—Case Reports—

# A Case of Autoimmune Hepatitis/Primary Biliary Cholangitis Overlap Syndrome during Treatment with Brodalumab for Generalized Pustular Psoriasis

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Psoriasis is a chronic inflammatory skin disease characterized by accelerated tumor necrosis factor-α (TNF-α)/interleukin (IL)-23/IL-17 axis, epidermal hyperproliferation, and dysregulated differentiation. Psoriasis is occasionally associated with autoimmune liver diseases such as autoimmune hepatitis (AIH) or primary biliary cholangitis (PBC), caused by autoimmunity against hepatocyte- or cholangiocyte-specific autoantigens, respectively. Overlap syndrome is a condition in which patients have features of both AIH and PBC. It has been reported that AIH, PBC, or the overlap syndrome can be triggered by certain drug therapies. A 65-year-old Japanese man developed increased serum levels of aspartate and alanine aminotransferases, and positive anti-nuclear and anti-mitochondrial M2 antibodies, along with neutropenia, at 4 weeks of treatment with an anti-IL-17 receptor A antibody brodalumab for generalized pustular psoriasis. Histological evaluation of the liver revealed interface hepatitis and non-suppurative destructive cholangitis, which is compatible with the overlap syndrome of AIH and PBC. This is the first case of AIH/PBC overlap syndrome during treatment with brodalumab for generalized pustular psoriasis. The relationship between brodalumab and AIH/PBC overlap syndrome should be further elucidated. The risk of autoimmune liver diseases in patients with psoriasis treated with brodalumab should be carefully considered. (J Nippon Med Sch 2021; 88: 569–573)

**Key words:** autoimmune hepatitis, primary biliary cholangitis, overlap syndrome, generalized pustular psoriasis, brodalumab

## Introduction

Psoriasis is a chronic inflammatory skin disease characterized by accelerated tumor necrosis factor-α (TNF-α)/interleukin (IL)-23/IL-17 axis, epidermal hyperproliferation, and dysregulated differentiation. Psoriasis is occasionally associated with autoimmune liver diseases such as autoimmune hepatitis (AIH) or primary biliary cholangitis (PBC)[1,2]. AIH is triggered by autoimmunity against hepatocyte-specific autoantigens, and is characterized by interface hepatitis on histology, hypergammaglobulinemia, and presence of autoantibodies such as anti-nuclear antibody, anti-smooth muscle antibody, or anti-liver kidney microsomal type 1 antibody. PBC is caused by autoimmunity against cholangiocyte-specific autoantigens, and is characterized by anti-mitochondrial antibodies, cholestasis, and chronic non-suppurative destructive cholangitis on histology. Some patients with AIH can develop features of PBC, and *vice versa*. These conditions are designated as overlap syndrome[3].

Patients with psoriasis have an increased probability of developing AIH; the reported incidence ratio compared to controls was 2.64 and 3.05 in mild and severe psoriasis, respectively in the Danish study[1]. Psoriasis is also a risk factor for PBC: the reported odds ratio was 4.6 in the Northeast England study[2]. Thus, patients of psoriasis might be more susceptible to AIH/PBC overlap syndrome compared to controls. It has been reported that 4.2% of the patients with AIH/PBC overlap syndrome have psoriasis[4]. However, no cases of AIH/PBC overlap syndrome associated with psoriasis have been reported

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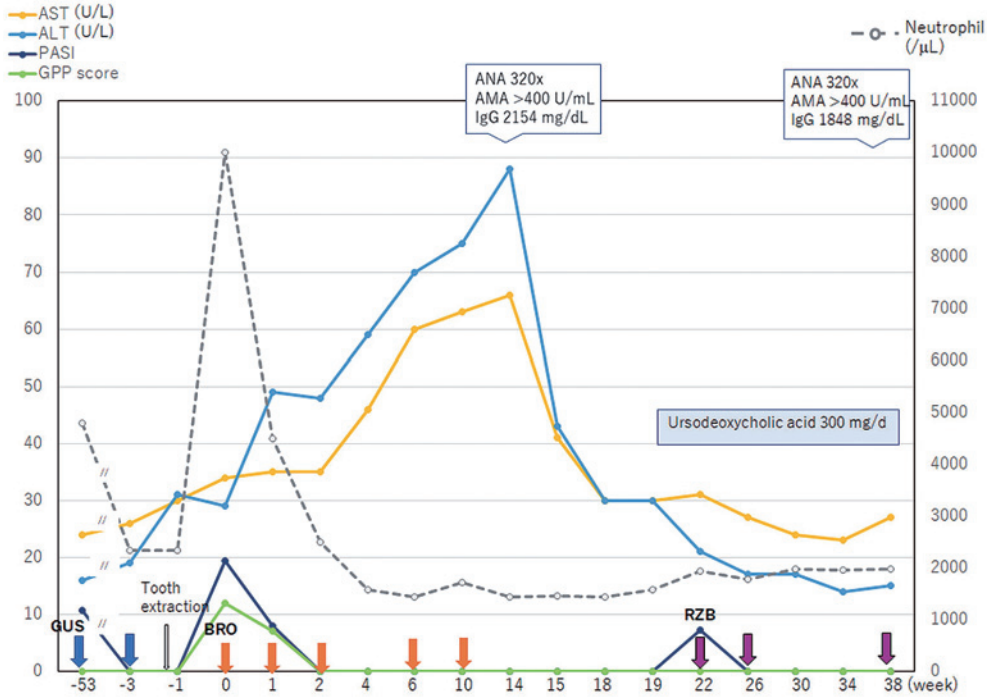


Fig. 1 The progress of psoriasis vulgaris and generalized pustular psoriasis (GPP), laboratory findings, and treatment. The beginning of the brodalumab (BRO) treatment was set as week 0. GUS, guselkumab; PASI, psoriasis area and severity index; RZB, risankizumab; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; AMA, anti-mitochondrial M2 antibody.

in the literature.

Some cases of AIH, PBC, or their overlap syndrome are reported to be induced by the administration of drugs such as minocycline for AIH[5], acetaminophen for PBC[6], or fluvastatin for overlap syndrome[7]. There are several cases of AIH, PBC, or their overlap syndrome induced by an anti-TNF-α antibody infliximab used as a therapy for psoriasis[8–10].

Brodalumab is a human monoclonal antibody against IL-17 receptor A (IL-17RA) and is used for the treatment of psoriasis. It blocks the effects of cytokines of the IL-17 family, mediated through IL-17RA, such as IL-17A, IL-17 F, IL-17A/F, IL-17C or IL-17E. We recently reported the first case of AIH, during treatment with brodalumab for psoriasis vulgaris[11]. We present here, the first case of AIH/PBC overlap syndrome during treatment with brodalumab for generalized pustular psoriasis (GPP).

## Case Report

A 65-year-old Japanese man with a 30-year history of psoriasis vulgaris was treated with an anti-IL-23p19 antibody guselkumab 100 mg at week 0 and 4, and every 8 weeks thereafter. He had indurated scaly erythema on the trunk and extremities, with a psoriasis area and severity index (PASI) of 11.8 before therapy (**Fig. 1**). However, he had no eruptions from week 12 to 52 of therapy. At week 52 of the treatment, he underwent a tooth extraction. Ten days later, he developed widespread pin-sized pustules on the erythematous areas of the trunk and extremities (> 75% of the body) (**Fig. 2**), with fever (body temperature 38.5°C) and elevated markers of inflammation on blood investigations: white blood cells 14,100/μL, neutrophils 71%, C-Reactive Protein (CRP) 12.16 mg/dL (normal 0-0.14). GPP was suspected based on the PASI score of 19.5 and total GPP score 12, classified as severe GPP, according to the severity criteria for GPP by the Japanese Dermatological Association[12]. He was switched from guselkumab to an anti-IL-17RA antibody brodalumab 210 mg, which was administered at weeks 0, 1, and 2. At week 2, he had no eruptions or fever, with normal neutrophil and CRP values. Histopathology of a pustule on the abdomen revealed subcorneal spongiform pustule filled with neutrophils (**Fig. 3**). Culture of the discharge from the pustule was negative for bacteria or fungi. The diagnosis of GPP was confirmed. At week 4 of brodalumab treatment, the blood investigation results showed increased values of aspartate aminotransferase (AST) (46 U/L; normal 13-30) and alanine aminotransferase (ALT) (59 U/L, normal 10-42) and neutropenia (neutrophils, 1,582/μL; white blood

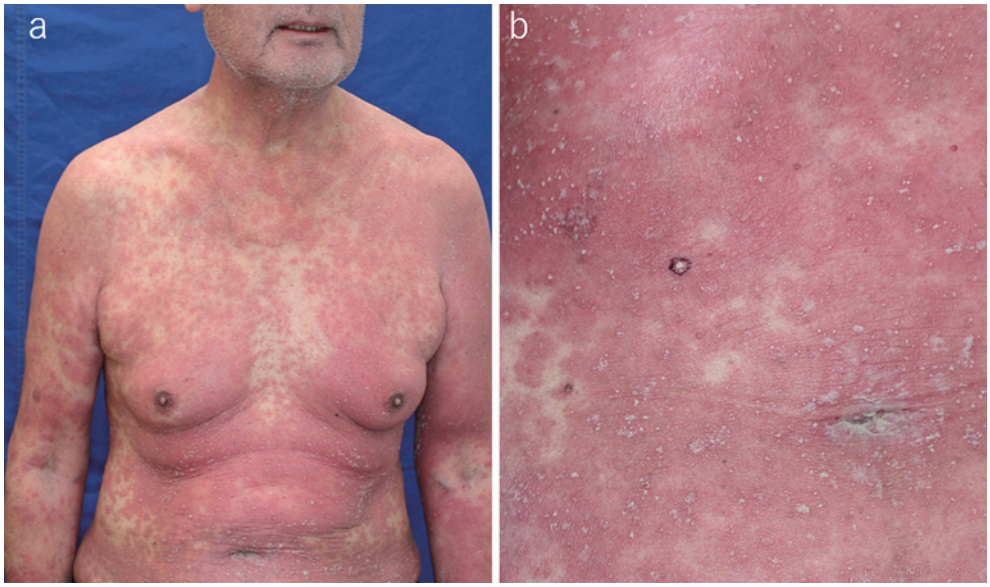


Fig. 2 (a, b) Widespread pustules on the erythematous areas on the trunk.

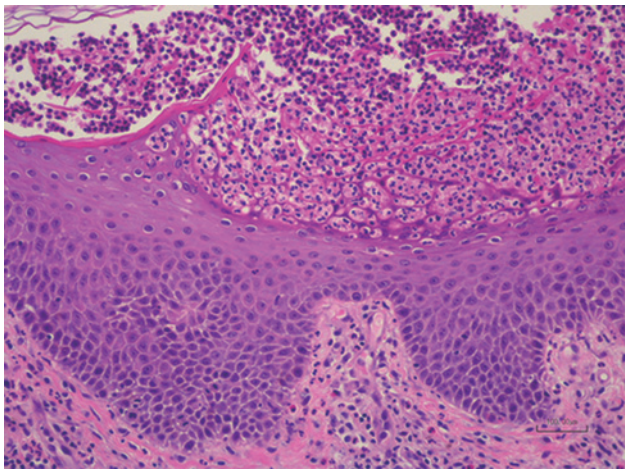

Fig. 3 Skin biopsy shows subcorneal spongiform pustule filled with neutrophils (hematoxylin and eosin; ×200).

cells, 5,400/μL; neutrophils, 29.3%; normal, 42%-74%). We suspected liver injury and neutropenia induced by brodalumab. Since the increase of aminotransferases was mild and neutrophil number was above the level for the discontinuation of brodalumab (1,000/μL), we decided to increase its dosing interval from 2 to 4 weeks instead of its discontinuation. The patient received further injections of brodalumab 210 mg at weeks 6 and 10. At week 14, the results of the blood investigations were as follows: AST 66 U/L, ALT 88 U/L, alkaline phosphatase 211 U/L (normal 106-322), γ-glutamyl transferase 23 U/L (normal 13-64 U/L), lactate dehydrogenase 191 (normal 124-222 U/L), total bilirubin 0.9 mg/dL (normal 0.4-1.5), neutrophils 1,436/μL, white blood cells 4,490/μL, neutrophil 32%, anti-nuclear antibody titer 1:320 speckled pattern, anti-mitochondrial M2 antibody > 400 U/mL (normal 0-7), anti-smooth muscle antibody (−), anti-liver kidney microsomal type 1 antibody (−), IgG 2,154 mg/dL (normal 861-1,747), IgA 137 mg/dL (normal 93-393), IgM 217 mg/dL (normal 33-183), Epstein-Barr virus IgM antibody (−), cytomegalovirus IgM antibody (−), hepatitis A, B, C, and E markers (−). AIH/PBC overlap syndrome was suspected and brodalumab treatment was discontinued. At week 18, both AST and ALT levels normalized to 30 U/L. Liver biopsy showed interface hepatitis with lymphoplasmacytic infiltration (**Fig. 4a**), and non-suppurative destructive cholangitis with lymphocytic infiltration, epithelial swelling, loss of small bile ducts, and ductular proliferation (**Fig. 4b**). According to the new scoring classification for PBC-AIH overlap syndrome proposed by Zhang *et al.*[3], the score of the patient was 22, which is interpreted as definitive overlap syndrome. At week 19, treatment with ursodeoxycholic acid 300 mg/day was initiated. At week 22, the neutrophil count was mildly recovered to 1,938/μL (WBC 6,000/μL, neutrophil 32.3%). The patient maintained normal AST/ALT levels for 3 months thereafter, although anti-nuclear and anti-mitochondrial M2 antibodies were still positive.

Twelve weeks after the last injection of brodalumab, the patient developed indurated scaly erythema on the extremities, with PASI score of 7.2, without pustules or fever. Recurrence of psoriasis vulgaris was suspected, and anti-IL-23p19 antibody risankizumab 150 mg was subcutaneously injected at weeks 0 and 4, and every 12 weeks thereafter. At week 4 of risankizumab treatment, the eruptions resolved. He had no eruptions or increased AST/ALT, but mild neutropenia of 1,900 to 2,000/μL until week 16 of risankizumab treatment.

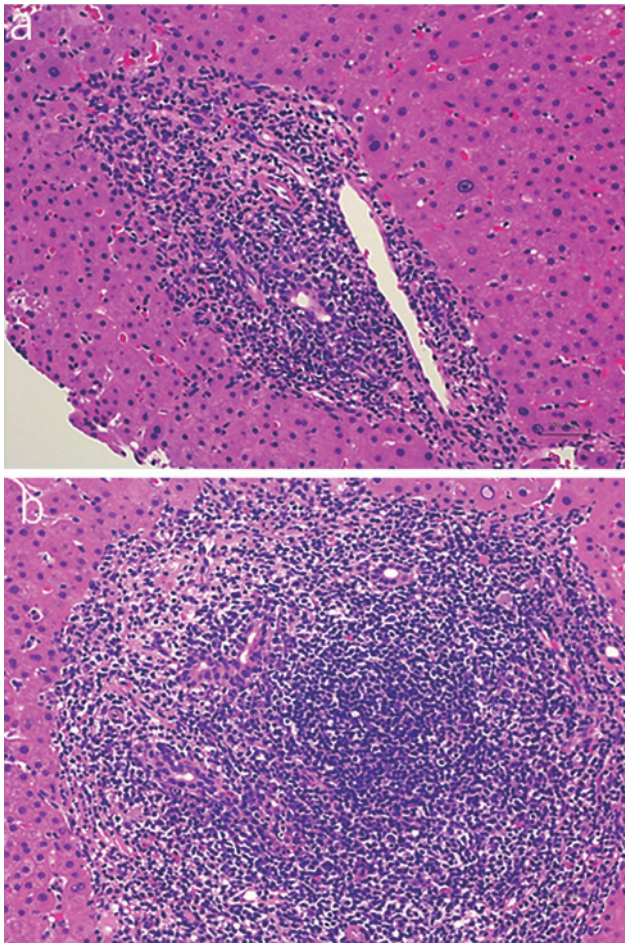


Fig. 4 Liver biopsy shows interface hepatitis with lymphoplasmacytic infiltration (a) and non-suppurative destructive cholangitis with lymphocytic infiltration, epithelial swelling, loss of small bile ducts, and ductular proliferation (b) (hematoxylin and eosin; ×200).

## Discussion

The etiopathogenesis of both, AIH and PBC involve enhanced activities of T helper cell type 1 (Th1) and Th17, and impaired activity of regulatory T cells (Tregs)[13–16], which is commonly seen in psoriasis patients. Psoriasis might thus share a common pathogenesis with AIH and/or PBC, and patients of psoriasis might be predisposed to these autoimmune liver diseases.

The present case developed AIH/PBC overlap syndrome during brodalumab treatment for GPP. Tooth extraction might trigger GPP via the release of angiogenic or chemotactic factors since GPP can be induced by medications, infections or injury[17] AIH, PBC, or their overlap is occasionally triggered by drugs[18]. The drug or its metabolite might covalently bind to the self-proteins in hepatocytes or cholangiocytes and form adducts, which might be presented as neo-antigens, inducing autoimmune inflammation[19]. The pathomechanism of drug-induced autoimmune liver diseases might also involve host-specific factors such as specific HLA types or abnormalities in the enzymes involved with drug metabolism or secretion, proinflammatory effector cells, and Tregs.

There have been some reports of AIH, PBC, or their overlap triggered by anti-TNF-α antibodies, infliximab, or adalimumab in patients of psoriasis[8,9]. In addition to immune-mediated mechanisms, anti-TNF-α antibodies might antagonize the effects of TNF-α to induce cytotoxic T cells eliminating autoreactive B cells, and subsequently allow the autoreactive B cells to produce autoantibodies against the autoantigens of hepatocytes or cholangiocytes[20,21]. We reported the first case that developed AIH during treatment with an anti-IL-17RA antibody brodalumab for psoriasis vulgaris[11]. However, there have been no reported cases of AIH/PBC overlap syndrome during treatment with anti-IL-17RA or anti-IL-17A antibodies. The present patient developed an increase in AST/ALT and neutropenia at 4 weeks of brodalumab therapy, which subsided after its discontinuation, indicating that the liver injury and neutropenia might have been induced by brodalumab. The updated Roussel Uclaf Causality Assessment Method score for hepatocellular injury due to drug-induced liver injury[19] was 7 in the present case, which corresponds to a causality grading of 'probable'. The Naranjo scale for adverse drug reaction (ADR)[22] in this case was 5, corresponding to probable ADR. Brodalumab treatment can cause neutropenia by suppressing granulopoiesis induced by IL-17A which enhances the production of granulocyte colony-stimulating factor and stem cell factor in the stromal cells of the bone marrow[23]. Although it is uncertain whether brodalumab induced the AIH/PBC overlap syndrome in the present case, brodalumab might unmask the latent AIH/PBC overlap syndrome in patients of psoriasis predisposed to this disease. One possible mechanism is that an anti-IL-17RA antibody brodalumab might block the regulatory activity of IL-17E, also known as IL-25, whose effects are mediated through IL-17RB/IL-17RA. IL-25 is constitutively expressed in the liver and inhibits autoimmune Th1 and Th17 responses by inhibiting the production of IL-12 and IL-23 by antigen-presenting cells[22], and suppresses D-galactosamine/lipopolysaccharide-induced fulminant hepatitis in mice by inducing myeloid-derived suppressor cells[24,25].

Alternatively, brodalumab might block the IL-17RA/IL-17RC-mediated effects of IL-17A to inhibit the pathological IFN-γ-dependent inflammation[26], leading to the promotion of Th1 cell-mediated autoimmune inflamma-

tion in the liver. It has recently been reported that aberrantly activated Th1 cells producing TNF-α are increased and play a pathogenic role in AIH[14]. It is postulated that Th1 cells play a key role at the onset of PBC[13]. It is reported that the knockout of *IL-17RA* in *Trypanosoma cruzi*-infected mice enhanced the expression of IFN-γ and TNF-α in the liver and aggravated the liver damage[27].

In conclusion, this was the first case of AIH/PBC overlap syndrome during brodalumab treatment for GPP. The relationship between brodalumab treatment and AIH/PBC overlap syndrome should be further elucidated. The risk of autoimmune liver diseases in patients with psoriasis treated with brodalumab should be carefully considered.

**Conflict of Interest:** The authors declare no conflict of interest.

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