Advances in Medicine and Engineering Interdisciplinary Research, 2025, Volume 3, Issue 3
DOI: 10.32629/ameir.v3i3.4065
ISSN Online: 2972-3825
ISSN Print: 2972-3833

Kounis Syndrome: A rare case of Omeprazol anaphylaxis

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Abstract: Anaphylaxis is a potentially fatal acute hypersensitivity reaction. Omeprazole has revolutionized the treatment of pathologies related to acid hypersecretion. Cases of anaphylactic reaction to proton pump inhibitors (PPIs) have been described. We present the case of a 30-year-old woman with acute gastroenteritis who immediately developed severe retrosternal pain, hypotension, and altered consciousness after taking intravenous omeprazole. There were signs of acute ischemia and increased markers of myocardial injury. She was admitted to the intensive care unit with good progress. Cases of severe anaphylaxis to PPIs are very rare; the mechanism is IgE-mediated, with a class effect and the possibility of cross-reaction with ranitidine. Kounis syndrome involves the association of type 2 acute myocardial infarction with anaphylactic shock. This adverse effect should be monitored, given the widespread use of PPIs, especially intravenously.

Key words: anaphylaxis; Kounis syndrome; Omeprazole

1 Introduction

Anaphylactic shock is a syndrome that includes hypotension, tachycardia or bradycardia and altered state of consciousness. It is also described as a set of 1 or 2 of the following symptoms: a) edema, erythema, urticaria and angioedema; b) laryngeal edema, spasm or bronchospasm [1]. There is a causal agent and it can occur within minutes or hours after exposure to that agent. Omeprazole is a known proton pump inhibitor (PPI), used in the treatment of pathologies related to excess gastric acid secretion. Kounis syndrome is also known as allergic angina syndrome or allergic myocardial infarction. This is defined as acute coronary syndrome (ACS) that occurs in association with allergic reaction/hypersensitivity and anaphylaxis/anaphylactic reactions, caused by the degranulation of mast cells and the release and interrelation of vasoactive mediators (histamine, leukotrienes, serotonin) and proteases (tryptase, kinase) [2][3]. We have 3 types [4-6].

Type I-Patients without cardiovascular risk factors and healthy coronary arteries in which the inflammatory cascade activated by the allergic reaction causes spasm of the coronary arteries, accompanied or not by an elevation of markers of myocardial injury;

Type II – Patients with pre-existing atheromatous coronary disease (known or not) in which the release of these mediators also produces coronary spasm, which occurs with normal cardiac enzymes or rupture of the atheroma plaque, manifesting as acute myocardial infarction;

Type III – Patients with stent thrombosis, in which the study of the thrombus on a slide reveals the presence of eosinophils and mast cells.

2 Clinical case

A 30-year-old Caucasian woman with a history of smoking, allergy to strawberries, cervical lesion (cervical intraepithelial neoplasia stage 1) and appendectomy in childhood. The patient came to the Emergency Department due to diarrhea, chills, epigastric pain and nausea that had been present for 24 hours after eating a salad. On observation, the patient was hemodynamically stable and apyretic. No significant changes were observed during cardiac and pulmonary auscultation. The abdomen was diffusely painful to palpation, with no defense or signs of peritoneal irritation. Omeprazole 40 mg intravenously (IV) was administered, which immediately caused hypotension (mean arterial pressure (MAP) less than 45 mmHg), severe retrosternal pain and altered state of consciousness. The following complementary diagnostic tests (DCT) were performed:

• Electrocardiogram (ECG) showing acute anterolateral ischemia with ST segment depression from v3 to v5 (Figure 1);

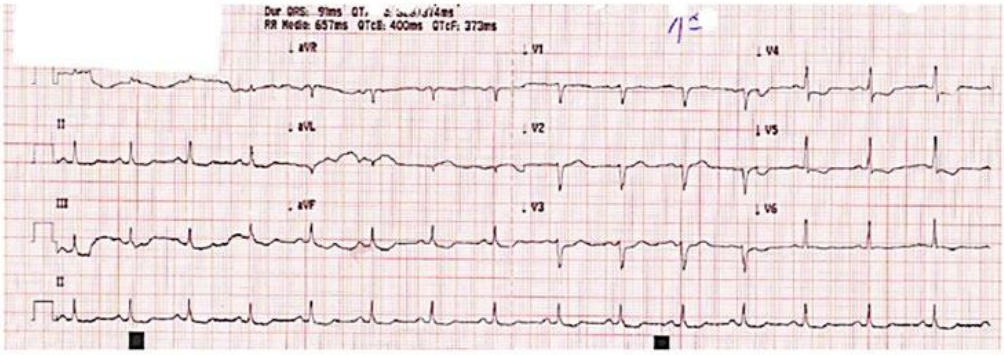

Figure 1. 12-lead electrocardiogram performed in an emergency setting, in sinus rhythm showing ST depression of the anterolateral wall.

• Analytically, the objective was to observe an increase in myocardial injury markers (CK-MB 5.1 ng/mL; troponin I 1.45 ng/mL); an increase in inflammatory parameters, with leukocytosis of 16,700 µ/L, neutrophilia, eosinophilia and C-reactive protein of 2.95 mg/dL; renal function and ionogram without alterations;

• Arterial blood gas analysis in room air showed no acid-base alterations, no hyperlactacidemia or hypoxemia.

Symptomatic treatment was immediately initiated, with administration of a loading dose of acetylsalicylic acid, clopidogrel and enoxaparin. Despite fluid therapy, the patient remained hypotensive and required initiation of norepinephrine, which subsequently achieved a MAP greater than 65 mmHg. Empirical treatment with piperacillin/tazobactam 4.5 g every 6 hours was also initiated, due to suspected septic shock. She was then transferred to the intensive care unit (ICU) due to her hemodynamic instability, and a transthoracic echocardiogram (TTE) and a computed tomography scan of the skull were subsequently performed, which revealed no pathological changes. Laboratory tests showed an increase in myocardial injury markers within 24 hours, with subsequent normalization (maximum troponin of 6.13 ng/mL – Table 1). Urine culture and stool virus testing were negative. A decrease in inflammatory parameters was also observed, and the patient was apyretic since the second day of admission to the ICU. Vasopressor support was gradually discontinued due to hemodynamic stability, while antibiotic therapy was maintained. After the 72-hour probability of rebound effect, the patient was transferred to the general Internal Medicine ward, with the following diagnoses: Kounis syndrome, anaphylaxis to omeprazole and acute gastroenteritis.

Table 1. Cardiac marker profile

	Day 0 ER	Day 1 ICU	Day 2 ICU/IM	Day 10 Discharge
CK-MB (0-3.4 ng/mL)	5.1	15.2	1.0	1.0
Troponin I (0-0.3 ng/mL)	1.45	6.13	0.55	0.01

Evolution of myocardial injury markers during the patient's hospitalization.

ER – Emergency Department; ICU – Intensive Care Unit; IM – Internal Medicine Inpatient Unit.

During her stay in the ward, she had good clinical and laboratory progress, with normalization of cardiac markers and electrocardiographic tracing (Figure 2). Blood cultures were negative, and Salmonella species was isolated in stool cultures, so antibiotic therapy was changed to doxycycline, which she continued for 7 days (the change occurred on day 4 of empirical antibiotic therapy with piperacillin/tazobactam). The patient presented with recrudescence of chest pain, with nonspecific characteristics. A repeat TTE detected "new" pleuropericardial effusion, of small dimensions; the ECG and markers of myocardial injury remained normal. She started treatment with ibuprofen, with resolution of the effusions. On the date of discharge, she was clinically and laboratory well, with a diagnosis of Kounis syndrome, anaphylaxis to omeprazole, polyserositis (pericardial effusion and pleuritic effusion) to be clarified, and salmonellosis, with an indication not to take PPIs or ranitidine. The patient did not attend the Internal Medicine and Immunoallergology appointments, therefore it was not possible to complete the study.

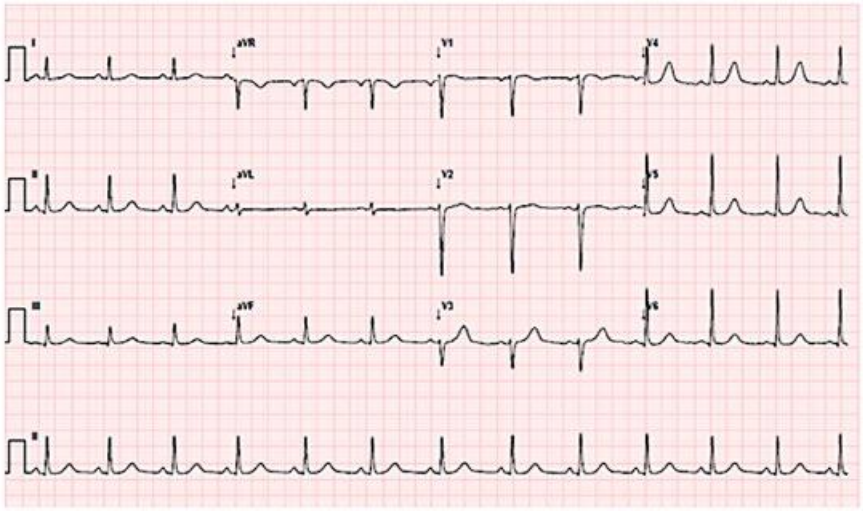

Figure 2. Electrocardiogram on discharge date, in sinus rhythm, with normalization

3 Discussion

Anaphylaxis to omeprazole and Kounis syndrome are the two main diagnoses in this case.

The patient was initially treated as having a type 2 acute myocardial infarction in the context of probable septic shock rather than anaphylactic shock, and therefore was not treated as a first-line agent with corticosteroid therapy and IV adrenaline. Takutsobo syndrome was ruled out after an echocardiogram showed no abnormalities (Figure 3). The type of Kounis syndrome was not clarified due to the impossibility of performing coronary angiography in a timely manner. Regarding the etiology of polyserositis, the following were considered: a) altered capillary permeability in the context of hypersensitivity; b) salmonellosis, with pericardial involvement [7]; c) autoimmune disease, however, only ANA+ 1/160 was found, with no other laboratory data of activity.

The mechanism of anaphylaxis to omeprazole is IgE-mediated (still unclear), with a class effect and the possibility of cross-reaction with other PPIs and even with ranitidine [8], with cases of delayed hypersensitivity to all PPIs having been described [9]. Until 1999, the known frequency of anaphylactic reaction to histamine 2 receptor antagonists

(ranitidine) and PPIs was between 0.2% and 0.7% [5]. According to a 2006 literature review, nine cases of anaphylactic shock to PPIs had been described, four of which were to omeprazole [5], with two more cases published in 2009 [10]. However, after a subsequent study with skin tests, it was found that the causal agent was, in most cases, the compound in the capsule (e.g. soybean oil, etc.) and not the PPI [11]. Regarding Kounis syndrome associated with anaphylactic reaction to omeprazole, there is one case reported in 2010 [12].

Kounis syndrome is increasingly observed in our clinical practice, but its incidence is not known. There are some cases described in Portugal of this entity associated with anaphylaxis to medications (quinolones, nonsteroidal anti-inflammatory drugs, metamizole magnesium) and wasp stings [13,14]. However, our case of Kounis syndrome due to anaphylactic reaction to intravenous omeprazole is the first described in Portugal. Although uncommon, this adverse effect should be treated with caution, given the widespread use of PPIs.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Ethical Responsibilities

Confidentiality of Data: The authors declare that they have followed the protocols of their institution regarding the publication of patient data.

Consent: Patient consent for publication obtained.