CASE REPORT

# The atopic heart: a curious case of coronary hypersensitivity

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## ABSTRACT

Kounis syndrome is a coronary hypersensitivity disorder involving coronary vasospasm secondary to inflammatory mediators released primarily from mast cells. We report a case of the type I variant of Kounis syndrome manifesting as angioedema with significant inferolateral ST elevation (2 mm) and raised cardiac biomarkers. Diagnosis requires a high index of suspicion and treatment is tactical. Caution should be exercised before using beta-blockers, morphine and epinephrine, which are empiric in cases of acute coronary syndrome and anaphylaxis, respectively. Our patient was treated with intravenous steroids and histamine blockers given the angioedema at presentation. The purpose of our case is to emphasise the importance of including Kounis syndrome in the differential diagnosis for acute coronary syndrome, and formulation of standard treatment guidelines for this under-recognised condition.

## KEYWORDS

Kounis syndrome, coronary hypersensitivity, acute coronary syndrome, troponin, allergic reaction, ST-elevation

**What was known on this topic?**

Kounis syndrome, first described in 1991, encompasses vasospastic angina, allergic myocardial infarction, and stent thrombosis with occluding thrombus infiltrated by eosinophils and/or mast cells. Kounis syndrome is heterogeneous with several agents implicated in the aetiology and chemical mediators in pathogenesis; however, in many, diagnosis is missed due to a lack of physician awareness (except in parts of Spain, Italy, Greece, and Turkey). Research is needed for formulating standardised diagnostic criteria and treatment guidelines, and this will help avoid missed diagnosis, allow better prediction of prognosis, and more appropriate therapy in the future.

**What does this case add?**

Kounis syndrome should always be included in the differential diagnosis of acute coronary syndrome as it is an under-recognised condition. The diagnosis of Kounis syndrome is tactical due to lack of awareness of this common entity in areas outside the Mediterranean region and lack of consistency in clinical presentation. Studies in the form of randomised controlled trials are needed to establish an international consensus on the treatment of Kounis syndrome.

## CASE REPORT

A 70-year-old woman presented to the emergency department with new-onset difficulty in breathing and worsening generalised pruritus. She had tachycardia with marked tongue swelling, generalised skin rash, laboured breathing and stridor. Hence, she was emergently intubated for significant upper airway oedema. Her medical history included asthma, hypertension with home medications notable for naproxen, ibuprofen, benazepril, folic acid, and hydroxyzine but no known allergies. We presumed angioedema, and started treatment with intravenous corticosteroids, histamine (H)1 and (H)2 receptor blockers.

Complete blood count, blood chemistry, troponin-I and chest X-ray were normal. However, the post intubation electrocardiogram (ECG) revealed sinus tachycardia with 2 mm ST-segment elevation in the inferior and lateral leads (*figure 1*). Troponin-I was now 5 ng/ml (normal 0-0.045) with the maximum being 5.6 ng/ml, and the

echocardiogram showed apical and septal wall hypokinesis suggestive of Takotsubo cardiomyopathy. The patient underwent emergent left heart catheterisation, which revealed normal coronary arteries, and an ejection fraction of 20%. The ECG changes returned to baseline after treatment (*figure 2*).

A diagnosis of type I Kounis syndrome was suggested based on concurrence of angioedema and ST-elevation myocardial infarction (STEMI) in the setting of normal coronary anatomy. Subsequent work up showed an IgE level of 221 IU/ml (normal < 114), and normal C1 esterase inhibitor, C3, C4 and tryptase. By day 4 of hospitalisation, she was weaned off mechanical ventilation and discharged.

## DISCUSSION

First described in 1991, Kounis syndrome is the concurrence of acute coronary syndromes (ACS) (angina and/or myocardial infarction) with allergic reactions (hypersensitivity, anaphylaxis or anaphylactoid reaction) due to coronary artery vasospasm caused by inflammatory mediators released during the allergic insult.[1] Kounis syndrome is a common, yet rarely diagnosed condition. Three variants are recognised: type I with normal or near-normal coronary arteries, type II with preexisting atheromatous disease, and type III with coronary stent thrombosis.[2] Various drugs (beta-lactam antibiotics, analgesics, contrast media, anti-cancer agents, proton pump inhibitors, angiotensin-converting enzyme inhibitors, thrombolytics), conditions (angioedema, urticarial, asthma, mastocytosis), and environmental exposures (hymenoptera stings, latex, poison ivy) can cause Kounis syndrome with recent offenders including histamine fish poisoning and losartan.[3]

The aetiology in our case was likely multifactorial with predisposing asthma, medications including naproxen and benazepril, and succinylcholine used for intubation, and angioedema at presentation. Common adverse effects of the above medications include: NSAIDs causing gastrointestinal ulcer/bleeding, rash, nephrotoxicity, hepatotoxicity; benazepril causing cough, hyperkalaemia, azotaemia, angioedema; folic acid causing nausea, anorexia; and succinylcholine causing muscle paralysis, rhabdomyolysis and malignant hyperthermia.

Pathogenesis of Kounis syndrome involves mast cells, which release mediators such as histamine and leukotrienes that constrict coronary vessels, and tryptase/chymase that cause plaque rupture/erosion.[4] Patients present with chest pain with or without elevation of troponins, along with dermatological and/or systemic manifestations of allergy. ECG changes range from ST elevation or depression to arrhythmias. Unlike ACS, the degree of ST elevation may not correlate with the troponin levels. In cases of Kounis syndrome with normal cardiac biomarkers and ECG, cardiac magnetic resonance imaging helps to confirm the diagnosis.[5] Furthermore, signs of cardiac disease and/or hypersensitivity may be absent, making Kounis syndrome an easily overlooked diagnosis. The differential diagnosis includes hypersensitivity myocarditis and isolated eosinophilic arteritis. Hypersensitivity myocarditis is usually clinically indistinguishable from Kounis syndrome, however, it is characterised by the presence of eosinophils, atypical lymphocytes and giant cells on myocardial biopsy. While eosinophilic arteritis involves

**Figure 1.** *Admission ECG showed sinus tachycardia with 2 mm ST-elevation in inferior (II, III, aVF) and lateral leads (V4, V5, V6)*

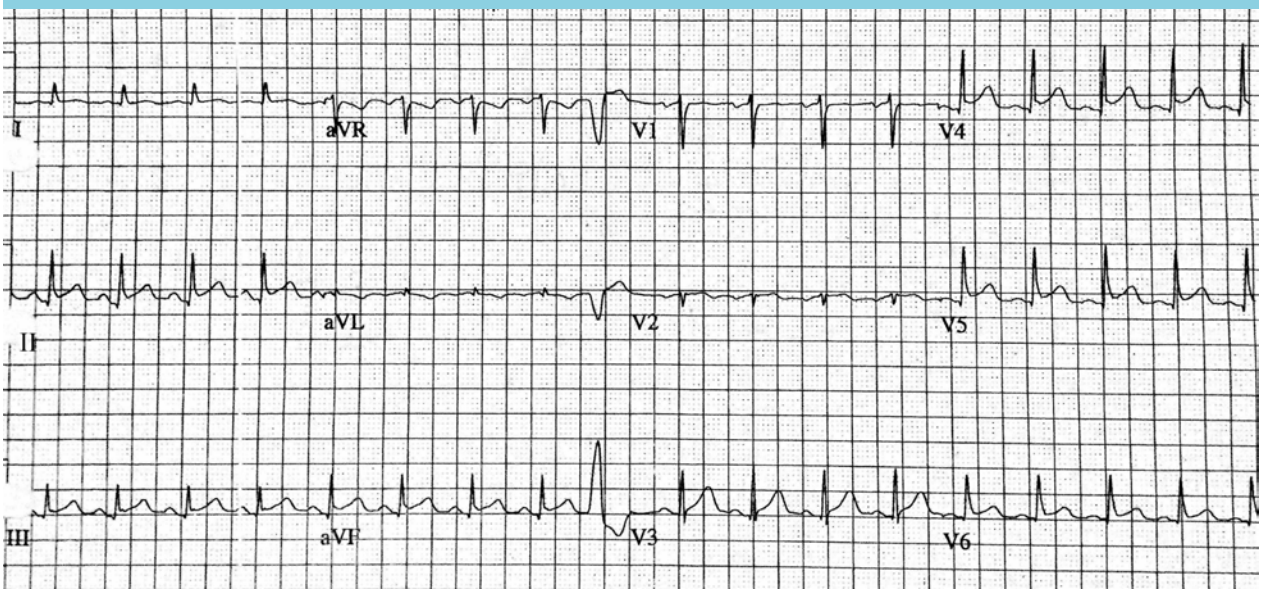
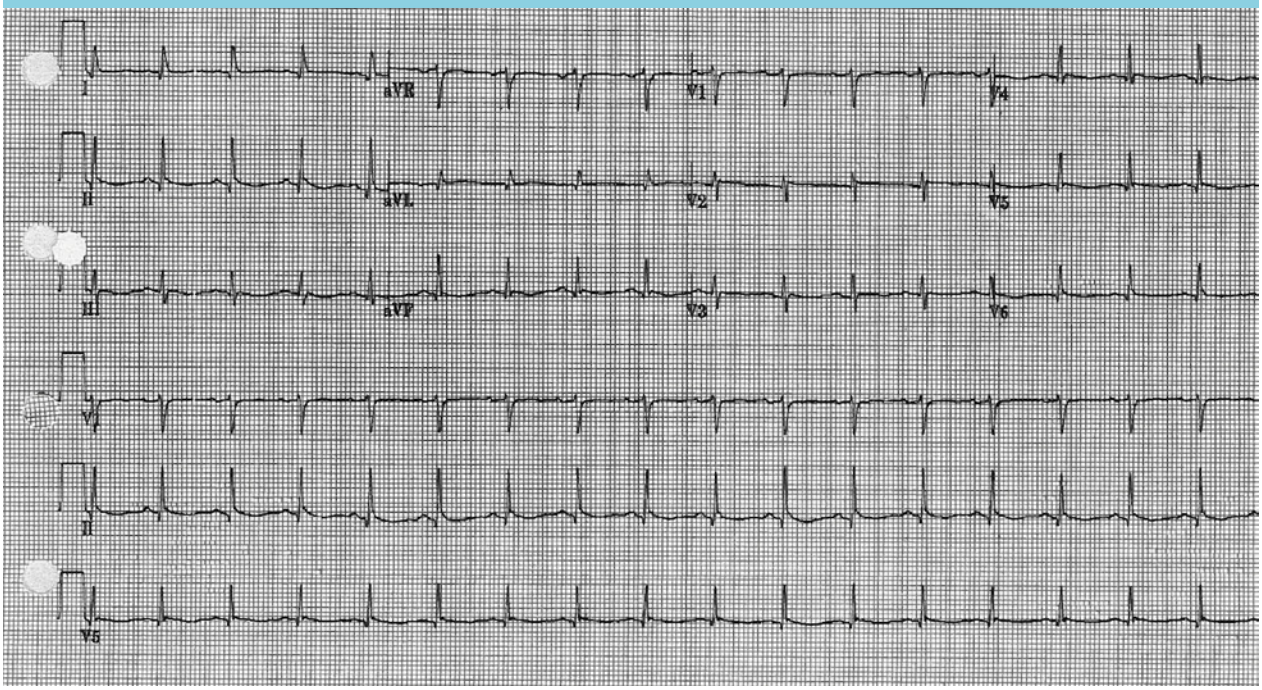


**Figure 2.** *Post treatment with steroids and histamine blockers, the ECG showed normal sinus rhythm with resolution of the ST elevation*




eosinophilic infiltration in all layers of the vessel wall with diffusely distributed mast cells. Further, Kounis syndrome is commonly associated with Takotsubo cardiomyopathy,[6,7] as seen in our case.

No biomarker accurately predicts the risk of Kounis syndrome, albeit recent reports link elevated serum tryptase levels to increased susceptibility to allergic reactions as well as asymptomatic ACS.[8] Further, treatment is challenging with a lack of uniform consensus on therapy. Most recommendations are based on anecdotal case reports or case series.[9] A 2009 review revealed intravenous steroids (76%), nitroglycerin (47%), H1-blockers (70%), and H2-blockers (35%) as the most commonly used treatment options.[10] Both beta-blockers (commonly used in ACS) and epinephrine (commonly used in anaphylaxis) should be avoided as they exacerbate coronary spasm due to unopposed alpha-adrenergic activity. Further, data supporting the use of prophylactic medications such as H1-blockers to avoid recurrence is lacking.[11] The prognosis of Kounis syndrome depends upon the patient's sensitivity, allergen concentration, number of allergens the patient is exposed to, magnitude of the initial allergic response as well as the syndrome's variance, with type I Kounis syndrome having a better prognosis than type II and type III.[12]

## DISCLOSURES

The authors declare no conflicts of interests. No funding or financial support was received.

## REFERENCES

1. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. Br J Clin Pract. 1991;45:121-8.
2. Nikolaidis LA, Kounis NG, Grandman AH. Allergic angina and allergic myocardial infarction: a new twist on an old syndrome. Can J Cardiol. 2002;18:508-11.
3. Kounis NG. Coronary Hypersensitivity Disorder: The Kounis Syndrome. Clin Ther. 2013;35:563-71.
4. Lopez PR, Peiris AN. Kounis Syndrome. South Med J. 2010;103:1148-55.
5. Akoz A, Bayramoglu A, Uzkeser M. Two questions for Kounis syndrome: can we use magnetic resonance imaging in the diagnosis and does ST elevation correlates with troponin levels? Am J Emerg Med. 2012;30:2086. e5-e7.
6. Kounis NG, Filippatos GS. Takotsubo and Kounis syndrome: is there any association? Circ. J. 2007;71:170.
7. Cheng TO, Kounis NG. Takotsubo cardiomyopathy, mental stress and the Kounis syndrome. Int J Cardiol. 2012;161:65-7.
8. Deliargyris EN, Upadhya B, Sane DC, et al. Mast cell tryptase: a new biomarker in patients with stable coronary artery disease. Atherosclerosis. 2005;178:381-6.
9. Cevik C, Nugent K, Shome GP, Kounis NG. Treatment of Kounis syndrome. Int J Cardiol. 2010;143:223-6.
10. Ridella M, Bagdure S, Nugent K, Cevik C. Kounis syndrome following beta-lactam antibiotic use: review of literature. Inflamm Allergy Drug Targets. 2009;8:11-6.
11. Gunaydin ZY, Bektas O, Akgedik R, Kaya A, Acar T. Recurrent Kounis syndrome. How should be the long-term treatment of Kounis syndrome? Int J Cardiol. 2014;177:1042-3.
12. Biteker M. Current understanding of Kounis syndrome. Exp. Rev. Clin. Immunol. 2010;6:777-88.