Non−ST-Elevation Myocardial Infarction-Like Syndrome in Scombroid Tuna Fish Poisoning

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Mistreated fish products ingestion can lead to a histaminergic illness known as Scombroid Syndrome (SS). The disease usually causes cutaneous rash, stomach cramps, nausea, vomiting, breathing disorder and further histamine-related symptoms. To date, however, SS has been disregarded among the potential triggers of acute coronary syndrome (ACS), in spite of prior published occasional case reports. In the present study we describe 3 consecutive patients presenting with signs and symptoms of ACS associated to SS. Two men and a woman with no history of coronary artery disease and food allergy were studied. Clinical characteristics, electrocardiographic presentation and outcomes are described. Non−ST-elevation myocardial infarction-like pattern was observed in all patients. The 2 men underwent unremarkable coronary angiography, whereas the woman was just monitored at emergency department. All individuals had uneventful follow-up. The present study confirms non−ST-elevation myocardial infarction-like ACS as a possible histaminergic toxic, not allergic, epiphenomenon of mistreated raw tuna fish ingestion, likely due to transient epicardial and/or microvascular coronary vasospasm. **(Am J Cardiol 2019;124:518−521)**

Mistreated fish products can lead to acute poisoning known as Scombroid Syndrome (SS). This consists of a histaminergic illness with challenging symptoms, somehow similar to those occurring with seafood allergies. Scombroid syndrome results from fish products consumption like mackerel and tuna fish, containing pathogen microorganisms that generate histamine and other spoiled substances usually causing cutaneous rash, stomach cramps, nausea, vomiting, diarrhea, hypotension, breathing disorder and/or headache, as in other histaminergic syndromes.[1−3] To the best of our knowledge, SS has been disregarded as a potential cause of acute coronary syndrome (ACS), in spite of occasional prior published case reports. In the present study we describe the first ACS case series following ingestion of mistreated tuna fish.

Methods

Because of official dispatch by the Local Authority and news media of potentially mistreated raw tuna fish products in the first week of June 2018, all patients referred to the Emergency Department (ED) at Messina University Hospital and Papardo Hospital (Messina, Italy) for SS were carefully studied. On admission, all patients complaining about gastroenteric disorders, cutaneous rash, diarrhea and further symptoms suggestive of fish food poisoning, underwent resting 12-lead electrocardiogram (ECG). Admission criteria to Coronary Care Unit were the presence of ST-T segment abnormalities associated with symptoms like chest pain, angina, and/or dyspnea. Clinical examination and transthoracic echocardiogram were then performed, and blood samples for cardiac biomarkers drawn. Persistent chest pain and increased Troponin levels, with or without wall motion abnormalities on echocardiography, were criteria for urgent coronary angiography.

Results

Three patients with no history of coronary artery disease (CAD) and food allergy were confirmed to have SS-related ACS at ED. The first one (case A) was a 56-year-old smoker man referred to the hospital for smooth urticarial reaction 1 hour after ingestion of raw tuna fish. On arrival, he also complained oppressive chest pain and palpitation. The second patient (case B) was a 58-year-old man likewise admitted for mild urticarial reaction, in combination with breathlessness, hypotension and marked asthenia initiated approximately 2 hours after tuna fish ingestion. The last patient (case C) was a 48-year-old woman with no risk factors, presenting with urticarial reaction, dyspepsia, diarrhea and moderate precordial oppression 3 hours after consumption of rare-cocked raw tuna fish. Demographic and clinical characteristics are displayed in Table 1.

Mild ST-segment elevation in lead aVR and depression in almost all precordial (V2-V6) and peripheral (D1, D2, aVL, aVF) leads were disclosed in everyone (Figure 1, left panels). Ensuing echocardiographic examination demonstrated trivial left ventricular wall motion anomalies in cases A and B (ejection fraction approximately was 50%), whereas no relevant abnormalities were seen in the woman. Patients A and B underwent coronary angiography within 12 hours from admission to Coronary Care Unit, but no remarkable lesions were observed (Figure 2). Once

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Table 1
Patients characteristics

Variable	Case A	Case B	Case C
Gender	M	M	F
Age (years)	56	58	48
Ischemic heart disease	0	0	0
Stroke/transient ischemic attack	0	0	0
Atherosclerosis	0	0	0
Hypertension	+	0	0
Smoke	+	+	0
Diabetes	+	+	0
Obesity	+	0	0
Hypercholesterolemia	+	0	0
Presentation			
Flushing	+	+	+
Abdominal cramps	0	+	+
Vomiting	0	+	+
Chest pain and/or dyspnea	+	+	+
Blood pressure (mm Hg)	115/60	70/30	90/60
Electrocardiographic findings			
ST-segment elevation [leads(mm)]	aVR (>1), V1 (<1)	aVR (>2)	aVR (0.5)
ST-segment depression (leads)	D1,D2,aVF, V3-V6	D1,D2,aVF, V2-V6	D2,aVF, V3-V6
Negative T wave	0	0	D2,D3,aVF
ST-segment normalization	<12 h	<12 h	<4 h
Laboratory samples			
Troponin T (<14 pg/mL)*	22−33−16	19−9−4	18−14
CPK (<200 U/L)*	95−98−87	110−90−70	88−75
CK-MB (<20 U/L)*	13−20−16	16−22−12	20−16
Myoglobin (23-72 ng/mL)	50−33−69	55−64−43	−
Coronary angiography			
Performed on arrival	+	+	−
Culprit lesion(s)	none	none	−

* Values (normal reference standards) refer to day 1-2-3, except from the woman (basal and 6-hour later samples).

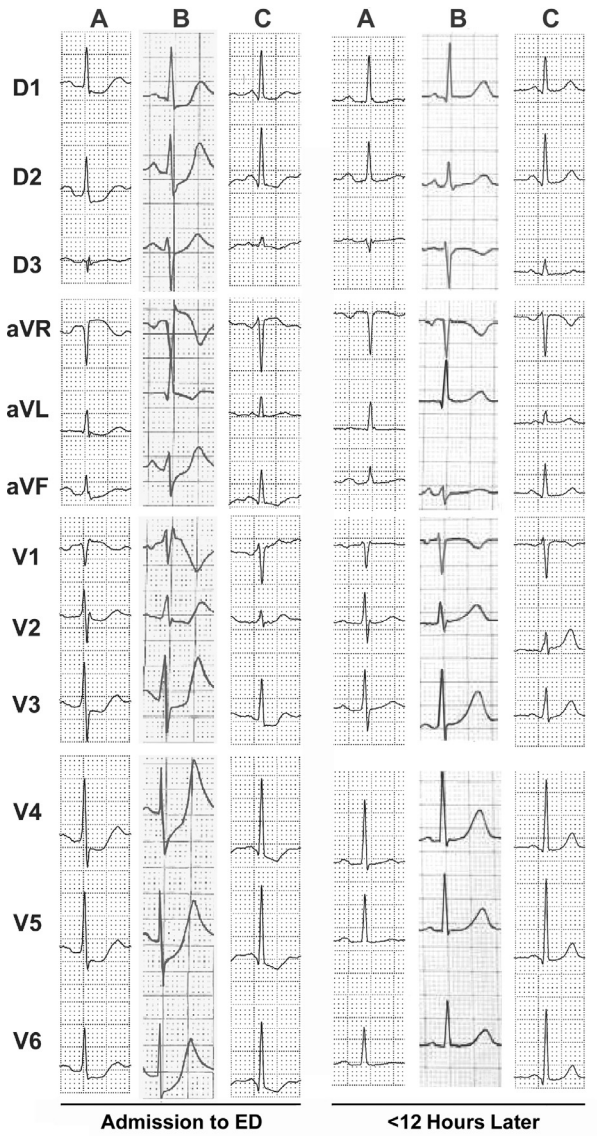

Figure 1. ECG recordings in the 3 patients on admission to Emergency Department *(left panels)* and within the next 12 hours *(right panels)*.

emergency physicians and cardiologists were noticed about the likelihood of further cases of mistreated tuna fish poisoning, the last patient (woman) did not undergo coronary angiography but was just treated with antihistamine drugs at the ED. Despite the absence of coronary artery stenosis, persistent hypotension in patient B required 24-hour treatment with plasma expanders, corticosteroids and antihistamine drugs. Short-term intravenous verapamil (1 mg/Kg) was administered to patient C for heart rate control. Electrocardiographic (Figure 1, right panels) and echocardiographic anomalies recovered within 12 to 24 hours from admission in both the male patients. Their in-hospital stay was uneventful and they were discharged on day 3. The woman was discharged 7 hours from the arrival to ED, once her clinical conditions and ECG findings had improved. No further events were noticed at 30-day follow-up.

Discussion

The SS was first described in 1979 as a food-allergy in Great Britain.[1−3] It has been established to cause up to 5% of all food poisoning in the USA.[4] The clinical picture usually consists of either gastrointestinal, dermatologic or breathing reactive disorders, often associated to headache and blood pressure changes.[3−5] In spite of currently known several cases of histamine-related food poisoning,[6] only occasional reports have been prior published showing an ACS as a complication of SS.[7−10] Also recently, Schwartz and colleagues did not mention fish poisoning among the potential triggers and/or vulnerability players of ACS.[11]

Present findings, however, do confirm that acute myocardial ischemia often occurs in the acute stage of SS ("*ischemic-SS*" subtype) as a histaminergic toxicity in CAD-free patients.

In agreement with previously published studies, coronary artery vasospasm, either epicardial or microvascular, seems to be the most likely pathophysiological mechanism of the transient ischemia. Besides, there are no indications about the typical ECG presentation on admission to Hospital in such patients. All cases from the present study showed non−ST-elevation myocardial infarction (NSTEMI)-like pattern, similar to that described by Gorgels et al in 1993 in patients with 3-vessel CAD.[12]

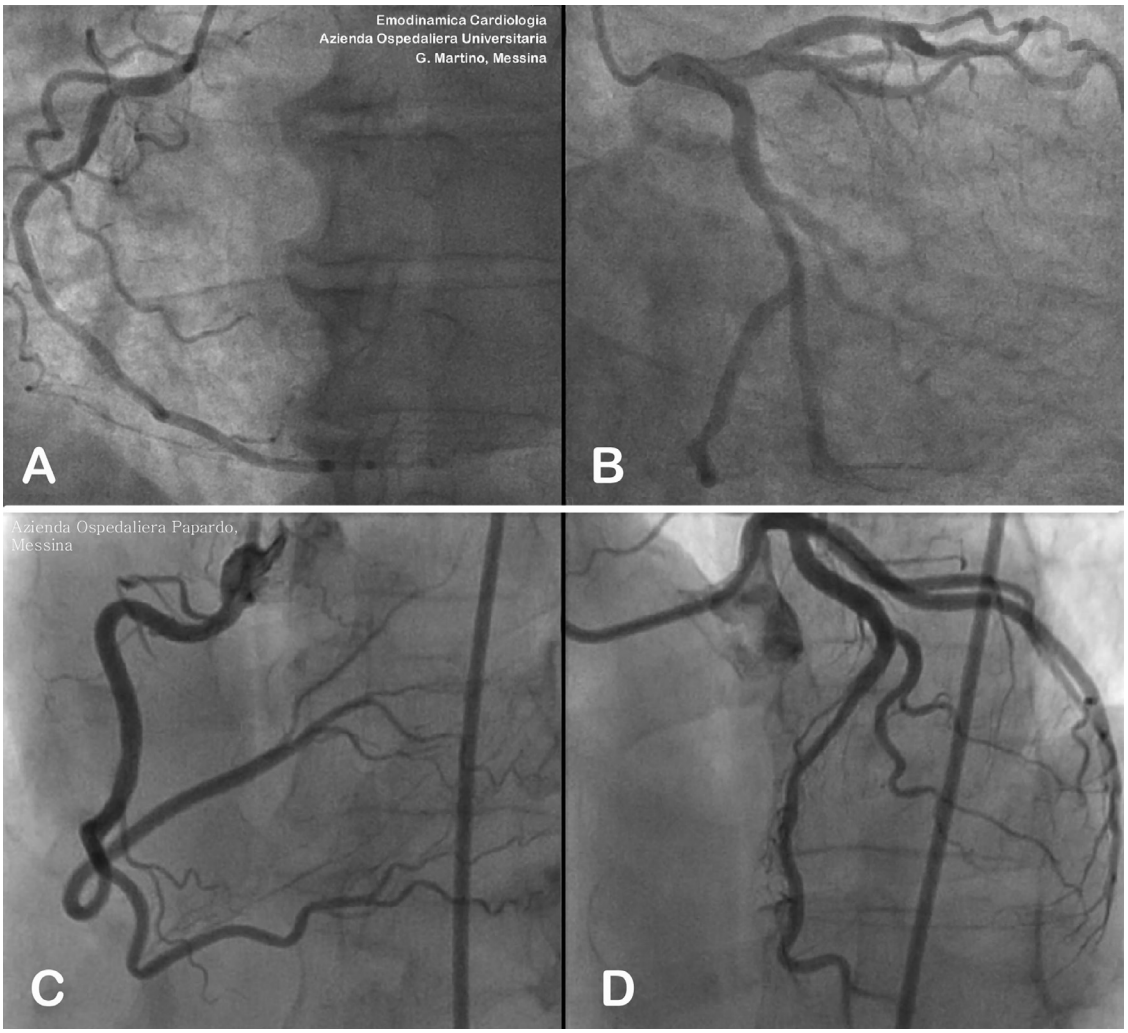

Figure 2. Normal coronary angiograms in the 2 male patients. Top panels, case A: right coronary artery *(A)*, left coronary artery *(B)*. Bottom panels, case B: right coronary artery *(C)*, left coronary artery *(D)*.

Interestingly, almost all known ischemic-SS individuals, included ours, were living in the Mediterranean Sea area, except from a single Australian patient. This peculiarity could be due to several fish species easily available in those regions, as well as abundant fish consumption in the Mediterranean diet. However, high-temperature environmental conditions (especially in Spring and Summer) imply a high-risk of mistreated fish production and storage.[3–6,13] The link between cardiovascular events and toxin triggers has been already established in infective conditions like those caused by Influenza virus, Chlamydia and other agents that can directly infect the atherosclerotic arteries. Exaggerated release of mediators in unstable plaques may lead to plaque erosion, rupture and ensuing thrombosis.[13,14]

The effects of abnormal histamine ingestion from raw fish poisoning are similar to those observed in the allergic reaction of the Kounis syndrome.[15,16] However, important differences between the 2 clinical entities have to be remarked. In the SS, abnormal enzymatic conversion of the free histidine into histamine is caused by the infected fish (or meat) products. The ''scombrotoxin'', a mixture of histamine and other amines (like putrescine and cadaverine), is produced by the decomposition of amino acids present in the tissue of fish products. Proliferation of Gram-negative bacteria and subsequent production of pathogen enzymes are usually linked to high-temperature raw fish or meat storage, whereas the same enzymes are inactivated by freezing. On the contrary, the Kounis disease is an allergic reaction that requires prior sensitization, mediators and inflammation cells to be activated. Degranulation of histamine may cause coronary vasospasm and plaque complications. In fact, erosion and rupture of pre-existing atherosclerotic lesions may even lead to intrastent or plaque thrombosis (Kounis type III variant), which has never been reported in the SS. Briefly, although free histamine is the "end-effector" in both conditions, SS patients usually show an anaphylactoid, not allergic, reaction.[15–19]

Further aspects should also be taken into account with respect to histamine fish-muscle content and individual tolerance to pathogen amines. The food regulations in the USA require histamine levels not exceeding 5 mg/100 g of fish, whereas 10 mg/100 g in Europe. Levels >50 mg/

100 g are toxic, even though some reaction is possible with lower concentrations, also considering the inhomogeneous distribution of the histamine through the same fish.[6,19]

Even though histaminergic illness gets on quick progression, life-threatening hemodynamic outcomes are possible in the acute stage of the disease requiring careful care assistance. Patients with chest pain and hypotension following ingestion of mistreated raw fish should be screened out for acute myocardial ischemia as soon as possible, being aware that antihistamine drugs and steroids are the first-choice medical therapy.[15] The need for coronary angiography has to be established on a case-by-case basis, considering that myocardial ischemia rapidly recovers. Although coronary vasospasm can also occur in chronic CAD patients, younger or healthy individuals should be prevented from unnecessary cath-lab admission.

The present case-series study confirms transient NSTEMI-like ACS as a potential epiphenomenon of mistreated raw tuna fish ingestion. Histaminergic epicardial and/or microvascular coronary vasospasm, just limited to the acute scombrotoxicity, appears to be the most likely underlying mechanism of the ischemic-SS.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.034.

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