



Letter to the Editor

Kounis Syndrome secondary to amoxicillin/clavulanic acid use in a child

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Abstract

The concurrence of acute coronary syndromes with allergic or hypersensitivity as well as with anaphylactic or anaphylactoid reactions is increasingly encountered in clinical practice and there are several reports associating mast cell activation with acute cardiovascular events in adults. It was first described by Kounis as “allergic angina syndrome” progressing to “allergic myocardial infarction”. The main mechanism proposed is the vasospasm of coronary arteries. This condition has not been described in childhood. We present a 13-year-old boy, admitted to our hospital with thoracic pain, 30 min after the ingestion of an oral dose of 500 mg of amoxicillin/clavulanic acid.

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1. Introduction

Allergic angina and allergic myocardial infarction, referred as “Kounis Syndrome”, have gained acceptance as a new cause of coronary artery spasm. Kounis and Zavras [1] described the “syndrome of allergic angina” 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. Allergic angina can progress to acute myocardial infarction which was named “allergic myocardial infarction” [2–3]. Causes of Kounis Syndrome [4] include drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, nonsteroidal anti-inflammatory drugs, skin disinfectants, thrombolytics, anticoagulants), various conditions (angioedema, bronchial asthma, urticaria, food allergy, exercise induced allergy, mastocytosis, serum sickness), and environ-

mental exposures (stings of ants, bees, wasps, jellyfish, grass cutting, millet allergy, poison ivy, latex contact, shellfish eating, viper venom poisoning). Kounis Syndrome due to amoxicillin/clavulanic acid use in the adults is rare, and its appearance in the children caused by this agent may be even rarer, and it has never been reported before. Such was the case in a child to be described herein.

2. Case report

A 13-year-old healthy boy who had never been hospitalized previously, was admitted to our emergency department because of severe chest pain and mild pruritic skin rashes. His complaints had started approximately 30 min after ingesting an oral dose of 500 mg of amoxicillin/clavulanic acid and lasted for 20 min. He was admitted to the emergency room 1 h after the onset of symptoms. On admission, he had no complaints, his physical examination was normal and his electrocardiogram showed ST segment elevations in leads II, III, aVF, V4, V5 and V6 (Fig. 1). He has no family history of coronary artery disease. Transthoracic echocardiography, performed in the coronary

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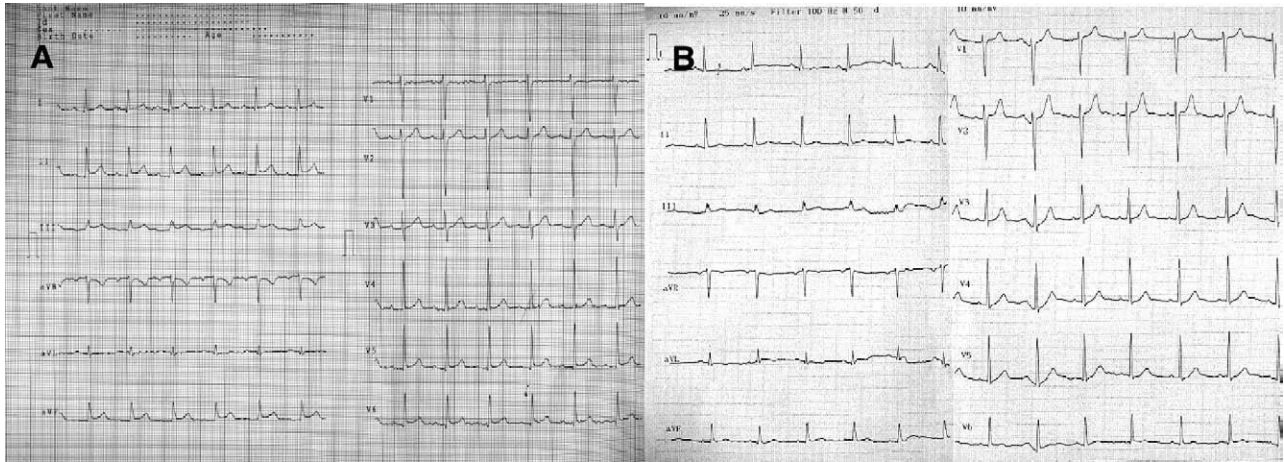


Fig. 1. Twelve-lead electrocardiography at presentation (A) showing ST elevation on II, III, aVF, V4, V5 and V6. Four days after the presentation electrocardiography (B) showed resolution of ST elevation.

intensive care unit, revealed inferior wall hypokinesia. Troponin-I estimated on arrival was 2.1 ng/ml (reference: 0–0.1 ng/ml), creatine kinase-MB fraction (CK-MB) was 30 U/L (reference: 0–25 U/L). In order to exclude coronary artery disease coronary angiography was performed, which revealed normal coronary arteries (Fig. 2).

Complete blood count, D-dimer, antithrombin III, lipoprotein (a), brain natriuretic peptide (BNP), serum cholesterol levels were normal. Antistreptolysin-O (ASO) titer, third and fourth complement component levels and antinuclear antibody, anti-DNA, *Salmonella* and *Brucella* agglutination tests were within normal limits. The serologic tests for viral etiology were negative for hepatitis A, B, C virus, human immunodeficiency virus (HIV), Coxsackievirus B, adenovirus and parvovirus B19. Cytomegalovirus (CMV) immunoglobulin (Ig) M and IgG, Epstein–Barr virus (EBV) viral capsid antigen (VCA) IgM and IgG, EBV nuclear antigen (EBNA) IgM and IgG tests were also negative.

Anticardiolipin IgG and IgM and lupus anticoagulants were negative. Factor VIII and fibrinogen levels were within normal limits. There was not protein C or protein S deficiency. Among

the thrombogenic gene panel studied (Factor V Leiden, factor V H1299R, prothrombin G20210A, factor XIII V34L, β -fibrinogen-455 G-A, MTHFR A 1298C, MTHFR C677T, PAI-1 4G-5G, GPIIIa L33P, ACE, ApoB R3500Q, ApoE), only MTHFR C677T homozygote mutation was disclosed.

Total IgE was 45 IU/ml (reference: 0–100) and amoxicillin specific IgE was negative, however serum tryptase was 31 μ g/L (reference: 5.6–13.5 μ g/L). Subsequent daily estimations of serum tryptase were within normal limits. Histamine was 0.1 ng/ml (reference: <0.2 ng/ml).

He was diagnosed to have Kounis Syndrome type I variant, secondary to amoxicillin/clavulanic acid ingestion. The patient was treated with oral antihistamines and 8 mg prednisolone every 6 h for 5 days. Troponin-I and CK-MB rose up to 13 ng/ml and 72 U/L, respectively. However, 4 days later, the repeated cardiac markers were within normal limits with resolution of electrocardiographic abnormalities (Fig. 1) and regression of inferior wall motion abnormality on echocardiographic changes. The boy was discharged from hospital in an excellent condition and after 1 month, in a following visit, he was doing well.

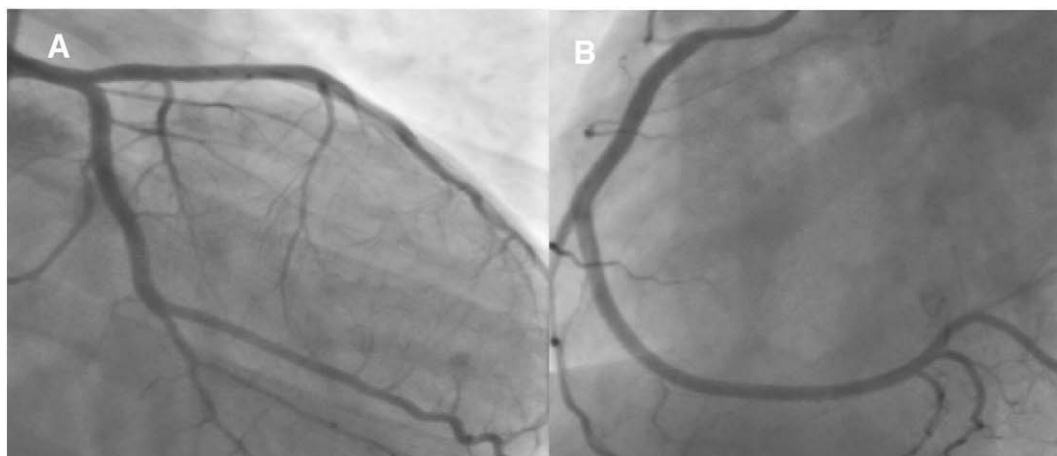


Fig. 2. His left (A) and right coronary arteries (B) were normal in coronary angiography.

3. Discussion

Kounis Syndrome is characterized by the concurrence of acute coronary syndrome with mast cell activation induced by inflammatory mediators released during allergic reaction [1–4]. Two variants of Kounis Syndrome have been described [4,5]. The type I variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease in whom the acute release of inflammatory mediators 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. The type II variant includes patients with culprit but quiescent pre-existing atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or plaque erosion or rupture manifesting as acute myocardial infarction.

In our patient all the markers for myocarditis were negative and he had no risk factors for coronary artery disease. His symptoms had started 30 min after the ingestion of an oral dose of 500 mg of amoxicillin.

Mast cells are found in most parts of the human body, including heart and vessels, and are involved in allergic and anaphylactic reactions through activation–degranulation [6]. Mast cell degranulation follows after antibody antigen reaction. However, sometimes direct action against the mast cell can happen [5,6]. This applies especially for drugs. Therefore the absence of amoxicillin IgE antibodies in our patient, does not exclude mast cell degranulation. Following mast cell degranulation several vasoconstricting and collagen degrading compounds are released locally and in the peripheral circulation. These compounds include preformed mediators such as histamine, neutral proteases (tryptase, chymase), platelet activating factor and newly synthesized mediators such as an array of cytokines and chemokines and others by the metabolism of arachidonic acid through activation of a phospholipase [5,6].

Tryptase levels were elevated, but histamine was undetected in our patient. Histamine is short lived and circulates only for 8 min following the allergic insult, but tryptase has a half-life of 90 min. The increased levels of tryptase suggest an acute allergic reaction, where tryptase has been incriminated to induce coronary artery spasm and/or plaque erosion or rupture [5–7]. Negative levels of histamine do not exclude the diagnosis of Kounis Syndrome due to short half-life of histamine.

Based on the above findings the diagnosis of type I variant of Kounis Syndrome induced by amoxicillin/clavulanic ingestion was made [8–11]. So far, the youngest patient with Kounis Syndrome reported in the literature was a 21-year-old female [11]. To the best of our knowledge the described patient is the first to be reported in an age of 13 years.

Our case highlights the fact that physicians should be aware of the allergic myocardial infarction. The diagnosis of this unique disease should be entertained when acute-onset chest pain is accompanied by allergic symptoms, electrocardiographic changes and elevated cardiac enzymes. All patients admitted to the emergency departments with chest pain and ST elevation on electrocardiography, should be interrogated for allergic insults.

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