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Case Reports

Kounis Syndrome: A Sting to the Heart

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Abstract

A 67-year-old woman experienced pruritus, an urticarial rash, and acute, pressure-like chest pain following an insect sting. Initial electrocardiographic findings were notable for ST-segment elevations in the inferior leads without reciprocal changes, but a follow-up electrocardiogram showed pronounced ST-segment elevations in the inferior leads with reciprocal changes. Her troponin I level peaked at 3,053 pg/mL, and she was transferred to a large academic center for percutaneous coronary intervention. Balloon angioplasty was performed for 95% thrombotic occlusion of the mid–right coronary artery, and a drug-eluting stent was placed. The patient's presentation was consistent with type II Kounis syndrome.

Keywords: Allergy; Kounis syndrome; ST elevation myocardial infarction

Introduction

Kounis syndrome is a rare type of dynamic coronary artery occlusion caused by an allergic prodrome; the occlusion can eventually lead to an acute myocardial infarction (MI). The condition is underrecognized, especially given the frequency of allergic reactions.[1] Greater awareness of Kounis syndrome will allow clinicians and frontline healthcare workers to promptly consider underlying acute coronary syndrome (ACS) in patients experiencing allergic reactions.

Case Report

A 67-year-old woman with a history of hypertension, hyperlipidemia, nonalcoholic steatohepatitis, elevated hemoglobin A_{1c} (5.8%), and obstructive sleep apnea was transferred to a quaternary medical center because of concern for an acute ST-segment elevation myocardial infarction (STEMI). The patient had been performing yard work and was stung by an insect 3 times in the right leg. Following the stings, she experienced severe pruritus of the lower extremities, upper chest, and ears that did not resolve with diphenhydramine. She also developed acute, pressure-like chest pain, 8 out of 10 in intensity, that radiated to her right arm. She reported nausea but no emesis.

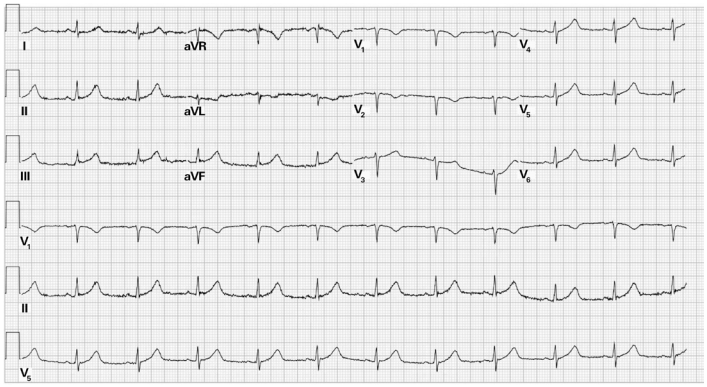

Fig. 1 Initial electrocardiogram shows minimal ST-segment elevations in the inferior leads.

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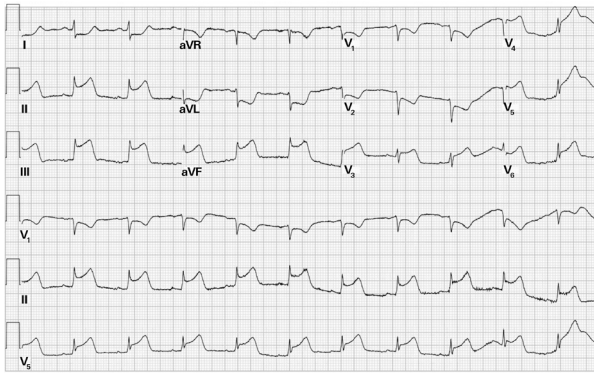

Fig. 2 Repeat electrocardiogram shows an inferior ST-segment elevation myocardial infarction.

When she arrived at the emergency department, an urticarial rash was noted on her torso, but there were no signs of angioedema or respiratory mucosal involvement. Initial electrocardiographic findings were notable for minimal ST-segment elevations in leads II, III, and aVF, with no reciprocal changes (Fig. 1). The patient received 0.3 mg of intramuscular epinephrine, which initially improved her pruritus and chest pain. However, the chest pain quickly changed in quality and severity: the patient described crushing, substernal chest pain with 10 out of 10 intensity. Repeat electrocardiography showed profound ST-segment elevations in leads II, III, and aVF, with reciprocal changes in leads I, aVL, V_1, and V_2 (Fig. 2).

The patient remained hemodynamically stable and did not have hypertension, even after receiving epinephrine. Nitroglycerin was not administered because of concerns for an inferior STEMI and possible right ventricular involvement. She was given intravenous morphine, which mildly abated her pain. Her initial high-sensitivity troponin I level was 2,442 pg/mL, eventually peaking at 3,053 pg/mL. An initial complete blood cell count and differential showed a leukocytosis of 16,900/μL with a neutrophil predominance (13,800/μL) and no eosinophilia. The patient was given a loading dose of aspirin (324 mg) and heparin, then transferred to a facility that could perform percutaneous coronary intervention (PCI); the facility was advised to activate their STEMI catheterization laboratory.

The diagnosis of an inferior STEMI was made at the accepting facility, and emergency PCI was performed via right radial artery access. The culprit lesion was a 95% thrombotic occlusion of the mid–right coronary artery (Fig. 3A). Balloon angioplasty was performed and a drug-eluting stent was placed (Fig. 3B), but thrombectomy was not required. The patient was given a loading dose of prasugrel in the catheterization laboratory and started on a tirofiban infusion that lasted 12 hours. The

Abbreviations and Acronyms

ACS	acute coronary syndrome
CAD	coronary artery disease
LAD	left anterior descending coronary artery
MI	myocardial infarction
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction

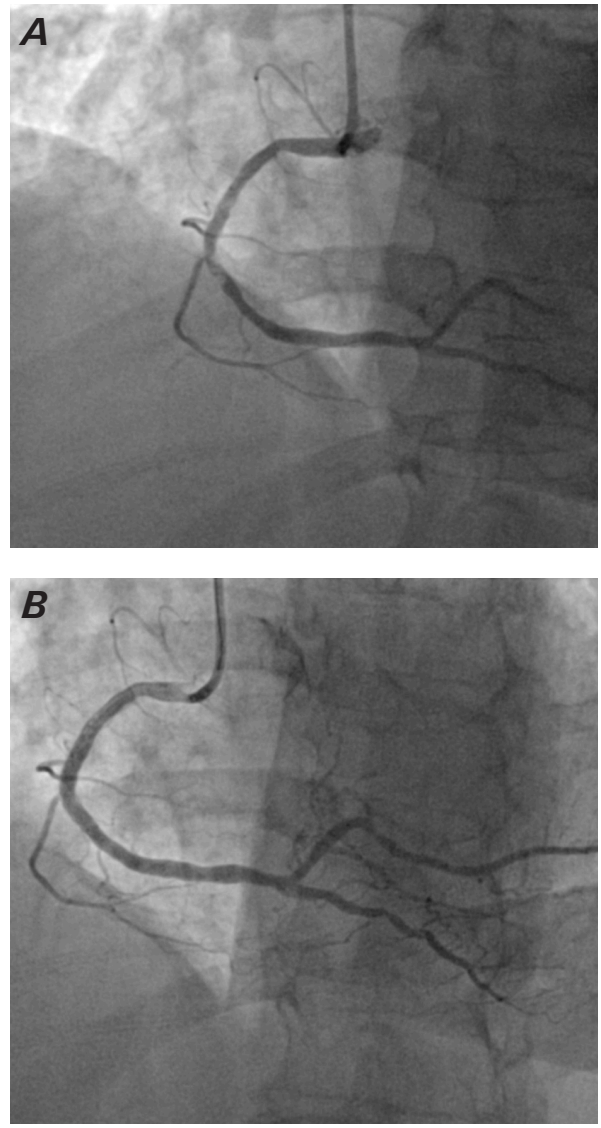

Fig. 3 A) angiogram obtained before percutaneous coronary intervention showing 95% thrombotic occlusion of the mid–right coronary artery; **B**) angiogram after percutaneous coronary intervention with balloon angioplasty and placement of a drug-eluting stent into the right coronary artery.

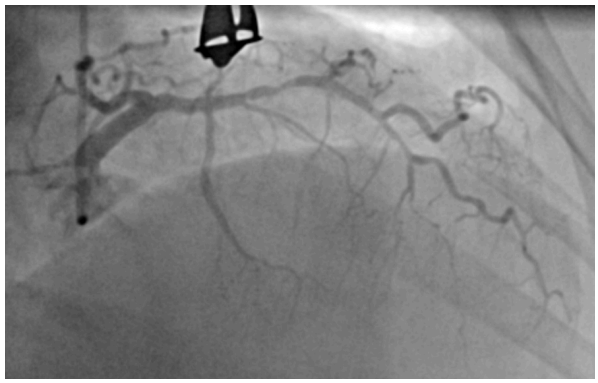

Fig. 4 Angiogram shows diffuse disease in the left anterior descending coronary artery.

left anterior descending artery coronary artery (LAD) appeared to be diffusely diseased throughout the mid- and distal portions, and there appeared to be a distal subtotal occlusion (Fig. 4), but intervention for the LAD was deferred to a later date.

On further questioning after PCI, the patient reported intermittent episodes of pressure-like chest pain, with radiation to the right shoulder, over several months before the incident that brought her to the hospital. She described weekly episodes that were often nonexertional and resolved quickly. She had never been formally evaluated by a cardiologist or had a workup for ischemia.

The patient remained stable and free from chest pain throughout the course of her hospitalization after PCI, and she did not require inpatient rehabilitation. She was discharged on dual antiplatelet therapy with aspirin (81 mg), prasugrel (10 mg), and atorvastatin (80 mg) daily, and metoprolol tartrate (25 mg) twice daily. She was discharged home with instructions to attend outpatient cardiac rehabilitation. The decision on whether to intervene in the LAD was deferred to the follow-up cardiology appointment.

Discussion

This report describes a 67-year-old woman who presented with symptoms and clinical evidence consistent with an acute STEMI during a suspected anaphylactic reaction to an insect sting. This clinical presentation is consistent with previous reports of Kounis syndrome, which has been described as ACS resulting from an allergic reaction to a drug, environmental exposure, or toxin.[1] The first report of an acute MI occurring in the setting of a protracted allergic reaction was published in 1950.[2] At that time, a possible underlying relationship between MI development and the concomitant allergic reaction was not clearly understood. It was not until 1991 that the first comprehensive review outlining the theorized etiology and pathophysiology of "allergic angina" was published, and the condition received its eponym of Kounis syndrome.[3]

Kounis syndrome is defined as ACS propagated by the activation of mast cells and platelets by inflammatory mediators (ie, histamine, arachidonic acid products, platelet-activating factor, and numerous chemokines and cytokines) that are released during an acute allergic insult.[4] The role of these inflammatory mediators in ACS has been elucidated in autopsy studies. Pathologic evaluation of the coronary arteries of 20 patients who suffered an acute MI, without any underlying evidence of an allergic reaction, showed an extremely high level of mast cell degranulation at the areas of plaque rupture. This led investigators to conclude that the proteases housed within mast cells could lead to plaque rupture and that this process is further amplified by an allergic insult.[5]

Of special note is the underlying role that mast cells play in Kounis syndrome. Mast cells are the primary activators of macrophages and T lymphocytes, acting through numerous chemokines and cytokines. In turn, macrophages and T lymphocytes act on mast cells, further propagating their activation. Mast cell degranulation is the key step of a hypersensitivity reaction that results in the release of numerous inflammatory mediators—in particular, histamine, which plays an active role in the expression of tissue factor, coronary vasoconstriction, and platelet activation. Other proteases released from mast cells can induce direct activation of matrix metalloproteinases, which further degrade the collagen cap and ultimately lead to plaque erosion and rupture.[6]

In 1998, Braunwald[7] officially recognized and categorized allergic angina as a specific category of dynamic coronary occlusion resulting from inflammatory mediators that are released during an allergic reaction; these mediators activate the smooth muscle within the coronary arteries, causing coronary vasospasm. The authors of a 2015 report noted that patients admitted to emergency departments with signs and symptoms indicative of anaphylaxis, angioedema, or urticaria have troponin I levels higher than those of nonaffected individuals.[8] This provides further evidence that the myocardium and coronary arteries are directly affected during anaphylaxis.

Kounis went on to describe 3 distinct subtypes of the syndrome.[9] Type I is seen in people with normal coronary arteries and no history of coronary artery disease (CAD). It is the direct result of coronary artery vasospasm caused by the allergic reaction. Type II is seen in people with known but stable CAD; it is the direct result of plaque rupture or erosion resulting from the allergic reaction. Type III is seen in people who have undergone PCI and is the direct result of platelet activa-

tion, from the allergic reaction, causing in-stent thrombosis.

Documented cases of Kounis syndrome are quite rare. A 2017 review estimated that there were 175 authentic cases reported in the literature.[10] However, the authors asserted that the syndrome is often underdiagnosed—if not outright missed—resulting in an overall underestimation of its incidence. Subsequent authors have estimated that Kounis syndrome occurs in up to 1.1% of patients with allergic hypersensitivity.[11] Given that the patient in this report eventually reported a history of angina, she likely experienced type II Kounis syndrome. With her underlying CAD, the cascade of inflammatory mediators from the allergic reaction to the insect sting resulted in plaque rupture and platelet activation.

Attention should be paid to the management of Kounis syndrome—in particular, type II. The patient in this report was initially treated with intramuscular epinephrine, which resolved her pruritus but resulted in a near-instantaneous change in the quality and severity of her chest pain. Intramuscular epinephrine should be used with caution in patients experiencing Kounis syndrome. Although it is considered first-line treatment for anaphylaxis, it can exacerbate coronary vasospasm and worsen cardiac ischemia,[12] all of which may have occurred in this patient. Corticosteroids and antihistamines, given with a routine ACS protocol, are the recommended initial treatments of choice for mild allergic reactions, with intramuscular epinephrine reserved for frank anaphylaxis.[13]

Conclusion

Kounis syndrome is a legitimate but underrecognized cause of coronary artery occlusion. The fact that allergic reactions are extremely common in local emergency departments means that clinicians need to be aware of the possibility of an allergic reaction triggering ACS, especially in people with known CAD. Through increased awareness of the syndrome, deleterious outcomes can be avoided and countless lives can be saved through the timely implementation of effective treatments.

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