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Captopril – not always short-acting ACE inhibitor

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CASE STUDY/PRACA KAZUISTYCZNA

Captopril — not always short-acting ACE inhibitor

Kaptopril — nie zawsze krótkodziałający inhibitor konwertazy angiotensyny

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Angiotensin-converting-enzyme inhibitors (ACEi) are among the most frequently prescribed drug groups in the world, indicated in patients with hypertension, coronary syndromes, heart failure and diabetic nephropathy [1]. ACEi-associated angioedema (ACEi-AAE) is a rare (0.1–0.7%), but potentially life-threatening side effect of ACEi and a contraindication to ACEi use [2]. We present a patient with ACEi-AAE after a single captopril administration.

A 47-year-old man was admitted to the cardiology department for a diagnostic work-out and qualification for mitral valve intervention. His medical records included bilateral nephrectomy due to polycystic kidney disease, chronic haemodialysis, resistant hypertension, type 2 diabetes and active smoking. On admission, he was in good general condition, with elevated blood pressure (170/103 mmHg) and a loud systolic murmur at the apex. He was administered 12.5 mg of captopril on top of his ACEi treatment (ramipril 5 mg o.d.) sublingually to decrease blood pressure. After about an hour, bilateral, non-itchy face blush and angioedema were observed in the oral area, including the lips and tongue (Figure 1A). As per local nursing protocol, the patient was immediately administered intravenous dexamethasone and antihistamines, followed by oral hydrocortisone, which did not have any immediate impact on symptom relief. No bradykinin antagonist was readily available. As there was no airway obstruction after the risk-benefit analysis, it was decided not to escalate with fresh frozen plasma administration. Two days later, he still presented with a swollen

tongue, albeit to a smaller extent (Figure 1B). The complete symptom relief was observed after five days.

Angioedema (AE) is a subcutaneous or submucosal swelling localized mainly in the head and neck area. AE occurs through two main mechanisms: histamine- and bradykinin-mediated [3]. Histamine-mediated AE is a type I hypersensitivity reaction often triggered by a subsequent encounter with a previously sensitized allergen. Upon re-exposure to the allergen, the mast cells degranulate initiating subsequent histamine release. It may lead to fatal airway obstruction and asphyxia-induced death. This type of AE occurs within minutes following allergen contact and responds well to antihistamine drugs, steroids and adrenaline, with symptom alleviation within 37 hours. Conversely, the second type of AE, including ACEi-AAE, is bradykinin-related. Bradykinin acts as a potent vasodilator and increases vascular permeability, resulting in plasma extravasation into subcutaneous and submucosal tissue, leading to swelling. ACE is the main enzyme that catabolizes bradykinin. ACE inhibition leads to bradykinin accumulation, manifesting as swelling in the facial and intestinal area, typically without urticaria. It may also involve upper airways, but less often than histamine-mediated AE. ACEi-AAE may develop after the first administration of ACEi and after months up to years of stable therapy [4]. The risk factors for bradykinin-mediated AE involve Afroamerican race, female sex, age >65 years, smoking, hereditary or acquired C1-inhibitor deficiency, which inhibits proteases responsible for bradykinin formation (e.g. factor XIIa and kallikrein) [5]. It poorly responds to antihistamines, glucocorticoids and adrenaline and resolves spontaneously within 2–5 days. The primary treatment of ACEi-associated AE is to discontinue the drug and carefully monitor the patient for potential airway obstruction, which might require intubation and mechanical ventilation. A synthetic bradykinin B_2-receptor antagonist, icatibant, is the only drug approved for the acute treatment of hereditary AE and was also effective for treating ACEi-AAE. It is administered as an on-demand subcutaneous single-dose injection, typically into the abdominal area. It can be self-administered or given by a healthcare professional. [6]. Recombinant plasma kallikrein inhibitor ecallantide was also evaluated in ACEi-AAE, but showed no clear benefit over placebo. Based on case reports, fresh frozen plasma might be useful in treating ACEi-AAE by supplying a C1-inhibitor and ACE to catabolize the accumulated bradykinin [7].

Since we did not have icatibant available, our patient was administered antihistamines and glucocorticoids, but based on the available literature reports and the slow symptom relief observed, spontaneous symptom relief cannot be excluded. Importantly, AE may also occur after angiotensin receptor blockers and sacubitril/valsartan had a similar rate as in the case of

ACEi, as demonstrated by the recent meta-analysis of 11 randomized clinical trials [2]. Considering the increasing prevalence of heart failure and the growing use of these drug groups, it is crucial to be aware of its potential side effects, including AE and to increase the availability of the tailored treatment, icatibant, in the emergency and cardiology departments.

In clinical practice, particularly within emergent scenarios characterized by hypertensive spikes, the co-administration of short-acting captopril with long-acting ramipril is occasionally executed, as demonstrated in this clinical case. This synergistic employment of different ACEis may potentiate the susceptibility to associated adverse effects, which include hyperkalemia, hypotension, acute kidney injury, and AE. It becomes crucial to identify and manage these complications, ensuring that therapeutic strategies and monitoring protocols are available and stringently implemented.

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A. B.

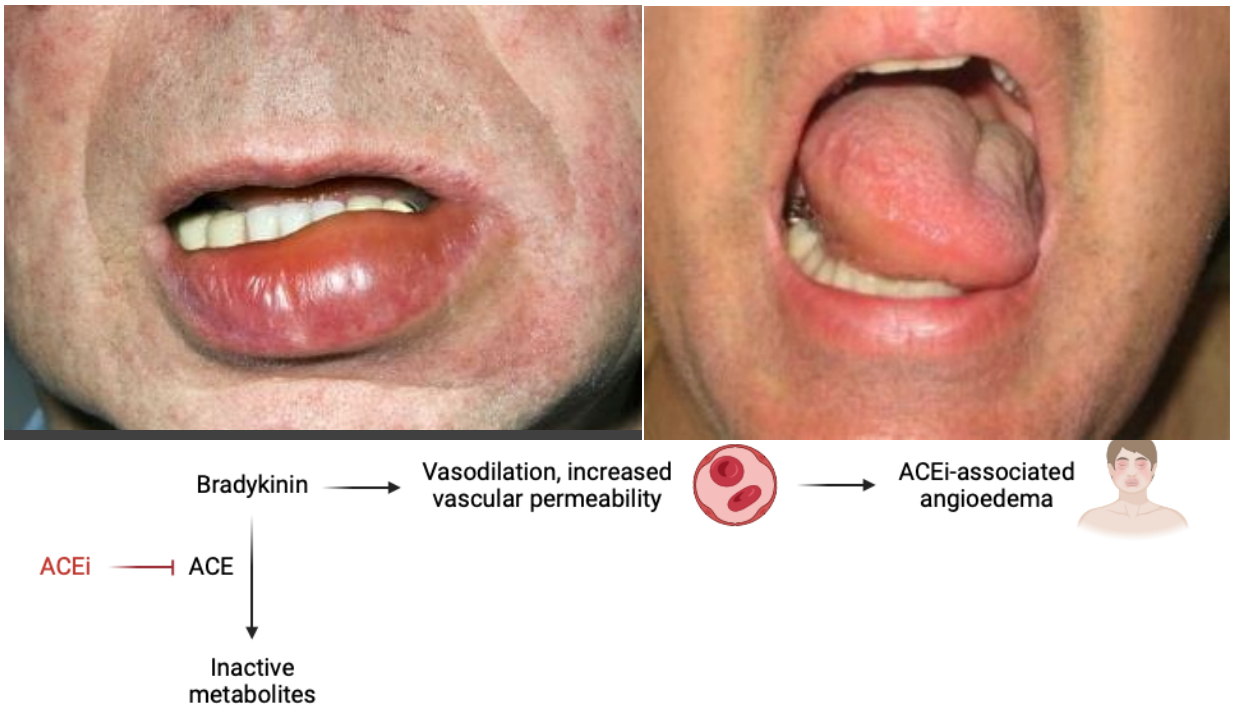

Figure 1. A: Angioedema following sublingual administration of 12.5 mg captopril on top of daily ramipril 5 mg. B: Gradual patient recovery after two days. C: Pathophysiology of ACE inhibitor-associated angioedema.