Psoriasis and Bullous Pemphigoid Developing Simultaneously During Systemic Administration with Bisoprolol and Losartan

Kordeva S\textsuperscript{1}, Broshtilova V\textsuperscript{2}, Tchernev G\textsuperscript{1,3}

\textsuperscript{1}Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606 Sofia, Bulgaria
\textsuperscript{2}Department of dermatology and venereology, military medical academy, 1606, sofia, Bulgaria
\textsuperscript{3}*Department of Dermatology and Venereology, Medical Institute of Ministry of Interior, General Skobelev 79, 1606, Sofia, Bulgaria

Abstract
Psoriasis and bullous pemphigoid are both chronic inflammatory skin disorders, involving abnormal immune responses. Their coexistence is often observed in the literature in the context of secondary development following an initial inflammatory process. In the majority of cases, the development of psoriasis seems to occur before the onset of bullous pemphigoid. While psoriasis is associated with autoimmune bullous diseases, it’s important to note that not every individual with psoriasis will develop bullous pemphigoid. Therefore the pathogenetic mechanism behind this association remains rather a mystery.

Several case reports/studies have been published describing the subsequent development of either psoriasis or bullous pemphigoid following initial monotherapy with beta blockers, sartans, or other drug class medications (which will not be mentioned in our case report as they are not relevant to the presented data).

We believe that our case is the first documented example of polymedicamentous development of 2 skin diseases within the intake of 2 antihypertensive drugs heterogeneous in class and action.

We present a 78-year-old female with plaque psoriasis followed shortly thereafter by a bullous pemphigoid after a 10-year period of antihypertensive therapy with bisoprolol and losartan. We believe that the cumulative effect of both medications may have contributed to the coexistence of these skin disorders.

Following the discontinuation of the initial antihypertensive therapy with bisoprolol and losartan and substituting it verapamil and moxonidine, along with the initiation of methotrexate and folic acid, the patient showed significant improvement.

Key words: psoriasis; bullous pemphigoid; drug-induced; bisoprolol; losartan

Introduction
Psoriasis is a frequently encountered chronic inflammatory skin condition, affecting 1-3% of the world’s population (1). Approximately one-third of the patients endure severe or moderate manifestations of the condition, with the moderate type affecting more than 10% of the body’s surface area (1). The most prevalent form of the condition is plaque psoriasis, affecting over 80% of patients (1). Spontaneous resolution is uncommon and the plaques generally remain either static or slowly enlarging (1).

Risk factors, such as smoking, alcohol consumption, dietary habits, infections, stress, and medications, have been linked to the development of the condition (2). Among the most frequently implicated drugs are the beta-blockers, non-steroidal anti-inflammatory drugs, lithium and synthetic antimalarials (3). Losartan, an angiotensin receptor blocker, was listed as probable, following the Naranjo adverse drug reaction probability scale score, among medications associated with triggering psoriasis (3).

Autoimmune bullous disorders represent a significant risk of morbidity and mortality, especially among the elderly population (4). Considering the aging demographics, there is an expected rise in the incidence of these conditions, particularly bullous pemphigoid (BP) (4). BP is a chronic skin disorder that is characterized by the development of tense blisters on erythematous or unaffected skin; however, there are cases where it can manifest with urticarial, papular or eczema-like eruptions (5).

Several medications have been identified as triggering factors for the development of bullous pemphigoid – furosemide, penicillins, ibuprofen and rarely beta-blockers (6). Both bullous pemphigoid
and beta-blockers are commonly encountered and prescribed among the elderly, therefore the dermatologists should consider beta-blockers as potential contributors to the development of this condition (6).

The coexistence of these two skin conditions – psoriasis and autoimmune bullous pemphigoid, has been well documented (7). In most cases the development of psoriasis seems to occur before the onset of bullous pemphigoid (5). Despite extensive searches though the medical literature, the precise reason for the association between these two diseases remains somewhat uncertain (8).

We present a 78-year-old female with newly discovered plaque psoriasis and bullous pemphigoid after long-term use of bisoprolol and losartan. The possible occurrence of the psoriatic lesions was from about one year prior to the consultation, while the bullous pemphigoid – one month prior to the consultation. Several biopsies were conducted to confirm both of the conditions. Before starting initial therapy for the management of these conditions, several consultations and tests were conducted.

HCV RNA was not detected, and the initial corticosteroid therapy with methylprednisolone was replaced with methotrexate and folic acid. A change in the medication regimen was implemented, substituting bisoprolol and losartan therapy with verapamil and moxonidine. Shortly after initiating the therapy and changing the antihypertensive regimen, the patient began to show gradual improvement.

Despite the uncertain nature of their connection, our case report will not primarily delve into the pathogenetic mechanisms of each disease (psoriasis and bullous pemphigoid), but rather on the common triggering factor they may share – the potential/possible/actual development following long-term oral intake of beta blockers (bisoprolol) and sartans (losartan). Drug-induced psoriasis and drug-induced bullous pemphigoid will be briefly reviewed and discussed, particularly in terms of their coexistence, polymorbidity and polymedication.

**Case report**

A 78-year-old female presented to the dermatology clinic with primary complaints of multiple solitary reddened lesions scattered over the whole body and scalp, which had been present for one month. The first appearance of a plaque located on the thigh area was noted one year ago.

She reported allergies to linden and certain anesthetics. Her medical history included duodenal ulcer, appendectomy in childhood, and arterial hypertension for 10 years. The patient is on systemic therapy with bisoprolol fumarate 10 mg administrated twice daily at morning and evening for the past 10 years prior to the consultation; losartan potassium 50 mg once daily in the morning administrated for 10 years prior to the consultation; vinpocetine 10 mg once in the morning; and pantoprazole 20 mg once in the morning.

The dermatological examination showed single rounded erosions on the skin of the whole body, mainly the gluteal, back and finger areas, with areas of hyperkeratosis and blister erosions (Fig.1a-e).

Additionally, extensive, infiltrative erythematous plaques with clear borders are noted in the intertriginous areas (Figure.2a-d). Under the breast area, these plaques are covered with yellow-greenish exudates (Figure.2a).

Routine blood tests were conducted, resulting without abnormalities. A contrast-enhanced CT scan of the thorax, abdomen, and pelvis was ordered. The results showed signs of emphysema; bilateral lung nodules; endobronchial lesion in the right lower lobe; bronchopulmonary, mediastinal, and pelvic lymphadenomagaly; cholelithiasis; adrenal nodules possibly indicative of adenomas; and kidney cysts.

Three biopsies were conducted, due to suspected bullous dermatosis. One of the biopsies confirmed bullous pemphigoid. The histological finding revealed an extensive parakeratotic crust covering superficial epidermal necrosis, accompanied by uniform acanthosis and eosinophilic exocytosis. Additionally, there was marked edema in the papillary dermis with focal subepidermal desquamation, as well as a moderate to dense perivascular mixed inflammatory infiltrate with abundant eosinophils in the upper dermal segment. Systemic treatment with intravenous methylprednisolone 30 mg and oral famotidine 40 mg/day was started, leading to observed improvement. The patient was advised to continue corticosteroid therapy at home following a prescribed dose reduction of 2 mg per week. A follow-up examination and paraclinical assessment were scheduled after 14 days.

Intertriginous erythema suggested a potential mycotic infection beneath the breast area. To address this, treatment with intravenous fluconazole 200 mg and topical application of clotrimazole 1 % cream once daily under the breast area was initiated. Additionally, a biopsy was taken from the same area. The histological findings were indicative for psoriasis. The psoriatic lesions were treated with topical application of calcipotriol/betamethasone gel once daily under the breast area for 14 days along with betamethasone/salicylic acid 0.5 mg/30 g ointment applied twice daily externally on the plaques. The patient experienced significant improvement with the psoriatic treatment.

To exclude paraneoplasia, a chest X-ray and abdominal ultrasound were performed, revealing abnormalities. Subsequent consultations were arranged with a gynecologist, gastroenterologist, and pulmonologist. The gynecological evaluation found no pathological changes, but a vaginal swab indicated contamination with Pseudomonas aeruginosa. As a result, a recommendation was made for a home treatment with one vaginal globule of nifuratel-nystatin and an outpatient consultation with a gynecologist, and initiation of systemic therapy with methotrexate. The proposed regimen consisted of methotrexate 10 mg administrated once weekly, divided into two doses, followed by administration of folic acid 400 mg twice daily for the remaining six days of the treatment.

**Case report**

A 78-year-old female presented to the dermatology clinic with primary complaints of multiple solitary reddened lesions scattered over the whole body and scalp, which had been present for one month. The first appearance of a plaque located on the thigh area was noted one year ago.

She reported allergies to linden and certain anesthetics. Her medical history included duodenal ulcer, appendectomy in childhood, and arterial hypertension for 10 years. The patient is on systemic therapy with bisoprolol fumarate 10 mg administrated twice daily at morning and evening for the past 10 years prior to the consultation; losartan potassium 50 mg once daily in the morning administrated for 10 years prior to the consultation; vinpocetine 10 mg once in the morning; and pantoprazole 20 mg once in the morning.

The dermatological examination showed single rounded erosions on the skin of the whole body, mainly the gluteal, back and finger areas, with areas of hyperkeratosis and blister erosions (Fig.1a-e).
week. A significant improvement was observed (Figure.1f), (Figure.2e,f).

The patient’s dermatological conditions could be triggered by her arterial hypertension’s medications, including bisoprolol fumarate and losartan potassium. Therefore, a regimen change was recommended, with verapamil hydrochloride 120 mg half a tablet a day and moxonidine 0.2 mg twice daily.
Psoriasis and Bullous Pemphigoid Developing Simultaneously During Systemic Administration with Bisoprolol and Losartan

Figure: 3a-c: Histology panel
A: Dermal hypersensitivity reaction x 100 x HE
B: Subepidermal clefting with moderate mixed inflammatory infiltrate, abundant of eosinophils in the papillary dermis x 400 x HE
C: Psoriasis vulgaris x HE x100

Discussion

Psoriasis is an immune-mediated chronic inflammatory skin disorder, characterized by a multifaceted etiology involving a complex interaction between genetic predisposition and environmental factors (9). Medications associated with the development of psoriasis are well-documented in the literature – antihypertensive drugs ([hydroxy]chloroquine), interferons, imiquimod, terbinafine, tumor necrosis factor-alpha antagonists, anti-programmed cell death protein 1 immune checkpoint inhibitors, beta-blockers (9) and sartans (10).

Drug-related psoriasis may closely resemble the pathological features of classical “non-drug-related” types of psoriasis (9). Moreover, some medications may have a significantly long latency period between the administration and the onset of the condition (9). To better differentiate drug related psoriasis, we can employ the Naranjo adverse drug reaction probability scale (9),(11). Drug-provoked psoriasis is a term used in the literature to collectively refer to both drug-induced and drug-aggravated psoriasis (12). Since the progression ceased upon discontinuation of the suspected medication (bisoprolol or/and losartan) in our patient, the more appropriate term to use would be drug-induced. Beta-blockers are described in the existing literature as major triggering or aggravating factors for the psoriasis development (13),(14).

Sartan-induced psoriasis is described as a triggering factor for a de novo manifestation of the condition (15). Interestingly, in the patients observed in the article, skin manifestations developed within 6 weeks and 9 months after the initiation of the sartan therapy, regardless of whether they had a family history of psoriasis (15). In our case report, it is possible that the development of the psoriatic lesions could be due to the losartan therapy. However, the 10-year duration of the antihypertensive medications administration leads to three hypotheses: the psoriatic lesions could be due 1) to the losartan therapy, but developed relatively late; 2) to the bisoprolol intake alone; or 3) it can be the result of the possible cumulative effect of both medications. Either way, terminating the medications led to a drastic improvement in the patient’s clinical condition.

Exacerbation of the disease has been associated with colonization of the skin and/or gut with Staphylococcus aureus, Malassezia, and Candida albicans (16). The current role of viruses such as papillomaviruses, endogenous retroviruses and HIV present in lesional skin is unknown (16). While exacerbation of the condition is possible, induction of the disease by microorganisms seems unlikely.

Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disease, characterized by generalized pruritic urticarial plaques and tense subepidermal blisters, predominantly observed in the elderly population (17). Understanding both predisposing and different triggering factors can significantly contribute to the understanding of the pathogenesis of the disease (17). Some of the drugs associated in the literature with BP onset are antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, anti-tumor necrosis factor (TNF)-alpha, immune checkpoint inhibitors targeting programmed cell death receptor 1 (PD-1) and its ligand (PD-L1), dipeptidyl peptidase 4 inhibitors (DPP-4i), beta blockers (atenolol, nadolol, practolol) and sartans (losartan) (17).

Given the polymorbid nature of most elderly patients, it’s important to consider the possibility that the condition may not be induced by a single medication but rather by the cumulative effect of multiple “triggering” medications.

The development of drug-induced bullous pemphigoid is associated with complex mechanisms, one of which is the molecular mimicry, in which the medications are perceived by the body as microbial agents (17),(18). Another theory, known as the “two step” theory, suggests that when two different drugs with similar molecular structures interact with the immune system, they may act as the primary and secondary “hits”, triggering and amplifying an immune response (17), (18).

Psoriasis and bullous pemphigoid are two clinically well-defined chronic inflammatory skin disorders, which can rarely co-exist in a patient (19). The precise pathogenic origin of the coexistence remains to be fully understood (19). Some authors suggest a possible connection between the autoimmune mechanism triggering bullous pemphigoid lesions and the ultraviolet light therapy, topical corticosteroids, or the inflammatory process inherent in psoriasis (19). Another hypothesis is that chronic inflammation in the dermo-epidermal junction may lead to exposure of antigens to autoreactive T cells, potentially triggering autoimmune blistering disease (20).

The management of coexisting bullous pemphigoid and psoriasis is achieved by discontinuing the causative drug agent and employing topical corticosteroids (21). Moderate to severe cases are managed typically with systemic corticosteroids and methotrexate (21). However, the use of biologics therapies for
Psoriasis and Bullous Pemphigoid Developing Simultaneously During Systemic Administration with Bisoprolol and Losartan

psoriasis, such as ustekinumab, secukinumab, and ixekizumab with coexisting bullous pemphigoid and psoriasis can result in the onset of new cases of BP (21). The clearance of both psoriatic and bullous lesions with acitretin suggested a direct connection between the psoriatic inflammatory process and the evolution of bullous lesions (22).

Despite the single case reports of patients with psoriasis or bullous pemphigoid, there appears to be no available data on their coexistence following polypharmacy therapy with bisoprolol and losartan. The discontinuation of the current therapy and switching to other drug classes appeared to be sufficient for the patient’s improvement, indicating that the bullous pemphigoid may have been triggered by 1) the inflammation inherent in psoriasis, by 2) mono- or polypharmacy with bisoprolol and/or losartan, or 3) by both factors. Either way, the concept of polypharmacy-induced skin-related multisite disease development, doesn’t seem entirely impossible.

Conclusion

We cannot definitively attribute the development of both conditions to any specific medication; we can only make conclusions based on the existing medical literature and the observed clinicopathological correlations presented in our patient. We believe that over the course of a 10-year antihypertensive therapy, the cumulative effect of both bisoprolol and losartan lead to the subsequent development of plaque psoriasis, followed shortly thereafter by bullous pemphigoid. After thorough review of the existing literature, we believe this represents the first documented case report of drug-induced psoriasis and bullous pemphigoid coexisting subsequent to polypharmacy with bisoprolol and losartan.

The purpose of this report is to raise awareness among future colleagues regarding the importance of careful consideration when prescribing certain drugs, emphasizing the potential/actual risks for adverse drug events and the importance of knowing how to manage them effectively if they do occur.

References

3. Lamba, Gurpreet MD; Palaniswamy, Chandrasekar MD*; Singh, Tarunjit MD; Shah, Dhaval MD; Lal, Sonia MD; Vinnakota, Ravi MD. Et.al Psoriasis Induced by Losartan Therapy: A Case Report and Review of the Literature. American Journal of Therapeutics 18(3): p e78-e80, May 2011. | doi: 10.1097/MJT.0b013e3181bc6c02