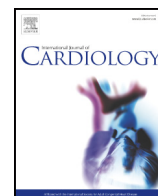




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Letters to the Editor

Underdiagnosis and pharmacovigilance. The case of allergic acute coronary syndrome (Kounis syndrome)

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Dear editor,

We read with great interest the manuscript by Ilhan E et al. [1] reporting the case of a 16 year-old child who developed a misdiagnosed Kounis syndrome (KS) induced by amoxicillin/clavulanic acid. The authors stated that KS is increasingly encountered in clinical practice and, as many experts currently do, they believe that KS is not an uncommon disease, but rather an under-diagnosed disease [2,3]. We strongly agree with this assumption and, as a Regional Centre of Pharmacovigilance, we would like to highlight the role of Pharmacovigilance Intensive Monitoring in the detection of under-diagnosed adverse drug reactions (ADR), including KS [4].

In particular, in the frame of an intensive ADR monitoring project activated in Tuscan County Emergency Departments, we encountered between December 2011 and February 2012, three cases of patients in a single hospital (Prato, Italy) who were diagnosed with unstable angina or acute myocardial infarction – according to analytical parameters, electrocardiographic abnormalities, and/or coronary angiography – in the context of an anaphylactic episode, after taking one or more pills of amoxicillin or amoxicillin/clavulanic acid.

A 57-year-old man, with cardiovascular (CV) risk factors (dyslipidemia and addiction to smoking) and a history of sensitivity to acetylsalicylic acid (ASA), received treatment for dental abscess with amoxicillin and clavulanic acid in December 2011. Fifteen minutes after taking 875/125 mg of the drug, he presented sudden chest pain,

nausea, diffuse skin rash and itching. Hypotension (75/50 mm Hg) and electrocardiographic abnormalities (initially a brief period of junctional rhythm and then sinus rhythm with ST segment elevation in leads D2, D3 and aVF, compatible with an acute inferior myocardial infarction) were observed on arrival at Prato Emergency Department (ED). The first blood tests were normal. After rapid administration of subcutaneous adrenaline, intramuscular antihistamines, intravenous corticosteroids and fluids the patient became hemodynamically stable. In 30 min since the ED admission, the patient was admitted to our Coronary Care Unit (CCU). Here he was asymptomatic and an electrocardiogram (ECG) was normal, so an urgent coronary angiography was not performed. A transthoracic echocardiography revealed asynergy in posterior and inferior segments at the basal level, with hypokinesia at the midventricular level, and a left ventricular ejection fraction of 55%. The day after, blood analysis showed a peak of troponine I of 3.78 ng/mL and the coronary angiography revealed the presence of normal lesion-free coronary arteries. Forty-eight hours later, serum troponine values had returned to normal.

In January 2012, a 58-year-old man, with CV risk factors (hypertension, treated with nebivolol/HCT 2.5/12.5 mg/day and doxazosin 2 mg/day, and strong addiction to smoking) and hyperthyroidism (treated with tapazole 5 mg/day), received treatment with amoxicillin and clavulanic acid, in prophylaxis for dental extraction. A few minutes after taking one pill (875/125 mg) of the drug, he presented dyspnea, chest pain and diffuse skin rash, so he was admitted to our ED. His vital parameters were within normal range but chest examination showed diffuse wheezing. First blood tests were normal and an ECG showed sinus rhythm with ST segment elevation in lateral leads. After administration of intravenous corticosteroids, intramuscular antihistamines and fluids, symptoms gradually improved and the patient was hospitalized in CCU. During all his in-hospital stay, the patient was asymptomatic. A coronary angiography showed coronary arteries without lesions. A chest X-ray was normal and cardiac enzymes remained normal. Serial ECG analysis revealed a persistent normal sinus rhythm (the above repolarization abnormalities disappeared within a few hours). After two days the patient was discharged with a diagnosis of anaphylactic reaction associated to transient ST segment elevation.

A 64-year-old man, ex-smoker for 20 years and mildly overweight, with no other known CV risk factor and no history of atopy, presented to our ED in February 2012. He complained of severe oppressive retrosternal chest pain radiating to the left arm, associated to weakness

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and excessive sweating, which occurred while painting a wall at home. The patient reported being treated with amoxicillin (1000 mg) for a dental procedure for a few days. He had taken a total of 5 tablets and he stopped the medication the day before hospital admission because of intermittent epigastric pain. In ED, he presented with normal vital signs. He was given a sublingual dose of isosorbide dinitrate (5 mg) and administered 500 mg of ASA intravenously. An ECG showed non-specific left ventricular repolarization abnormalities. Thirty minutes later chest pain stopped and the patient was hospitalized in our Short Intensive Observation-High Dependency Unit (SIO-HDU). In treatment with ASA and low molecular weight heparin, monitoring of myocardial markers revealed increased levels of troponin I (0.14 ng/mL) after about 12 h. Based upon patient's clinical data, the consultant cardiologist decided for giving a clopidogrel loading dose of 600 mg before angiography. Heart catheterization revealed the subocclusion of anterior interventricular artery and circumflex artery in middle tracts. Dual percutaneous angioplasty and stenting were performed with optimal result.

Myocardial ischemia or infarction may be more common than suspected, in hypersensitivity, anaphylactic or anaphylactoid reactions and could explain some unexpected cardiac arrests or mortalities observed in these situations [5]. Recent studies have shown that the same mediators are increased in both allergic coronary and non-allergic coronary syndromes, and a common pathway seems to exist [6]. Is therefore Kounis syndrome the tip of the iceberg of a common pathway between allergic and non-allergic coronary syndromes that may be implicated in cases of coronary spasm and plaque erosion or rupture? Many questions about the exact pathophysiologic mechanism

of Kounis syndrome remain unanswered. The increasing number of cases published in the last few years shows that this condition should be taken into consideration in the differential diagnosis of ischemic heart disease.

In conclusion, it is our opinion that Kounis syndrome should be borne in mind especially when diagnosing patients with no CV risk factors who experience acute coronary syndrome and who report ingestion of a drug or a food accompanied by symptoms of anaphylaxis.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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