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## Letter to the Editor

## The conundrum of hypersensitivity cardiac disease: Hypersensitivity myocarditis, acute hypersensitivity coronary syndrome (Kounis Syndrome) or both?

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## ABSTRACT

Hypersensitivity or allergic inflammatory processes can affect the cardiac structures during allergic insults. The myocardium, the conduction system and the coronary arteries can be the targets of these insults resulting in Kounis syndrome (hypersensitivity coronary syndrome) or hypersensitivity myocarditis. Kounis syndrome and hypersensitivity myocarditis can be clinically indistinguishable and masquerade each other. Simultaneous occurrence of both entities has not been reported. We report on a patient who presented with signs and symptoms of type I variant of Kounis syndrome but cardiac magnetic resonance imaging showed that he had hypersensitivity myocarditis.

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## 1. Introduction

Hypersensitivity is synonymous to allergy and denotes an excessive reaction associated with gross tissue changes after antigen–antibody (IgE or IgM) reaction. The cardiac tissue can be easily affected by hypersensitivity processes, while the myocardium and the coronary arteries are especially vulnerable as well. There are two clinical entities of hypersensitivity etiology, 1) Hypersensitivity coronary syndrome or Kounis syndrome [1], a concurrence of acute coronary syndrome with conditions associated with mast cell degranulation involving interrelated and interacting inflammatory cells and including hypersensitivity or allergic and anaphylactic or anaphylactoid insults and 2) Hypersensitivity myocarditis [2], an inflammatory disease affecting the myocardium and the cardiac conduction system manifesting as an allergic complication of drug therapy.

The following unique report is of a patient who presented with clinical and laboratory findings suggesting of acute coronary hypersensitivity syndrome (Kounis syndrome) but who was proved, with cardiac magnetic resonance (CMR) imaging, at a later stage, to have myocardial changes compatible with hypersensitivity myocarditis. The clinical course, the laboratory and differentiating findings of these two relative entities are discussed.

## 2. Case report

A 28 year-old male had an episode of acute bronchitis with temperature of 38 °C and his family physician prescribed amoxicillin 1gr b.i.d. Six hours later the patient felt generalized itching accompanied by

erythematous rash covering the whole body surface. He was given 500 mg of hydrocortisone sodium succinate intramuscularly followed by oral cetirizine 10 mg b.i.d. The following 24 h, rash and itching started to subside. However, he was feeling unwell and he was admitted to our hospital for further evaluation.

On examination, he had not any significant past medical history and was not smoker. He did not give any history of atopy and did not have any previous hospitalizations. His family history was free of any cardiac or chest disease. One hour after admission he developed severe retrosternal pain radiating to the neck and elbows. He started sweating with difficulty in breathing. His blood pressure was 120/80 mm Hg, the pulse 69 beats/min regular and on auscultation there was neither pericardial rub nor murmurs. The electrocardiogram showed ST elevation of 3 mm in leads II, III, AVF, V7–V9 compatible with acute inferior myocardial infarction (Fig. 1). He was, immediately, given 5 mg of nitroglycerin sublingually and 325 mg of aspirin and was transferred to the coronary care unit. The above symptoms were persisting and infusion of nitroglycerin was started at a rate of 2 mcg/min. However, electrocardiographic changes and symptoms did not subside and he was thrombolysed with 40 mg of tenecteplase. Half an hour later the patient developed sinus bradycardia of 40 beats/min with dizziness and diaphoresis. With 0.5 mg of atropine iv bradycardia and symptoms subsided and the electrocardiographic changes reverted to normal (Fig. 2). Transthoracic echocardiography revealed hypokinesia and segmental akinesia involving the inferior wall with an estimated ejection fraction of 55%. Next day cardiac catheterization revealed normal coronary arteries. The blood results showed peak CPK 855 IU/L (normal range 21–232), CPK-MB 90 IU/L (normal range 0–6), troponin 21.35 (normal range >0.05), eosinophils 7% (normal range 3–5). Cardiac magnetic resonance imaging, two weeks later, showed hypokinesia of the inferolateral wall and late gadolinium enhancement in the subepicardial corresponding area

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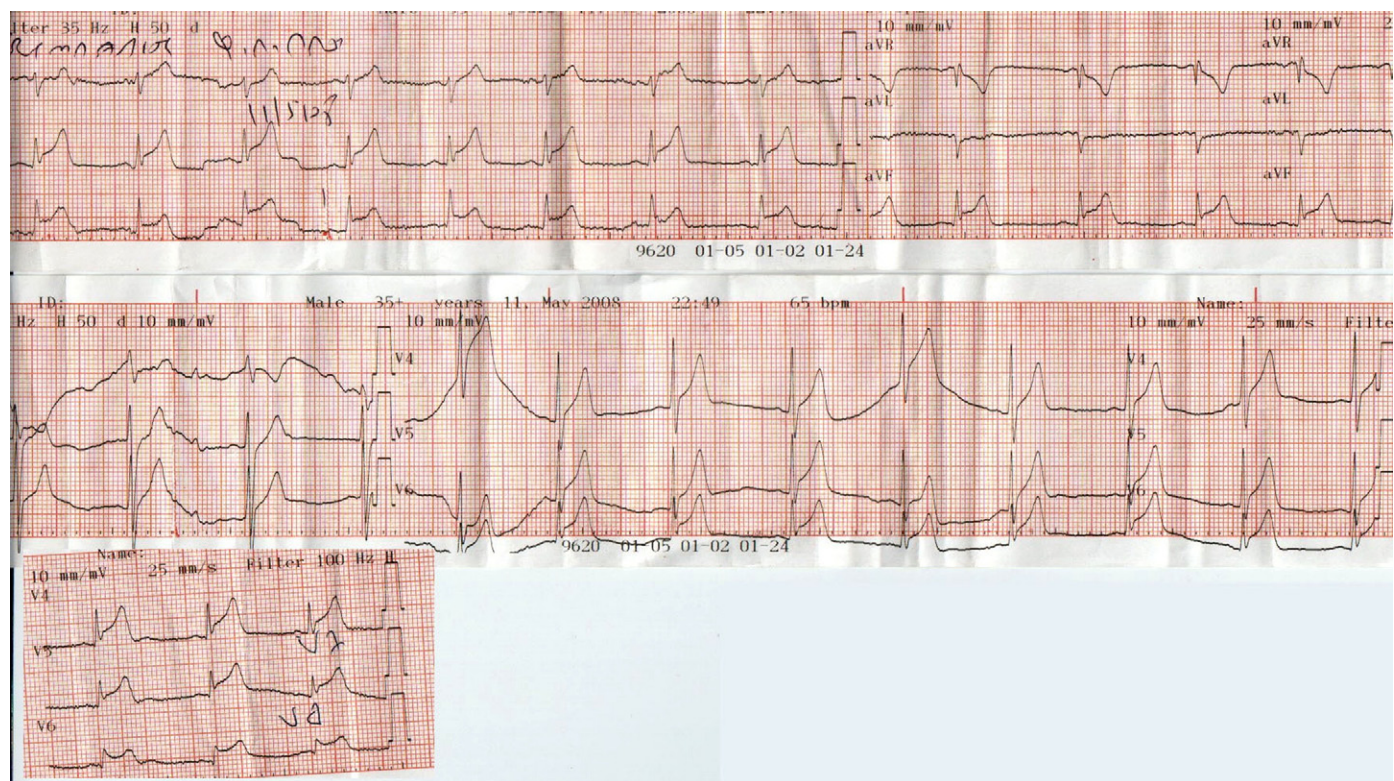


**Fig. 1.** Electrocardiogram showing ST elevation of 3 mm in leads II, III, AVF V7-V9 compatible with acute inferior myocardial infarction.

(Fig. 3, arrows) compatible with myocardial inflammation due to focal myocarditis. A second CMR study 6 months later showed complete resolution of the inflammation (Fig. 4).

### 3. Discussion

The described patient developed severe retrosternal pain following an allergic reaction to amoxicillin administration for acute bronchitis. Electrocardiography and blood tests, including cardiac enzymes and troponin, confirmed the diagnosis of an acute myocardial infarction of type I variant of Kounis syndrome [3–9]. This variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease in whose the acute release of inflammatory mediators during the allergic reaction can induce either coronary artery spasm without increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. Initially, the patient was suspected to have suffered episodes of coronary artery spasm and was treated with sublingual nitroglycerin followed by nitroglycerin infusion. However,

this does not exclude transient coronary occlusion by thrombus. Indeed, the administration of thrombolytic therapy with tenecteplase relieved the symptoms and reverted the electrocardiographic changes to normal which denotes clot lysis.

Cardiac magnetic resonance imaging, performed two weeks after discharge, showed hypokinesis in the inferolateral wall with late gadolinium enhancement in the sub-epicardial corresponding area which was reverted to normal 6 months later. This finding was compatible with myocardial oedema and myocyte damage suggesting myocarditis. Although infectious disease accounts for most cases in previously healthy patients, myocardial inflammation may also be triggered by reversible or irreversible toxic, ischaemic or mechanical injury, drug related inflammation or other immune reactions. Since this patient had a recent history of skin allergic reaction to amoxicillin, drug-induced hypersensitivity myocarditis was the leading diagnosis. Cardiac magnetic resonance can differentiate acute myocarditis from acute myocardial infarction. Microscopic [10], animal [11] and clinical studies have confirmed the role of late gadolinium enhancement CMR as a gold standard for in vivo diagnosis of myocardial infarction. In patients

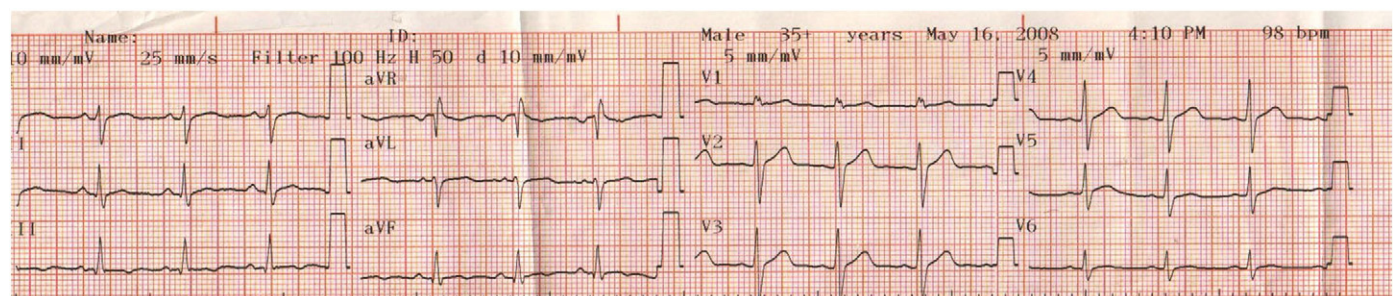


**Fig. 2.** The electrocardiographic changes have reverted to normal after thrombolysis with tenecteplase.



**Fig. 3.** Cardiac magnetic resonance imaging, two weeks later, showing late gadolinium enhancement in the sub-epicardial corresponding area (arrows) compatible with myocardial inflammation due to focal myocarditis.

with myocarditis, several studies had demonstrated a highly specificity of late gadolinium enhancement for diagnosing such injury in myocarditis [12–16]. In acute myocarditis, the distribution of gadolinium uptake is patchy and does not conform to any particular coronary territory but usually appears in the sub-epicardial or mid-wall myocardial layers and never in the sub-endocardial area alone [17]. In contrast, in acute myocardial infarction, the gadolinium late enhancement is always in the sub-endocardial area. This late enhancement area corresponds to the infarct-related artery. Late gadolinium enhancement not only allows differentiating ischemic injury [18] but may also indicate the possible aetiology of the non ischemic insult. Follow-up studies, at least 4 weeks after the onset of the disease, may be useful to differentiate

uncomplicated involvement of the myocardium and may be of prognostic value [19].

There is a discrepancy in the results of some studies concerning sensitivity, specificity and accuracy of CMR in detecting myocarditis. A study [20] showed 44%, 100% and 71% respectively while another study [21] showed 88% sensitivity. Others [22] have attributed this discrepancy to the fact that, in borderline myocarditis, myocyte injury is not present thus making the contrast enhancement not visible.

Our patient showed a dramatic improvement after urgent thrombolysis and this suggests that a thrombotic coronary occlusion was most likely responsible for his clinical presentation. Perhaps the immediate tenecteplase administration had a crucial immediate effect on the thrombotic occlusion which did not allow the injury to extend and affect the sub-endocardial territory.

In conclusion, hypersensitivity myocarditis and hypersensitivity coronary syndrome (Kounis syndrome) seem to be two clinical entities which share the same etiology and symptomatology thus making their differential diagnosis difficult [23].

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [24].

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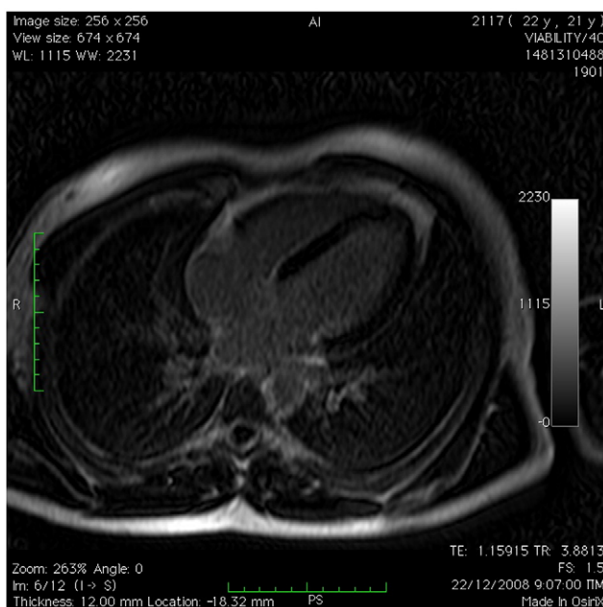


**Fig. 4.** Cardiac magnetic resonance imaging, six months later showing complete resolution of the inflammation.

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