



Ustekinumab associated bullous pemphigoid in a psoriasis patient and a review of the literature

Psoriasis hastasında ustekinumab ile ilişkili gelişen büllöz pemfigoid ve literatür derlemesi

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Abstract

Ustekinumab is a Food and Drug Administration-approved (2009) novel treatment for psoriasis patients. This anti-interleukin-12/23p40 monoclonal antibody is effective in the treatment of plaque psoriasis and psoriatic arthritis. Several drugs, including anti-tumor necrosis factor-alpha agents, used for psoriasis have been reported to induce or cause bullous pemphigoid (BP). A psoriasis patient presented with bullous lesions appearing on the extremities, groin, and axillary region four weeks after ustekinumab therapy. The patient was diagnosed with drug-induced BP. Ustekinumab was discontinued and the patient was treated with topical steroids and acitretin. The BP lesions did not recur in the twelve-month follow-up, after cessation of the steroids. Even though several drugs are related to the induction of BP, ustekinumab is included in this list recently. The resolution of BP after discontinuation of ustekinumab favors the diagnosis of drug-induced BP.

Keywords: Psoriasis, ustekinumab, adverse effect, bullous pemphigoid

Öz

Ustekinumab, psoriasis hastaları için Gıda ve İlaç İdaresi tarafından 2009 yılında onaylanan yeni bir tedavi ajanıdır. İnterlökin-12/23'ün p40 subünitini hedef alan bu monoklonal antikor, plak psoriasis ve psoriatik artrit tedavisinde etkilidir. Literatürde şimdiye kadar anti-tümör nekroz faktörü-alfa grubu ilaçların da içinde yer aldığı pek çok ilaç büllöz pemfigoid (BP) gelişiminden sorumlu tutulmuştur. Kliniğimize bir psoriasis hastası ilk ustekinumab enjeksiyonundan dört hafta sonra ekstremiteler, kasık ve aksillar bölgede büllöz lezyonlar ile başvurdu. Hastaya ilaçla indüklenen BP tanısı koyuldu. Ustekinumab kesildi ve hasta topikal steroid ve asitretin ile tedavi edildi. BP steroid kesilmesinden sonraki on iki aylık takipte tekrarlamadı. BP'ye sebep olan ilaçların olduğu listeye ustekinumab çok yakın bir zamanda eklenmiştir. Ustekinumabın kesilmesinden sonra BP'nin tekrarlamaması ilaç ilişkili BP tanısını desteklemektedir.

Anahtar Kelimeler: Psoriasis, ustekinumab, yan etki, büllöz pemfigoid

Introduction

Psoriasis is a common chronic inflammatory dermatologic disease. The pathogenesis of psoriasis is complicated and not fully understood yet. However, the underlying pathology

involves T cells and T cell interactions with innate immunity^{1,2}.

Bullous pemphigoid (BP), on the other hand, is an acquired autoimmune dermatitis with autoantibodies against the basement membrane zone³. BP mainly affects the elderly.

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Received/Geliş Tarihi: 03.11.2017 **Accepted/Kabul Tarihi:** 09.10.2018 **ORCID ID:** orcid.org/0000-0001-6561-196X

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Turkderm-Turkish Archives of Dermatology and Venereology published by Galenos Yayınevi.

The pathogenesis of drug-induced BP is not fully understood but a strong correlation with medications exists. Over the years, more than 50 medications have been associated with BP^{4,5}. Classically, drug-induced BP arises in a patient with multiple drug regimens and a newly introduced drug. Medication-related BP mainly occurs in a younger group of patients when compared to classical BP. The lesions respond well to systemic steroids and relapses rarely occur after discontinuation of the inciting drug.

Ustekinumab is a novel treatment for psoriasis and psoriatic arthritis in the structure of anti-interleukin-12 (IL-12)/23p40 monoclonal antibody. Several drugs and light therapy used for psoriasis have been reported to induce or cause BP.

Case Report

A 58-year-old patient with a 10-year history of psoriasis was admitted to our outpatient clinic with itching and bullous lesions on the trunk and extremities along with generalized psoriatic plaques. In the past, the patient had used methotrexate (cumulative dose 1500 mg), cyclosporine, and acitretin for psoriasis. His medical history included chronic renal failure, hypertension, and hepatosteatosi. He used amlodipine for his hypertension for years and occasionally used paracetamol for headache and arthralgia.

For psoriasis, the recent choice of treatment was adalimumab. However, after three months of adalimumab therapy, the treatment was switched to ustekinumab (Stelara®; Janssen Biotech, Inc., Horsham, PA) because of resistant and generalized psoriatic lesions. A one-month interval existed between the last dose of adalimumab and ustekinumab injection.

One month after the initial injection of 45 mg ustekinumab, bullous lesions formed on erythematous urticarial plaques and psoriatic lesions appeared. The lesions were prominent on the axillary fossa and inguinal region. Laboratory tests revealed mild anemia (Hg: 12.7, normal ranges: 13.1-17.2 g/dL), eosinophilia (4.8, normal ranges: 0-3%), and increased serum C-reactive protein (9.2, normal ranges: 0-3

mg/L) levels. Serum creatinine level was also elevated to 2.07 mg/dL. Skin biopsies from the lesional and perilesional skin were examined (Figure 1). Light microscopic examination revealed bullae with subepidermal cleavage and dermal infiltrate of eosinophils. In addition, direct immunofluorescence study of the perilesional skin showed subepidermal linear immunoglobulin G (IgG), C3, and C4 staining. The diagnosis was BP with dermatopathological findings. Our patient received a Naranjo adverse drug reaction probability scale score of 8 and a modified Naranjo scale score of 5, indicating a probable drug reaction^{6,7}.

After the initial administration of ustekinumab, the treatment was discontinued. The bullous lesions were treated with topical mometasone furoate, clobetasol propionate, and oral acitretin (35 mg/day) was started for the psoriatic plaques. After two weeks of treatment, development of new lesions stopped and pruritus decreased. BP improved clinically. The topical steroid application was ceased after three weeks. Bullous lesions disappeared with slight hyperpigmentation and the patient continued treatment with acitretin for psoriasis. No relapses occurred in the twelve-month follow-up.

Inflammatory subtype of acquired epidermolysis bullosa (AEB) can simulate BP both histopathologically and clinically in some cases and it was an important differential diagnosis in our case. To differentiate these two diseases, salt split test in pathological examination is necessary because in both conditions, linear IgG deposition is observed in the basement membrane. A limitation of our case was the lack of salt-split, ELISA or Western blotting to confirm the diagnosis of BP. We favored the diagnosis of BP because AEB is a chronic disease which requires long-term systemic immunosuppressive treatment to suppress symptoms. On the other hand, in our patient, the lesions disappeared without the need for immunosuppressive treatment after ustekinumab was halted and acitretin treatment did not worsen the scenario. We received informed consent form from patient.

Discussion

Several mechanisms have been proposed for the etiopathogenesis of drug-related BP. In certain individuals, some drugs may cause an unwanted immune dysregulation leading to inactivation of the endogenous regulatory processes, resulting in a BP phenotype^{8,9}. Other drugs may act as antigenic haptens that bind and modify proteins in the basement membrane. This may expose a previously hidden antigenic site and induce an autoimmune cascade¹⁰.

Ustekinumab, a fully human IgG1κ monoclonal antibody, binds to the common p40 subunit of IL-12 and IL-23, blocking the activation of the receptors of these cytokines in dendritic cells and monocytes. Recently, ustekinumab has been reported to induce BP in a patient with psoriatic onycho-pachydermo-periostitis after 18 months of use. Similar to our case, the patient had previously used an anti-tumor necrosis factor (TNF) inhibitor (infliximab) before ustekinumab¹¹.

The coexistence of psoriasis and BP has been reported in approximately 40 patients³. It is still debated whether the co-occurrence of these two diseases is a coincidence or a pathogenic relationship. In both diseases, the basement membrane zone is involved in the pathogenesis. Disruption of the basement membrane and keratinocytes with treatment and/or previous dermatosis may change the antigenicity of the basement membrane and facilitate autoantibody production³.

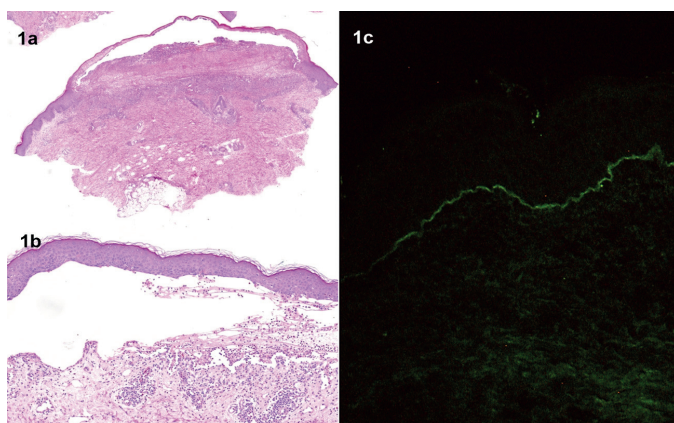


Figure 1. a) Subepidermal blister formation (hematoxylin and eosin, x40), b) an inflammatory infiltrate composed predominantly of eosinophils and neutrophils in the dermis and bullous cavity (hematoxylin and eosin, x100), c) bullous pemphigoid, direct immunofluorescence. There is linear deposition of Immunoglobulin G in the basement membrane zone with direct immunofluorescence

Table 1. Literature review of cases with biologic drug-induced bullous pemphigoid

Case	Drug	Age	Disease	Duration of biologic drug	Location	Tx BP	Tx psoriasis	Reference
1	Adalimumab	50	Psoriasis	3 months	Trunk, limbs	TS, SS	-	Stausbol-Gron et al. ¹³
2	Adalimumab	49	U. Colitis	1,5 years	The superior forehead, scalp, trunk, hands and feet	TS, SS, Azt, IVIG	-	Wessman et al. ¹⁴
3	Etanercept	79	Psoriasis	3 days	Generalized	Dds	-	Wilmer et al. ¹⁵
4	Etanercept	61	Rheumatoid arthritis	2 months	Trunk and extremities	SS	-	Mochizuki et al. ¹⁶
5	Etanercept	63	Psoriasis	2 months	Arms and upper back	TS	-	Kluk et al. ¹⁷
6	Etanercept	65	Rheumatoid arthritis	2 years	Trunk, upper and lower limbs and oral mucosa	SS + Mtx	-	Bordignon et al. ¹⁸
7	Efalizumab	51	Psoriasis	1 week	Generalized	TS	Acitretin	Duong et al. ⁵
8	Efalizumab	82	Psoriasis	6 weeks	Palms,soles generalized	TS, SS, Mtx	Mtx	Monnier-Murina et al. ¹⁹
9	Secukinumab	65	Psoriasis	1 week	Upper limbs and trunk	TS	Secukinumab	Ho PH and Tsai ²⁰
10	Ustekinumab	63	Psoriasis	18 months	Trunk, extremity	SS	-	Nakayama et al. ¹¹
11	Ustekinumab	62	Psoriasis	40 weeks	Upper thighs, lower neck, and upper trunk	TS	-	Le Guern et al. ²¹
12	Ustekinumab	58	Psoriasis	1 month	Intertriginous areas, generalized	TS	Acitretin	Our case

Tx: Treatment, BP: Bullous pemphigoid, TS: Topical steroids, SS: Systemic steroids, Azt: Azathioprine, IVIG: Intravenous immunoglobulin, Dds: Dapsone, Mtx: Methotrexate

This is supported by reports of blisters initially appearing on psoriatic lesions¹². The patient in this case had blisters on both psoriatic plaques and a psoriasis-naive erythematous base. This may be explained by BP antigen spreading to psoriasis-free areas after the initial pathological process. The reported cases of patients with biologic drug-induced BP are summarized in Table 1^{5,11,13-21}. Most of the patients received these drugs for psoriasis (9/12), only 2 patients were reported to have rheumatoid arthritis and 1 ulcerative colitis. In most of the cases, the biologic drug was stopped after development of BP lesions and psoriasis was treated with an alternative drug. In only one case, secukinumab was reported to be the culprit drug, however, treatment with secukinumab was started again after a while but rechallenge did not result in reemergence of BP lesions.

The immune system is a very sensitive system prone to imbalance. It is already known that TNF-targeted treatments used in psoriasis and rheumatoid arthritis are related to autoimmune diseases with an increased incidence of anti-double-stranded-DNA production and exacerbation of multiple sclerosis²². Biologics modify the immune system through cytokines and TNF- α inhibition. The immune system may mediate different pathways in susceptible individuals when one path is blocked by a drug action, leading to unexpected autoimmune processes. It is not possible to definitely say that ustekinumab is the direct cause of BP in this patient. However, rapid onset of BP after the initiation of ustekinumab therapy and amelioration of lesions

after cessation of the treatment and lack of recurrence favors drug-induced BP.

Acknowledgements: We would like to thank Prof. Dr. JC Prinz for critical reviewing of the paper.

Ethics

Informed Consent: We received informed consent form from patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.V., A.O.H., Concept: S.V., M.G., Design: S.V., H.Ş., Data Collection or Processing: M.G., P.K., Analysis or Interpretation: S.V., N.K., Literature Search: S.V., P.E., Writing: S.V., M.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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