Adrenal Insufficiency Secondary to Abrupt Dose Reduction of Topical Corticosteroid Therapy after Starting Brodalumab for Psoriasis: A Case Report

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Abstract
The risk of treating psoriasis with biologic drugs in patients treated with topical corticosteroids over prolonged periods requires careful attention to their underlying adrenal insufficiency because the development of adrenal insufficiency symptoms frequently occurs after cessation of the topical corticosteroids: the dose and duration of topical corticosteroid therapy and etretinate use correlate with risk. In this case report, we present a 65-year-old man with psoriatic erythroderma who developed arthralgia, joint pain, muscle pain, fatigue, and headache after starting brodalumab and a reduction of topical potent corticosteroid doses in the treatment of psoriasis. Because his plasma cortisol levels were decreased and the levels and various signs recovered by administration of physiological doses of hydrocortisone replacement, we concluded that these clinical signs observed after starting brodalumab could be clinical manifestations of adrenal insufficiency secondary to an abrupt reduction in the amount of a topical corticosteroid, but not adverse effects of brodalumab. We found another 2 cases with psoriatic erythroderma who developed secondary to adrenal insufficiency after starting biologic drugs and a reduction of topical corticosteroid doses in the literature. Notably, the side effects of brodalumab include arthralgia, headache, and fatigue, and suspicion of side effects may include the clinical manifestations of adrenal insufficiency. Clinicians have to predict adrenal insufficiency secondary to an abrupt reduction of topical corticosteroids after remarkable improvement of psoriasis by biologics. The routine monitoring of plasma cortisol levels is necessary for all
erythrodermic psoriasis patients treated with topical corticosteroids over prolonged periods before starting biologics.

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Introduction

Symptoms of adrenal insufficiency are common after cessation of topical corticosteroid therapy, particularly when administered at high doses and over prolonged periods. Therefore, patients with psoriasis who are switched to a biologic agent after cessation of long-term treatment with topical corticosteroids require careful monitoring for adrenal insufficiency. Signs and symptoms of adrenal insufficiency usually develop slowly, often over several months, but they may appear suddenly with the onset of stress, even that associated with the common cold. Because diffuse myalgia and arthralgia can also often be presenting signs of rheumatic disease [1], these signs may be erroneously interpreted as a paradoxical reaction or side effect of biologics. Indeed, arthralgia was the most common adverse event mentioned in a pharmacovigilance report based on 2 years of data collected on brodalumab in the USA [2]. In that report, headache, fatigue, nausea, and myalgia were also observed and acknowledged to be similar to the symptoms of adrenal insufficiency secondary to cessation of topical corticosteroids. However, why these symptoms occurred after initiating brodalumab remained unclear.

In this case report, we describe a 65-year-old man with psoriasis who developed arthralgia, joint pain, muscle pain, fatigue, and headache after showing initial good progress when started on brodalumab and with an abrupt reduction in the dose of a potent topical corticosteroid. He was found to have a profoundly decreased plasma cortisol level, which recovered after administration of physiological doses of hydrocortisone, along with resolution of his signs and symptoms. The clinical signs observed in this patient after starting brodalumab could have been clinical manifestations of adrenal insufficiency secondary to the abrupt dose reduction of topical corticosteroid rather than an adverse effect of brodalumab.

Case Report

The patient was a 65-year-old man with a 40-year history of stable plaque psoriasis. Before his first visit to our hospital, he had used 0.5% clobetasol propionate ointment at an estimated dose of 15 g/week and oral etretinate 20 mg/day continuously for 35 years. His psoriasis had not responded to combination therapy with cyclosporine or apremilast. On physical examination, he had diffuse, scaly erythematos plaques on his trunk, arms, and legs (Fig. 1a, b). His Psoriasis Area and Severity Index (PASI) score was 26.2. He had no joint symptoms at his initial presentation. Marked skin atrophy was noted on the extremities due to the long-term use of topical clobetasol propionate and oral etretinate. He was diagnosed with refractory psoriatic erythroderma and started on brodalumab. His psoriatic lesions cleared rapidly, so the estimated dose of the topical corticosteroid was decreased from 15 g to 5 g/week. Six weeks after initial presentation, he developed a cold with a sore throat and fever and gradually became immobilized, with increasing stiffness and pain in the large joints of the upper and lower extremities, muscle pain, general fatigue, and headache. Limited range of motion of the shoulder joints was noted (Fig. 1c). On admission, the results of laboratory investigations were white cell count $5.02 \times 10^3/\mu L$, eosinophil $462/\mu L$ (normal range 70–450), hemoglobin $12.2 \text{ g/dL}$ (13.7–16.8), platelets $246 \times 10^3/\mu L$, alanine aminotransferase $9 \text{ U/L}$,
aspartate aminotransferase 10 U/L, creatinine 0.74 mg/dL, urea nitrogen 14 mg/dL, total protein 5.5 g/dL (6.6–8.1), albumin 2.9 g/dL, C-reactive protein 0.74 mg/dL (0.00–0.14), creatine kinase 53 U/L (59–248), sodium 142 mmol/L, potassium 4.1 mmol/L, serum cortisol 0.5 μg/dL (4.5–21.1), and adrenal cortical hormones 25.1 pg/mL (7.2–63.3). Blood tests showed
Elevated eosinophils, hypoproteinemia, hypoalbuminemia, and hypocortisolemia. The patient's joint symptoms were evaluated by a rheumatologist who performed physical examination and musculoskeletal ultrasonography. The results did not show the sign of enthesitis or inflammation of the joints; therefore, psoriatic arthritis, reactive arthritis, or osteoarthritis was ruled out. Computed tomography revealed bilateral adrenal atrophy. The adrenocorticotropic hormone stimulation test confirmed decreased secretion of cortisol at 30 min–120 min (1.6–1.7 μg/dL, normal range 4<) and decreased response to adrenocorticotropic hormone, suggesting adrenal insufficiency. The diagnosis was thus adrenal insufficiency secondary to abrupt dose reduction of topical corticosteroid after marked improvement on brodalumab. He was started on low-dose corticosteroid therapy (hydrocortisone 15 mg) and his symptoms of adrenal insufficiency resolved, with range of motion also restored in the shoulder joints (Fig. 1d). Brodalumab was continued, and his PASI scores indicate no recurrence of psoriasis. The patient provided written informed consent to the publication of this case report.

**Discussion**

Brodalumab is a human, anti-interleukin (IL)-17 receptor monoclonal antibody that blocks the shared IL-17 receptor A and thus targets not only IL-17A and IL-17F but also IL-17C [3]. Therefore, in addition to being an effective treatment for patients with psoriasis, brodalumab could also have beneficial effects in those with atopic dermatitis and those with paradoxical reactions to other anti-IL-17A therapies. Given that the side effects of brodalumab include injection site reaction, Candida infection, upper respiratory tract infection, arthralgia, neutropenia, headache, and fatigue, suspicion of side effects is warranted in patients on brodalumab who complain of arthralgia and headache, especially if the arthralgia spreads rapidly (Table 1). An alternative possibility is that such patients have pre-existing risk factors that predispose them to paradoxical development of psoriatic arthritis when treated with brodalumab, which is more effective than other anti-IL-17A treatments and more similar in effect to anti-IL-23p19 therapies [4].

A search of the literature identified 2 further patients with psoriasis who developed adrenal insufficiency secondary to starting a biologic and with abrupt reduction in the dose of a topical corticosteroid. Including the present case, all 3 patients were Japanese men, aged 41–68 years. The clinical symptoms, triggering events, topical corticosteroid doses, and response to hydrocortisone replacement are summarized in Table 2. The main indication for the biologic agent was psoriatic erythroderma. Two of the 3 patients also received etretinate, which allowed more efficient absorption of corticosteroids [5, 6].

Considering that our patient developed arthralgia and headache after his good start on brodalumab and the abrupt dose reduction of the topical corticosteroid, the most likely explanation is that long-term use of the potent topical corticosteroid led to adrenal insufficiency, thereby causing development of myalgia, arthralgia, and joint stiffness. Previous studies have

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**Table 1. Clinical symptoms of adverse reactions of brodalumab, adrenal insufficiency, and a present case**

| Adverse reactions of brodalumab [2] | Symptoms in adrenal insufficiency | Symptoms in a present case |
|------------------------------------|----------------------------------|---------------------------|
| Arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections | Arthralgia, myalgia, fatigue, muscle contractures | Arthralgia, myalgia, fatigue, headache |

Common symptoms were underlined.
Table 2. Demographic and clinical characteristics of 3 patients with psoriasis who developed adrenal insufficiency secondary to starting on a biologic agent

| Case | Age, years/sex | Underlying condition | Disease severity and therapy before use of biologics | Biologic agent | Onset of adrenal insufficiency | Symptoms of adrenal insufficiency | Serum cortisol level, mg/dL | Triggering event | Response to hydrocortisone replacement |
|------|----------------|----------------------|------------------------------------------------------|----------------|-------------------------------|---------------------------------|-------------------------------|-----------------|--------------------------------------|
| 1, Ref. [5] | 41/M | Psoriatic erythroderma | 33.6 | Clobetasol propionate, 10 g/day, 20 years | Etretinate | Infliximab | 2 weeks after starting infliximab | Vomiting, diarrhea, malaise | 1.8 | None | Good |
| 2, Ref. [6] | 68/M | Psoriatic erythroderma | ND | Clobetasol propionate, dose ND, 30 years | ND | Secukinumab | ND | Anorexia, weight loss, arthralgia | Decreased | ND | ND |
| 3, Present case | 65/M | Psoriatic erythroderma | 26.2 | Clobetasol propionate, 2 g/day, 40 years | Etretinate | Brodalumab | 6 weeks after starting brodalumab | Malaise, anorexia, arthralgia, headache, myalgia | 1.1 | Common cold | Good |

M, male; ND, not described; PASI, Psoriasis Area and Severity Index.
found the musculoskeletal symptoms of adrenal insufficiency, such as arthralgia, joint stiffness, and low back pain [7–9], although this has not been widely recognized. Another study demonstrated that the major initial manifestations of adrenal insufficiency were severe generalized myalgia, fatigue, and muscle contractures in the lower extremities [1]. Many dermatologists might not consider adrenal insufficiency in similar cases unless serum cortisol level is measured.

The present case emphasizes the importance of considering adrenal insufficiency secondary to a reduction of topical corticosteroids after remarkable improvement of psoriasis by brodalumab. This case highlights the need for routine monitoring of plasma cortisol levels in all patients with symptoms suggestive of adverse events after starting brodalumab, particularly in those who have been treated with potent topical corticosteroids. Depending on the clinical signs observed after starting brodalumab, the possibility of secondary adrenal insufficiency should not be overlooked in the differential diagnosis of diseases that present with arthralgia, headache, fatigue, and myalgia, particularly in patients treated with long-term potent topical corticosteroids, such as clobetasol propionate, at doses of more than 15 g/week as in our case. Untreated adrenal insufficiency can result in life-threatening low blood pressure and high blood potassium levels [10].

**Statement of Ethics**

The study conforms to the guidelines established by the Declaration of Helsinki. This retrospective review of patient data did not require ethical approval in accordance with local guidelines of the Institutional Review Board at Kawasaki Medical School. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Mariko Yamane and Hiroaki Hayashi carried out studies and participated in the data collection. Mariko Yamane and Yumi Aoyama drafted the manuscript. Mariko Yamane and Hiroaki Hayashi participated in the design of the study. Mariko Yamane, Hiroaki Hayashi, and Yumi Aoyama have read and approved the final manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
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