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Case Report

Kounis syndrome and hypersensitivity myocarditis – One and the same? Insights from cardiac magnetic resonance imaging

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ABSTRACT

Myocarditis and acute coronary syndrome are both described in the setting of concurrent hypersensitivity reactions to a variety of allergenic triggers (hypersensitivity myocarditis and Kounis syndrome respectively). Mast cell degranulation is thought to be pivotal in the pathogenesis of both clinical entities. Cardiac magnetic resonance imaging (CMR) has assumed a key role in the assessment of chest pain syndromes, providing a useful non-invasive tool to aid clinical decision-making. Despite increasing availability and uptake of CMR, only a small fraction of published Kounis syndrome cases report CMR findings, and confirmation of myocardial infarction remains elusive. We present a case of presumed Kounis syndrome with comprehensive CMR imaging that provides an insight into why these two well-described clinical entities share many clinical features – perhaps they are one and the same. <**Learning objective:** Myocarditis and acute coronary syndrome (ACS) in the setting of hypersensitivity reactions share similar clinical characteristics. Endomyocardial biopsies are often not undertaken in this patient group, and differentiation has typically been at the clinicians' discretion. Cardiac magnetic resonance imaging can provide an insight into the underlying pathogenesis, with currently available evidence suggesting myocarditis is a prerequisite for ACS, rather than being stand-alone clinical entities.>

Introduction

Myocarditis and acute coronary syndrome are both described in the setting of concurrent hypersensitivity reactions to a variety of allergenic triggers. Mast cell degranulation is thought to be pivotal in the pathogeneses of both clinical entities – the former resulting in myocardial inflammation and the latter in coronary artery vasospasm, allergic myocardial infarction, or stent thrombosis (Kounis syndrome variants I, II, and III respectively). Clinical presentation, electrocardiograph (ECG) changes, and biochemical markers are virtually identical in both descriptions. It is recommended that patients presenting with any grade of systemic allergic reaction associated with clinical, laboratory, and ECG evidence of myocardial ischemia be diagnosed with Kounis syndrome [1].

Since Kounis syndrome was first described in 1991 [1] there have been significant advancements in both cardiac magnetic resonance imaging (CMR) technology and accessibility, which now assumes a key role in the non-invasive diagnosis of acute myocarditis, and more widely in the assessment of undifferentiated chest pain syndromes. Despite these advances and mounting case reports in the literature, there remains a paucity of CMR data in Kounis syndrome. To date, three cases fulfilling clinical criteria for Kounis syndrome have reported CMR imaging. Two cases were consistent with hypersensitivity myocarditis rather than myocardial infarction, one of which was proven on endomyocardial biopsy [2,3]. The third case cited tapering myocardium, hypokinesis in the distal inferior wall and apex, and a small pericardial effusion as evidence of myocardial ischemia, all features that could – and are more likely to – reflect myocarditis, particularly in the absence of late gadolinium enhancement (LGE), an elevated troponin level, or abnormal ECG findings [4]. Surprisingly there are no cases of Kounis syndrome with objective evidence of isolated myocardial ischemia or infarction. Our case presentation, CMR findings, and subsequent literature review provide an insight into why these two clinical entities are often inseparable – perhaps they are one and the same.

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Case report

A 58-year-old man presented to the emergency department with influenza-like symptoms, dizziness, chest pain, dyspnea, and an erythematous rash. Cardiovascular risk factors included hypertension and hypercholesterolemia. He was hypotensive (blood pressure 85/45 mmHg), tachycardic, and hypoxic (SaO2 82–84%). An ECG showed ST segment elevation in the inferior leads with reciprocal ST depression in V1, V2, and aVL (Fig. 1). He was taken for emergency cardiac catheterization that revealed only mild (20%) proximal right coronary artery stenosis without evidence of ruptured vulnerable plaque or vasospasm. Left coronary arteries were angiographically smooth and systolic function on left ventriculogram was normal (ejection fraction = 74%). Blood tests subsequently revealed an elevated troponin T that peaked at 681 ng/ml (normal <0.1 ng/ml).

Prior to his presentation, he reported a nine-day history of an influenza-like illness for which he consulted his general practitioner, who prescribed amoxicillin with clavulanic acid. His symptoms began abruptly after taking the first dose, having completed a course of the same antibiotic without incident three weeks earlier. Initial serum tryptase level was elevated at 111 μg/L (normal <12 μg/L), normalizing by day three. Subsequent allergen specific IgE was positive to penicilloyl G (6.7 kU/L), penicilloyl V (91.5 kU/L), and amoxicilloyl (49 kU/L), consistent with an immediate hypersensitivity reaction to amoxicillin. Full blood examination and biochemistry were unremarkable. The clinical presentation, ECG, coronary angiogram, and blood work findings were consistent with a diagnosis of type I Kounis syndrome. He remained stable throughout his admission without symptoms or signs of heart failure.

CMR imaging was performed on the fourth day to evaluate the etiology of myocardial necrosis, and specifically to assess for evidence of myocarditis or myocardial infarction. This showed overall normal left ventricular systolic function (ejection fraction = 61%) with hypokinetic mid to distal inferior wall segments. Contrast agent was administered (0.15 mmol/kg Gd-DTPA; Magnivist; Schering AG, Berlin, Germany) with evidence of early gadolinium enhancement (EGE) and myocardial edema in these regions. Delayed imaging was performed after 10 min, showing transmural late gadolinium enhancement (LGE) in the distal inferior wall, with patchy mid-wall and sub-epicardial LGE in adjacent segments (Fig. 2). Repeat CMR three months later showed normal left ventricular systolic function, resolution of edema and EGE, but persistence of transmural and subepicardial LGE in the distal inferior wall (Fig. 2). These findings were suggestive of both myocarditis (subepicardial and mid-wall LGE) and myocardial infarction (subendocardial LGE extending transmurally).

Discussion

Kounis syndrome has been defined as "the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult" [1]. More than 300 cases of Kounis syndrome have been reported in the literature without racial or age predilection, and in response to a variety of allergens. Degranulation of mast cells and release of inflammatory mediators such as histamine, tryptase, serotonin, and leukotrienes are postulated to promote the coronary artery vasospasm thought to underlie type I variant Kounis syndrome, although causation has not been established in humans or experimental models [1]. An elevated serum tryptase level was evidence of mast cell activation in our patient.

Like Kounis syndrome, a variety of allergens have been implicated in hypersensitivity myocarditis, the most common cause of acute medication-related myocardial injury [2]. Rather than predominantly affecting the coronary arteries as postulated in Kounis syndrome, the allergic reaction manifests as myocardial inflammation with or without pericardial and conduction system involvement [3]. Myocardial inflammation of any cause has been known to mimic acute coronary syndrome (ACS). For example, endomyocardial biopsies of 24 consecutive patients with suspected ACS but normal coronary arteries showed evidence of viral genomes in 71% of cases, suggesting myocarditis as the cause [5]. Sarda and colleagues showed 40% of 45 patients presenting with presumed ACS but normal coronary arteries had scintigraphic evidence of focal or heterogenous myocarditis [6]. Furthermore, Yilmaz et al. provoked coronary vasospasm with intracoronary acetylcholine in 71% of patients presenting with atypical chest pain and biopsy-proven myocarditis, compared with 40% of patients with similar symptoms but normal biopsy results, suggesting

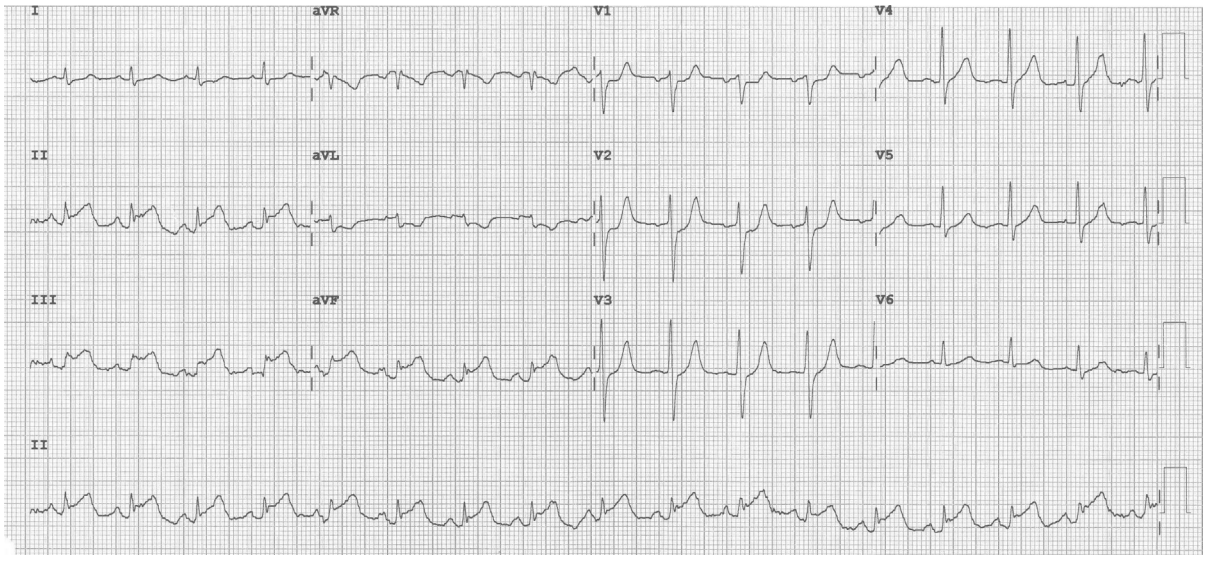

Fig. 1. Presenting electrocardiogram showing inferior ST elevation with reciprocal depression.