



## Valsartan/Hydrochlorothiazide Induced Pemphigus Foliaceus

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### Introduction

The term pemphigus refers to a group of autoimmune intraepidermal blistering diseases of skin and mucous membranes in which there is loss of adhesion between keratinocytes, following disruption of desmosomes, as a consequence of autoantibody binding to various antigens on the cell surface. Drug-induced pemphigus mimics idiopathic pemphigus clinically, histopathologically and immunologically. Exogenous factors as burns, UV radiation and X-rays can be involved in the development of pemphigus. Other factors as drug intake (thiol drugs or SH drugs, phenol drugs and nonthiolnonphenol drugs) are involved in inducing or triggering pemphigus outbreak, frequently resembling pemphigus foliaceus (PF) [1-4]. Antihypertensives have been reported to cause pemphigus vulgaris or pemphigus foliaceus [5]. We report a case of valsartan/hydrochlorothiazide- induced pemphigus foliaceus

### Case Report

A 70-year-old man with personal history of NSAIDs allergy, asthma, endocarditis, hypercholesterolemia, hyperuricemia and hypertension presented to us with a skin eruption. He has not family history of autoimmune diseases. His antihypertensive medication regimen included enalapril that was stopped because of cough and he was started to be treated with oral valsartan 160 mg plus hydrochlorothiazide during the 12 month period before he presented to us with lesions on the scalp an itchy skin rash. Dermatological examination revealed erythematous, scaly crusted plaques and erosions over the face and on the chest, back and shoulders (Figure 1). Mucosal lesions were not observed. Skin biopsy showed eosinophilic spongiosis of the epidermis and subcorneal blistering with acantholysis at the upper epidermis (Figure 2). The histopathologic examination was consistent with PF. Direct immunofluorescence revealed intercellular staining for IgG and C3 at the upper epidermis (Figure 3). Laboratory investigations showed eosinophilia. Renal and liver functions test, serum levels of complements C3 C4 and antinuclear antibodies revealed no abnormalities. ELISAs detected antiDsg1 antibodies (index 8.55) but not anti Dsg-3. IFN gamma release test nor drug-induced lymphocyte stimulation test were not available. Pemphigus foliaceus was diagnosed. Treatment with oral prednisone 30 mg daily plus azathioprine 100 mg (as a glucocorticoid -sparing agent) was started and valsartan was discontinued, resulting in gradual improvement. Skin lesions recurred after valsartan was reintroduced by cardiologist 6 month later.

### Discussion

Valsartan is an angiotensin II receptor blocker (ARB), a newer class of antihypertensives. Rarely some skin condition such as angioedema, urticarial, photosensitive rash, lichenoid eruption, pseudolymphomatous eruption and bullous pemphigoid, induced by valsartan have been



Figure 1: Erythematous an scaly crusted plaques on her back.

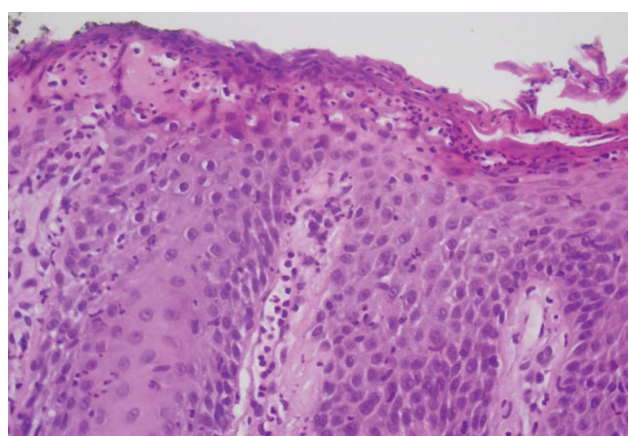
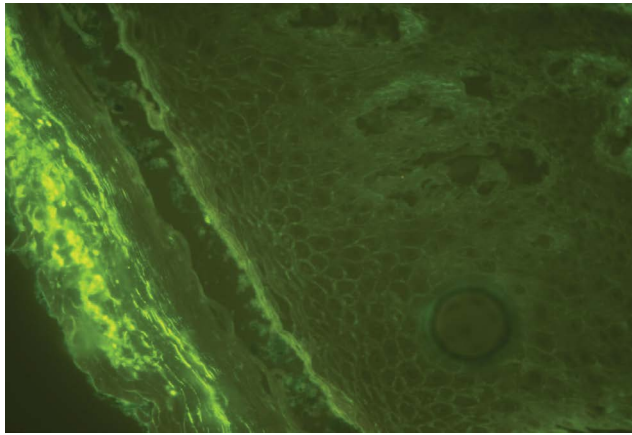


Figure 2: Subcorneal blister formation and acantholytic keratinocytes. Eosinophilic spongiosis of the epidermis.



**Figure 3:** Direct immunofluorescence results for IgG.

reported [6-13]. ARBs or sartans, widely prescribed as a substitute of angiotensin-converting enzyme inhibitors (ACEi), were reported as possible triggers of PF in patients treated with candesartan and telmisartan, losartan and valsartan [5,14].

Pemphigus foliaceus is a rare autoimmune blistering disease in which the binding of autoantibodies to desmoglein 1 (Dsg1) results in acantholysis (loss of intercellular adhesion between keratinocytes) and development of subcorneal blisters. Clinical findings include superficial bullae, and more often erosive lesions leaving areas of crusting over an erythematous base, localized on the chest, back, shoulders, face and scalp. Nikolsky' sign (blistering of the skin as a response to slight rubbing or pressure) is usually positive. The diagnosis is based on clinical picture, histopathological findings and presence of autoantibodies detected by direct or indirect immunofluorescence [15]. The most common variant of drug-induced pemphigus is pemphigus foliaceus (PF) with anti desmoglein 1 auto antibodies, caused by thiol containing drugs [3] although pemphigus vulgaris (PV) has also been described. Associated drugs most commonly offenders are penicillamin, captopril and penicillins, and rarely pyritinol, thioprolone, rifampicin, cephalosporins, gold, methimazole, levodopa, opioids phenobarbital, cytokins, piroxicam, aspirin, nifedipine, propranolol and angiotensin converting enzyme inhibitors other than captopril. Lesions may develop from 1 day to 6 months after administration of the culprit drug [16].

Yoshimura et al. [3] found that 8 of 17 patients with drug-induced pemphigus showed foliaceus-like appearance and responsible drugs were thiol-containing drugs in 16 (bucillamine, d-penicillamine, cetapril, thiopronine and captopril).

Feng et al. [17] studied 6 cases of drug induced pemphigus. Five out of 6 cases of drug induced pemphigus presented as pemphigus foliaceus, were sensitive to low doses of corticosteroids and had good prognosis.

Criteria for diagnosis of drug-induced pemphigus include a history of exacerbation while using the same drug in addition to blistering, acantholysis and positive direct IF on the skin showing cell surface staining of IgG, C3 deposition [17].

The *in vitro* IFN-gamma release from the patient's lymphocytes test has been shown to be of diagnostic value in drug-induced skin reactions [2]. 32-2B immunolabeling is useful for diagnosing drug-induced pemphigus and a normal pattern is an indicator of a good prognosis [18].

Most of patients go into remission upon withdrawal of the offending drug but some patients must be treated with systemic corticosteroids, other immunosuppressants or agents as antimalarial drugs, rituximab, mycophenolate mofetil intravenous immunoglobulin.

## Conclusion

Many drugs can induce pemphigus. A drug origin should be

considered in every new patient with pemphigus and in every flare-up of the disease. The diagnosis of drug-induced pemphigus is challenging. The interval between the administration of drug and the onset of cutaneous manifestations is not well defined. The majority of the patients with drug-induced pemphigus show pemphigus foliaceus-like clinical and histopathological features with anti-Dsg 1 autoantibodies. A meticulous clinical history can detect the presence of facilitating or triggering factors. A prolonged latency period between the administration of the drug and the onset of the cutaneous manifestations may occur. Discontinuing the offending drug reduce the need for medical treatment.

## References

1. Ruocco V, Ruocco E, Lo Schiavo A, Brunetti G, Guerrero LP, et al. (2013) Pemphigus: etiology, pathogenesis, and inducing or triggering factors: facts and controversies. *Clin Dermatol* 31: 374-381.
2. Brenner S, Goldberg I (2011) Drug-induced pemphigus. *Clin Dermatol* 29: 455-457.
3. Yoshimura K, Ishii N, Hamada T, Abe T, Ono F, et al. (2014) Clinical and immunological profiles in 17 Japanese patients with drug-induced pemphigus studied at Kurume University. *Br J Dermatol* 171: 544-553.
4. Landau M, Brenner S (1997) Histopathologic findings in drug-induced pemphigus. *Am J Dermatopathol* 19: 411-414.
5. Pietkiewicz P, Gornowicz-Porowska J, Bowszyc-Dmochowska M, Dmochowski M1 (2015) A retrospective study of antihypertensives in pemphigus: a still uncharted odyssey particularly between thiols, amides and phenols. *Arch Med Sci* 11: 1021-1027.
6. Kalra A, Cooley, Palaniswamy C, Kalra A, Zanotti-Cavazzoni SL (2012) Valsartan-induced angioedema in a patient on Angiotensin-Converting-Enzyme Inhibitor for years: Case report and literature review. *Am J Ther* 19: 189-192.
7. Irons BK, Kumar A (2003) Valsartan-induced angioedema. *Ann Pharmacother* 37: 1024-1027.
8. de la Serna Higuera C (2000) [Angioedema and urticarial reaction induced by valsartan]. *Med Clin (Barc)* 114: 599.
9. Martínez Alonso JC, Domínguez Ortega FJ, Méndez Alcalde J, Fuentes Gonzalo MJ (2003) Angioedema due to valsartan. *Allergy* 58: 367.
10. Frye CB, Pettigrew TJ (1998) Angioedema and photosensitive rash induced by valsartan. *Pharmacotherapy* 18: 866-868.
11. Gencoglan G, Ceylan C, Kazandi AC (2009) Linear lichenoid drug eruption induced by valsartan. *Clin Exp Dermatol* 34: e334-335.
12. Sawada Y, Yoshiki R, Kawakami C, Fukamachi S, Sugita K, et al. (2010) Valsartan-induced drug eruption followed by CD30+ pseudolymphomatous eruption. *Acta Derm Venereol* 90: 521-522.
13. Femiano F (2003) [Mucocutaneous bullous pemphigoid induced by valsartan. A clinical case]. *Minerva Stomatol* 52: 187-190.
14. Bae YI, Yun SJ, Lee SC, Park GT, Lee JB (2008) Pemphigus foliaceus induced by an angiotensin II receptor blocker. *Clin Exp Dermatol* 33: 721-723.
15. James KA, Culton DA, Diaz LA (2011) Diagnosis and clinical features of pemphigus foliaceus. *Dermatol Clin* 29: 405-412, viii.
16. Ahronowitz I, Fox L (2014) Severe drug-induced dermatoses. *Semin Cutan Med Surg* 33: 49-58.
17. Feng S, Zhou W, Zhang J, Jin P (2011) Analysis of 6 cases of drug-induced pemphigus. *Eur J Dermatol* 21: 696-699.
18. Maruani A, Machet MC, Carlotti A, Giraudeau B, Vaillant L, et al. (2008) Immunostaining with antibodies to desmoglein provides the diagnosis of drug-induced pemphigus and allows prediction of outcome. *Am J Clin Pathol* 130: 369-374.