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An unusual presentation of allergic reactions: Kounis syndrome

過敏反應的一個不尋常表現：Kounis 綜合徵

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Kounis syndrome is a rare cause of angina pectoris and acute coronary syndrome associated with acute allergic reactions. We present a case of one middle-aged male with this syndrome presenting with ST elevation on electrocardiogram after amoxicillin intake. It is important that clinicians be aware of the possible link between allergic disorders and acute coronary syndromes. Therefore, an allergic insult should be considered during diagnostic and therapeutic steps in managing acute coronary syndromes in appropriate clinical context. Acute coronary syndromes associated with this syndrome should be managed per relevant guidelines and timely coronary angiography should be performed in majority of cases. (Hong Kong j.emerg.med. 2015;22: 371-375)

Kounis綜合徵是心絞痛和急性冠脈綜合徵的一種罕見病因，與急性過敏反應有關。我們報告一個中年男性Kounis綜合徵案例，表現為攝入阿莫西林後心電圖ST段抬高。臨床醫生知道過敏性疾病和急性冠脈綜合徵之間可能有關是重要的。因此，在診斷和治療急性冠脈綜合徵時，當有合適的臨床情境，應該考慮過敏性反應。當急性冠脈綜合徵與此綜合徵結合，應該按照相關的指引進行治理，大多數情況下應及時進行冠狀動脈造影。

Keywords: Coronary artery disease, coronary vasospasm, drug hypersensitivity

關鍵詞：冠狀動脈疾病、冠狀動脈痙攣、藥物過敏

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Introduction

Kounis syndrome is a rare cause of angina pectoris and acute coronary syndrome associated with acute allergic reactions. However, it is often underdiagnosed and underreported due to lack of awareness of its presence. First described by Kounis et al 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] it has been increasingly recognised as a potential cause of angina pectoris,[2] acute coronary syndromes,[3] and possibly stent thrombosis.[4] We describe here a case with allergic reaction associated with ST elevation in electrocardiogram (ECG) and near-normal coronary arteries on coronary angiography.

Case report

A 41-year-old male patient presented to our emergency department with pruritus and redness of skin after taking amoxicillin. He simultaneously had substernal chest pain of crushing-squeezing character which started minutes after the skin symptoms began and gradually worsened, with no radiation to arms, back, or neck. At presentation, he had ongoing substernal pain exceeding half an hour. His vital signs were as follows: heart rate: 87/min, respiratory rate:16/min, body temperature: 37.0°C, blood pressure: right arm (sitting): 135/90 mmHg, left arm 130/85 mmHg. His physical examination revealed acute urticarial plaques that had a tendency to coalesce. He had no perioral or uvula swelling, nor did he have rhonchi in chest examination.

Three to five days before the index presentation with pruritus, he presented to our emergency department with the same complaints of skin redness and urticarial plaques but without chest pain. He was diagnosed to have acute urticaria for which he was given phenyramine 45.5 mg intravenously (IV), ranitidine 100 mg IV, and methylprednisolone IV (1 mg/kg), each time with rapid success. At the time of presentation, he was on both long and short-acting antihistamines; namely desloratadin 5 mg orally a day and clemastin 1 mg orally two times a day. He also gave a history of chest pain after accidental contact with a β-lactam antibiotic one year ago. No previous skin prick test had been performed to identify allergic triggers, nor did he give a history of allergic event with therapeutic doses of any drugs, including antibiotics.

An ECG within 10 minutes of first medical contact revealed ST elevation in inferior derivations (Figure 1). He was given aspirin 300 mg (chewing tablet), heparin 5000 U in conjunction with methylprednisolone 1 mg/kg, phenyramine 45.5 mg IV, and ranitidine 100 mg IV. Troponin I and creatinine kinase/myocardial bioenzyme at 45 minutes of the pain were normal (<0.010 and <3.4 ng/ml, respectively). Urgent arrangements were made for primary percutaneous coronary intervention (PCI). Coronary angiogram revealed minor coronary artery

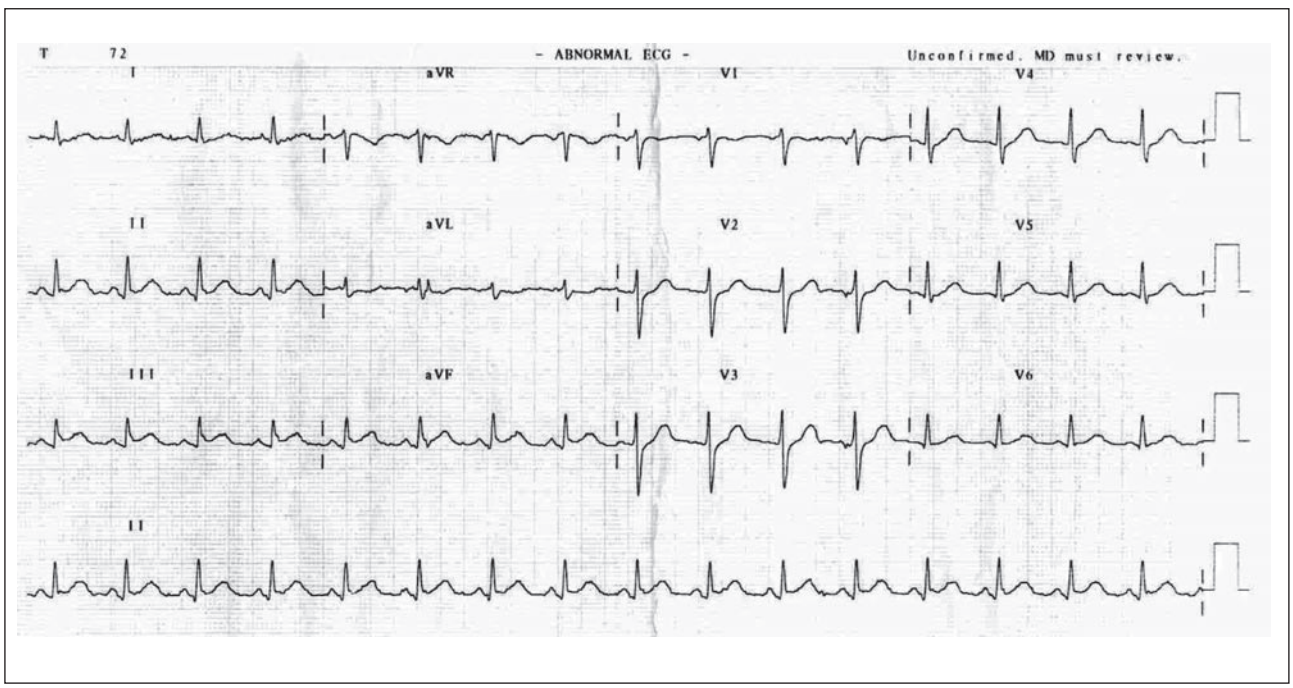


Figure 1. Electrocardiogram taken at presentation. Note ST elevations in inferior leads.

disease with luminal irregularities in all coronary arteries. No thrombi or vasospasm was detected (Figure 2). He had a normal control electrocardiogram (Figure 3). Cardiac enzymes at 8 and 12 hours after the start of chest pain were 0.071 and 0.108 ng/ml (upper limit of normal=0.100 ng/ml). He had no recurrent symptoms under antihistaminic and antithrombotic (aspirin 100 mg) therapy and was discharged. A later echocardiogram revealed normal left ventricular function with an ejection fraction of 58%. He continued aspirin therapy along with antihistaminic therapy. A skin prick/intradermal test with a β-lactam antibiotic was not performed due to fear of inducing a recurrent acute coronary event. Skin prick tests with a panel of commercial extracts of airborne and food allergens (Allergopharma, Italy) failed to show any offending agent. He was free of any symptoms as of the date of the writing of this report.

Discussion

Acute coronary syndrome induced by allergy is a less defined clinical entity. Kounis syndrome is described as the co-occurence of acute coronary syndrome with allergic insults including allergic and hypersensitivity reactions, and anaphylaxis.[1] It is caused by mast cell activation, resulting in mast cell degranulation and release of chemical mediators, including histamine, leukotrienes as well as tryptase and chymase that activate metalloproteinases which degrade collagen and induce plaque rupture.[5,6] Histamine is known to be a powerful vasodilator in the peripheral circulation but it exerts a constrictor action on smooth muscle of coronary arteries via H1 receptors, leading to vasospasm.[5]

Two types of Kounis syndrome have been identified. Type 1 occurs in people with normal coronary arteries. Type 2, on the other hand, includes patients with preexisting coronary artery disease with plaques or flow-limiting stenoses which are eroded or ruptured by inflammatory mediators or coronary vasopasm.[7] Our case was consistent with Type 2, as no obstructive coronary lesions were identified on coronary angiography, with some luminal irregularities being present.

So far, cases with Kounis syndrome presenting with ST elevation myocardial infarction (STEMI) and

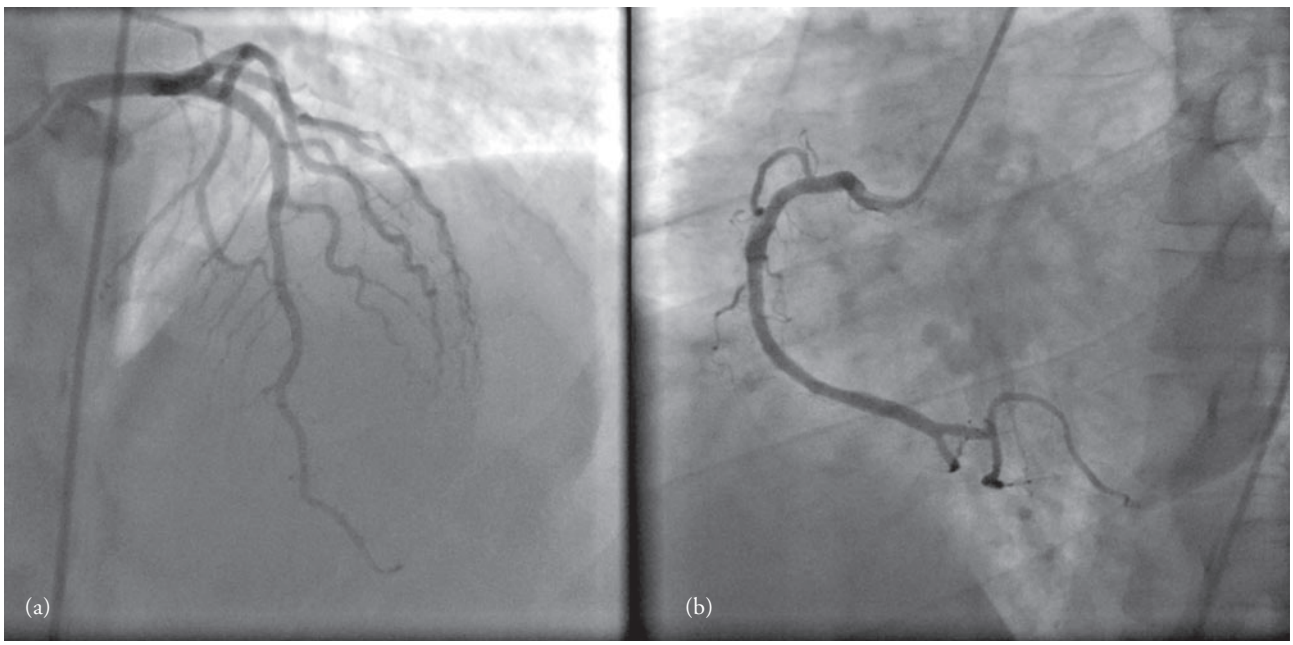


Figure 2. Left (a) and right (b) coronary arteries. Both arterial systems were free of flow-limiting stenoses, albeit having minor lumen irregularities.

coronary stent thrombosis have been reported.[4,8] The overall prognosis of the disease is favourable, most of the cases being asymptomatic at long term under antihistaminic therapy. The allergenic triggers include both topical and food allergy. A variety of food or environmental substances and drugs including penicillin derivatives, environmental allergens, some food allergens, and genetic mutations have been reported to cause Kounis syndrome.[8-13] Our patient had also penicillin allergy.

Our case presented with ST segment elevation, which is the common ECG manifestation. It is intriguing to see temporary or permanent ST elevation associated with Kounis syndrome as the primary mechanism of acute coronary syndromes associated with this syndrome involves histamine-induced coronary vasospasm. A case series from Turkey reported that all six patients with Kounis syndrome presented with acute ST elevation and troponin elevation.[14] Likewise, a case series from Spain included 5 patients with Kounis syndrome, 80% whom presented with ST elevation and 100% with an elevated troponin levels.[12] However, cases with ST depression and T wave changes have also been reported. As mentioned above, chymase and tryptate activate metalloproteinases and cause plaque rupture that can cause unstable angina pectoris (USAP) and Non-ST elevation myocardial infarction (NSTEMI). Calogiuri et al[15] reported a case with Kounis syndrome associated with intravenous administration of piperacillin/tazobactam, leading to unstable angina with ST depressions and normal troponin level.

In patients with allergic reactions suspected to have Kounis syndrome a rapid ECG should be taken to rule out acute ECG changes, particularly ST elevation. Patients presenting with a clinical picture and ECG changes suggestive of an ACS should be treated per relevant guidelines. In patients suggestive of Kounis syndrome, simultaneous with acute coronary syndrome management, therapy for acute allergic reactions should be commenced without delay as the definite therapy of the syndrome depends on therapy of the acute allergic reaction. As the trigger for both theoretical vasospasm and plaque rupture is allergic reactions and resulting vasoactive amines, the therapy for allergic reactions is an integral and perhaps more

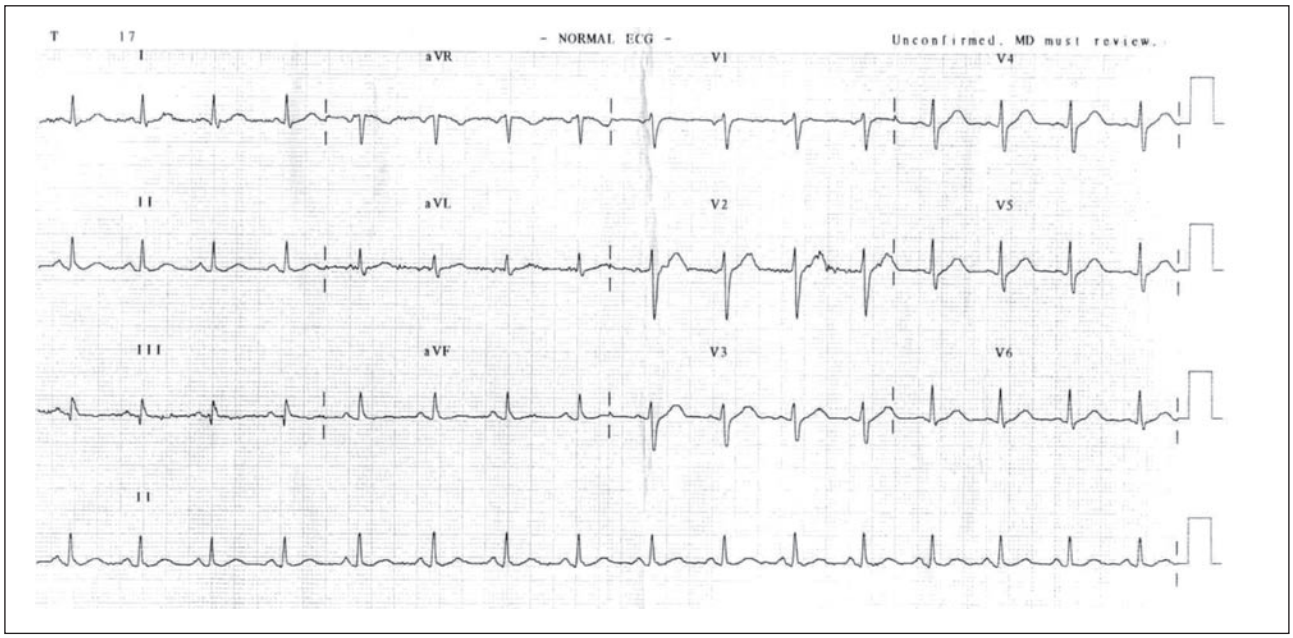


Figure 3. Control electrocardiogram taken after angiography. Note the complete resolution of ST elevation in inferior leads.

important part of the therapy. As the physiopathology of this rare entity is vasospasm rather than occlusive thrombus formation, it would be prudent to proceed directly with coronary angiography rather than administering fibrinolytic agents.

Conclusions

Kounis syndrome should be considered in patients with simultaneous allergic reactions and chest pain. It is crucial to understand that every type of coronary events may take place, namely STEMI, non-STEMI or unstable angina. If acute coronary syndrome is suggested by the ECG, subsequent management of the patient involves simultaneous treatment of allergic reaction and acute coronary syndrome. Coronary angiography is central in treating patients with STEMI.

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