

Allergic myocardial infarction in childhood: Kounis syndrome

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Abstract Kounis Syndrome was first described by Kounis as “allergic angina syndrome” progressing to “allergic myocardial infarction”. This report describes the first children in the literature presented with Kounis syndrome.

Keywords Allergy · Childhood · Kounis Syndrome · Myocardial infarction

Introduction

Kounis syndrome (KS), which comprises allergic angina and allergic myocardial infarction, can present as acute coronary syndrome (ACS) with concurrent anaphylactic/anaphylactoid reactions. Here, we describe the first children in the literature presented with KS.

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Case reports

The first patient was a 9-year-old previously healthy girl who was stung on the head and neck several times by honeybees. On clinical evaluation in the emergency room, she had erythematous rash over the face, neck, and arms. She complained of chest pain radiating to neck. Electrocardiogram showed elevation of ST segment in II, III, aVF, and V5–V6 leads compatible with acute inferior myocardial infarction. Echocardiographic examination performed at intensive care unit revealed hypokinesia of the inferior wall with an estimated ejection fraction of 50%. The results of blood examination showed increased troponin I of 4.3 ng/ml, CK-MB of 342 U/l, serum tryptase of 45 µg/l, and IgE of 190 IU/ml. Coronary angiography revealed normal coronary arteries. The patient was treated with oral antihistamines and prednisolone. Five days after admission, cardiac markers and serum tryptase levels were within normal limits with resolution of electrocardiographic abnormalities and regression of inferior wall motion abnormality on echocardiography.

The second patient was a 13-year-old boy admitted to our hospital with mild pruritic skin rashes and thoracic pain started 10 min after the ingestion of an oral dose of 500 mg of amoxicillin/clavulanic acid. 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. Transthoracic echocardiography 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). Coronary angiography revealed normal coronary arteries.

Total IgE was 45 IU/ml (reference=0–100 IU/ml) and amoxicillin-specific IgE was negative. However, serum

tryptase was 31 µg/l (reference=5.6–13.5 µg/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 KS 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. Four days later, the repeated cardiac markers were within normal limits with resolution of electrocardiographic abnormalities and inferior wall motion echocardiographic changes, and the patient was discharged on the fifth day.

The third patient was an 11-year-old healthy boy who had never been hospitalized previously, admitted to our hospital because of chest pain, pruritus, and palpitations. While interrogating about the risk factors, we learned that an oral amoxicillin/clavulanic acid was administered just before the clinical setting has initiated. Electrocardiography showed ST segment elevation in leads V2–V5 compatible with acute anterior myocardial infarction. Coronary arteries were completely normal on the angiography. Transthoracic echocardiography, performed in the coronary intensive care unit, revealed anterior wall hypokinesia. Troponin I, CK-MB, and tryptase estimated on arrival were elevated (5 ng/ml, 780 U/l, and 42 µg/l, respectively). Amoxicillin-specific IgE was also positive. We have treated him with corticosteroid, mast cell stabilizer (ketotifen 2 mg tb, 1×1 PO), and histamine (H2) antagonist (famotidine 20 mg tb 2×1 PO). ST segment elevation and anterior wall hypokinesia was regressed in a few days without any complications.

The last patient was a 10-year-old boy who was stung by wasps on his head and forearm. He was immediately transferred to hospital by his parents. He was admitted with mild pruriginous erythematous rash and chest pain. Electrocardiogram showed ST segment elevations in leads II, III, aVF, V5, and V6. Transthoracic echocardiography and coronary angiography were normal. The results of blood examination showed increased troponin I of 1.1 ng/ml, CK-MB of 42 U/l, serum tryptase of 33 µg/l, and IgE of 321 IU/ml. Blood eosinophils were also raised to 10%. However, blood histamine and complement proteins C3 and C4 were normal. He was treated with oral antihistamines and prednisolone. On the fifth day of admission, he was discharged with complete recovery and regression of electrocardiographic abnormalities.

Discussion

After the first report of acute myocardial infarction during a prolonged allergic reaction to penicillin was published in 1950 [9], the concurrence of allergic reactions and acute coronary syndromes called Kounis syndrome (KS) has gained acceptance as a new cause of coronary artery spasm

[5, 6]. Kounis and Zavras [6] 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” [4, 6]. There are several causes that have been reported as capable of inducing KS [3]. These include a number of drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, non-steroidal anti-inflammatory drugs, skin disinfectants, thrombolytics, anti-coagulants), various conditions (angio-edema, bronchial asthma, urticaria, food allergy, exercise induced allergy, mastocytosis, serum sickness), and environmental exposures (stings of ants, bees, wasps, jellyfish, grass cutting, millet allergy, poison ivy, latex contact, shellfish eating, viper venom poisoning). Although this condition has been rarely described in adults, the first child with KS has been recently described [1]. In this report, we describe the first children in the literature presented with KS which reminds one to keep in mind KS in the differential diagnosis of acute chest pain in children.

KS is characterized by the concurrence of acute coronary syndrome with mast cell activation induced by inflammatory mediators released during allergic reaction [3]. Two variants of KS have been described [3–6]. 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 atherosclerotic disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins, plaque erosion, or rupture manifesting as acute myocardial infarction. However, since type II variant includes patients with pre-existing atherosclerotic disease, we think that it is almost impossible to encounter the type II variant in childhood.

None of the patients described were on regular medications. They did not have previous history of allergy, bronchial asthma, dermatitis, eczema, diabetes, or premature coronary artery disease. They did not also have family history of coronary artery disease or allergic reactions. Complete blood count, D-dimer, antithrombin III, lipoprotein (a), brain natriuretic peptide, serum cholesterol levels, Antistreptolysin-O (ASO) titer, C3 and C4 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, coxsackievirus B, adenovirus, and parvovirus B19. Anti-cardiolipin IgG and IgM and lupus anticoagulants were negative. There was no protein C or protein S deficiency or Factor V Leiden mutation.

Intradermal skin tests with insect venoms (bee, wasp) were performed, in the volar side of the forearm, by injection of the relative venoms for the first and the last patient. The tests, for both hymenoptera venoms, were considered positive because the longest wheal diameter was greater than 5 mm after 15 min. Based on the above findings, the diagnosis of type I variant of KS was made for all patients.

Mast cell degranulation follows after antibody antigen reaction. However, sometimes direct action against the mast cell can happen [2, 8]. This applies especially to drugs. Therefore, the absence of amoxicillin IgE antibodies in the second 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 [2, 7]. Tryptase levels were elevated in all patients, but histamine was undetected. 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 [2, 3]. The utility of serum mast cell tryptase to diagnose anaphylaxis had a sensitivity of 73% and specificity of 98%, and serial measurements of total serum tryptase in serum or plasma may increase the sensitivity and the specificity of the test [3]. Negative levels of histamine and tryptase does not exclude the diagnosis of KS due to short half-life of histamine.

Hymenoptera venoms mainly contain peptides, proteins, and vasoactive amines including histamine, acetylcholine, norepinephrine, and dopamine [7]. These substances are responsible for direct venom cardiotoxicity and several of the proteins and peptides are allergenic. The major allergen of honeybee venom is phospholipase A2. Other allergens

include melitin, hyaluronidase, and apanin [7]. Although most severe reactions of hymenoptera stings occur with the first sting, patients who have previously experienced insect stings are at increased risk for severe allergic reactions from future stings. Most fatalities occur in adults but children and adolescents experienced more insect sting reactions [7]. Our two patients admitted with hymenoptera sting were experiencing the first time of bee sting in their lives.

We have treated all of the children with oral antihistamines, prednisolone, and mast cell stabilizers. They were quite healthy at the sixth month control.

Our study highlights the fact that pediatricians 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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