Kounis syndrome associated with COVID-19 infection: cause or coincidence?

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SOUHRN

Kontext: Otrava histaminem v rybím mase, známá i jako scombroid syndrom, je potravinami přenášené onemocnění vyvolané toxicitou histaminu, jež je výsledkem konzumace zkaženého masa některých druhů ryb. V některých případech to může vést k rozvoji život ohrožujících anafylaktických reakcí. V odborné literatuře se běžně uznává a přijímá možnost korelace s postižením koronárních tepen; případy jsou sice vzácné, ale ještě vzácnější jsou případy ve spojení s infekcí novým lidským koronavirem, tedy s onemocněním COVID-19 jako pátou doloženou pandemií od chřipkové pandemie z roku 1918. V tomto článku jako první popisujeme případ akutního koronárního syndromu u infikovaného pacienta s onemocněním COVID-19. Pro výskyt akutních koronárních příhod spolu s alergickými reakcemi nebo s reakcemi hypersenzitivity se používá termín Kounisův syndrom, v málo případech byl však spojen se scombroid syndromem.
Kazuistika: Na naše oddělení emergency byla dopravena mladá žena s erytematózními lézemi, mírným svěděním, nauzeou, diaforézou a slabostí, které se dostavily po konzumaci jídla s tuňákem v konzervě. Její klinický stav se zhoršil a došlo u ní k rozvoji akutního koronárního syndromu vyvolaného koronárním vazospasmem. Po prvním negativním výsledku vyšetření orofaryngeálního stěru na RNA SARS-CoV-2 a při čekání na laboratorní vyšetření orofaryngeálního stěru během hospitalizace byla u ní o několik dní později zjištěna pozitivita na infekci virem SARS-CoV-2. S akutním koronárním syndromem se u pacientů se scombroid syndromem setkáváme vzácně a ještě vzácněji ve spojení s infekčním onemocněním COVID-19. Tento případ prokázal spojitost otravy histaminem v rybím mase s Kounisovým syndromem a infekcí virem SARS-CoV-2, což nám umožnilo rozhodnout o dalším léčebném postupu.
Proč by si měl lékař na akutním příjmu být vědom této skutečnosti? Pokud není tento syndrom rychle a včas diagnostikován, jedná se o život ohrožující stav. Lékař na akutním příjmu si musí být vědom této skutečnosti, aby mohl správně vyhodnotit anamnézu postižených pacientů. Pouze pečlivě odebraná anamnéza nás může dovést ke správné diagnóze a změnit naše rozhodování o léčbě.

Keywords:
Acute coronary events
Allergic myocardial infarction
Kounis syndrome
SARS-CoV-2 infection
Scombroid syndrome
Vasospastic allergic angina

ABSTRACT

Background: Histamine fish poisoning, known as scombroid syndrome, is a foodborne disease caused by histamine toxicity that results from eating specific types of spoiled fish. In some cases it can lead to the development of life-threatening anaphylactic reactions. In literature the possibility of correlated coronary involvements is widely recognized and accepted, cases described are rare, but even more rare if combined with the novel human coronavirus disease COVID-19 infection, the fifth documented pandemic since the 1918 flu pandemic. In this report, we describe a case of acute coronary syndrome in infected patient with COVID-19, for the first time. The occurrence of acute coronary events with allergic or hypersensitivity reactions has been described as the Kounis syndrome, but in few cases it has been associated with scombroid syndrome.
Case report: A young woman came to our Emergency Department with erythematous lesions, mild itching, nausea, diaphoresis and weakness, after a meal with canned tuna. Her clinical situation worsened and she developed acute coronary syndrome due to vasospasm. After the first negative result for rapid oropharyngeal swab test of SARS-CoV-2 RNA, waiting for molecular oropharyngeal swab during her hospitalization, a few days later she was tested positive for SARS-CoV-2 infection. Acute coronary syndrome in patients with scombroid syndrome is rare to find and more rare if associated with COVID-19 infection. This case demonstrated a linkage of histamine fish poisoning with Kounis syndrome and SARS-CoV-2 infection, allowing us to foster the treatment decision-making process.
Why should an emergency physician be aware of this? This syndrome can represent a life-threatening, if not promptly and early known. An emergency physician must have this knowledge, to evaluate accurately the anamnesis of affected patients. Only a circumspect anamnesis can lead us to correct diagnosis and change our decision-making process for treatment.

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Introduction

Histamine fish poisoning is a foodborne disease caused by histamine toxicity from eating specific types of spoiled fish. This syndrome, typically benign, such an allergic reaction, is characterized by a variety of manifestations as flushing, headache, and gastrointestinal symptoms.[1] In some cases it can lead to the development of life-threatening anaphylactic reactions or acute coronary syndrome, referred to as Kounis syndrome.[2] Acute coronary syndrome or ST-segment elevation myocardial infarction, resulting from allergic reaction or pseudo-allergic reaction like histamine fish poisoning is rarely described.[3] The interaction between scombroid syndrome and SARS-CoV-2 infection is not clearly understood. The novel human coronavirus disease COVID-19 has become the fifth documented pandemic since the 1918 flu pandemic. It's believed to be a spillover of animal coronavirus and later adapted the ability of human-to-human transmission. Because the virus is highly contagious, it rapidly spreads and continuously evolves in the human population.[4]

Case report

A 22-year-old woman presented with mild itching, nausea, diaphoresis and weakness, after eating a meal with canned tuna. Within 30 minutes, her symptoms intensified, she also became pale, and her forehead, chin, and neck were erythematous. Carried to the hospital by ambulance, betamethasone 4 mg IM was administered to her and facial erythema had subsided. First she was tested negative for rapid oropharyngeal swab test of SARS-CoV-2 RNA and she was admitted to the hospital. Waiting for molecular oropharyngeal swab result, during her hospitalization in emergency department, her pulse rate was 103 beats/min, blood pressure 110/60 mmHg, TC 36.0 °C, SpO_2 98%, RR 16. The patient had a past medical history with reported foods intolerances, without any cardiovascular risk factors like hypertension, dyslipidemia, diabetes or tobacco attitude. She reported that canned tuna was homemade, and that it had remained open for several days. Except for slightly diaphoretic skin, her physical exam was unremarkable: lungs were clear to auscultation bilaterally; heart rate was regular, sinus tachycardia has been noted, with no murmurs or adventitial sounds. Her abdomen was soft, not tender and not distended. Extremities were slightly cold but pulses were present, with no edema. Laboratory cell blood count (CBC) and comprehensive metabolic panel (CMP) were normal. A few hours later her admission, she tested positive for molecular oropharyngeal swab test of SARS-CoV-2. Chest X-ray was normal. Electrocardiogram was performed: sinus tachycardia, normal atrioventricular conduction was noted. Within one hour after the meal, she developed chest and abdominal pain with a feeling of impending doom. She became hypotensive (blood pressure 70/30 mmHg) with development of shortness of breath and a recurrence of urticarial plaques in her forehead. It was been administered O_2 insufflation, volume expanders, hydrocortisone 1 mg/kg IV and H1 and H2 antihistamines, (diphenhydramine 2 mg/kg and ranitidine 1 mg/kg IV). Another Electrocardiogram was performed and it was suggestive of subendocardial ischemia in infero-anterior-lateral leads (Fig. 1). Echocardiographic study has been performed at bedside showing apical and infero-antero septal segments ipokinesis. A minimal increase of the myocardial necrosis biomarkers values was found: troponin I 1.6 ng/ml, reference value (RV) <1.2; creatine kinase-MB 19 ng/ml, RV <6; and myoglobin 212 ng/ml, RV <70 concentrations in controls seriate. We started the administration of nitroglycerin IV doses being titrated according to the response, aspirin, low-molecular-weight heparin, and oxygen therapy. Admitted in CCU, emergency coronary angiography was performed and revealed normal epicardial arteries (Fig. 2). SARS-CoV-2 infection combined with hypersensitivity reactions may have been involved in this clinical presentation, as a trigger for vasospastic

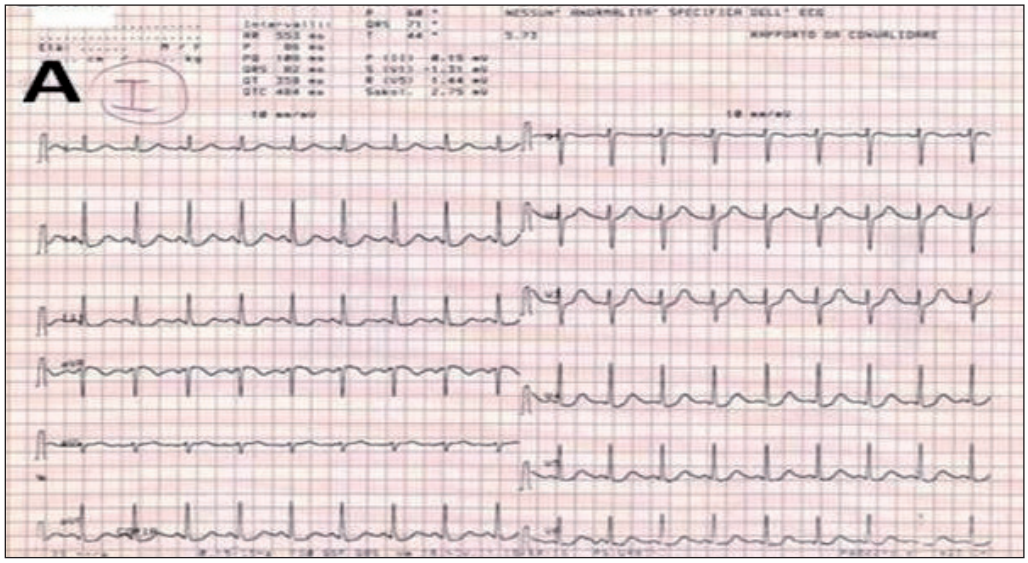

Fig. 1 – Electrocardiogram was suggestive of subendocardial ischemia in infero-anterior-lateral leads.

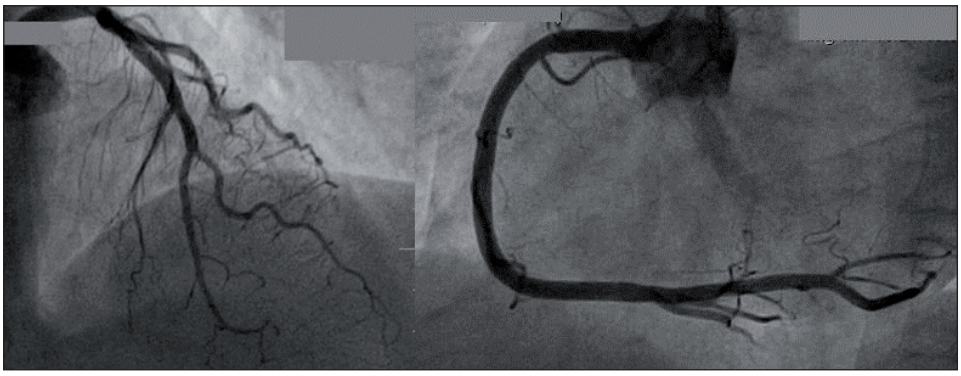

Fig. 2 – In emergency room, coronary angiography were performed revealing normal epicardial arteries.

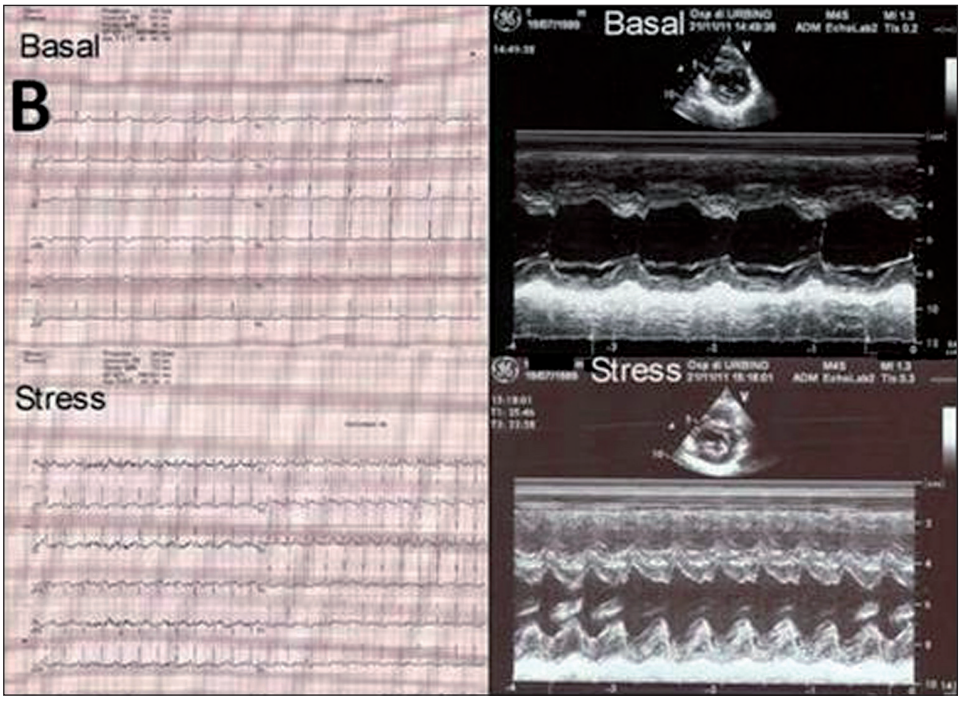

Fig. 3 – On the third day, the patient underwent a pharmacological echocardiographic stress test with dobutamine which was completely negative for inducible ischemia.

reaction. The possibility of a scombroid poisoning was an option thus we examined the tuna eaten. High histamine concentration was found in tuna leftover (>5 000 ppm). We performed also research of salmonella, shighella, protozoa, helminths etc., but all results were negative. No pathogens were isolated from the food samples. No other cases associated with this product were identified. On the third day, electrocardiogram and echocardiographic study shown normal pattern, as well as values of myocardial necrosis biomarkers were normalized. The patient underwent a pharmacological echocardiographic stress test with dobutamine (Fig. 3), which was completely negative for inducible ischemia. Before discharge, with normal findings at electrocardiogram, echocardiographic study, serum chemistry, she tested negative for molecular oropharyngeal swab test of SARS-CoV-2 RNA and she was discharged home.

Discussion

Scombroid syndrome is a foodborne disease caused by the ingestion of spoiled fish, usually of the families *Scombridae* and *Scomberesocidae*, in the absence of organoleptic abnormalities. Scombroid-fish poisoning causes are not clearly understood, but high histaminic concentrations are constant findings in intoxicated foods. Histamine, since 1940s, was detected as a trigger of this syndrome.[5] Nonetheless, scombroid syndrome is not an allergic reaction but it has symptoms that mimic those of a food allergy. These occur on average 90 min after consumption of the food and resolve in a few hours but they may persist for up to more than 48 hours. The symptoms consist of headache, diffuse erythema, hyperemia, nausea, vomiting, diarrhea, abdominal soreness and severe bronchospasm, hypotension.[1] Respiratory dis-

tress, vasodilatory shock have been observed.[6,7] Recent research has shown that Kounis-like syndrome can affect also the mesenteric[8] and cerebral arteries.[9] In literature, the possibility of a concomitant coronary involvement in scombroid syndrome is widely recognized and accepted, but cases described specifically in this sense are very rare. Many inflammatory mediators (such as histamine, cytokines etc.) released during allergic reaction may induce a vasospatic reaction, through direct activation of coronary vascular smooth muscle.[10] The pathophysiological mechanisms of myocardial injury caused by SARS-CoV-2 are not well known. Myocardium SARS-CoV-2 infection is dependent on ACE-2 receptors. The interaction between SARS-CoV-2 and ACE-2 in the heart could contribute to SARS-mediated myocardial inflammation and damage.[11] With ACE-2 downregulation decreases cardioprotective effects of angiotensin 1–7 and increases inflammatory cytokines production as TNFα, may be responsible for the myocardial damage, and TGF-β,[12,13] included in a common pathway of interstitial fibrosis development in the myocardium and could potentially be a mode of cardiac damage.[14] Even cardiac mast cells located around the coronary arteries could have a role; they can be activated by a variety of stimuli, including various allergens and complement factors.[15] Kounis syndrome shows that linkage between acute coronary events and hypersensitivity or allergic reaction. To our knowledge a few cases have been associated with coronary vasospasm and scombroid syndrome.[3,16–18] In Kounis syndrome, an acute allergic or hypersensitivity reaction may cause different kinds of cardiovascular symptoms. It's difficult to make a clinical diagnosis and often it's made retrospectively, being really life-threatening for patients affected. These different kinds of clinical manifestations were clustered in three types according to severity of coronary lesions (from vasospasm to an acute coronary thrombosis) and previous history of coronary artery disease.[3] Scombroid syndrome in the United States represents one of the major chemical foodborne illnesses[19] caused by the consumption of poisoned fish products, which contain high free histamine concentration, responsible for the clinical manifestations.[5–20] *Scombridae* and *Scomberesocidae* included tuna, mackerel, skipjack, and bonito fishes are among the most involved species. Inappropriate fish storage can lead to an increased grown of enterobacteria. Bacteria in spoiled fishes can decarboxylate high percentage of free histidine to histamine. Free amino acid concentration is variable between different fish species; high histidine concentration is typical of not settled species to protect the tissues from the sudden increase of lactic acid.[21–25] Histamine excess seems to have a key role in the development of symptoms, but it has not been possible to reproduce the illness in humans, with similar doses to those ingested in fish poisoned. These results suggest that some substances present in fish increase histamine toxicity in human, promote its absorption, or inhibit its inactivation by histamine *N*-methyltransferase and diamine oxidase.[26–28] There isn't a gold standard in pharmacological treatment, but antihistamines drugs represent first line treatment in this case. Allergic manifestations such urticaria increase with steroids as well as coronary vasospasm. In these cases H1/H2 receptor blockers, nitrates, calcium channel blockers can be administrated. However, the administration of β-blockers may exaggerate coronary spasm due to unopposed activity of α-adrenergic receptors. Epinephrine, which is the drug of choice and may save lives in anaphylaxis, may aggravate ischemia and worsen coronary vasospasm in Kounis syndrome.[29–35]

Why should an emergency physician be aware of this?

This syndrome can represent a life threatening, if not promptly and early known. An emergency physician must have this knowledge, to evaluate accurately the anamnesis of affected patients. This case represents also that, probably, in patients with normal coronary arteries without any predisposing factors for coronary artery disease, the acute release of inflammatory mediators due to SARS-CoV-2 infection may induce coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins.

Only a circumspect anamnesis can lead us to correct and prompt diagnosis and change our decision-making process for treatment.

Even this knowledge should be part of the cultural baggage of emergency physicians.

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