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

Giorgio Fiore, Carlo Gaspardone, Silvana Di Maio, Michele Oppizzi, Alberto Margonato
Clinical Cardiology Unit, IRCCS San Raffaele University Hospital, Milan, Italy

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.

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 lymphocytosis 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 (amphetamine, cocaine, barbiturates, benzodi-azepines, cannabinoids, opioids) resulted negative. Coronary Computed Tomography Angiography (CCTA) revealed no signifi-
cant 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 recorded 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 moni-
toring 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 prod-
ucts, 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 intra-
venous CCS and H1 antagonists along with normal echocardi-
ographic findings guided the decision to a more conservative strat-
egy. Because of the high elevation of Troponin T at two hours and
the feasibility of urgent CCTA at our institution, this was the exam-
ination of choice that excluded coronary thrombosis and athero-
sclerotic disease, making the diagnosis of vasospastic (type 1)
Kounis syndrome very likely. In addition, lymphocytic leukocyto-
sis and increased lymphocyte-total leukocytes ratio has been
linked to anaphylaxis4 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 man-
agement 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 simi-
lar pathophysiological mechanisms and the diagnosis and treat-
ment 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

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, rocuronium bromide, succinylcholine, suxamethonium, trimethaphan) | Nuts | Anaphylaxis                        |
| Antibiotics (beta-lactams, trimethoprim–sulfamethoxazole, sulperazon, vancomycin, amikacin) | Mushrooms | Bronchial asthma                    |
| Anticoagulants (heparin)     | Sgombroid reaction | Chronic Autoimmune Urticaria        |
| Contrast Media (iodinated contrast, ultrasound contrast) | Vegetables | Intracoronary stenting             |
| Corticosteroids              |                     | Mastocitosis                        |
| Immunoglobulins and biologic drugs |                     | Serum sickness                      |
| Thrombolytics                |                     | Echinococcal cyst rupture           |
| Others (antineoplastics, amiodarone, clopidogrel, enalapril, esmolol) |                     | Hymenoptera and scorpion sting      |
|                             |                     | Jellyfish sting                     |
|                             |                     | Snake venom                         |
|                             |                     | Latex                               |
|                             |                     | Millet and other respiratory allergies |

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.
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. 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. 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

Due to the absence of significant coronary atherosclerosis, we decided not to administer a long-term antplatelet therapy to our patient. Furthermore, Aspirin through inhibition of cyclooxygenase may shunt arachidonic acid degradation to the Leukotriene pathway producing mediators of anaphylaxis. 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 are future promising therapies to avoid vasospasm and to stabilize inflamed vulnerable atherosclerotic plaques. Along with a non-urgent full cardiologic workup, cardiac MRI was counseled to spot subclinical myocardial damage or scar. The role of cardiac SPECT remains 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. 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, beta-blockers) 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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