Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4646-20
Intern Med 59: 2611-2618, 2020
http://internmed.jp

【 CASE REPORT 】

Drug-induced Bullous Pemphigoid and Lupus Erythematosus Occurring under Anti-TNF-α and IL-6 Therapy in a Patient with Rheumatoid Arthritis

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Abstract:
A 65-year-old Japanese woman, who was diagnosed with rheumatoid arthritis and Sjögren's syndrome with various autoantibodies including anti-DNA antibody, developed bullous pemphigoid (BP) and hematological abnormalities like lupus erythematosus after adalimumab therapy. The discontinuation of adalimumab resolved those disorders but polyarthritis thereafter relapsed. The introduction of abatacept was not effective, but tocilizumab was found to be effective for polyarthritis, however, thereafter both bullous disease and severe pancytopenia developed. Discontinuation of tocilizumab was effective, but polyarthritis again developed, and baricitinib resolved it. There is an increasing number of reports of drug-induced BP and lupus erythematosus, and biologics might trigger an alteration in the pathophysiological/clinical course of rheumatic disorder.

Key words: rheumatoid arthritis, Sjögren's syndrome, bullous pemphigoid, lupus erythematosus, biologics, drug-induced autoimmune reactions

(Intern Med 59: 2611-2618, 2020)
(DOI: 10.2169/internalmedicine.4646-20)

Introduction

Biologics have significantly improved the outcomes of patients with rheumatoid arthritis (RA), however, many patients do not respond to biologics from the outset or lose their response over time, the latter often being attributed to the immunogenicity of biologics. The immunogenicity of biologics often induces anti-drug antibodies and has been linked to serious adverse events including infusion/allergic reactions, thrombotic events, and autoimmune reactions, including drug-induced lupus erythematosus (DILE) (1-3). The management of RA patients who develop drug-induced autoimmune reactions and the safety of re-challenging these patients with other biologic therapies remain largely unknown and understudied.

Bullous pemphigoid (BP) is a kind of subepidermal immunobullous disorder which usually occurs in elderly individuals and presents with multiple tense bullae (4). Subepidermal bulla of BP is characterized by inflammatory eosinophil-predominant infiltrate, linear deposits of IgG and/or C3 at the basement membrane zone (BMZ) in direct immunofluorescence, and circulating autoantibodies targeting the BMZ proteins BP180 (BP antigen 2 or type XVII collagen) and BP230 (BP antigen 1) in an enzyme-linked immunosorbent assay and indirect immunofluorescence/split skin substrate (4). There has been growing evidence of a higher prevalence of neurologic diseases in patients with BP and some reports have suggested an increased frequency of certain cancers, dermatoses, and various autoimmune and inflammatory disorders (5, 6). Moreover, more than 50 different drugs have been associated with the appearance of BP and this number is very likely to increase (7). Although several pathogenetic mechanisms have been proposed in the

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Received: February 11, 2020; Accepted: May 20, 2020; Advance Publication by J-STAGE: July 7, 2020
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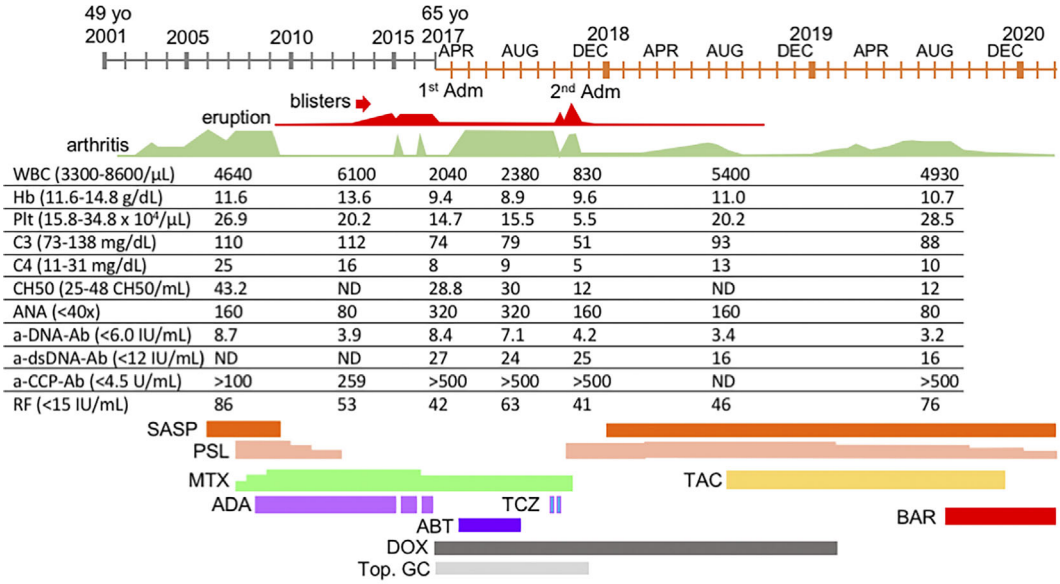

WBC (3300-8600/μL)	4640	6100	2040	2380	830	5400	4930
Hb (11.6-14.8 g/dL)	11.6	13.6	9.4	8.9	9.6	11.0	10.7
Plt (15.8-34.8 x 10^4/μL)	26.9	20.2	14.7	15.5	5.5	20.2	28.5
C3 (73-138 mg/dL)	110	112	74	79	51	93	88
C4 (11-31 mg/dL)	25	16	8	9	5	13	10
CH50 (25-48 CH50/mL)	43.2	ND	28.8	30	12	ND	12
ANA (<40x)	160	80	320	320	160	160	80
a-DNA-Ab (<6.0 IU/mL)	8.7	3.9	8.4	7.1	4.2	3.4	3.2
a-dsDNA-Ab (<12 IU/mL)	ND	ND	27	24	25	16	16
a-CCP-Ab (<4.5 U/mL)	>100	259	>500	>500	>500	ND	>500
RF (<15 IU/mL)	86	53	42	63	41	46	76

Figure 1. Clinical course. The clinical course of this patient is summarized as indicated. ABT: abatacept, a-CCP-Ab: anti-cyclic citrullinated peptide antibody, ADA: adalimumab, Adm: admission, a-dsDNA-Ab: anti-double strand DNA antibody, a-DNA-Ab: anti-DNA antibody, ANA: anti-nuclear antibody, BAR: Baricitinib, DOX: doxycycline, Hb: hemoglobin, MTX: methotrexate, ND: not determined, Plt: platelet, PSL: prednisolone, RF: rheumatoid factor, SASP: salazosulfapyridine, TAC: tacrolimus, TCZ: tocilizumab, Top. GC: topical glucocorticoid, WBC: white blood cell, yo: years old

past, it is not yet clear by which mechanisms drugs affect the development of BP, but it is likely that such patients have an underlying susceptibility for the development of BP and the drugs act as triggers (7).

We herein report an interesting case of an RA patient primarily complicated with Sjögren's syndrome (SS) who presented with various auto-antibodies and thereafter developed a bullous disease and lupus erythematosus under treatment with a tumor necrosis factor (TNF)-α inhibitor and an interleukin (IL)-6 inhibitor, but the patient did not develop these diseases under treatment with a CD28 co-stimulation modulator and a Janus kinase (JAK) inhibitor.

Case Report

A 49-year-old Japanese woman was pointed out to have dry mouth at admission due to herpes zoster in 2001. The Saxon's test and sialoscintigraphy revealed xerostomia, and the laboratory data showed hypergammaglobulinemia, and positivity of anti-nuclear antibody (ANA), anti-SS-A antibody. The patient was diagnosed with SS based on the revised Japanese criteria for SS (8). The subsequent clinical course is summarized in Fig. 1 and described below. Then, bilateral polyarthritis of the hands and fingers developed, and X-rays of the hands showed joint space narrowing and bone erosions. A serological test showed that anti-citrullinated peptide antibody (ACPA) was positive. The patient was newly diagnosed with RA at 51 years of age and thereafter was treated with salazosulfapyridine (SASP) at 54 years of age, and subsequently, methotrexate (MTX) and a low dose of prednisolone (PSL) were initiated. However, the polyarthritis continued and joint destruction soon became evident (Fig. 2). Next, the subcutaneous administration of adalimumab (ADA) every other week was added at 56 years of age, and the symptoms thereafter resolved.

However, urticaria-like itchy rashes developed after the initiation of ADA. Moreover, after the discontinuation of SASP and PSL at 57 years of age, bullae gradually developed (Fig. 1). Since those skin abnormalities was suspected to have been induced by ADA, ADA was temporarily discontinued but thereafter was again restarted due to a relapse of arthralgia. However, since she further presented with mild pancytopenia, the patient was admitted to our hospital at 65 years of age. The patient did not have any history of allergic reactions for drugs, atopic diseases, nor asthma, and did not have familial history of autoimmune diseases. Physical examination revealed that, although swan-neck and hammer toe deformities, hallux valgus, and limitation in the range of motion of the elbows were seen, the patient did not show any arthralgia, joint tenderness, or swelling. Bullae and flare with pruritus were seen on the face, extremities, and trunk (Fig. 3). Laboratory tests revealed leukopenia, normocytic normochromic anemia, and mild thrombocytopenia (Fig. 1, Table 1). The positive autoantibodies were rheumatoid factor, ACPA, platelet-associated IgG (PAIgG), and anti-SS-A, anti-DNA, and anti-double strand DNA (dsDNA) antibodies. Hypocomplementemia was also detected (Table 1). A dermatologist performed a physical examination and skin biopsy of the bullous eruption on the right forearm. According to Japanese guidelines for the management of pem-

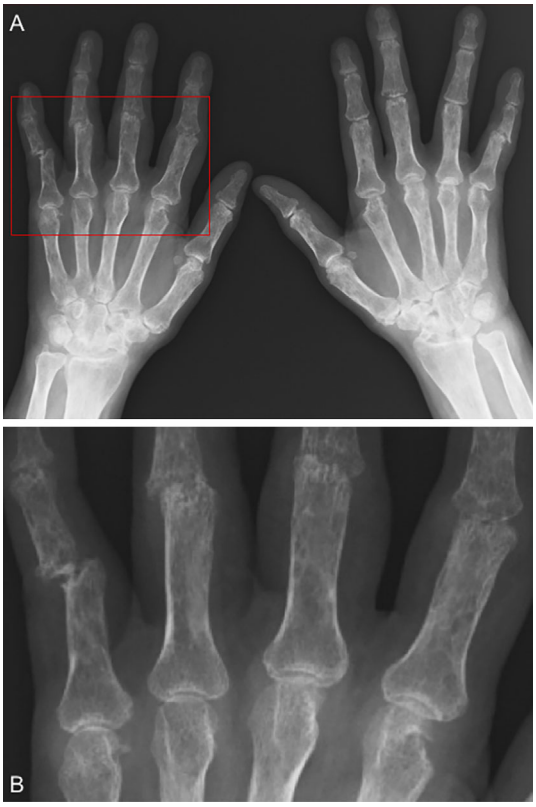

Figure 2. X-ray images of the patient's hands. Joint space narrowing and destruction were observed, which were considered to be compatible with RA. Joint destruction in the left hand is highlighted by red square in (A) and such sites are magnified in (B).

phigoid (9), BP was diagnosed based on the presence of subepidermal bulla with inflammatory eosinophil-predominant infiltrate (Fig. 4A, B), linear deposits of IgG and IgM at the BMZ by direct immunofluorescent microscopy (Fig. 4C), circulating anti-BMZ IgG antibodies-epidermal pattern by indirect immunofluorescent microscopy (Fig. 4D). An additional serum examination disclosed the positivity of anti-BP 180 antibody (22.7 U/mL; normal, <9.0 U/mL) (Table 1). We diagnosed the patient to have BP and it was suspected to be a side effect of ADA. At this point, her clinical and laboratory manifestations (leukopenia, hypocomplementemia, ANA, and anti-dsDNA antibody) were also considered to fulfil the Systemic Lupus Collaborating Clinics (SLICC) 2012 and the European League Against Rheumatism/the American College of Rheumatology (EULAR/ACR) 2019 criteria of systemic lupus erythematosus (SLE) (10, 11). Together with her history of immunological abnormalities (Fig. 1), she was also suspected to suffer from DILE or to apparently have SLE.

As indicated in Fig. 1, we eliminated ADA, and then the administration of topical glucocorticoid and oral doxycycline therapy was initiated. Thereafter, the pancytopenia and skin manifestations were immediately resolved, however, the polyarthritis relapsed. We initiated the subcutaneous administration of abatacept (ABT) every week. Although no skin and laboratory abnormalities developed, the efficacy of ABT

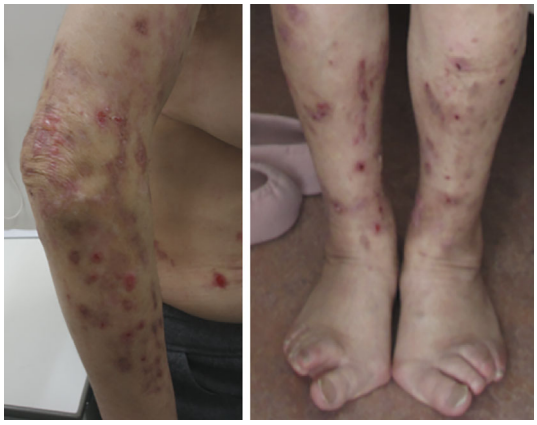

Figure 3. Representative images of skin manifestations. Bullous lesions and scars were observed in the extremities.

was not sufficient. Six months later, ABT was switched to the subcutaneous administration of tocilizumab (TCZ) every other week. After the first injection of TCZ, mild oral mucosal ulcers and an erosive skin rash were seen, but such manifestations improved after a few days and the polyarthralgia significantly improved. Then, we performed the second injection of TCZ, however, oral mucosal ulcers, bullous eruptions, and an erosive rash thereafter developed. Moreover, severe pancytopenia with hypocellular bone marrow, hypocomplementemia, and liver dysfunction were also observed, while titers of anti-DNA and anti-dsDNA antibodies did not change (Fig. 1). We suspected these new symptoms to be side effects of TCZ, and initiated 10 mg/day of PSL in addition to discontinuing both TCZ and MTX. Then, these findings and the laboratory data improved. One year later, polyarthritis flared again despite having once improved. We restarted SASP and added 1 mg/day of tacrolimus (TAC). Those treatments were temporally effective but insufficient for the polyarthritis, we started to administer baricitinib (BAR) which successfully eliminated the polyarthritis without any side effects for six months, and TAC and PSL could thus be discontinued and tapered, respectively.

Discussion

In this case, although the patient was primarily diagnosed with RA and SS and presented with anti-DNA antibody, she did not fulfill the diagnostic criteria of SLE and other autoimmune disorders at an earlier stage. However, after the treatment with biologics, BP developed and she also became complicated with SLE (10, 11). Blistering eruptions are extremely rare in RA and SS (12, 13), however, bullous diseases including BP may sometimes be associated with SLE (14, 15). Moreover, since many drugs can cause drug-induced BP and lupus erythematosus (3, 7), our findings suggest that both ADA and TCZ could induce BP and SLE in an RA patient primarily presenting with SS manifestations.

Lupus-like syndrome and anti-TNF-α induced lupus erythematosus were the most commonly observed diseases

Table 1. Laboratory Findings on the First Admission.

Complete blood count		Biochemistry		Serology	
WBC	**2,040 /μL**	**TP**	**9.0 g/dL**	**CRP**	**0.52 mg/dL**
Neutrophil	**47.1 %**	**Alb**	**3.0 g/dL**	**RF**	**42 IU/mL**
Lymphocyte	**26.3 %**	T-Bil	0.5 g/dL	C3	74 mg/dL
Monocyte	4.2 %	AST	27 IU/L	**C4**	**8 mg/dL**
Eosinophil	10 %	ALT	17 IU/L	**CH50**	**28.8 U/mL**
RBC	**2.86 ×10⁶/μL**	LDH	259 IU/L	**IgG**	**4,490 mg/dL**
Hb	**9.4 g/dL**	Cr	0.43 mg/dL	**IgA**	**806 mg/dL**
MCV	95.5 fL	BUN	11 mg/dL	IgM	62 mg/dL
MCH	**32.9 pg**	Na	135 mEq/L	**IgE**	**2,141 IU/mL**
Hct	**27.3 %**	K	3.9 mEq/L	**ANA**	**320 × (homo, spe)**
Plt	14.7 ×10⁴/μL			**ACPA**	**>500 U/mL**
				a-SS-A Ab	**>1,200 U/mL**
Urinalysis				a-SS-B Ab	4.9 U/mL
Protein	(±)			**a-DNA Ab**	**8.4 IU/mL**
Blood	(-)			**a-dsDNA Ab**	**27 IU/mL**
				a-Sm Ab	8.2 U/mL
				a-RNP Ab	<2.0 U/mL
				PA-IgG	**122 ng/10⁷cells**
				a-Des-1 Ab	<3.0 U/mL
				a-Des-3 Ab	<3.0 U/mL
				a-BP180 Ab	**22.7 U/mL**

Bolds indicate abnormal value. WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, Hct: hematocrit, Plt: platelet, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic dehydrogenase, Cr: creatinine, BUN: blood urea nitrogen, CRP: C-reactive protein, RF: rheumatoid factor, Ig: immunoglobulin, ANA: antinuclear antibodies, ACPA: anti-citrullinated protein antibody, a-: anti, Ab: antibody, SS: Sjögren's syndrome, ds: double strand, Sm: Smith, RNP: ribonucleoprotein, PA: platelet-associated, Des: desmogrein, BP: bullous pemphigoid

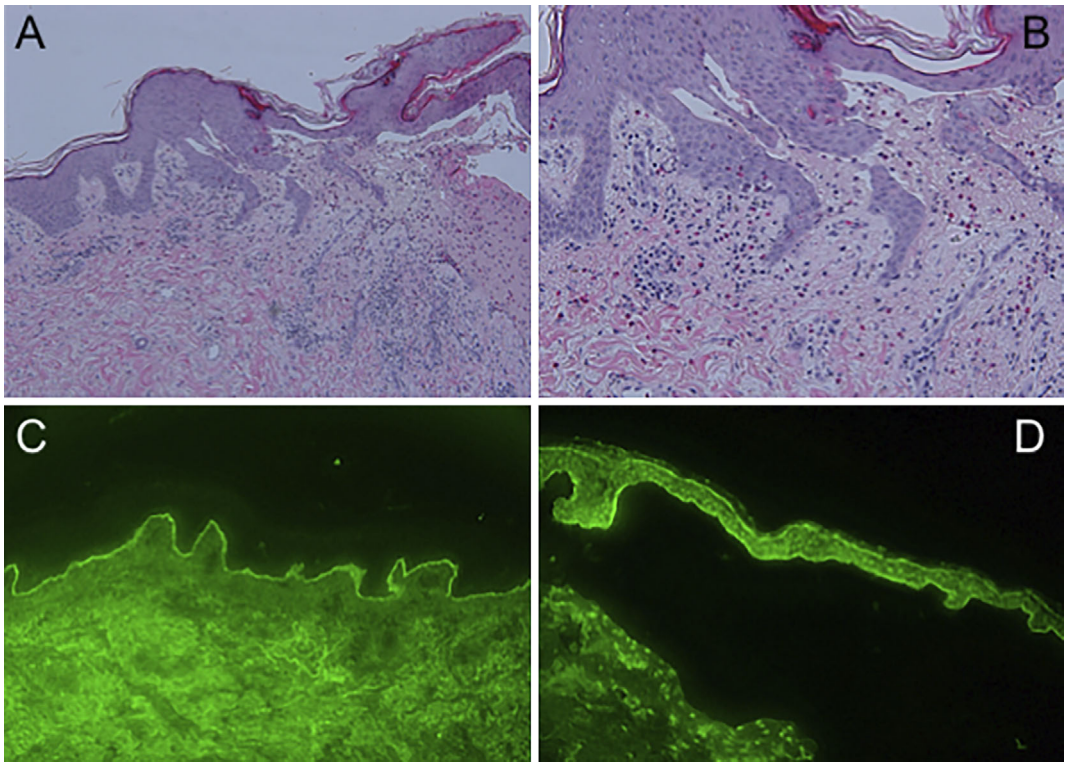

Figure 4. Histological findings of the bullous eruptions. Hematoxylin and Eosin staining showed severe inflammation with eosinophils in subepidermal blisters [×100 (A) and ×200 (B)]. Linear deposits of IgG at basement membrane zone (direct immunofluorescence, ×100) (C) and at the epidermal side of the blister (indirect immunofluorescence/split skin substrate, ×100) (D) were observed.

Table 2. Case Reports of Bullous Pemphigoid Induced by TNF Inhibitors.

No	Age	Sex	Primary diagnosis	TNF inhibitors	Duration of TNF inhibitors	Other drugs	Blisters	Treatment for BP	Treatment for primary disease	References
1	65	F	SS, RA	ADA	1 year	amlodipine besylate, candesartan cilexetil, rebamipide, cevimeline hydrochloride hydrate, ambroxol, eldecalcitol, MTX	trunk, face, extremities	topical glucocorticoid and oral doxycycline	•prednisolone: effective but relapsed •abatacept: ineffective •SASP, tacrolimus: effective but relapsed •tocilizumab: effective but BP relapsed •baricitinib: effective	present case
2	81	M	UC	ADA	2 weeks	irbesartan, bisoprolol, torasemide, atrovastatine, acetylsalicylic acid, mirtazapine, mesalazine, kaliumchloride, and levothyroxine for 6 years	trunk, extremities	prednisolone 80 mg/d and MTX 15 mg/w	not described	17
3	49	M	UC, PSC	ADA	1.5 years	metoprolol, pantoprazole, levothyroxine, and ursodiol	trunk, limbs, hands, feet	prednisolone 80 mg/d, intravenous immunoglobulin, and azathioprine 150 mg/d	not described	18
4	79	F	psoriasis with localized BP, type 2 DM	ETN	3 days	not described	generally	dapsone 100 mg/d	not described	19
5	54	F	UC	IFX	20 days	not described	trunk, limbs	prednisone	ADA: effective for ulcerative colitis without BP	20
6	61	F	RA with history of BP	ETN	2 months	not described	trunk, extremities	prednisolone 45 mg/d	not described	21
7	63	F	PsA	ETN	2 months	not described	arms, upper back	superpotent topical corticosteroids	•ADA; ineffective for psoriasis •ustekinumab: effective for psoriasis without side effects	22
8	71	F	RA	ADA	3 years	hydroxychloroquine, venlafaxine, bisoprolol, hydrochlorothiazide, risedronate, calcium carbonate-vitamin D3, acetylsalicylic acid and paracetamol	back, neckline, flexor forearms, lower legs, oral mucosa	topical corticosteroids and dapson 75 mg/d	not described	23
9	65	F	RA	ADA	1 year	prednisolone, MTX, folic acid, lansoprazole	knees, wrists, elbows, back	prednisolone 60 mg/d	not described	24
10	50	M	PsA	ADA	12 weeks	not described	trunk, limbs	prednisolone 15 mg/d and topical clobetasol	not described	25
11	65	F	RA	ETN	2 years	none	trunk, limbs, oral mucosa	oral steroid and MTX	not described	26

F: female, M: male, SS: Sjögren's syndrome, RA: rheumatoid arthritis, UC: ulcerative colitis, PSC: primary sclerosing cholangitis, BP: bullous pemphigoid, DM: diabetes mellitus, PsA: psoriatic arthritis, ADA: adalimumab, ETN: etanercept, IFX: infliximab, MTX: methotrexate

in a registry of autoimmune diseases associated with anti-TNF-α (16). On the other hand, only few cases have reported the onset of BP after initiation of TNF-α inhibitor treatment. We summarized the case reports of TNF-α inhibitor-induced BP in the literature and along with the finding of this case in Table 2 (17-26). Our case is the first

Table 3. Drug Efficay and Adverse Reactions in This Case.

Drugs	Arthritis	Blisters	Lupus-like symptoms
ADA	treatable	induce	suspect
TCZ	treatable	induce	induce
ABT	not enough	no relation	no relation
BAR	treatable	no relation	no relation

ADA: adalimumab, TCZ: tocilizumab, ABT: abatacept, BAR: baricitinib

one complicated with SS and presenting the presence of various autoantibodies, it remains unknown whether manifestations of SS could be the risk of drug-induced BP. Age and sex appear to not be associated with any bias. The time course for the development of BP after the administration of TNF-α inhibitors could be quite variable, at least between several days and 3 years. There seems to be no specific drug associated with TNF-α inhibitor-induced BP. Although restarting anti-TNF-α treatment with another agent except for culprits does not always induce a relapse of TNF-α inhibitor-induced BP (20, 22), re-challenging the involved biologics often induces recurrence with a quicker onset and more severe symptoms (27). To the best of our knowledge, the occurrence of such paradoxical reactions, including BP and lupus erythematosus, in patients treated with TCZ is extremely rare (28). Since the factors associated with the occurrence of a paradoxical reaction in patients with TCZ remain to be elucidated, further studies are thus needed.

We herein described our findings of an interesting clinical course of a patient receiving multiple biologics and JAK inhibitor treatment. In which, ADA and TCZ induced BP and SLE, while ABT and BAR did not (Table 3). The precise pathogenic mechanisms of drug-induced BP and SLE remain unclear, but are likely to involve genetic factors and individual mechanisms linked to the class of drugs (29). TNF-α inhibitors may trigger autoimmune bullous diseases including BP, probably using the same pathway that is involved in other types of autoimmune diseases secondary to TNF-α inhibitors, such as lupus erythematosus, interstitial lung disease, anti-phospholipid syndrome, inflammatory myopathies, autoimmune hepatitis and thyroiditis (7, 16, 19). Classically, the modulation of the homing of Th1 and Th2 cells may explain the induction of autoimmune disease (30, 31). The inhibitory properties of TNF-α or IL-6-targeted therapies suggest that the immunological state of the treated patients shifts from Th1 to Th2 dominance, which is known to be involved in BP (32). However, TNF-α and IL-6 inhibitors do not always act as a simple Th1 inhibitor, and other mechanisms of action of TNF-α inhibitor induced lupus-like syndrome have been proposed. Several lines of evidence indicate that type I interferon (IFN), especially IFN-α, plays a central role in the pathogenesis of SLE (33). It has been reported that IFN-α production was sustained when endogenous TNF-α was neutralized (34), and that treatment with TNF-α inhibitors is associated with increased expression of type I IFN-induced genes in patients with SS and RA (35-37), suggesting a pivotal role of TNF-α inhibitors in its paradoxical reactions. Although the profiles of IFN-α in BP patients have yet not been addressed, BP could develop following IFN-α therapy (38). Moreover, IgE antibodies against BP180 are known to be associated with more severe forms of BP, and IgE auto-antibodies can trigger type I interferon responses capable of exacerbating self-destructive autoimmune responses (39, 40). Although the mechanisms of paradoxical reactions in patients with TCZ also have not been addressed, one possibility might be postulated. After TCZ administration in both RA and Castleman disease patients, IL-6 receptor was saturated with TCZ and IL-6 signaling was completely inhibited, but serum both the IL-6 and IL-6 receptor markedly increased, suggesting that various cytokines including interferons might be also up-regulated under TCZ treatment (41). Considering these reports, we may speculate that TNF-α and IL-6 inhibitors could induce BP and SLE via the introduction of the predominance of IFN-α. It is also conceivable that CD28 co-stimulation modulators and JAK inhibitors did not trigger the development of BP and SLE in this patient, since CD28 co-stimulation modulators do not directly affect IFN-α signaling and JAK inhibitors can down-regulate such pathway (42, 43). In addition, in this case, the effectiveness of ADA, TCZ, and BAR was sufficient to successfully treat the arthritis, but ABT was insuficcient (Table 3). Concerning SLE, the efficacy of TCZ or ABT for SLE has not been established and TNF-α inhibitors should be avoided for SLE because of its ability to induce lupus erythematosus (44, 45). On the other hand, BAR may be a promising treatment for SLE (46, 47). These findings indicate that BAR was the only drug to improve RA without inducing BP and SLE in this case.

Finally, several pathogenetic mechanisms in paradoxical reactions of biologics have been proposed, in which a delicate immunological balance becomes disturbed in all patients with the disease and the inhibition of TNF-α and/or IL-6-dependent signaling may further deranges such balance (1, 7). In RA cases with complicated pathological conditions such as SS, SLE, and BP as in this case, JAK inhibitors, which affect to multiple inflammatory cytokines, interferons, and hormone receptors, may be better than biologics targeting a single inflammatory molecule. We must further investigate the mechanisms of these types of disorders and accumulate a larger number of similar reports in order to clarify the details of these diseases.

Written informed consent to publish this case report has been obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

Acknowledgements

We express our appreciation to the members of Tanaka Laboratory for their helpful suggestions and clerical assistance.

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