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Case Report

Autoimmune Hemolytic Anemia in a Patient with Generalized Pustular Psoriasis Treated with Brodalumab: A Case Report

Toru Sugimoto[1], Yuri Kinoshita[1], Keigo Ito[1], Hidehisa Saeki[2] and Azusa Ogita[1]

[1]Department of Dermatology, Nippon Medical School Musashikosugi Hospital, Kawasaki, Japan
[2]Department of Dermatology, Nippon Medical School, Tokyo, Japan

Psoriasis is a condition characterized by chronic inflammation of the skin, epidermal hyperproliferation, and dysregulated differentiation driven by acceleration of the tumor necrosis factor-alpha/interleukin (IL)-23/IL-17 axis. Herein, we report a case of generalized pustular psoriasis initially managed with etretinate, apremilast, and risankizumab in a Japanese man. Because of side effects, a therapeutic transition was made to brodalumab at 7 months after the initial consultation. His dermatological symptoms improved; however, hemoglobin concentration decreased to 7.6 g/dL after 4 months of treatment. Diagnostic investigation revealed warm autoimmune hemolytic anemia (AIHA). To our knowledge, this is the first report of AIHA during treatment with brodalumab for generalized pustular psoriasis. The etiological association between AIHA and psoriasis is unclear. Future studies should investigate whether AIHA accompanies pustular psoriasis or results from drug-induced AIHA secondary to brodalumab administration. Our findings suggest that the risk of AIHA in patients with psoriasis treated with brodalumab warrants careful consideration.
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Introduction

Autoimmune hemolytic anemia (AIHA) comprises a spectrum of disorders characterized by acquired autoantibodies reacting against red blood cell antigens, leading to their premature destruction and shortened lifespan. Autoantibody generation may affect one side or both sides of the antigen–antibody interaction, thus contributing to the heterogeneous character of AIHA. This heterogeneity spans pathogenesis, pathophysiology, clinical course, and prognosis[1,2].

Autoantibodies exhibit binding to self-red blood cells, inducing aggregation or dissolution, particularly at temperatures at or below approximately 37°C. Despite the commonality in autoantibody appearance, AIHA exhibits substantial diversity in antibody types, reaction temperature ranges, positions of hemolysis, and age at disease onset[3].

Recent studies reported associations between AIHA onset and use of anti-tumor necrosis factor-alpha inhibitors in psoriasis vulgaris and anti-IL-17A inhibitors in psoriatic arthritis[4,5]. Brodalumab, a human monoclonal antibody against IL-17 receptor A (IL-17RA), is used to treat psoriasis by blocking the effects of cytokines in the IL-17 family, mediated through IL-17RA, including IL-17F, IL-17A/F, IL-17C, and IL-17E.

To our knowledge, there are no documented cases of AIHA coexisting with generalized pustular psoriasis (GPP). Herein, we present a case of AIHA onset during

Correspondence to Toru Sugimoto, s-toru@nms.ac.jp
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treatment with brodalumab for GPP.

Case Report

A Japanese man in his 70s had experienced persistent itching for the previous 20 years. Approximately 3 years earlier, he was diagnosed as having atopic dermatitis by his primary care doctor and was prescribed celestamine, antihistamines, and steroid ointments. Two months earlier, he developed erythematous patches over his whole body, leading him to seek examination and treatment at our clinic. During the initial visit, because of prolonged use of celestamine, there was no characteristic exanthema, making diagnosis challenging. We suspected polymorphic chronic skin eruption, and a reduction in steroid dose and changes in steroid ointments were made to determine the pathophysiology (**Figures 1 and 2**). Four months after the initial visit, he presented with fever (38.5°C), generalized erythema, and numerous small pustules. Blood analysis showed elevations in inflammatory markers (white blood cell count 14,810/μL, neutrophils 74.2%, C-reactive protein [CRP] 12.13 mg/dL). A biopsy specimen of the pustules revealed Kogoj's spongiotic pustules within the epidermis, leading to a diagnosis of GPP. We started treatment with etretinate; however, uncontrolled stomatitis emerged in the fourth week, necessitating discontinuation of treatment. During hospitalization, we transitioned to apremilast and initiated daily phototherapy. However, by the fourth week, the patient's fever and exanthema worsened. This prompted a therapeutic switch to risankizumab. By the eighth week of risankizumab therapy, progression of fever and exanthema prompted a therapeutic switch to brodalumab, after which fever and exanthema gradually improved. However, by the fourth month of brodalumab therapy, despite normal inflammatory markers (white blood cell count 8,610/μL, neutrophil ratio 64.3%, CRP 0.86 mg/dL), hemoglobin decreased to 7.6 g/dL, requiring blood transfusion. Irregularities in antibody screening revealed a profusion of antibodies on the patient's red blood cell surface, rendering the results inconclusive. This raised suspicion of AIHA. Additional findings included a total bilirubin value of 1.69 mg/dL, positive direct and indirect Coombs test results, a cold agglutination titer of 16-fold, and a reticulocyte count of 10.9%. A diagnosis of warm autoimmune hemolytic anemia (wAIHA) was made.

After the diagnosis of wAIHA, we discontinued brodalumab and initiated cyclosporine 100 mg (~2 mg/kg) and prednisolone 30 mg (~0.5 mg/kg/day). Because of the side effects of cyclosporine, which include hypertension and renal impairment, meticulous adjustment was necessary to balance exanthema control, leading to maintenance at 75 mg. After starting prednisolone, a tapering regimen was started every 2 weeks. By the 12th week, hemoglobin levels had normalized after AIHA, and reticulocyte counts had significantly improved. At this writing, the patient is undergoing maintenance therapy with 6 mg of prednisolone.

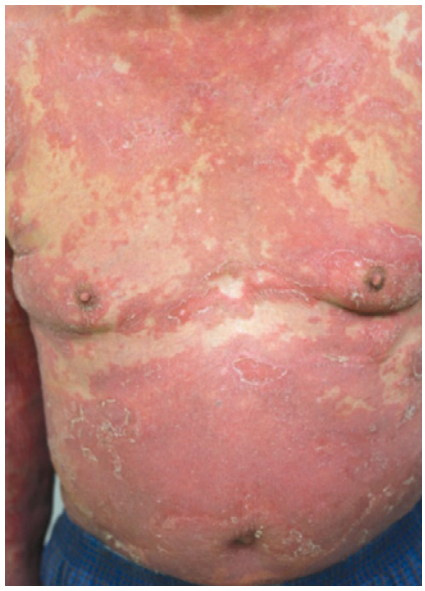

Figure 1 Widely distributed pustules on the erythematous areas on the trunk

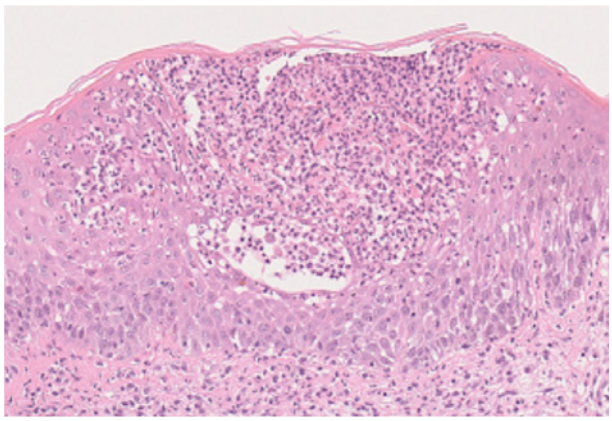

Figure 2 Staining of a skin biopsy specimen shows a subcorneal spongiform pustule filled with neutrophils

Discussion

AIHA is a subtype of immune-mediated hemolytic anemia characterized by the development of self-reactive antibodies targeting specific red blood cell antigens. This immune response accelerates red blood cell destruction via antigen–antibody reactions, drastically reducing their

lifespan. While the precise cause of AIHA is unclear, its pathogenesis involves multifactorial changes in antigen–antibody dynamics, leading to the polymorphic nature of its clinical presentation and prognosis. The mechanisms triggering autoantibody expression remain to be identified.

Despite commonalities in autoantibody manifestation, AIHA exhibits diverse antibody types, range of activity, positions of hemolysis, and age at onset[1–3]. In the present case, a patient undergoing brodalumab therapy for GPP developed AIHA. Although the pathogenesis is unclear, levels of peripheral blood Th17 cells are higher in AIHA patients than in healthy subjects. This elevation is correlated with disease activity and severity, implicating Th17 cells as crucial contributors to AIHA onset. Moreover, studies have reported involvement of IL-17 cells in AIHA pathogenesis. Notably, transfer of Th17 cells from AIHA-induced mice to normal mice resulted in an 80% increase in incident AIHA, whereas administration of IL-17-neutralizing antibodies reduced incidence to approximately 18%[4,5]. Recent studies have highlighted the involvement of IL-17 cells in autoimmune diseases. In type 1 diabetes and autoimmune liver diseases, emergence of novel T cell cytokines such as IL-17 and IL-9, as well as elevation of existing cytokines, has been reported[6,7]. Autoimmune liver diseases such as autoimmune hepatitis and primary biliary cholangitis are characterized by increased activation of Th1 and Th17 cells and a reduction in regulatory T cells, mirroring features observed in psoriasis patients[8–11]. Thus, psoriasis shares underlying pathogenic mechanisms with autoimmune diseases such as autoimmune hepatitis and type 1 diabetes, which suggests that psoriasis patients are more vulnerable to these autoimmune diseases.

By inhibiting the effects of IL-17A, brodalumab may suppress pathological IFN-γ-dependent inflammation. This increases the proportion of IL-17A in peripheral blood, which may be linked to AIHA onset. Although further comprehensive investigation is necessary to clarify the association between brodalumab therapy and AIHA, our findings suggest that careful consideration of the risk of AIHA is warranted for patients with psoriasis treated with brodalumab.

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