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A case of bullous pemphigoid in a psoriatic patient treated with etanercept

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Abstract

The prevalence of Bullous Pemphigoid (BP) as a most common autoimmune bullous skin disease has increased in recent years. Drug-induced BP is an uncommon form of BP. A 25-year-old psoriatic woman was admitted to Imam Khomeini hospital complex affiliated to the Tehran University of Medical Science with a chief complaint of generalized blistering lesions. She had received Etanercept for psoriasis during the last three months before admission. Moreover, she declared that her erythematous papules developed after a single injection of ondansetron one month ago and expanded until her admission time. After initiating topical and systemic corticosteroids, her lesions improved over one month. The results of a lesional biopsy were compatible with BP. Due to the history of complete clinical response with Adalimumab, she was switched to Adalimumab after discharge and had a complete response during the 6-month follow-up period. Since there are reports regarding the bilateral association between BP and psoriasis without a secondary cause, we cannot consider this patient as a definite drug-induced BP case.

Keywords: Bullous pemphigoid; Psoriasis; Etanercept; Adverse drug reaction; Tumor necrosis factor.

Introduction

Bullous Pemphigoid (BP) the most common pemphigoid disorder has an incidence rate varying from 4-42.8 cases per 1 million people per year. There are growing number of BP reports due to the aged population, an increase in drug-induced cases, and an improvement in disease diagnosis [1,2]. Although BP itself rarely leads to mortality, it may enhance both mortality and morbidity rate due to co-morbidities (especially neurological disorders) and therapeutic side effects [3].

The pathogenesis of the disease includes the formation of autoantibody from the IgG class against two structural components of the hemidesmosome known as BP180 and BP230, providing structural adhesion between basal keratinocytes and basement membrane in the dermal-epidermal junction. Antibody formation leads to neutrophil chemotaxis and degradation of the Basement Membrane Zone (BMZ) [2,3].

Classical clinical presentation of BP is the appearance of a generalized tense, serous or hemorrhagic bullae following a non-bullous, pruritic phase with a duration of days to months which might lead to misdiagnosis of the disease. Mucosal involvement is rarely reported in BP [4].

Diagnosis of BP relies on clinical features, histopathological

evaluation, immunofluorescence assays, and quantification of circulating autoantibodies against BP180 and/or BP230 [2,4]. Although there is no worldwide-accepted approach to treat BP, topical/ systemic corticosteroid is the mainstay of the treatment. Moreover, Doxycycline, Dapsone, and immunosuppressants are other therapeutic choices [1,3].

Various drugs have been associated with the development of BP. The cross-reactivity of antibodies that target drugs with antigens in the BMZ is the rationale for drug-induced BP. Drug-induced BP may develop months to years after drug exposure [5]. Tumor necrosis factor α (TNFα) inhibitors can generate antibodies against themselves leading to an immune response. There are reports regarding TNFα inhibitors induced autoimmune diseases including systemic lupus erythematosus, Dermatomyositis/polymyositis, vasculitis, etc [6]. The present study aims to describe a psoriatic patient with BP who has received etanercept.

Case presentation

A 25-year-old woman (wt=60 kg) with a history of psoriasis from four years ago was admitted to Imam Khomeini hospital complex affiliated to the Tehran University of Medical Sciences. The primary chief complaint of the patient was generalized blistering lesions. She has a family history of psoriasis and Bechet's disease. After her psoriasis diagnosis four years ago, she received topical Clobetasol 0.05 % for nearly 3 years. After a case of flare-up, she was switched to oral methotrexate (7.5-15 mg weekly) for six months. Due to an incomplete response to methotrexate, she has switched to Adalimumab 40 mg SC every two weeks for 6 months. She has a complete clinical response with Adalimumab. Due to the Adalimumab shortage in a period, she switched to Etanercept 50 mg SC weekly for the last three months before her admission. The last dose of Etanercept was administered five days before admission. She was also receiving Metformin tablet 500 mg BD and Cyproterone acetate 50 mg daily during the last 6 months for polycystic ovary syndrome (PCOS). The patient had a history of intramuscular injection of Ondansetron Amp 4 mg due to anorexia, nausea, and vomiting one months before admission. Five days following the injection, the patient developed itchy erythematous papules at the injection site, which expanded over time. The lesions became towel-like gradually despite using Hydroxyzine tablet 10 mg BD. During her admission, she has pruritic, tense, and flaccid blisters and bullae on her face, chest, abdomen, and upper and lower extremities (Figures 1,2) although there was no mucosal involvement. During admission blisters became like rings (Annular lesions) and groups of small new lesions appeared were like 'cluster of jewels' or 'crown of jewels'. Therefore, with this clinical view, the diagnosis of linear IgA bullous disease (LABD) was raised clinically.

On the admission day, she was hemodynamically stable (BP = 120/85 mmHg, HR = 84 beat/min, RR = 14 breath/min), afebrile (Temperature = 36.8 °C oral). She has normal lab data during admission and hospitalization including Coagulation Tests (PTT, INR), CBC (WBC, RBC, PLT, Hb, Lymphocyte, Neutrophil, MCV, MCH, MCHC), ESR, CRP, LFT(AST, ALT, Total Bilirubin, Direct Bilirubin, ALP), Serum Creatinine, BUN, VBG, Na, K, Mg, P, Ca, Uric acid, Lipid profile (VLDL, HDL, LDL, Total cholesterol, Triglyceride), Rheumatologic markers (ANA, Anti ds DNA, P-ANCA, C-ANCA, Anti-Ro/SSA, Anti-La/SSB, C3, C4, and CH50). PPD test, HBsAg, HIV Ag/AB, and Anti HCV were all negative. Punch biopsy specimens from her abdomen lesion was sent for pathology. She was hospitalized in the dermatology ward with a primary diagnosis of BP.

Figure 1: Flaccid blisters and bullae on the patient's body.

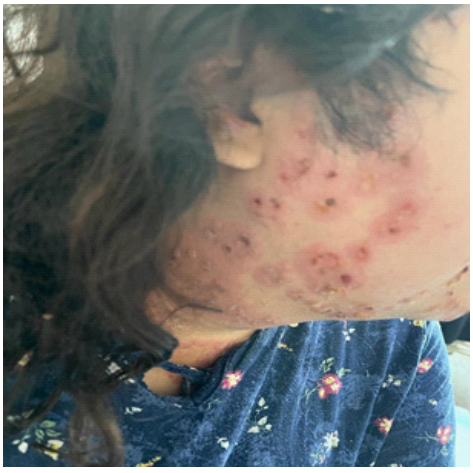

Figure 2: Flaccid blisters and bullae on the patient's upper extremity.

Therapeutic interventions and treatments

The patient received Clindamycin capsule 300 TDS, Cetirizine tablet 10 mg BD, and Prednisolone tablet 30 mg daily since her admission. She also received topical medication including Clobetasol 0.05 % ointment BD, Mupirocin 2% ointment BD, and Zinc Oxide 25 % ointment QID. The dermatology team requested pharmacotherapy consultation for the possibility of drug-induced reactions. Based on pharmacotherapy consultation, considering the patient's medical history, drug administration schedule, previous reports regarding Etanercept-induced BP and the association between psoriasis and BP, and the progressive nature of lesions despite Ondansetron discontinuation for one month, it is not possible to determine the definite causative of the reaction. So, it was recommended that subsequent doses of Etanercept as well as Ondansetron not be administered until the results of the biopsy were prepared.

Pathology reports suggest skin tissue with denuded epidermis (subepidermal bullae) with preserved dermal papillae containing thickened vessels with perivascular and interstitial

infiltration of lymphohistiocytes and many eosinophils. Results of the immunofluorescence study suggest linear C3 and IgG at the dermal–epidermal junction without IgA or IgM deposition. Consequently, subepidermal bullae with denuded epidermis and eosinophilic dermal infiltration were compatible with bullous pemphigoid. After two weeks of hospitalization, most of the BP lesions had disappeared and the patient was discharged.

Due to the concerns regarding further psoriasis flare-ups, and considering her previous optimal clinical response with Adalimumab, it was supplied and restarted one month after being discharged at a dose of 40 mg SC every two weeks. After 6 months of the follow-up period, her psoriasis was optimally controlled without any flare-ups and the BP lesion resolved completely.

Discussion

BP might be one of the TNFα inhibitors' adverse effects or a pathologic process in terms of psoriasis. It has been suggested that TNFα plays a key role in both diseases. There are reports regarding the development of non-drug-induced BP in patients with psoriasis [7].

A bilateral relationship between psoriasis and BP prevalence has been reported. Results of a cohort study suggest that patients with BP are at a 2.6-fold increased risk of developing psoriasis. Moreover, patients with a history of psoriasis were 1.5 times as likely to have BP as those without psoriasis. Male gender, young age, smoking, hypertension, and prolonged systemic/topical corticosteroid use were prevalent in patients with concurrent BP and psoriasis [8].

Nearly frothy cases of concurrent psoriasis and BP has been reported. Although there is a bilateral relationship, in most cases, psoriasis develops first and BP emerges after a duration ranging from 1-60 years. Disruption of the BMZ is common in psoriatic patients which may trigger autoantibody formation leading to BP [9].

There are reports regarding autoimmune disease (e.g. cutaneous vasculitis, lupus-like syndrome, BP, etc.) as an adverse effect of TNFα inhibitors [6].

Until now 17 cases (median age 57 years) of BP associated with anti- TNFα have been reported. In most cases, discontinuation of drug and corticosteroid administration subsided the disease's progress. Among TNFα inhibitors Etanercept (17.6 %) has the minimum number of case reports as compared with Adalimumab (58.8%) and Infliximab (23.5%). The duration between drug initiation and clinical presentation ranges from 3 days to 209 weeks. Out of these 17 patients, 5 were suffering from psoriasis before BP emergence [10].

Another study investigating biologic drugs-induced BP in psoriasis patients suggests that most of the reported cases were assessed as "probable" consistently in both the Naranjo scale and the Karch-Lasagna algorithm [11].

There is a report about Etanercept-induced BP in a 63-year-old woman with recalcitrant psoriasis who had treatment failure with methotrexate and phototherapy. Her clinical presentations were initiated after two months of treatment with Etanercept (25 mg twice weekly). After one month the patient was switched to Adalimumab resulting in an acceptable clinical response [12].

Moreover, there is a report regarding BP induction in a 79-year-old white woman with psoriasis 3 days after Etanercept (25 mg) initiation. She has a successful treatment with Dapsone [13].

It has been suggested that the levels of TNFα in serum and blister fluid of patients with bullous autoimmune disorders increased. Amazingly there are reports about the therapeutic role of Etanercept in pemphigoid. A study by Sacher etal. Suggest a rapid response to Etanercept in a 72-year-old woman with cicatricial pemphigoid who has a therapeutic failure with Mycophenolate mofetil, Azathioprine, and topical Cyclosporine [14].

Another study showed the therapeutic role of Etanercept in a 64-year-old man with concurrent psoriasis and BP. It has been reported that after therapeutic failure with Mycophenolate mofetil, prednisone was started and Etanercept (25 mg weekly) was administered during corticosteroid taper down. Although during prednisone taper down the patient start to develop new blisters, after increasing the Etanercept dose (50 mg twice weekly) both psoriasis and BP were completely controlled even after corticosteroid discontinuation [7].

Two more cases of successful treatment of BP with Etanercept exist in psoriatic patients after treatment failure with conventional treatments including Cyclosporine, methotrexate, corticosteroid, and phototherapy [10].

Several hypotheses exist regarding TNFα inhibitors induced BP including apoptosis-induced autoantibody formation, unbalanced cytotoxic T-cell response-induced autoantibody production, and antigenic role of TNFα blockers which bind to BMZ and trigger further immune responses. Autoantibody formation leads to the activation of the inflammatory cascade responsible for clinical symptoms. An increase in TNFα level is a part of the inflammatory cascade which induces secretion of helper T cell (Th)1 associated cytokines. This might be the rationale behind therapeutic reports regarding TNFα inhibitors in BP. TNFα can drive eosinophils to secrete either Th1 or Th2 cytokines, depending on the chemokine profile of the microenvironment. Thus, an individual's unique inflammatory state may affect the downstream consequences of TNFα inhibition and can explain the ability of anti-TNFα agents to both treat and promote BP [10-15].

The clinical features of blisters in this case were consistent with LABD. However, the result of biopsy suggests BP. Additionally, the lack of linear deposition of IgA at the dermo-epidermal junction, which is a mandatory diagnostic criterion for LABD, ruled out the disease. Like BP, LABD may be associated with autoimmune diseases (e.g. psoriasis) and TNFα inhibitors may both induce and treat the disease [16,17].

In this study, the calculated Naranjo scale score was 4 for Etanercept and 3 for Ondansetron suggesting a possible adverse drug reaction for both agents. Although a direct drug-related effect is possible in this case, the predisposing role of psoriasis should not be ignored. On the other hand, the relationship between the onset or offset of the disease and the drug administration schedule should not be considered. As mentioned, the primary itchy erythematous papules develop at the site of the Ondansetron injection one month before admission, but we didn't find any previous reports regarding Ondansetron-associated BP. Moreover, we cannot ethically re-challenge either Etanercept or Ondansetron for identifying causal agents.

Despite two previous cases of Etanercept-associated BP in psoriatic patients which has 63 and 71-year-olds we describe

a 25-year-old woman. As mentioned, similar to this case one of these cases was successfully treated with Adalimumab, as another TNFα inhibitor. Our patient's complete therapeutic response before admission during treatment with Adalimumab and 6 months follow-up after discharge might weaken the probability of drug reaction with Etanercept. On the other hand, as a hypothesis for the probable causal role of Etanercept and the therapeutic role of Adalimumab, it can be considered that although both agents work through TNFα, Adalimumab is a neutralizing antibody while Etanercept is a fusion protein of extracellular ligand binding domain of the TNFα receptor. Close monitoring of skin conditions is highly advisable in patients receiving biologic therapies for psoriasis. Further studies are required to fully distinguish between the drug and psoriasis-induced BP.

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References

1. Murrell DF, Ramirez-Quizon M. Management and prognosis of bullous pemphigoid. UpToDate, Waltham, MA. https://www.uptodate. com/contents/management-and-prognosis-of-bullous-pemphigoid. 2014.
2. Miyamoto D, Santi CG, Aoki V, Maruta CW. Bullous pemphigoid. Anais brasileiros de dermatologia. 2019; 94: 133-46.
3. Bağcı IS, Horváth ON, Ruzicka T, Sárdy M. Bullous pemphigoid. Autoimmunity reviews. 2017; 16: 445-55.
4. Bernard P, Antonicelli F. Bullous pemphigoid: A review of its diagnosis, associations and treatment. American journal of clinical dermatology. 2017; 18: 513-28.
5. Pecoraro V, De Santis E, Melegari A, Trenti T. The impact of immunogenicity of TNFα inhibitors in autoimmune inflammatory disease. A systematic review and meta-analysis. Autoimmunity reviews. 2017; 16: 564-75.
6. Stone JH. Tumor necrosis factor-alpha inhibitors: Induction of antibodies, autoantibodies, and autoimmune diseases. UpToDate®, Version. 2008; 16: 1-9.
7. Yamauchi PS, Lowe NJ, Gindi V. Treatment of coexisting bullous pemphigoid and psoriasis with the tumor necrosis factor antagonist etanercept. Journal of the American Academy of Dermatology. 2006; 54: S121-2.
8. Kridin K, Ludwig RJ, Schonmann Y, Damiani G, Cohen AD. The bidirectional association between bullous pemphigoid and psoriasis: a population-based cohort study. Frontiers in Medicine. 2020; 7: 511.
9. Wilczek A, Sticherling M. Concomitant psoriasis and bullous pemphigoid: coincidence or pathogenic relationship?. International journal of dermatology. 2006; 45: 1353-7.
10. Zhang J, Wang SH, Zuo YG. Paradoxical phenomena of bullous pemphigoid induced and treated by identical biologics. Frontiers in Immunology. 2022; 13.
11. Husein-ElAhmed H, Steinhoff M. Bullous pemphigoid induced by biologic drugs in psoriasis: A systematic review. Journal of Dermatological Treatment. 2022; 33: 2886-93.
12. Kluk J, Goulding JM, Bhat J, Finch TM. Drug-induced bullous pemphigoid: Cases triggered by intravenous iodine and etanercept. Clinical and experimental dermatology. 2011; 36: 871-3.
13. 13-Wilmer EN, Becker N, Chen A, Kroumpouzos G. Etanercept-induced generalization of chronic, localized, anogenital bullous pemphigoid in a psoriatic patient. JAAD Case Reports. 2016; 2: 25-7.
14. Sacher C, Rubbert A, König C, Scharffetter-Kochanek K, Krieg T, et al. Treatment of recalcitrant cicatricial pemphigoid with the tumor necrosis factor α antagonist etanercept. Journal of the American Academy of Dermatology. 2002; 46: 113-5.
15. 15-Wilmer EN, Becker N, Chen A, Kroumpouzos G. Etanercept-induced generalization of chronic, localized, anogenital bullous pemphigoid in a psoriatic patient. JAAD Case Reports. 2016; 2: 25-7.
16. 16-Kwinta BD, Queen D, Husain S, Gallitano SM. Drug-Induced Linear IgA Bullous Dermatosis Mimicking Stevens-Johnson Syndrome Treated with Etanercept: A Case Report. The American Journal of Dermatopathology. 2023; 45: 189-91.
17. 17-Lammer J, Hein R, Roenneberg S, Biedermann T, Volz T. Drug-induced linear IgA bullous dermatosis: a case report and review of the literature. Acta Dermato Venereologica. 2019; 99: 508-15.