Lisinopril-Induced Pemphigus Foliaceus in a Patient with Diabetes Mellitus and Kaposi-Juliusberg Varicelliform Eruption

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Abstract

Drugs have often been implicated as the cause of pemphigus. Lisinopril is a drug of the angiotensin-converting enzyme inhibitor class primarily used in the treatment of hypertension, congestive heart failure, heart attacks, and also in preventing renal and retinal complications of diabetes mellitus. Various side-effects have been described in the English medical literature related to lisinopril, but only one case with pemphigus foliaceus as an adverse reaction to lisinopril. To the best of our knowledge, we present the second case of lisinopril-induced pemphigus foliaceus complicated with Kaposi-Juliusberg varicelliform eruption in a patient diabetes mellitus type II.

A 60-year-old man presented with diffuse erythema on the face, trunk and extremities. Disseminated erosions, 2-5 mm in diameter, and umbilicated vesicles were present. Erosions with remnants of the blister roof were partially found on the trunk. Semiannular erosions were present. On the posterior part of the trunk (paravertebral and vertebral) there were infiltrated, partially grouped, sharply delineated yellowish-reddish plaques, up to 2 cm in diameter. Direct and indirect immunofluorescence test as well as histological analysis revealed a drug-induced pemphigus foliaceus. After treatment of Kaposi-Juliusberg eruption and impetiginization, lisinopril was discontinued. Rapid involution of the skin lesions, was observed. Since, only minor skin lesions still persisted after 6 months of follow-up and treatment, the diagnosis of drug-induced pemphigus foliaceus was established.

It usually takes 1 - 6 months for angiotensin-converting enzyme inhibitors to induce pemphigus. All drugs taken by the patient, including homeopathic agents, over-the-counter drugs, and even medications that were discontinued should be taken into consideration. Medical history taking should be repeated in cases where there is no response to therapy.

Key words

Porokeratosis; Dermoscopy; Cryotherapy; Treatment Outcome
the active metabolite of enalapril, which contains an amide group (3). Lisinopril is a drug of the angiotensin-converting enzyme (ACE) inhibitor class primarily used in the treatment of hypertension, congestive heart failure, heart attacks, and also in preventing renal and retinal complications of diabetes mellitus (4). Various side-effects have been described in the English medical literature, related to lisinopril (3,5,6), but only one case with pemphigus foliaceus as an adverse reaction to lisinopril (3).

We present the second case of lisinopril-induced pemphigus foliaceus complicated with Kaposi-Juliusberg varicelliform eruption in a patient with diabetes mellitus type II.

Case report

This is a case report of a 60-year-old man from the surroundings of Trstenik, Serbia. On admission to our Clinic the patient was subfebrile, with diffuse erythema on his face, trunk and extremities. Also, disseminated erosions, 2-5 mm in diameter, and umbilicated vesicles were present. Erosions with remnants of the blister roof were found partially on the trunk. Semi-annular erosions were also present on the trunk. On the posterior part of the trunk (paravertebral and vertebral) there were infiltrated, partially grouped, sharply delineated yellowish-reddish plaques, up to 2 cm in diameters. No mucosal lesions were detected.

Personal history revealed a ten-year history of diabetes mellitus and a 2-year history of hypertension. Family history: both parents suffered from arterial hypertension; mother also suffered from diabetes mellitus and asthma. The patient observed the skin condition 1,5 years before admission, and claimed to be allergic to bisoprolol. The first skin lesions appeared in 2007, as erythema, scales and pruritus on the trunk, scalp and upper extremities. The patient was treated for atopic dermatitis with local therapy on occasional dermatological appointments. In September 2011, the patient’s skin condition worsened and he presented with high fever. He was admitted to the Dermatology Department and was treated for atopic erythroderma for 8 days with 100 mg of methylprednisolone daily followed by a gradual taper, antihistamine chlorpheniramine maleate tablets 2x25 mg regularly, and chlorpheniramine injections 20 mg/day if necessary. Also, procaine benzylpenicillin 1600 000 i.u. was administered. The patient’s standard therapy included metformin tablets 1000 mg/day for diabetes mellitus and lisinopril tablets 10 mg/day for arterial hypertension. Topical corticosteroid and emollient therapy were administered, too. Histology revealed parakeratosis, intact stratum granulosum, and chronic dermal inflammation. This was diagnosed as drug-induced generalized exfoliative dermatitis. The therapy was not changed, as pruritus and skin lesions gradually resolved, and the patient was afebrile. However, 5 days later, disseminated papulo-vesicular eruption appeared. The new lesions mostly involved the face, scalp and trunk and the eruption was accompanied by high fever. On discharge, the patient was recommended to receive metformin tablets 1000 mg/day, Aciclovir tablets 5x200 mg, and B complex vitamins.

Upon admission to our Clinic, the patient presented with erythroderma, umbilicated vesicles and rounded yellowish crusts, erosions with remnants of blister roofs, while some of erosions were semiannular (Figures 1a and 1b). On the proximal parts of the extremities and trunk there were some erythematous patches with scales (Figure 1a).

Laboratory tests revealed the following abnormal results: low erythrocyte count - 3.5 x 1012/L, low hemoglobin levels - 106 g/L, low serum iron level - 4.1 µmmol/L, slightly reduced total iron binding capacity - 44 µmmol/L, blood glucose levels highly elevated up to 27.4 mmol/L, HgbA1c was elevated. Other biochemical results including hepatogram, renogram, proteinogram, lactate dehydrogenase and creatine kinase were within normal ranges.

Immunology tests results: antistreptolysin O (ASO) titre was normal; serum IgE level was elevated - 725 IU/ml (normal range up to 100); antinuclear factor on Hep-2 cells and anti - SS-A (Ro) antibodies, were negative.

Virology tests: anti Herpes simplex virus type-1 immunoglobulin (Ig) G titer of 1: 640 showed four-fold decrease after one month; anti Herpes simplex virus type-2 immunoglobulin G titer was 1: 40 and remained unchanged.

Hormone tests: thyroid-stimulating hormone, free thyroxine and adrenocorticotropic hormone were within normal ranges.

Direct immunofluorescent test revealed IgG in the intercellular substance of epidermis. No IgA,
Figure 1a. The patient on admission: umbilicated vesicles, erosions and blister remnants on erythematous infiltrated skin

Figure 1b. The patient on admission: erosion with remnants of the blister roof, some semiannular in shape, umbilicated vesicles and erythroderma
IgM and complement component C3 deposits were observed, thus indicating a diagnosis of autoimmune pemphigus. Indirect immunofluorescence test was positive with a titer of 1 : 160. Histological tests revealed epidermal hyperkeratosis and acanthosis, whereas in the corneal layer subcorneal clefts were observed with acantholytic cells. Acantholysis was present focally in the stratum spinosum. Dermal blood vessels were surrounded by lymphocytes and eosinophils. Histology was consistent with pemphigus foliaceus (Figure 1c). The first therapy included aciclovir tablets 5x200 mg, antibiotics: (trimethoprim-sulfamethoxazole), metformin tablets 1000mg/day, and insulin (due to unsatisfactory glycemic control). Upon resolution of erosions and umbilicated vesicles, after 10 days, prednisone therapy 40 mg/day and azathioprine 150 mg/day were initiated with gastro- and osteoprotection. Local therapy included: antiseptic lotions and creams containing an antibiotic and a corticosteroid component.

Two weeks after admission, the patient developed new, small blisters on the trunk and erythematous, sharply demarcated plaques on the face, neck and trunk (Figures 2a and 2b). Subsequent histological specimens, taken from the face and trunk, revealed identical findings (Figure 2c). As this finding was consistent with drug-induced pemphigus foliaceus, lisinopril was discontinued. Hydrochlorothiazide 25 mg was introduced if necessary. Lisinopril was discontinued because based on the patient’s history, the skin condition dramatically worsened 6 months after lisinopril was introduced. The plaque lesions started resolving rapidly, no new blisters appeared, and after 2 weeks, the patient was dismissed from the hospital. At the 6-month follow-up, the patient presented with small plaques (up to 1 cm in diameter) with minimal infiltration. Indirect immunofluorescence test was positive, with a titer of 1 : 20. Thus, based on all previously mentioned, we established the diagnosis of a drug-induced pemphigus in a patient with diabetes mellitus and Kaposi-Juliusberg varicelliform eruption.

Discussion
Kaposi-Juliusberg varicelliform eruption or eczema herpeticum are well known to be associated with several chronic dermatoses including atopic dermatitis,
pemphigus foliaceus, seborrheic dermatitis, Darier disease and congenital ichthyosiform erythroderma (7). Some of the cases end up being fatal (7). To the best of our knowledge, this is the second published case of lisinopril-induced pemphigus foliaceus (3), and the first one with the abovementioned association.

According to different authors, there are three groups of chemical structures in drugs that can cause pemphigus: sulfhydryl radicals (thiol drugs or SH drugs) (8), phenol drugs (7), and non-thiol nonphenol drugs (2). Another classification divides drugs causing pemphigus into drugs with sulphydryl group, drugs containing an active amide group and non-thiol, non-amide drugs (9). Examples of sulfhydryl radical drugs include captopril, enalapril, penicillamine, and gold sodium thiomalate. Aspirin, rifampicin, levodopa, and heroin are examples of phenol drugs (8). Nonsterioidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, glibenclamide, and dipyrone are examples of non-thiol non-phenol drugs (8). More than 200 cases of drug-induced pemphigus have been reported, with penicillamine accounting for almost 50%. In patients who take penicillamine for longer than 6 months, it is estimated that 7% develop pemphigus (10).

Different mechanisms have been proposed in inducing acantholysis and they differ related to the used drug. Thiol drugs are capable of causing acantholytic changes in skin explants (11). The proposed mechanisms include: inhibition of enzymes that aggregate keratinocytes; activation of enzymes, such as plasminogen activator, which disaggregates keratinocytes; disturbance of cell adhesion by formation of thiol-cysteine bonds instead of cysteine-cysteine bonds, and formation of neoantigen by an immunological reaction. Pemphigus serum and captopril induce heat shock protein 70 and inducible nitric oxide synthase overexpression, thus, triggering apoptosis in human keratinocytes (12). Recently, captopril (ACE inhibitor containing thiol group) was found to modulate acetylcholinesterase in human keratinocytes, in vitro (13). Human keratinocytes synthesize and secrete non-neuronal acetylcholine, which acts as a local cell signaling molecule, regulating functions like proliferation, cell adhesion, motility, desmosomal cell contact, and glandular secretion (13). Captopril induces a strong acetylcholinesterase upregulation leading to acetylcholine degradation and
its reduced secretion. This suggests that acantholysis induced by ACE-inhibitors might be linked to altered levels of acetylcholine (13). Phenolic drugs were proposed to release cytokines from keratinocytes, such as tumor necrosis factor (TNF) alpha and interleukin (IL)-1 (14). It is known that they participate in the regulation and synthesis of complement and proteases like plasminogen activator, which take part in acantholysis (15). Calcium channel blockers may cause pemphigus, because calcium is necessary for the activity of enzymes, which play a role in keratogenesis; desmogleins are calcium dependant (11).

Up to now, the following ACE inhibitors were reported to induce pemphigus foliaceus: captopril (16), lisinopril (3), enalapril (17), and fosinopril (18). As a thiol containing ACE inhibitor, captopril was found to induce skin adverse changes (pemphigus, as well), whereas other ACE inhibitors were investigated related to this point in the last two decades. In 1992, enalapril was found to be a powerful in vitro acantholytic agent (non-thiol, but amide containing drug) (19). In 1999, in vivo enalapril-induced acantholysis was reported (20). In 2001, aggravation of a severe childhood pemphigus vulgaris by enalapril was described (21). Fosinopril has neither a thiol nor an amide component (3) and is unable to block the adhesion molecules in vivo like captopril, thus pointing to different mechanism in inducing acantholysis (22).

Historically, lisinopril was the third ACE inhibitor (after captopril and enalapril) and was introduced in the early 1990s. Lisinopril (C_{21}H_{35}N_{3}O_{7}) contains an amide group. It is a lysine derivative of enalaprilat, the active metabolite of enalapril (3, 23). According to world literature, one case of lisinopril-induced PF was described in a 66-year–old man (3). The diagnosis was established after skin biopsy and direct immunofluorescence. Indirect immunofluorescence was not performed. Unfortunately, the follow-up was limited to 3 weeks because the patient died of bronchopneumonia. Sera from patients with pemphigus foliaceus recognize epitopes of desmoglein-1. Rare cases of pemphigus foliaceus develop antibodies to desmoglein-3 or have both desmoglein-3 and desmoglein-1 antibodies. Patients with pemphigus vulgaris who have lesions limited to the mucous membranes have only desmoglein-3

Figure 2c. Histology of facial plaque lesions (see 2a). Subcorneal cleft with acantholytic (HE, x400).
antibodies, while patients with antibodies to both desmogleins usually develop widespread mucocutaneous lesions (24). Circulating and tissue-bound antibodies to desmoglein 1 and desmoglein 3 found in spontaneous pemphigus foliaceus and pemphigus vulgaris respectively, are also found in drug-induced pemphigus, like in our case, suggesting a similar molecular mechanism (3). Although most patients with drug-induced pemphigus have tissue-bound and/or low-titre circulating autoantibodies with the same antigenic specificity as do patients with idiopathic pemphigus, it has been reported that in the case of penicillamine-induced pemphigus, 10% do not have tissue-bound, and more than 30% do not have circulating autoantibodies (25).

According to international data on side effects of lisinopril (26) a total of 82,414 people reported side effects when taking lisinopril up to September 17th, 2012. Among them, 35 people (0.04%) had pemphigoid, and 11 people (0.01%) had pemphigus. One of the reported cases of pemphigus would be our patient. It took 6 - 12 months for lisinopril to induce pemphigoid (100% patients) and 1 - 6 months to induce pemphigus (100% patients). Female predominance has been observed for pemphigoid cases (67.65%) and male predominance in pemphigus cases (83.33%). Most patients were over 60 years of age: 100% in pemphigoid cases and 91.67% in pemphigus cases (26).

Anatomically, pemphigus lesions are predominant on the trunk. Normal skin explants taken from former pemphigus patients from different areas of their bodies (back and buttocks), when cultured with enalapril presented different thresholds of acantholysis. Lesions on the back showed diffuse acantholysis, while mild to moderate acantholysis was detected on the cultured explants taken from the buttocks. No structural changes were found in control cultures (27). This study demonstrated certain preferential anatomic localizations of pemphigus lesions. Also, in the opinion of the authors of this article, drug-induced pemphigus, shares the same anatomical preference in genetically predisposed persons, especially if induced by ACE inhibitors.

Of special interest is that ACE inhibitors can induce circulating antibodies directed to antigens of the superficial epidermal cells in patients without skin changes, as published recently (28). A group of 68 patients treated with ACE inhibitors and 48 controls were included in the study. Indirect immunofluorescence showed that 33 sera (52.38%) presented autoantibodies directed to an antigen of the cytoplasm of the superficial epidermal keratinocytes. Two of the 33 positive sera had autoantibodies to desmoglein 1 and/or 3 in enzyme-linked immunosorbent assay - ELISA test. Immunoblot analyses were negative. All the 48 control sera were found to have no circulating antibodies using the three assays. This study clearly indicates that ACE inhibitors may induce production of circulating autoantibodies even in patients without clinical manifestations of pemphigus (28). Autoantibody development is not related to the duration of ACE inhibitor administration (28) in these patients. Recently, one case of pemphigus foliaceus induced by an angiotensin II receptor blocker (candesartan) has been published (29). Angiotensin II receptor blockers are widely prescribed as antihypertnesives as a substitute for ACE inhibitors (29).

Vitamin D may be able to prevent ACE inhibitor-induced cell detachment and apoptosis in keratinocytes. The results of an Israeli study in vitro confirm that calcitriol protects keratinocytes from captopril-induced cell detachment and apoptosis (30). It is important to have a detailed history of all drugs taken by the patient, including homeopathic agents, OTC drugs, and even medications that were discontinued. In cases where there is no response to therapy repeated drug history taking should be considered (2). Every case of de novo pemphigus should be first estimated as drug-induced. Usually, it takes 1 - 6 months for ACE inhibitors to induce pemphigus (26). If previous dermatosis exists, such as atopic dermatitis, the diagnosis may be delayed. In our patient, solitary, sharply demarcated plaques showed a characteristic histology of pemphigus foliaceus. At the 6-month follow-up, the patient presented with small plaques (up to 1 cm) with minimal infiltration, while indirect immunofluorescence test was positive, with a titer of 1 : 20. It has been estimated that approximately 40 to 50% of patients with thiol-drug-induced pemphigus recover spontaneously when the drug is withdrawn with rapid decline in desmoglein antibody levels (24). Only 15% of cases induced by...
non-thiol drugs remit following drug withdrawal. Perhaps drugs act to trigger disease in genetically predisposed individuals (24). Our case also shows that specimen collection should be repeated in doubtful cases, when new lesions on the skin do not correspond to the previous clinical diagnosis.

**Abbreviations**

ACE - Angiotensin-converting enzyme  
OTC - Over-the-counter  
PF – Pemphigus foliaceus

**References**


Lizinopril kao uzrok pemphigus foliaceus kod pacijenta sa dijabetes melitumom i Kaposi-Juliusberg variceliformnom erupcijom

Sažetak

Uvod: Lekovi se sve češće navode kao uzročnici pemfigusa. Lizinopril je inhibitor angiotenzin-konvertujućeg enzima (ACE - eng. angiotensin-converting enzyme) koji se koristi u lečenju hipertenzije, kongestivne srčane bolesti kao i u prevenciji renalnih i retinalnih komplikacija u dijabetesu melitus. Do sada su opisane različite reakcije na lek, ali samo jedan slučaj pemphigusa foliaceus (PF). Prikazujemo drugi slučaj u svetu PF indukovanog lizinoprilom komplikovanog Kaposi-Juliusbergovom variceliformnom erupcijom kod pacijenta sa diabetsom melitus tip 2.


Lizinopril (C21H35N3O7) je lizinski derivat enalaprilata, aktivnog metabolita enalapril. Različiti neželjeni efekti na lizinopril su do sada opisani, ali samo jedan slučaj PF .

Prikaz slučaja: Muškarac, star 60 godina iz okoline Trstenika primljen je sa supfebrilnim temperaturama. Brojne diseminovane umbilikovane vezikule i eritem bili su prisutni na koži lica, trupa i ekstremiteta, a semi-anularne erozije na koži trupa. Jasno ograničeni žućkasto-crvenkasti plakovi, mestimično grupisani, veličine do 2 cm, bili su lokalizovani na zadnjoj strani trupa (paravertebralno i vertebralno). Osim pojačanih injekcija na obe konjunktive, na ostalim vidljivim služnicama nisu uočene patološke promene. Iz anamnestičkih podataka saznalo se da boluje od dijabetesa melitus tip 2 ukupno 10 godina, a od hipertenzije 2 godine, i da je od lekova redovno uzimao metformin i lizinopril. U porodičnoj anamnezi naveo je da su oba roditelja imala povišen pritisak, dok je majka boovala od dijabetesa melitus i astme. Od 2007. godine kada su se pojavile prve promene na koži, lečen je pod dijagnozom atopijski dermatitis i to uglavnom lokalno. Međutim, pogoršanje kožnog stanja nastupilo je 1,5 mesec pre prijema na našu kliniku, kada je zbog febrilnosti, upućen prvo u regionalnu bolnicu gde je pod dijagnozom eritrodermije lečen pored lokalne terapije i sistemski kortikosteroidima, antihistaminicima i antibioticima. Histologija koja je radena tom prilikom, upućivala je na eksfolijativni dermatitis kao reakciju na lek. Nakon 5 dana, došlo je do pogoršanja opštega stanja pacijenta, febrilnosti, sa erupcijom novih kožnih lezija po tipu papulovezikulozne erupcije, te je premešten na Kliniku za dermatovenereologiju KCS u Beogradu. Po prijemu, uočene su semianularne erozije sa ostacima krovova bula kao i pojedinačni žućkasto-crvenkasti plakovi do 2 cm u prečniku na trupu i ekstremitetima, i diseminovane umbilikovane vezikule.

Laboratorijske analize su ukazale na postojanje blage hiposideremijske anemije, i povišen IgE tital od 725 IU/ml (normalne vrednosti do 100). Imunološke analize su bile uredne, dok je virusološkim analizama zapažen četvorostruki pad titra HSV-1 tokom boravka u bolnici.

Direktna, indirektna imunofluorescencija kao i histologija bile su kompatibilne sa PF .

Lečenje: Nakon primene aciklovir tableta, antibiotika prema antibiogramu i metformina (kojeg je pacijent redovno uzimao) kao i insulina (nezadovoljavajuća glikoregulacija), uključen je prednisolon 40 mg/dan kao i azatioprin 150 mg/dan, antiseptičke boje i kombinovane antibiotsko-kortikosteroidne kreme. Nakon 2 nedelje i rezolucije prvobitnih promena, uočene su nove − superficijelne bule kao i eritematozni, jasno ograničeni plakovi na licu, trupu i ekstremitetima. Histologija sa plakova potvrdila je nalaz PF moguće indukovanog lekovima. Na osnovu
ponovljenih anamnestičkih podataka uočeno je da je do pogoršanja promena na koži došlo 6 meseci pošto je u terapiju uveden lizinopril. Lek je isključen, nakon čega je nastupilo rapidno poboljšanje: nestajanje plakova, epitelizacija erozija i prestanak javljanja novih bula. Nakon 6 meseci praćenja, utvrđeno je da na koži i dalje postoje retke, minimalno infiltrovane promene na trupu i ekstremitetima.

Na osnovu svega iznetog, postavljena je dijagnoza PF pokrenutog lizinoprilom kod pacijenta sa dijabetesom melitus i Kaposi-Juliusbergovom variceliformnom reakcijom.


Cirkulišuća i za epidermis vezana antitela protiv dezmogleina 1 i dezmogleina 3, koja su prisutna kod pacijenata sa spontanim pemfigusom foliaceus odnosno vulgarnim pemfigusom, mogu se dokazati i kod pacijenata sa lekovima izazvanim pemfigusom kao što je to slučaj kod našeg pacijenta. Ipak, treba znati da prema podacima iz literature, kod pacijenata sa pemfigusom izazvanim penicilaminom (najčešće inkriminisani lek), direktni imunofluorescenti test ostaje negativan kod 10% a indirektni kod 30% obolelih.

Posle 6 meseci od ukidanja lizinoprilu, naš pacijent je idalje imao retke, minimalno infiltorovane male plakove (dijametra nekoliko mm) na trupu i ekstremitetima. Titar antidezmogleinskih antitela bio je nizak i iznosio je 1 : 20. Poznato je da se samo kod približno 40−50% pacijenata sa pemfigusom izazvanim lekovima koji poseduju tiol (SH) grupu bolest spontano povlači posle ukidanja inkriminisanog leka. Kada su u pitaju ostali lekovi, ovaj procenat nije viši od 15%.

Zaključak: Kod svakog de novo slučaja pemfigusa, mora se isključiti uloga leka kao potencijalnog pokretača odnosno uzroka bolesti, s obzirom da svi lekovi koje je pacijent uzimao uključujući i vitamine i homeopatske lekove, pa čak i lekove koje je pacijent prestao da uzima, mogu biti pokretači bolesti. Kod svih pacijenata kod kojih ne dolazi do očekivanog terapijskog odgovora na primenjenu terapiju, treba ponovo insistirati na detaljnim anamnestičkim podacima.

Ključne reči
Lizinopril + neželjena dejstva; Pemphigus + hemijski izazvan; Inhibitori angiotenzin konvertirajućeg enzima; Dermatitis; Kapošijeva variceliformna erupcija