]. Excessive amounts of Th17 cells trigger inflammation in hair follicles, and high serum IL-17 levels are detected in patients with AA [8]. However, in certain cases, it was reported that AA develops from using IL-17 inhibitors to treat psoriasis, which can be regarded as a paradoxical reaction [9, 10], and AA was ameliorated by switching to other biologics [9]. These reports suggest that IL-17 and Th17 cells may not play a major role in AA pathogenesis. Recently, AA scalp lesions have been shown to contain significantly increased levels of Th1 and Th2 cytokines, with no elevation in Th17 or Th22 cytokine levels compared to normal scalp tissues [11]. The cytotoxic CD8+ T cells play a major role in AA development since interferon-gamma (IFN-γ^{high}) CD8+ T cells are abundant in alopecia skin lesions [12]. IL-17-producing Th17 cells may be the initiator and induce Th1 cells and IFN-γ^{high} CD8+ T cells to damage the hair follicle in AA. Therefore, in case 1 with UC, blocking of Th1 activity by the use of a TNF-α inhibitor might cause the shift of Th1 burden to Th2 cytokine-dominant AD and may be an initial step in the development of Th17-dominant AA.

Th1 and Th17 cells are involved in the development of RA [3, 6]. In case 2 with RA, the decrease in Th1 activity owing to the use of a TNF-α inhibitor might cause the Th1 burden shift to Th2 dominance and induce AD and urticaria development. The pathogenesis of chronic urticaria has not been studied in detail. A key receptor present in chronic urticaria is the immunoglobulin E receptor FcεRI, although there is evidence that FcεRI is not always involved in mast cell activation and histamine release; multiple pathways leading to mast cell activation have been identified [13].

In our two cases, a detailed cytokine examination was not performed serologically or histologically. Generally, AD and AA are chronic and recurrent skin diseases and little is known about the adverse effects of TNF-α inhibitors. However, in our first case, the symptoms resolved promptly without recurrence after discontinuation of the TNF-α inhibitor treatment, which might suggest that the disease was caused by the TNF-α inhibitor.

Statement of Ethics

The research was conducted in accordance with the Declaration of Helsinki. The patients provided written informed consent to publication of their case studies, including publication of images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E. Masukawa and K. Yamanaka took care of the patients. E. Masukawa, Y. Matsushima, K. Habe, and K. Yamanaka wrote the manuscript.

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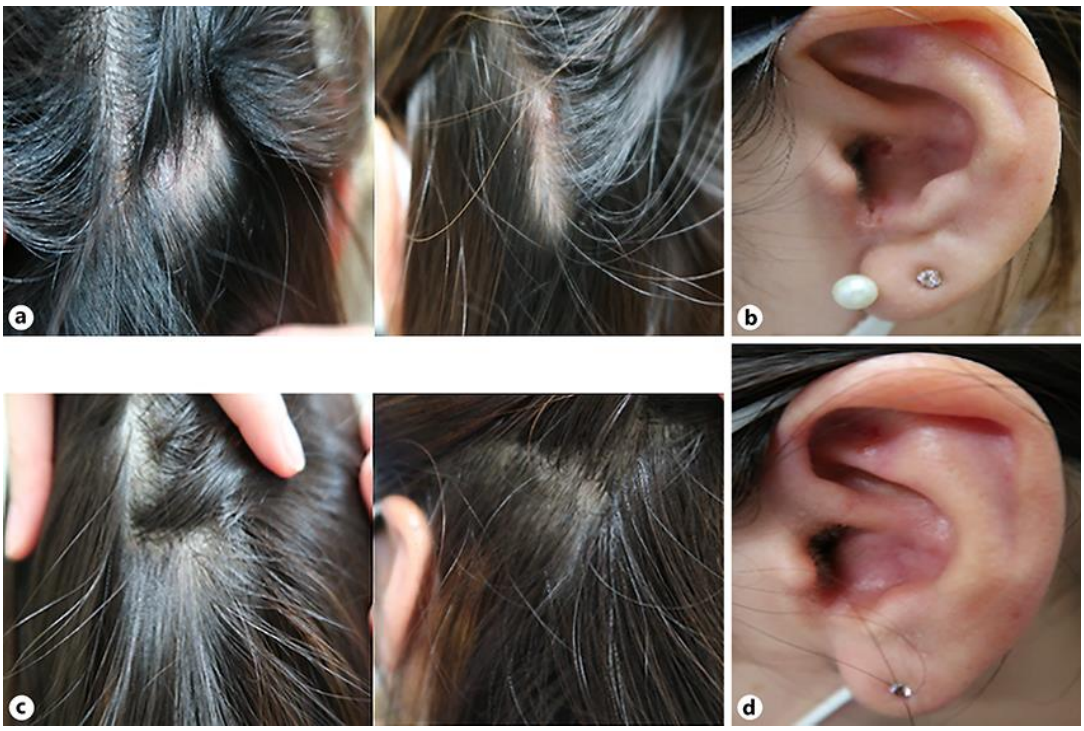

Fig. 1. Case 1. After using infliximab, alopecia areata developed and worsened. At her first visit to our department, hair loss spots (2 cm in diameter) were scattered on the temporal and occipital regions of the head (**a**). In the past 5 months before her first visit, the skin eruptions on her ears had been worsening. Exudative erythema and crusts were found on both ears (**b**). After her medication had been switched to vedolizumab, symptoms of both alopecia areata and atopic dermatitis improved without any specific medication (**c**, **d**).

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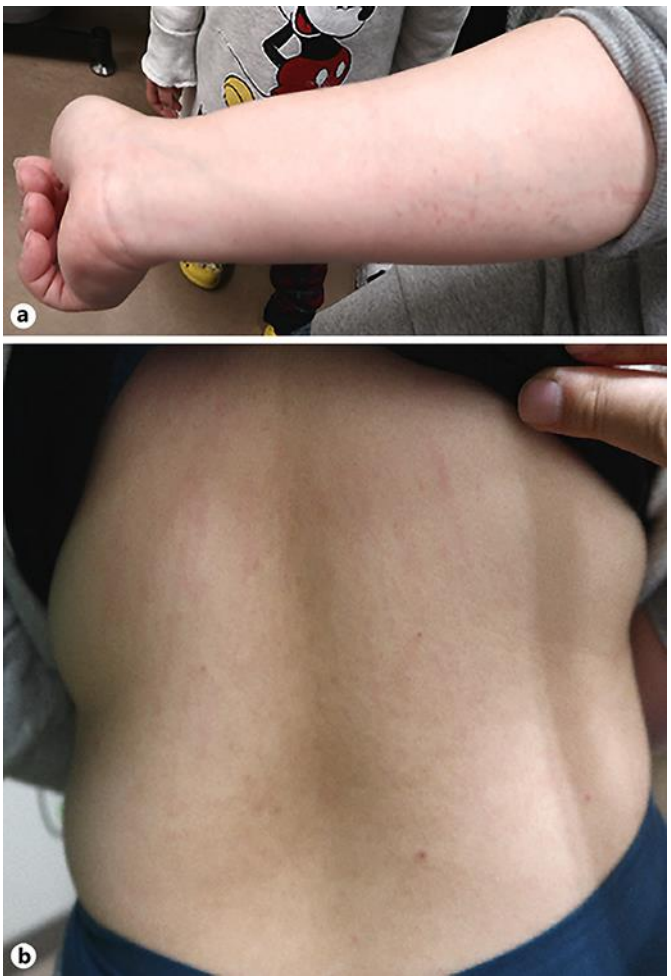

Fig. 2. Case 2. Two months after using etanercept, the patient felt itching over the whole body. At her first visit to our department, wheals were observed over her whole body (**a**). At her second visit, erythema with scales was observed on the back, which is a typical symptom of atopic dermatitis (**b**).