



<http://dx.doi.org/10.1016/j.jemermed.2015.02.044>

Clinical Communications: Adults

MYOCARDIAL INFARCTION IN THE SETTING OF ANAPHYLAXIS TO CELECOXIB: A CASE OF KOUNIS SYNDROME

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Abstract—Background: Acute coronary syndromes in the setting of an allergic or hypersensitivity reaction are known as Kounis syndrome. The syndrome involves release of inflammatory mediators after an allergen exposure that leads to coronary artery vasospasm or platelet activation. A variety of foods, drugs, and environmental exposures have been implicated in this condition. **Case Report:** The case involves a 62-year-old woman with dyspnea, chest pain, and transient ST-segment elevation after ingesting celecoxib. Her symptoms resolved with treatment for a suspected allergic reaction. Although she did have mild elevation of serum cardiac biomarkers, subsequent cardiac catheterization demonstrated normal coronary arteries. **Why Should an Emergency Physician Be Aware of This?:** This is the first reported case of ST-segment elevation myocardial infarction after allergy to celecoxib. Knowledge of Kounis syndrome will better prepare physicians in both its identification and clinical management. © 2015 Elsevier Inc.

Keywords—Kounis syndrome; celecoxib; ST-segment elevation; anaphylaxis; hypersensitivity reaction

INTRODUCTION

Kounis syndrome is the occurrence of acute coronary syndrome secondary to an allergic or hypersensitivity reaction (1). The syndrome is caused by inflammatory mediators released during mast cell activation that induce coronary artery vasospasm and platelet activation (1). A variety of foods, drugs, and environmental exposures have been implicated in this condition (2). Despite

numerous case reports, Kounis syndrome remains a poorly recognized clinical entity. We report a case of Kounis syndrome in an adult female shortly after ingesting celecoxib. Awareness of this phenomenon and its proposed treatments will better prepare physicians in both identification of Kounis syndrome and its clinical management.

CASE REPORT

A 62-year-old female with a medical history of hypertension, hypothyroidism, osteoarthritis, and Samter's syndrome (i.e., bronchial asthma, nasal polyposis, and aspirin sensitivity) sought medical attention after experiencing sudden shortness of breath 15 min after taking her prescribed celecoxib. There were no other recent ingestions or known exposures that may have precipitated an allergic response. The patient further noted persistent chest tightness, emesis, skin flushing, and pruritus. She had been taking celecoxib on an intermittent basis for arthritis over the previous 6 months. She denied any previous reaction to this medication. Her only known allergy was an anaphylactic response to aspirin 20 years earlier, which she noted was similar to her current symptoms. The patient was otherwise healthy, does not smoke, and has no significant family history of medical illnesses. She was a seasonal resident on an island off the coast of Maine.

On initial assessment by island emergency medical services, the patient appeared to be in significant respiratory distress with flushed and diaphoretic skin, but no visible urticaria or angioedema. Initial vital signs included a heart

RECEIVED: 17 April 2013; FINAL SUBMISSION RECEIVED: 9 January 2015;

ACCEPTED: 27 February 2015

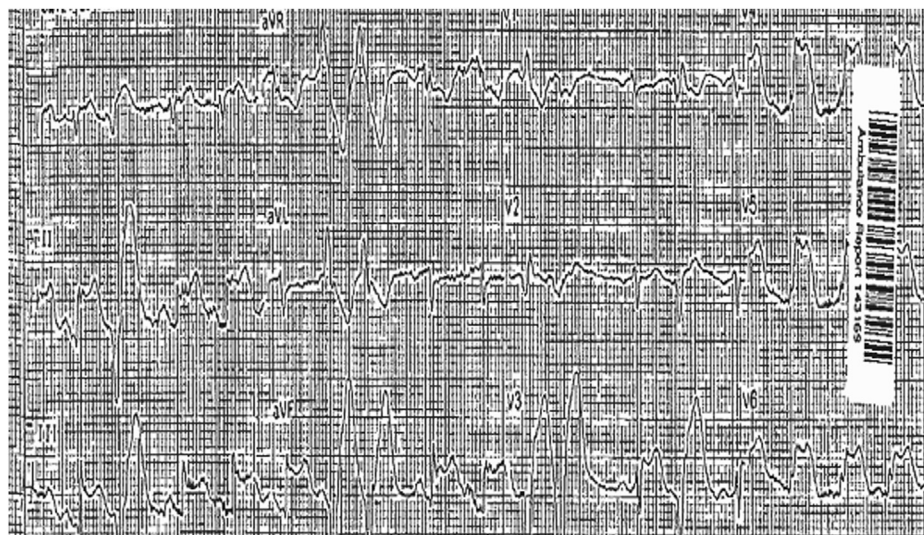


Figure 1. Prehospital 12-lead electrocardiogram showing >4 mm of ST-segment elevation in inferior (II, III, aVF) and anterolateral (V3, V4, V5, V6) leads and ST-segment depression in aVL.

rate of 170 beats/min, blood pressure 82/62 mm Hg, respiratory rate of 20 breaths/min, and oxygen saturation of 86% on ambient air. Cardiac and pulmonary auscultation were unremarkable. Transport time from the scene to the nearest hospital was prolonged due to the need for both rescue boat and ambulance transfers. En route to the hospital, the patient received supplemental oxygen, 1 liter of normal saline, 50mg of intravenous diphenhydramine, and a 2.5 mg albuterol sulfate nebulization. Her hemodynamics and oxygenation improved during transport. Upon arrival to the mainland, a prehospital 12-lead electrocardiogram (ECG) revealed sinus rhythm with 4-mm ST-segment elevations in the inferior and anterolateral leads accompanied by premature ventricular contractions. Reciprocal changes were evident in aVL (Figure 1).

The patient arrived at a nearby tertiary care center 1 h and 15 min after the onset of her symptoms. At that time, her dyspnea and chest discomfort had markedly improved although ST-segment elevations and depression persisted on ECG (Figure 2). Chest x-rays and routine laboratory studies were without abnormalities. Cardiac biomarkers returned mildly elevated, with a troponin T of 0.41 ng/mL, peak total creatinine kinase 218 U/L, and creatinine kinase MB equaling 10.5 ng/mL. While awaiting cardiac consultation, she was administered i.v. doses of methylprednisolone (125mg), unfractionated heparin (60U/kg bolus then 12U/kg/hr drip), and eptifibatide (180mcg/kg bolus followed by 2mcg/kg/min drip) as well as clopidogrel (600mg) taken orally. Aspirin was never given due to reported allergy. Serial ECGs revealed normalization of

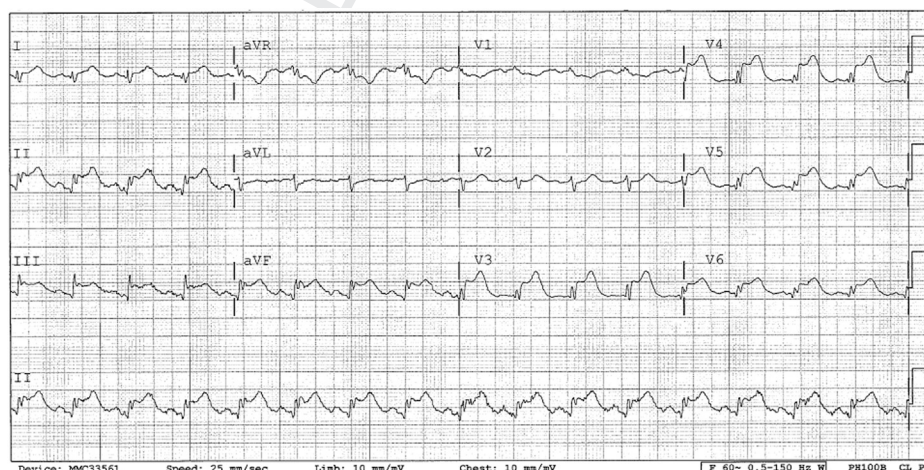


Figure 2. Initial electrocardiogram obtained on arrival to the emergency department and over an hour after symptom onset reveals persistent ST-segment elevation in leads II, III, aVF as well as leads V3–V6. Reciprocal ST-segment depression in aVL continues.

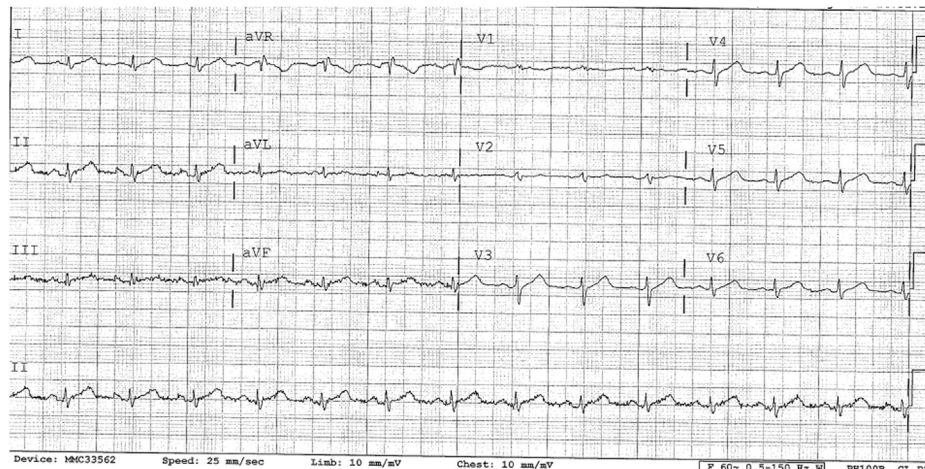


Figure 3. Repeat electrocardiogram 2 h after hospitalization demonstrates marked regression of ST-segment elevation.

ST elevation within 2 h of hospital arrival (Figure 3). Cardiac consultation was obtained in the emergency department. Immediate cardiac catheterization was deferred, given the patient's symptomatic improvement as well as resolution of ischemia on ECG.

The patient was continued on i.v. heparin and eptifibatide. A transthoracic echocardiogram performed later that day revealed akinesis of the apical third of the left ventricle with a preserved ejection fraction. The next morning, cardiac catheterization and angiography demonstrated normal coronary arteries (Figure 4). The patient was discharged home in good condition on a steroid taper.

DISCUSSION

The occurrence of allergic reaction concomitant with myocardial infarction was first observed and published in 1950 during a protracted hypersensitivity response to

penicillin (3). Decades later, Kounis and Zavras coined the syndromes of *allergic angina* and *allergic myocardial infarction* to describe the coincidental occurrence of acute coronary events with allergic or hypersensitivity reactions (4,5). Today, such phenomena are referred to as Kounis syndrome (1).

The pathophysiology of Kounis syndrome centers on the activation and degranulation of mast cells during an allergic insult. Once triggered via immunoglobulin E crosslinking, the complement system, or other mechanisms, mast cells release potent inflammatory substances both locally and in the peripheral circulation (1). These chemical mediators, which include histamine, thromboxane, leukotrienes, and neutral proteases can induce coronary artery spasm and platelet activation in susceptible individuals (6,7). Various medications, environmental exposures, and medical conditions can provoke Kounis syndrome (2). Although several nonsteroidal anti-inflammatory drugs can precipitate this condition, this

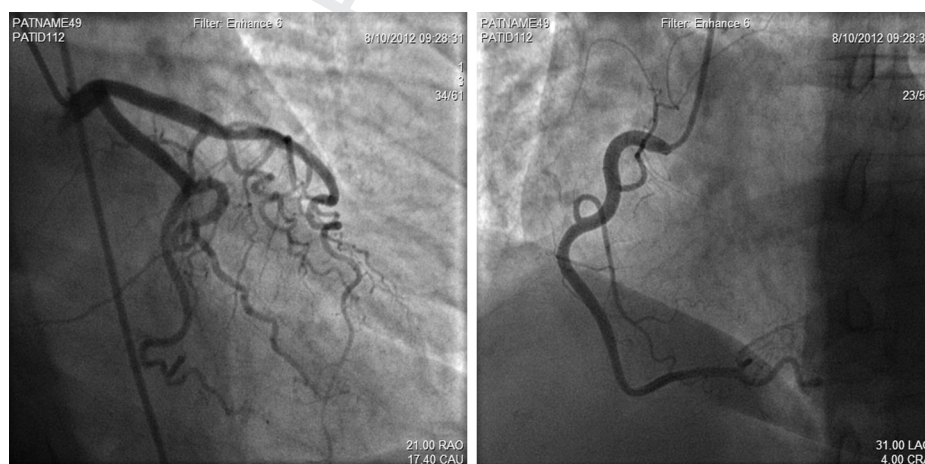


Figure 4. Cardiac catheterization with coronary angiography performed the following day shows normal patency of left anterior descending and left circumflex arteries (left image), as well as a normal right coronary artery (right image).

case is the first known report connecting celecoxib with Kounis syndrome.

Three subtypes of Kounis syndrome exist in the medical literature. The type I variant encompasses individuals who have normal coronary arteries and are free of atheromatous risk factors, and in whom the acute release of inflammatory mediators induces coronary artery spasm with or without elevation of serum cardiac biomarkers (1). Type II variant consists of subjects with pre-existing coronary artery disease in whom proinflammatory compounds induce either coronary vasospasm or atheromatous plaque erosion and rupture (1). More recently, a third subtype of Kounis syndrome involving coronary stent thrombosis owing to drug allergy has been proposed (8).

Severity of symptoms involving Kounis syndrome can range from mild angina with hives and pruritus to life-threatening anaphylaxis associated with left ventricular dysfunction and cardiogenic shock (9). Individuals with atopy are at increased risk of developing Kounis syndrome compared to normal individuals, and often experience worse symptoms due to an amplified inflammatory response (10,11). Prognosis depends on several elements, including magnitude of the initial response, patient sensitivity, comorbidity, site of antibody-antigen reaction, allergen concentration, and the route of allergen entrance (12). Although adults are more frequently affected, events in children have also been documented (13,14).

Medical management of patients with Kounis syndrome is often challenging because the clinician must consider and treat both cardiac and allergic insults simultaneously. To date, no definitive guideline exists, and current strategies for treating Kounis syndrome derive from published case reports. Therapies aimed at suppressing the hypersensitivity response consist of histamine receptor blockers, corticosteroids, epinephrine, and intravascular volume replacement (15,16). Pharmacotherapeutic measures in acute coronary syndromes include anti-platelets, anti-coagulants, and when appropriate, agents that decrease myocardial oxygen consumption (nitrates, beta-blockers, calcium channel blockers) (15,16). Cardiac catheterization along with intracoronary vasodilator infusion has helped treat type I Kounis (16). Angioplasty and thrombus evacuation may have utility for type II variants. Administration of epinephrine for Kounis syndrome is a complex issue. Although a lifesaving medication in anaphylaxis, epinephrine's α -adrenergic effects can exacerbate coronary vasospasm and worsen myocardial ischemia (17,18). Current anaphylaxis guidelines have no absolute contraindications against administration of epinephrine, and support its application in life-threatening situations (19).

Long-term treatment and prevention of Kounis syndrome should be tailored to the specific subtype affecting the patient. In type I, allergen avoidance might be sufficient. For more complicated cases of Kounis syndrome,

the use of mast cell-stabilizing medications has been suggested. Inhibition of mast cell degranulation avoids the release of inflammatory mediators and helps prevent adverse sequelae, such as coronary vasospasm and plaque erosion (15). Mast cell stabilizers can also have value in managing unstable angina and myocardial infarction of nonallergic etiology (15). Several of the vasoactive substances known to cause Kounis syndrome are found at elevated concentrations in patients experiencing acute coronary syndromes—unrelated to hypersensitivity (20–22). This approach has been shown to reduce the incidence of thrombotic events in laboratory animals after experimental mast cell activation (23).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

It is important to consider the diagnosis of Kounis syndrome in patients presenting with chest discomfort, ECG changes and accompanying allergic symptoms. While the severity of cases is variable, prompt recognition and medical intervention is essential for optimizing patient outcomes. Treatments should be directed at both suppression of the allergic reaction and relaxation of the coronary vasculature. The use of epinephrine in Kounis syndrome is a challenging decision and probably best reserved for life-threatening situations.

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