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KOUNIS SYNDROME FOLLOWING MOXIFLOXACIN AND DEFLAZACORT ADMINISTRATION

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ABSTRACT

Kounis syndrome (KS), characterized by the simultaneous occurrence of acute coronary syndrome (ACS) and allergic reactions, can be triggered by a range of factors and drugs. We report on the case of a patient who arrived at our emergency department (ED) with symptoms of an allergic reaction after taking moxifloxacin and deflazacort orally. In the ED, the patient experienced a 5-minute episode of oppressive chest pain. A 12-lead electrocardiogram (ECG) was registered, and elevated troponin levels were detected in the blood, suggesting myocardial damage. The patient was admitted to the internal medicine department for observation, and a second 12-lead ECG demonstrated a significant variation in the repolarization pattern. The day after, a coronary angiography revealed no significant stenosis, thus supporting, along with elevated serum tryptase levels, the diagnosis of KS. This case report highlights two potential triggers for KS and emphasizes the critical importance of early recognition and prompt treatment of KS.

KEYWORDS

Kounis syndrome, allergic reaction, coronary disease

LEARNING POINTS

- *Kounis syndrome can be triggered by moxifloxacin and/or deflazacort.* This case report documents the onset of Kounis syndrome following the administration of moxifloxacin and deflazacort.
- *Diagnosing and treating Kounis syndrome can be challenging.* Its diverse triggers and clinical manifestations complicate accurate diagnosis. Effective treatment involves addressing both cardiac and allergic symptoms, with the understanding that medications used for cardiac issues may exacerbate allergic reactions, and vice versa.
- *Nonspecific electrocardiogram (ECG) alterations should not be underestimated.* In the context of an allergic reaction, ECG alterations, including nonspecific ones, might be an early warning sign.

INTRODUCTION

Kounis syndrome (KS) is a clinical condition defined by the occurrence of acute coronary events within the context of hypersensitivity reactions. This syndrome arises from the release of inflammatory mediators during an allergic reaction, which can lead to coronary artery

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spasms, plaque ruptures, or thrombosis. According to the literature, KS can be triggered by various allergens, including drugs, environmental exposures, insect stings, and foods such as fish, shellfish, fruits, vegetables, and canned goods *(Table 1)*. Despite its recognized prevalence, KS is frequently underdiagnosed due to its wide range of clinical presentations and overlap with other acute coronary syndromes. Even if KS can be easily suspected in patients presenting with clear signs and symptoms of hypersensitivity and chest pain, a wide variability of electrocardiogram (ECG) abnormalities makes diagnosis challenging for emergency physicians. Electrocardiographic anomalies may range from ST-segment abnormalities on the ECG to various degrees of heart block and arrhythmias. KS is categorized into three main types based on the underlying coronary pathology: type I, where the allergic reaction causes coronary artery spasm in individuals without preexisting coronary artery disease; type II, occurring in patients with atherosclerotic disease, where allergic mediators lead to plaque erosion or rupture; and type III, which involves patients with coronary stents, where hypersensitivity reactions can result in stent thrombosis. Advanced diagnostic methods such as coronary angiography (CAG), cardiac magnetic resonance imaging (CMR), myocardial scintigraphy (MS), and measurements of serum tryptase, histamine, cardiac enzymes, and cardiac troponins are useful for confirming KS. Treatment remains challenging and must be tailored to the specific type of KS. No treatment guidelines have been published to date.

We present a case of KS type I in the context of a hypersensitivity reaction to moxifloxacin and deflazacort. We discuss the electrocardiographic abnormalities, further analysis, and treatment performed in the ED and during the first 24 hours after diagnosis.

CASE DESCRIPTION

A 60-year-old male with a history of recurrent sinusitis presented to our ED with hives, malaise, and sneezing. Symptoms have developed 45 minutes after taking moxifloxacin 400 mg and deflazacort 30 mg, according to the suggestion of the primary ear nose and throat specialist for acute sinusitis.

On arrival, the patient's vital signs and the physical examination were unremarkable. Blood tests did not suggest inflammation, and renal function and electrolytes were in the normal range. In the ED, methylprednisolone 40 mg and clemastine 2 mg were promptly administered intravenously, alleviating hypersensitivity symptoms. During the following hour of observation in the ED, the patient experienced a sudden episode of oppressive chest pain for about 5 minutes. A 12-lead ECG was registered, revealing secondary repolarization abnormalities *(Fig. 1)*, not definitely imputable to ischemic ST-segment alteration. In the patient's previous medical records, no 12-leads ECG was found for comparison, only a prior medical report, mentioning "nonspecific repolarization abnormalities".

We determined high sensitivity troponin T (hs-TnT) according to the production company cut-off (Roche® hs-TnT): levels were slightly elevated at baseline (17 ng/l vs. 14 ng/l), with no significant increase after 3 hours (21 ng/l). The cardiologist consultant recommended treatment with acetylsalicylic

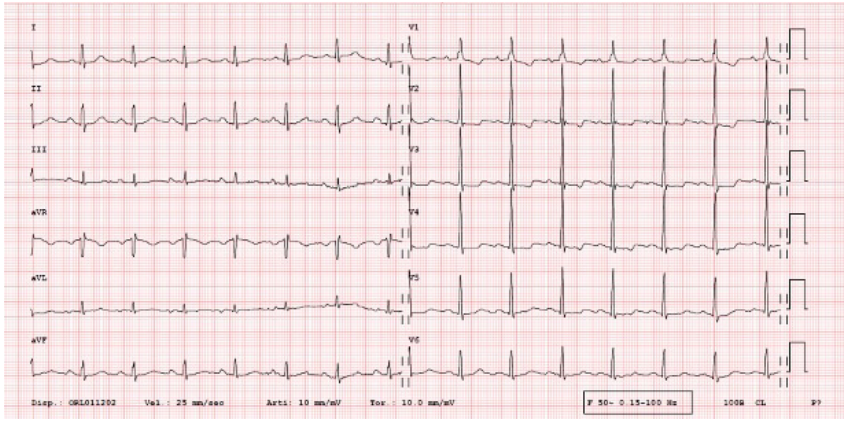


Figure 1. Twelve-lead electrocardiogram showing a sinus rhythm with a heart rate of 87 bpm, PR interval of 176 ms, QRS duration of 98 ms, and QTc of 456 ms. The axis is normal. There is evidence of right ventricular hypertrophy suggested by an enlarged R wave in V1/V2 and secondary repolarization abnormalities.



Figure 2. Twelve-lead electrocardiogram showing a sinus rhythm with a heart rate of 65 bpm, PR interval of 188 ms, QRS duration of 68 ms, and QTc of 427 ms. The axis is normal. There is evidence of right ventricular hypertrophy suggested by an enlarged R wave in V1/V2. There are non-specific T wave abnormalities in anterolateral leads (I, aVL, V2-V6).

acid 500 mg and early intravenous administration of heparin sodium. The patient was admitted to the medicine ward in stable condition, without symptoms. During the following hours, the patient experienced a new onset of oppressive chest pain; a 12-lead ECG was registered, showing more pronounced T-wave changes in the anterolateral leads *(Fig. 2)*. The following day, hs-TnT levels normalized (14 ng/l). Coronary angiography revealed no significant coronary artery injury. Serum tryptase levels were elevated (20.20 µg/l vs. 11.4 µg/l), confirming the presence of an allergic reaction.

The patient was diagnosed with vasospastic myocardial infarction due to KS, likely triggered by moxifloxacin and/or deflazacort. Upon discharge, he received standard care for coronary artery disease and subsequently returned to his normal life.

DISCUSSION

KS is an acute coronary syndrome occurring in the context of an allergic or anaphylactic reaction. Its pathogenesis involves the release of IgE-antigen immune complexes, which activate inflammatory mediators such as histamine, mast cells, basophils, macrophages, and the cytokine system[1]. This activation, triggered by allergen exposure, can induce coronary artery spasm or myocardial infarction.

The term "Kounis syndrome" was first introduced in 1950 and formally described in 1991 by Dr. Nicholas Kounis[2]. He observed the correlation between allergic reactions and acute myocardial infarction and termed the condition "histamine-induced angina syndrome", highlighting its association with endothelial dysfunction or microvascular angina. The syndrome represents a unique intersection of cardiovascular and allergic pathologies. Since its initial description, numerous case studies and reviews have expanded the understanding of KS, identifying a range of triggers, which we summarize in *Table 1*. Closely related to this study, prior studies have highlighted cases of allergic reactions and KS following the administration of corticosteroids[3]. Additionally, previous literature has also associated allergic reactions and KS with quinolones[4], with only 2 cases linking KS to moxifloxacin. In the first case, diagnosed as KS type 1, the ECG showed ST-segment elevation in two leads[5], whereas in the second, classified as type 2, it revealed T-wave inversion in two leads[6].

Cardiovascular symptoms and signs vary widely, from mild angina to severe myocardial infarction and sudden cardiac death, which can complicate diagnosis and contribute to underdiagnosis.

KS-related deaths are rare and difficult to assess post-mortem but combining various investigative methods -

Drugs	Diseases	Food consumption	Environmental exposure
• *Analgesics:* aspirin, dipyrone. • *Anaesthetics:* etomidate, isoflurane, propofol • *Antibiotics:* penicillins (ampicillin, amoxicillin), quinolones (ciprofloxacin, moxifloxacin), aminoglycosides (amikacin), cephalosporins (cefazolin, cefoxitin, cefuroxime), glycopeptides (vancomycin), trimethoprim-sulfamethoxazole • *NSAIDs:* diclofenac, naproxen • *Anti-neoplastics:* 5-fluorouracil, carboplatin, cisplatin, cyclophosphamide, interferon • *Contrast media* • *Glucocorticoids:* betamethasone, hydrocortisone • *Skin disinfectants:* chlorhexidine, povidone iodine • *Muscle relaxants:* cisatracurium, rocuronium, succinylcholine • *Proton pumps inhibitors:* lansoprazole, omeprazole • *Thrombolytic agents and anticoagulants:* heparin, streptokinase, urokinase, lepirudin, bivalirudin • *Others:* allopurinol, enalapril, esmolol, insulin, nicotine patches, mesalamine, bupropion, tetanus toxoid	• Angioedema • Urticaria • Bronchial asthma • Churg-Strauss syndrome • Exercise-induce anaphylaxis • Food allergy • Anisakiasis • Scombroid syndrome • Hay fever • Mastocytosis • Stents and intracardiac devices • Takotsubo myocardiopathy	• Fish • Fruits • Vegetables • Mushrooms • Tomato salad • Ice-cream	• Hymenoptera and jellyfish stings • Snake and scorpion venom • Poison ivy • Latex • Metals • Grass cutting

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs-

Table 1. Triggers of Kounis syndrome, as described in the literature.

such as gross and microscopic examination, biochemistry, and immunohistochemistry - can provide valuable insights. Key findings include signs of coronary atherosclerosis or myocardial ischemia, along with immunohistochemical evidence of anaphylactic immune cell activation and the release of inflammatory mediators in the coronary arteries and myocardial tissue. This approach helps reduce the number of undiagnosed cases in post-mortem assessments of deceased patients[7].

The management of KS is challenging, and addressing both cardiac and allergic manifestations, along with considering potential drug interactions, is the cornerstone for diagnosis and treatment in the ED[1]. Treatment varies by type[8]: type I is generally managed with intravenous corticosteroids and vasodilators (e.g., calcium channel blockers and nitrates), while types II and III require treatment for acute coronary syndrome. In KS, epinephrine and beta-blockers may worsen ischemia and coronary vasospasm, and morphine can induce significant mast cell activation and degranulation, worsening the allergic reaction. Therefore, these medications should be avoided, if possible, with sulphite-free epinephrine and fentanyl being appropriate alternatives[9].

In our case, the patient presented with symptoms of an allergic reaction followed by chest pain, ECG changes, and slightly elevated troponin levels. Chest pain is a commonly reported symptom in anaphylaxis; however, in our case, the ECG abnormalities were not immediately suggestive of ischemic cardiac disease. With no prior medical history and a coronary angiogram showing no atherosclerotic disease, the elevated tryptase helped us to make the diagnosis of KS type I. Given our patient's lack of exposure to other allergens, we suspect that the syndrome was triggered by moxifloxacin and/or deflazacort. Using the Naranjo score, a tool for estimating the probability of adverse drug reactions[10], we classified the association as "probable" for both drugs, with a score of seven for each. This finding, combined with the simultaneous administration of the two medications, makes it challenging to determine the precise trigger. Previous research identifies both classes of these drugs, quinolones and corticosteroids, as potential inducers of KS. This case report contributes to the existing literature by providing further evidence that these two drugs may trigger KS.

Overall, this case underscores the importance of considering a broad spectrum of potential triggers for KS and highlights the need for heightened awareness of nonspecific ECG alterations in the context of allergic reactions. Given the risk of severe outcomes if not promptly recognized and treated, clinicians should be vigilant for KS in patients with systemic allergic reactions and signs of acute coronary syndrome.

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APPENDIX

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