

Kounis Syndrome: Simultaneous Occurrence of an Allergic Reaction and Myocardial Ischemia in a 46 Year Old Patient after Administration of Contrast Agent

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KEY WORDS: Kounis syndrome, gadoterate meglumin, acute coronary syndrome, hypersensitivity

IMAJ 2013; 15: 725–726

The association of an acute coronary syndrome and an allergic reaction following the administration of penicillin was first described in 1950. In 1991, Kounis and Zavras coined the term Kounis syndrome for the simultaneous occurrence of the entities allergic angina and allergic myocardial infarction [1]. We report the first case, to the best of our knowledge, in which the allergen was gadoterate meglumin, a contrast agent commonly used in magnetic resonance imaging.

PATIENT DESCRIPTION

A 46 year old woman presented with chest pain, nausea and fatigue that lasted an hour. Her medical history was significant for hypophyseal prolactinoma and well-controlled type II diabetes (HbA1c 6.5%) without signs of target organ damage. She had previously undergone a workup on common allergic reactions to iodine contrasts, metamizole, ampicillin, co-amoxiclav, azithromycin, doxycycline, sulfamethoxazole, cefalexin, diclofenac, hyoscine butylbromide, tramadol, acetylsalicylic acid and

poison ivy. The patient was a non-smoker and did not drink alcohol. Her body mass index was 28.9 kg/m², her family history was unremarkable and she took only 850 mg metformin twice a day.

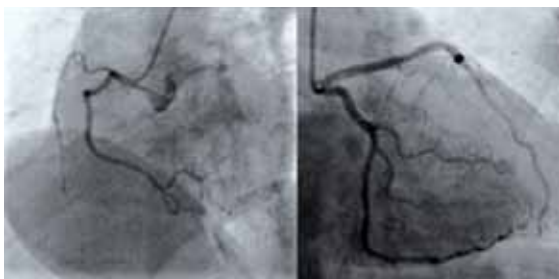
Two hours before admission, she received 15 ml of contrast agent Dotarem® (Guerbet Group, France; gadoterate meglumine) for brain magnetic resonance imaging with 125 mg methylprednisolone intravenous premedication. Ten minutes later she developed generalized urticaria and angioedema progressing to shock. She was hemodynamically and respiratorily stabilized with the prompt administration of epinephrine 1 mg intramuscularly, chlorpiramine chloride 10 mg IV, methylprednisolone 125 mg IV and 0.9% NaCl 1000 ml IV. On arrival at the emergency room she was conscious, normotensive (resting rate 120/80 mmHg), eupneic, with symmetric pulsations; her pulse was 90/min and oxygen saturation 90%. Twelve-lead electrocardiogram revealed 1.5 mm ST

segment depression in inferolateral leads [Figure A] and laboratory workup was significant for leukocytosis (18.7 x 10⁹/L) and hyperglycemia (15.8 mmol/L). Her cardiac troponin level (cTnT) was within normal limits (0.074 µg/L) as were lactate dehydrogenase (191 U/L), creatine kinase (72 U/L) and only a discrete elevation of aspartate aminotransferase (37 U/L) and alanine aminotransferase (51 U/L). The lipid panel was within limits for a secondary prevention and arterial blood gas analysis revealed low pO₂ (7.3 kPa) and 88% hemoglobin saturation. Chest X-ray was normal for her age. The patient was admitted to the coronary unit where she received standard conservative treatment for acute coronary syndrome. Acetylsalicylic acid was omitted due to her known allergy and glycemia was regulated with adjusted doses of fast-acting insulin. Repeated workup after 4 hours showed elevation of cTnT (0.311 µ/L), AST (61

AST = aspartate aminotransferase



[A] 12-lead ECG showing ST segment depression in inferolateral leads



[B] Coronary catheterization, showing the patent's right coronary artery (left), left anterior descending coronary artery and circumflex artery also without significant stenoses (right)

U/L), ALT (70 U/L), LDH (311 U/L) and persistence of ECG changes. Cardiac catheterization performed after premedication (hydrocortisone and chloropyramine chloride) 6 days after admission showed smooth epicardial arteries without hemodynamically significant stenoses [Figure B]. The patient had no further complaints and ECG changes subsided completely. Echocardiography revealed the preserved systolic and diastolic function of a normal sized heart without regional wall motion abnormalities. The patient had an uneventful recovery and she was discharged after 10 days.

COMMENT

To date three forms of Kounis syndrome have been described. Type I occurs in patients without risk factors and normal coronary arteries, hence acute release of inflammatory cytokines causes coronary spasm and possible organ damage; type II occurs in patients with existing coronary artery disease (70% of all cases); and the recently described type III occurs in patients suffering from coronary artery thrombosis, including stent thrombosis where the aspirated thrombus contains a significant amount of mastocytes and eosinophils [2].

Although the pathogenesis of Kounis syndrome is not completely understood, it has been suggested that activated vaso-

ALT = alanine aminotransferase
LDH = lactate dehydrogenase

constrictive pathogens, serotonin, histamine, leucotriens and angiotensin II cause endothelial dysfunction and smooth muscle hypercontractility [3]. Histamine and leucotriens are potent vasoconstrictors, while triptase and chymase activate tissue metalloproteinases which can induce collagen degradation, or plaque erosion or rupture, thus prompting an acute coronary incident. More than 300 cases of Kounis syndrome following exposure to various substances have been described; these substances were usually drugs (antibiotics, anesthetics, analgesics, corticosteroids, contrast agents, acetylsalicylic acid), insect venoms, food, and drug-eluting stents. Gadoterat meglumine (Dotarem) is a contrast agent for MR imaging that in rare cases leads to severe allergic reactions. To the best of our knowledge, this is the first case of acute coronary syndrome following an allergic reaction to gadoterate meglumine. Our patient, who had multiple drug allergies, could have theoretically developed acute coronary syndrome to prophylactically given corticosteroids. Although such cases have been described before, we believe it is highly unlikely because she usually took steroids without significant side effects. One could also attribute coronary hypoperfusion to anaphylactic shock or adrenalin-induced vascular spasm. Nevertheless, considering the patient's atopy and clinical course, we believe that the underlying disorder was a coronary

spasm induced by anaphylactic mediators. This case could be classified as type II Kounis syndrome due to the presence of a risk factor (diabetes), but complete absence of coronary lesions indicates type I Kounis syndrome.

The idea of a pathophysiological link between allergic and non-allergic coronary spasm raises many questions. Kounis syndrome might be nature's way of showing us a model to explain the cascade of events leading to plaque rupture. The assumption that excessive release of anaphylactic mediators accompanies every acute coronary syndrome is substantiated by the literature and calls for new therapeutic modalities [4].

Blockage of the histamine pathway by H1 receptor antagonists and chromoglycate could theoretically prevent or ameliorate coronary incidents. High risk patients, such as those with drug-eluting stents, would benefit from this treatment the most. We conclude that research of allergic angina and allergic myocardial infarction opens a new chapter in understanding the pathophysiology of acute coronary syndrome and the development of a new and effective treatment.

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“He that is the author of a war lets loose the whole contagion of hell and opens a vein that bleeds a nation to death”

Thomas Paine (1737-1809), English-American political activist, author, political theorist and revolutionary