Kounis syndrome after almonds ingestion: From the diagnostic approach to new therapeutic options

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Abstract

Acute coronary syndromes can develop with an unusual and challenging presentation. Kounis syndrome is a mostly overlooked Acute Coronary Syndrome (ACS) in the setting of anaphylactic or anaphylactoid reactions in response to an allergic insult that can lead to severe complications including cardiac arrest. A 52-year-old-man presented to the emergency department of our hospital because of acute transient loss of consciousness that developed some minutes after almonds ingestion. The complex diagnostic workup led to the diagnosis of vasospastic Kounis syndrome, an infrequent type of acute coronary syndrome, mostly overlooked, with challenging diagnostic and therapeutic features. Peculiarities on clinical presentation, the approach adopted by the emergency physician and the consultant cardiologist to achieve the correct diagnosis and our proposed management with a brief revision of the literature will be reported. Unusual clinical presentations of acute coronary syndromes represent part of the pitfalls that an emergency physician can face during the everyday practice. Prompt identification of these conditions is always struggling but of crucial importance to improve patient prognosis with a correct diagnostic work-up and therapeutic management.

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Introduction

Acute coronary syndromes can develop with an unusual and challenging presentation. Kounis syndrome is a mostly overlooked Acute Coronary Syndrome (ACS) in the setting of anaphylactic or anaphylactoid reactions in response to an allergic insult. It is part of the pitfalls that an emergency physician or a cardiologist of emergency departments can face during the everyday practice.

This case will underline how to promptly recognize and correctly manage these situations even in the absence of specific guidelines.

Case Report

A 52-year-old man with no previous medical and cardiovascular history and no cardiovascular risk factors presented to the emergency department of our institution because of acute transient loss of consciousness. The episode was preceded by acute onset of low thoracic/epigastric pain associated with nausea, vomiting, cold sweating and intense tremors. He referred to have eaten almonds about ten minutes before the onset of symptoms. At his arrival he appeared worried, confused and sweaty. Arterial blood gas analysis revealed mild compensated metabolic acidosis (pH 7,3, CO2 30mmHg, HCO3- 18mmol/L, COHb 0,4%), p02 78mmHg and abnormal lactate levels (7mmol/L). Neurological evaluation and brain CT ruled out ischemic or hemorrhagic stroke. ECG showed sinus tachycardia with mild ST elevation in V1-V2-V3, hyperacute T in precordial leads and reciprocal ST depression in inferior and lateral leads (Figure 1). Complete blood count underlined lymphocytic leukocytosis without anemia and with normal eosinophil count (WBC 15 x 10^9/L, 65% Lymphocytes, reference value 4,8-10,8 x 10^9/L), C-reactive protein 44mg/L (reference value <6mg/L) and high-sensitive Troponin-T was negative at first measurement and highly increased at 2 hours-check (7ng/L to 532ng/L, reference value 0-14ng/L).

In the suspicion of anaphylaxis, intramuscular epinephrin and intravenous corticosteroids (CCS, Methylprednisolone 60mg) and antihistamine H1 (Chlorphenamine 10mg) therapy was administered by the emergency physician. A second ECG was recorded about 30 minutes later and showed complete normalization of the previous alterations and transthoracic echocardiography performed by the consultant cardiologist highlighted normal biventricular function without kinetic abnormalities. Toxicological screening for

common drugs (amphetamines, cocaine, barbiturates, benzodiazepines, cannabinoids, opioids) resulted negative. Coronary Computed Tomography Angiography (CCTA) revealed no significant epicardial coronary stenosis with mild atherosclerosis of the left anterior descending artery (Figure 2). The patient was kept under observation for 48h. No arrhythmias were registered and he remained asymptomatic without new ECG alterations. After 10h, Troponin T was more than halved and serial assays presented a constant descending trend. A final diagnosis of coronary spasm secondary to allergic reaction was done (Kounis syndrome, type I). The patient was discharged about 60 hours after the ED access with a calcium channel antagonist (Diltiazem 60mg tid) therapy and indication to undergo a Cardiac MRI, a 24-hour Holter monitoring and a complete immuno-allergologic evaluation.

Discussion

Clinical presentation and how to reach diagnosis

Kounis syndrome is an Acute Coronary Syndrome (ACS) in the setting of anaphylactic or anaphylactoid reactions in response to an allergic insult, including food, insect bites or drugs (Table 1).[1] Subsequent mast cell and platelet activation induces the release of inflammatory mediators such as histamine, arachidonic acid products, platelet-activating factor, cytokines and chemokines.[2] In this context, coronary artery spasm in predisposed subjects (type I), plaque rupture (type II) or stent thrombosis (type III) can occur.[3] A variety of ECG alterations may be observed, including ST-segment elevation or depression, any degree of heart block and cardiac arrhythmias.[2] Prompt identification of this overlooked syndrome and correct patient management is always struggling. In our case, the absence of cardiovascular risk factors and atypical chest pain features made the suspicion of ACS low. However, the ECG at the presentation was suggestive of ST-elevation myocardial infarction. In this setting, an urgent coronary angiography might have been performed to exclude coronary thrombosis. Nevertheless, the rapid reversal of symptoms and ECG alterations after infusion of intravenous CCS and H1 antagonists along with normal echocardiographic findings guided the decision to a more conservative strategy. Because of the high elevation of Troponin T at two hours and the feasibility of urgent CCTA at our institution, this was the examination of choice that excluded coronary thrombosis and atherosclerotic disease, making the diagnosis of vasospastic (type 1) Kounis syndrome very likely. In addition, lymphocytic leukocytosis and increased lymphocyte-total leukocytes ratio has been linked to anaphylaxis[4] and together with high C-reactive protein levels, temporal correlation with almond ingestion, gastrointestinal symptoms (but absence of other allergic manifestations) strengthen the diagnosis of anaphylaxis and subsequent coronary vasospasm as the cause of the clinical presentation. Serum triptase levels were not tested but could have been of great interest to rapidly confirm diagnosis.

Case management and therapy

There is no established treatment in this atypical ACS, as management according to the most recent guidelines for ACS does not appear totally appropriate in this context.[5] Our proposed approach is reported in Figure 3. It is not surprising that vasospastic Kounis syndrome may overlap with Prinzmetal angina, as they share similar pathophysiological mechanisms and the diagnosis and treatment should therefore be directed in the same way.[6] A limitation of our approach was probably the choice of CCTA. An invasive study of the coronary flow reserve with provocation tests for epicardial

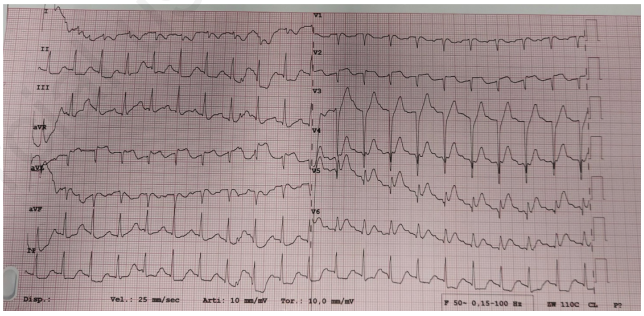

Figure 1. ECG at presentation. ST segment elevation in anterior precordial leads, hyperacute T waves and reciprocal ST segment depression in inferior and lateral leads.

Table 1. Some possible triggers of Kounis Syndrome according to reported cases.

Drugs	Food	Clinical conditions and environment
Analgesics *(Aspirin, NSAIDs)*	Fresh and dried fruit	Anisakis
Anesthetics *(isoflurane, midazolam, propofol, remifentanil,*	Nuts	Anaphylaxis
rocuronium bromide, succinylcholine,	Mushrooms	Bronchial asthma
suxamethonium, trimethaphan)	Sgombroid reaction	Chronic Autoimmune Urticaria
Antibiotics *(beta-lactams, trimethoprim–*	Vegetables	Churg Strauss syndrome
sulfamethoxazole, sulperazon, vancomycin, amikacin)		Intracoronary stenting
Anticoagulants (heparin)		Mastocitosis
Contrast Media (iodinated contrast, ultrasound contrast)		Serum sickness
Corticosteroids		Echinococcal cyst rupture
Immunoglobulins and biologic drugs		Hymenoptera and scorpion sting
Thrombolytics		Jellyfish sting
Others *(antineoplastics, amiodarone, clopidogrel, enalapril, esmolol)*		Snake venom
		Latex
		Millet and other respiratory allergies

and microvascular vasospasm may better identify patients that could benefit from vasodilating drugs. Intravenous CCS and histamine H1 antagonists, reducing the acute inflammatory burden, may partially revert allergic and anginal symptoms and arterial vasospasm.[7] On the contrary, epinephrine, administered to our patient in the suspicion of anaphylactic shock, can worsen coronary vasospasm. Glucagon infusion or Methoxamine may also be considered in patients who are receiving beta-blockers or are in shock refractory to epinephrine.[8] In the case of severe anginal pain extreme caution should be reserved to the use of Morphine and opiates, which can induce massive mast cell degranulation and aggravate the allergic reaction. Fentanyl and its derivatives are preferred drugs while intravenous paracetamol (acetaminophen) can cause severe hypotension.[8]

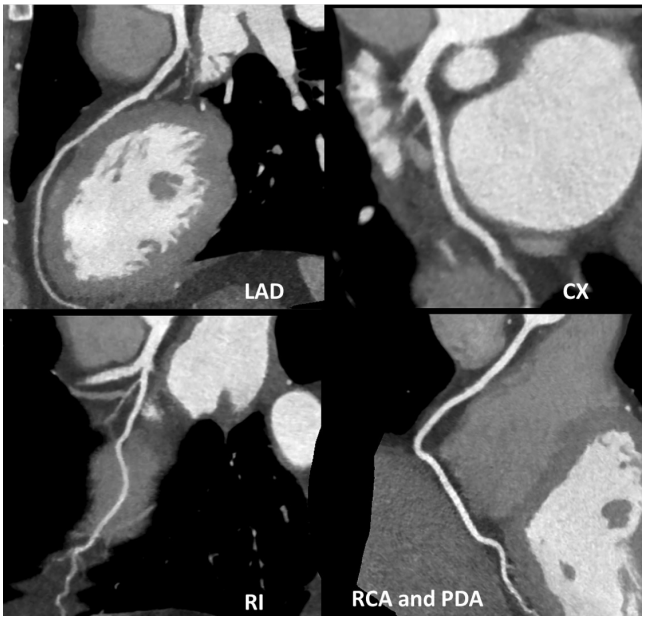

Figure 2. Coronary computed tomography angiography. Absence of atherosclerotic obstructive disease of the epicardial coronary arteries. LAD: left anterior descending artery; CX: left circumflex artery; RI: ramus intermedius of the left coronary artery; RCA: right coronary artery; PDA: posterior descending artery.

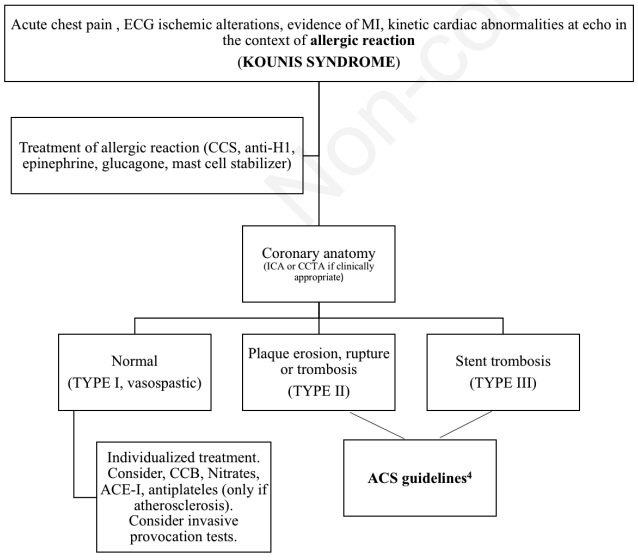

Figure 3. Proposed algorithm for the management of KOUNIS syndrome during the acute phase. ECG: electrocardiography; MI: myocardial infarction; CCS: corticosteroids; ICA: invasive coronary angiography; CCTA: coronary computed tomography angiography; CCB: calcium channel blocker; ACE-I: angiotensin converting enzyme inhibitors; ACS: acute coronary syndrome.

Due to the absence of significant coronary atherosclerosis, we decided to not administer a long-term antiplatelet therapy to our patient. Furthermore, Aspirin through inhibition of cyclooxygenase may shunt arachidonic acid degradation to the Leukotriene pathway producing mediators of anaphylaxis.[9] Concerning long-term therapy, non-dihydropyridine calcium channel blocker (or nitrates) are the drug of choice to reduce the risk of new coronary spasms. Beta-blockers are instead generally contraindicated in this setting, as they can elicit unopposed coronary alpha-1 mediated vasospasm and offset the beneficial effect of epinephrine. Mast cell stabilizers (e.g. sodium cromoglycate) may be considered for future prevention in predisposed atopic subjects, but their efficacy in the acute setting is questionable. Monoclonal antibodies that avert mast cell degranulation by masking the IgE binding site[10] are future promising therapies to avoid vasospasm and to stabilize inflamed vulnerable atherosclerotic plaques.[11,12] Along with a non-urgent full cardiologic workup, cardiac MRI was counseled to spot subclinical myocardial damage or scar. The role of cardiac SPECT remain anecdotal and debatable; nowadays ICA or CCTA, completed by MRI in residual doubtful cases, appear the best management to rule-in or rule-out ACS, as reported by ESC guidelines for N-STE ACS.[5] Finally, full allergologic evaluation with serum tryptase, skin prick test and IgE screening is mandatory to strengthen diagnostic suspect, identify etiologic triggers and avoid new events.

Conclusions

We presented the case of a type I (vasospastic) Kounis syndrome. This is an infrequent type of ACS, mostly overlooked, with challenging diagnostic and therapeutic workup. Drugs commonly used as first line therapy for ACS (Aspirin, betablockers) do not appear completely appropriate in this context. A personalized management based on the clinical scenario is encouraged in the absence of specific guidelines. Coronary computed tomography angiography in the emergency setting to exclude major coronary stenosis or plaque instability and rupture permits to safely discharge patients after clinical stabilization and acute pharmacological management. Intravenous CCS and H1 antagonists together with vasodilators like calcium channel blockers or nitrates (if blood pressure is satisfactory) appears adequate drugs. Long term treatment after discharge should be discussed with a cardiologist and immunologist, if appropriate, and individualized based on patient characteristics, pathophysiological considerations, identified causes, presence of atherosclerotic disease and residual cardiac function.

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