



# Ramipril-induced cutaneous vasculitis: about an observation

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## **Abstract :**

Angiotensin- Converting Enzyme (ACE) inhibitors are very frequently used as a standard therapy in treatment of hypertension and heart failure. They are also prescribed in the management of diabetic nephropathy to prevent its progression. Moreover, they have other indications.

Side effects of ACE inhibitors drugs like dry cough, hyperkalemia, hypotension, renal failure, proteinuria are very common. They can cause other side effects such cutaneous manifestations that are rare and not very recognized. However, they rarely cause cutaneous vasculitis. We report the case of 65-year-old male who had history of dilated cardiomyopathy with severe left ventricle dysfunction, treated with ramipril with good tolerance at first and who developed cutaneous vasculitis after second introduction.

**Keywords:** Ramipril -ACE- cutaneous vasculitis- side effect- allergic reaction

## **Introduction :**

Angiotensin-converting enzyme (ACE) inhibitors are very frequently used as standard therapy of hypertension, heart failure and diabetic nephropathy besides other indications.

Their side effects are various. They can cause a multitude of dermatological side effects. Cutaneous adverse reactions attributed to ACE inhibitors include skin rashes, pruritus, life-threatening angioedema, lichenoid eruptions, urticaria, photosensitivity, hair loss and bullous eruptions. (1,2)

## **Case report:**

We report the case of a 65-year-old patient who has been followed since 07/2020 for dilated cardiomyopathy with severe LV dysfunction and atrial fibrillation; he was treated with beta-blockers, an ACE (ramipril), digoxin and anticoagulation. ACE was then stopped due to arterial hypotension after one month.

In January 2021, he was admitted to cardiology B for left cardiac decompensation.

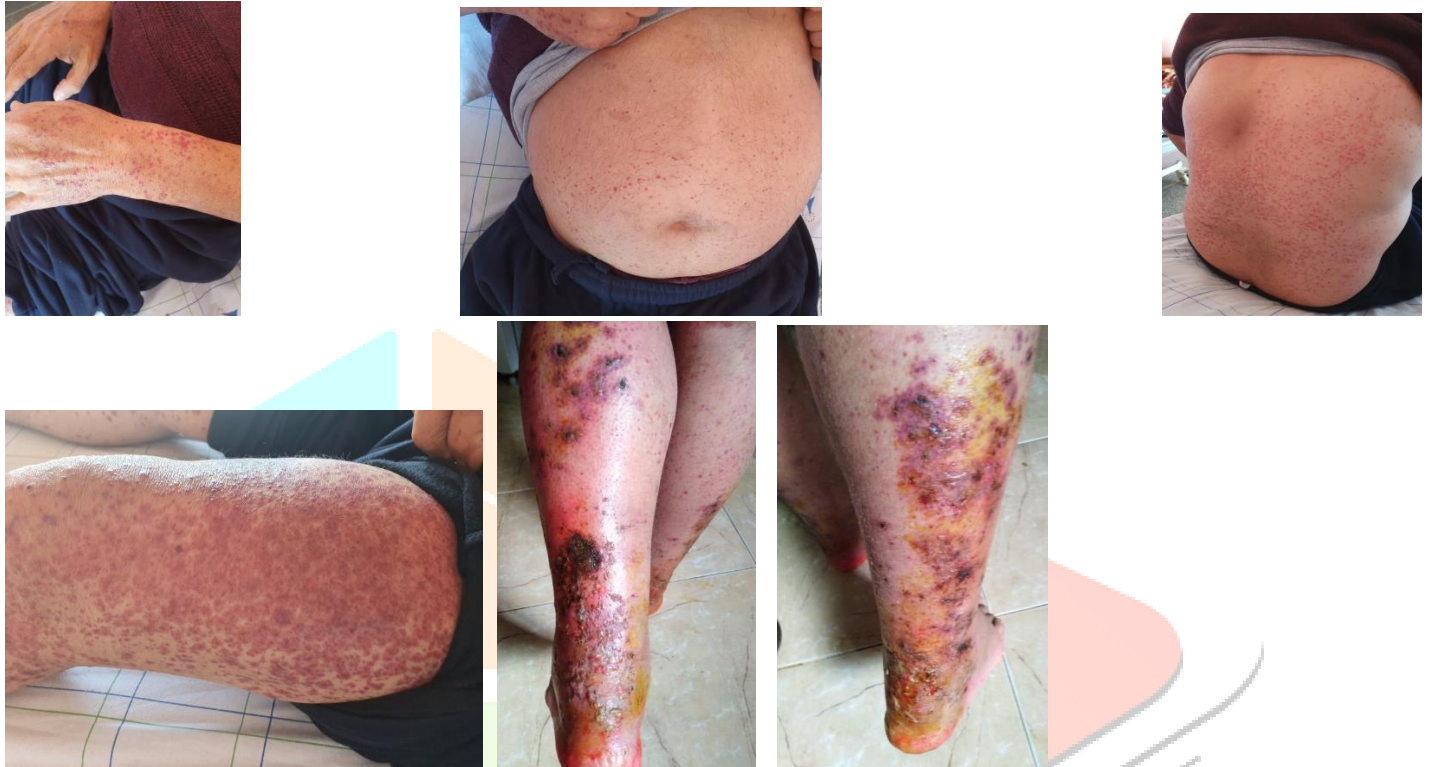
The patient received intra-venous diuretics, potassium supplementation, digoxin, aldactone, anti-vitamin K anticoagulation and ramipril-type converting enzyme inhibitor.

One week after re-introduction of ramipril, he developed painful symmetrical purpuric eruption on the lower and upper limbs and the back (**figures 1 to 6**). Clinical examination showed a bullous purpura of the lower limbs with erosions covered with melicera scabs and infiltrated purpura on the back, abdomen and upper limbs, without fever or other hemorrhagic signs.

The blood count, platelet count and hemostasis test were correct. The renal and hepatic tests were without abnormalities. Skin biopsy showed neutrophilic vasculitis secondary to drug intake.

The pharmacovigilance center was alerted and confirmed the accountability of ramipril as the most implicated drug. The rash improved slowly after cessation of treatment and initiation of antibiotic therapy based on amoxicillin + clavulanic acid.

He was discharged and at follow up good clinical evolution with no recurrence.



**Fig. 1-6:** Cutaneous eruptions caused by Ramipril in our patient.

### **Discussion :**

Cutaneous vasculitis is defined as an inflammatory process that affects the vessel wall leading to its infiltration and destruction with hemorrhagic and ischemic events (4).

Its incidence ranges from 39,6 to 59,8 per million per year (5).

It affects the skin with varying levels of associated systemic manifestations. It can range in severity from simple, benign, short-lived and self-limited skin involvement to serious life-threatening form with multiple organ failure (5). Its physiopathological mechanism is still poorly understood. Vasculitis can affect the small- or medium-sized vessels of the skin. Vasculitis affecting the small vessels of the skin (arterioles, capillaries, postcapillary venules) tends to cause lesions such as purpura, petechiae, and possibly shallow ulcers. Livedo reticularis, nodules, and deep ulcers are usually caused by vasculitis of deeper, medium or large vessels.

Vasculitis is classified as primary disorder (idiopathic) or secondary one that associated with infections (streptococcal infection, viral hepatitis), hypersensitivity to drugs or underlying disease (paraneoplastic phenomenon, rheumatologic or other auto-immune disease) (5).

According to the literature, it is mainly idiopathic with a frequency of 40%, 20% is secondary to drug consumption, 22% is associated with respiratory infection, 12% is associated with systemic disease such as lupus and rheumatoid arthritis, Sjogren's syndrome, less than 5% occurs in a background of cancer or inflammatory disease (6).

It manifests as a palpable purpura usually affecting the lower limbs. careful questioning and clinical examination should look for the triggering factor such as infections, symptoms related to concomitant disease and drugs (7). Skin Biopsy with specimen is the gold standard for the diagnosis of cutaneous

vasculitis and also necessary for the detection of cutaneous vascular immune complexes by direct immunofluorescence (6).

Cutaneous reactions related to angiotensin-converting enzyme inhibitors include various skin lesions from simple rashes to bullous eruptions.

According to data in literature, experiments in vitro have revealed that ACE inhibitors- induced adverse reactions in the skin are mostly based on two different non-immunological mechanisms. The first mechanism is explained by the fact that drugs containing thiols groups (sulfhydryl), such as Captopril, can evoke acantholysis by mechanisms interfering with the disulfide and thiol group balance (8, 9). On the other hand, Enalapril and Ramipril are containing an amide group, appear to be an even stronger acantholytic agent than captopril or other thiol drugs. The mechanisms of Ramipril induced acantholytic effects are still a matter of debate and seem to involve the inhibition of transglutaminase activity (8). Therefore, ACE inhibitors may cause bullous eruptions by direct interference with cell cohesion without any involvement of immunologic mechanisms (2).

Further types of skin effects by ACE inhibitors have been reported only as single case reports. These include maculo-papular (10), lichenoid eruptions (11), pityriasis rosea-like (12), psoriasiform (13), and vasculitis (10), onycholysis (14), erythema multi-forme (15), photosensitivity (16) and hair-loss (17). Pruritus has also been recorded and is of special importance because it often precedes angioedema (19,18). Thus, patients should be advised to report pruritus immediately, since in the case an interruption of ACE-inhibitor therapy must be considered.

### **Conclusion :**

Cutaneous side effects of ACE inhibitors are rare and clinical presentation is variable. Cutaneous vasculitis secondary to ACE inhibitors is uncommon. The exact mechanism is not clear and is still matter of discussion. Their appearance requires immediate cessation of treatment to avoid the risk of progression to severe complications.

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