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CASE REPORT
Coronary heart disease

Friend or foe: food-dependent exercise-induced anaphylaxis associated with acute coronary syndrome aggravated by adrenaline and aspirin: a case report

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Background Although aspirin and adrenaline are the guideline-recommended treatments for acute coronary syndrome (ACS) and anaphylaxis, both regimens can contribute to clinical worsening in the setting of concurrent ACS and anaphylaxis which is called allergic angina or Kounis syndrome.

Case summary A 62-year-old woman with food-dependent exercise-induced anaphylaxis developed ACS after intramuscular injection of adrenaline for the treatment of anaphylaxis, whereas administered aspirin for the treatment of ACS exacerbated anaphylaxis.

Discussion Our case underlines the importance of tailored treatment based on the underlying pathophysiology of individual patients. Clopidogrel and glucagon might be a better alternative for the treatment of Kounis syndrome.

Keywords Case report • Kounis syndrome • Allergic angina • Food-dependent exercise-induced anaphylaxis

Learning points

- Aspirin and adrenaline are the guideline-recommended therapy for acute coronary syndrome (ACS) and anaphylaxis, but there are risks of worsening of anaphylaxis by aspirin and of ACS by adrenaline for the treatment of Kounis syndrome.
- Clopidogrel and glucagon can be alternatives for the treatment of Kounis syndrome, yet further research is necessary.
- Our case shows the importance of tailored treatment based on the individual underlying pathophysiology.

Introduction

Evidence-based guidelines give standardized treatment strategies; however, they do not work for everyone, and clinical decisions should always be tailored to suit individual patients.

Current guidelines from the European Society of Cardiology recommend aspirin for all patients with acute coronary syndrome (ACS) at an initial dose of 150–300 mg and a maintenance dose of 75–100 mg daily if no contraindication is recorded.[1] Similarly, adrenaline is recommended by the European Academy of Allergy and Clinical Immunology as the first-line therapy for all patients experiencing

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anaphylaxis.[2] Here, we present a case of ACS associated with anaphylaxis aggravated by aspirin and adrenaline, showing the importance of individual pathophysiology.

Timeline

Timeline	Events
5 years ago	The patient experienced intermittent feeling of chest tightness at night several times over 5 years, without any prior history of medical consultation.
A few hours ago	The patient ate mango fruit for lunch, then played tennis.
Initial presentation	Presented to the dermatology department with itchiness and urticaria spreading throughout the whole body which developed while playing tennis. Oral administration of antihistamine (fexofenadine hydrochloride 20 mg and mequitazine 6 mg) did not alleviate her symptoms.
One hour later	Developed dyspnoea with wheezing lung sound and chest tightness. A diagnosis of food-dependent exercise-induced anaphylaxis was made. Intramuscular administration of 0.3 mg adrenaline was given.
5 min later	Prompt improvement in wheezing lung sound and dyspnoea was observed, but chest tightness conversely exacerbated with acute ischaemic electrocardiogram (ECG) change. Intravenous administration of nitroglycerine (1 mg/h) and nicorandil (2 mg/h) resulted in complete disappearance of chest tightness and normalization of ECG change. A 200 mg aspirin was loaded for suspected acute coronary syndrome.
A few hours later	Whole-body urticaria and palpebral oedema aggravated. Severe abdominal pain occurred with stepwise worsening. Additional dose of antihistamine (5 mg IV q 12 h) and hydrocortisone sodium succinate (500 mg IV daily) were administered for 3 days.
3 days later	Whole-body urticaria persisted. Aspirin (75 mg daily) was suspected cause of prolonged allergic reaction.
4 days later	Aspirin withdrew. Clopidogrel (75 mg daily) was substituted as antiplatelet therapy. Only fexofenadine hydrochloride (20 mg daily) was continued for anti-allergic treatment. No allergic symptoms nor chest symptoms recurred.
2 weeks later	Coronary angiography revealed no obstructive diseases. A 50 μg acetylcholine provoked subtotal occlusion of distal right coronary artery leading to the diagnosis of coronary vasospasm. No allergen-specific IgE was detected. Skin prick test, oral food challenge, and oral food and exercise challenge were not performed due to patient's discretion.

Case presentation

A 62-year-old woman, who had a 5-year history of intermittent chest tightness at night without any prior history of medical consultation, presented to our hospital with itchiness and urticaria in the whole body that she had developed while playing tennis a few hours after eating mango fruit. Oral administration of antihistamine (fexofenadine hydrochloride 20 mg and mequitazine 6 mg) did not alleviate her symptoms, and the patient developed dyspnoea with wheezing lung sound and chest tightness. A diagnosis of food-dependent exercise-induced anaphylaxis (FDEIA) was made. Intramuscular administration of adrenaline 0.3 mg improved her wheezing lung sound and dyspnoea but exacerbated chest tightness. Electrocardiogram (ECG) showed ST depression and T-wave inversion in the inferior leads and V3–V6 leads consistent with acute ischaemic change (*Figure 1*). Transthoracic echocardiography revealed left ventricular ejection fraction of 87% with no apparent regional wall motion abnormality. Laboratory data showed no elevation in cardiac enzymes. Intravenous administration of vasodilators, including nitroglycerine (1 mg/h) and nicorandil (2 mg/h), resulted in complete disappearance of chest tightness and normalization of ECG findings with no need for emergent coronary angiography (CAG). In addition to vasodilators, aspirin (200 mg loading dose and 100 mg daily for the following 3 days) was administered orally for suspected ACS. Subsequently, urticaria and palpebral oedema aggravated, and severe abdominal pain occurred with stepwise worsening, which was managed with additional chlorpheniramine maleate (5 mg IV q 12 h) and hydrocortisone sodium succinate (500 mg IV daily) for three days due to persistent urticaria, after checking there was no previous history of aspirin allergy. Aspirin was suspected to prolong the allergic reaction and was replaced by clopidogrel (75 mg daily) leading to the resolution of allergic symptoms. The patient continued oral antihistamine (fexofenadine hydrochloride 20 mg daily) and clopidogrel (75 mg daily). Two weeks later, CAG was performed revealing no obstructive lesions. However, subtotal occlusion of the distal right coronary artery was induced by 50 μg acetylcholine resulting in ischaemic ECG changes and chest pain, consistent with vasospastic angina (*Figures 2* and *3*, and Supplementary material online, *Figures S1–S3*). Allergen-specific immunoglobulin E (IgE) tests for mango, kiwi, peach, avocado, tomato, wheat, and nuts were all negative. Skin prick test, oral food challenge, and oral food and exercise challenge were not performed due to the patient's discretion of anaphylaxis' risk. The patient was educated to avoid exercise after eating, especially mango fruit. Clopidogrel was withdrawn without any evidence of clinical worsening over 1 year.

Discussion

Allergic angina, also known as Kounis syndrome, is defined as ACS associated with allergic reaction or anaphylaxis requiring treatment for both ACS and allergic reaction.[3] Kounis syndrome is classified into three types—Type 1: coronary spasm without plaque erosion or rupture; Type 2: coronary spasm with plaque erosion or rupture; and the recently added Type 3: stent thrombosis or in-stent restenosis due to allergic sequela.[4] In Types 2 and 3 Kounis syndrome, long-term antiplatelet therapy and revascularization procedures are necessary depending on the initial presentation, whereas Type 1 Kounis syndrome can be managed with medical therapy including vasodilators, antihistamines, and corticosteroids. Only two cases of Kounis syndrome accompanied by FDEIA, like our case, have been reported in the literature.[5,6] The first case was a 70-year-old man who developed ST-segment elevation myocardial infarction during a FDEIA attack, while taking aspirin for a previous history of cerebral infarction. Coronary angiography revealed thrombosed occlusion at the proximal left anterior descending artery, which was successfully treated with thrombectomy and bare-metal stent placement, suggesting Type 2 Kounis syndrome. Histological examination of the aspirated thrombus to investigate the causal link between allergic reaction and plaque rupture was not available in this case. The second case was a 49-year-old man presenting ST-segment elevation in leads V2-V4 after adrenaline administration which was treated with medical therapy. No obstructive coronary artery disease (CAD) was detected by cardiac magnetic resonance imaging, suggesting Type 1 Kounis syndrome. Though the clear associations were not depicted in the reports, aspirin and adrenaline might have worked as complicating factors.

Non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin, promote anaphylaxis in patients with FDEIA via increasing antigen uptake across the intestinal epithelium and promoting histamine release from mast cells and basophils.[7] In addition, aspirin and other NSAIDs may induce dysregulation of arachidonic acid metabolism, leading to bronchoconstriction and bronchial hyperreactivity.[8] A causative link between exacerbation/prolongation of allergic reaction and aspirin is not clear in our case; however, the fact that the whole body urticaria and abdominal pain worsened after aspirin administration and completely diminished after aspirin withdrawal convince us that aspirin was a complicating factor. Previous reports

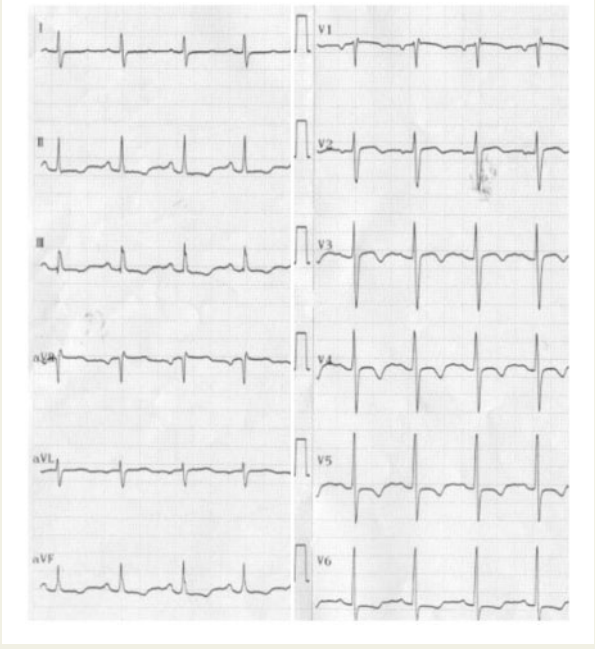

Figure 1 Electrocardiogram recorded during chest pain. An electrocardiogram revealed ST-segment depression in leads II, III, aVF, and V5–V6 and T-wave inversion in leads II, III, aVF, and V3–V6.

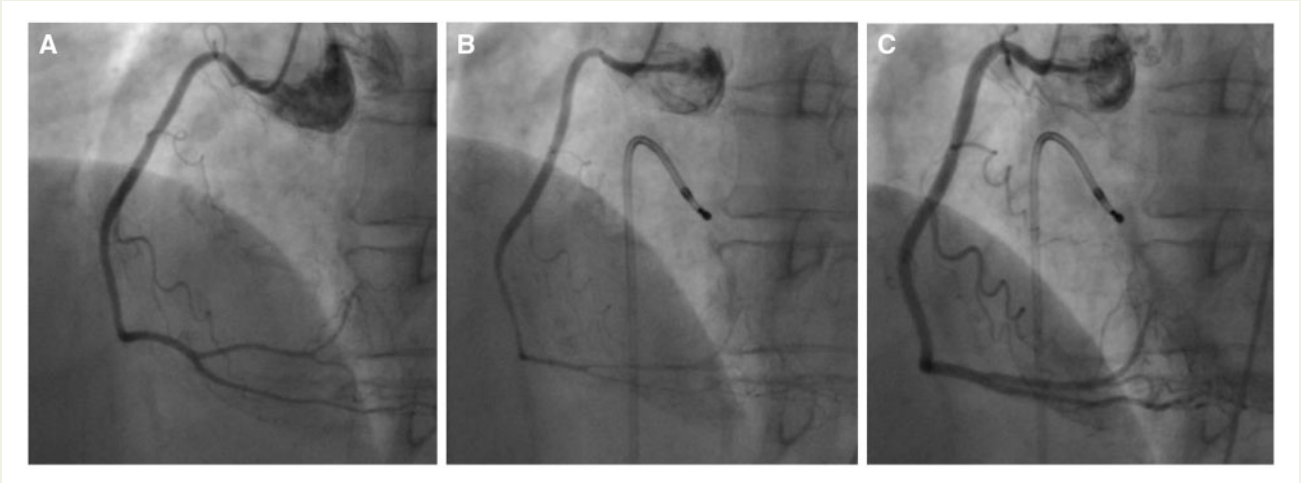

Figure 2 (*A*) Baseline right coronary angiogram showing no obstructive coronary artery diseases. (*B*) After coronary infusion of 50 μg acetylcholine, subtotal occlusion was induced at the distal right coronary artery. (*C*) After coronary infusion of nitroglycerine, coronary spasm was resolved, leaving no coronary obstruction in the right coronary artery.

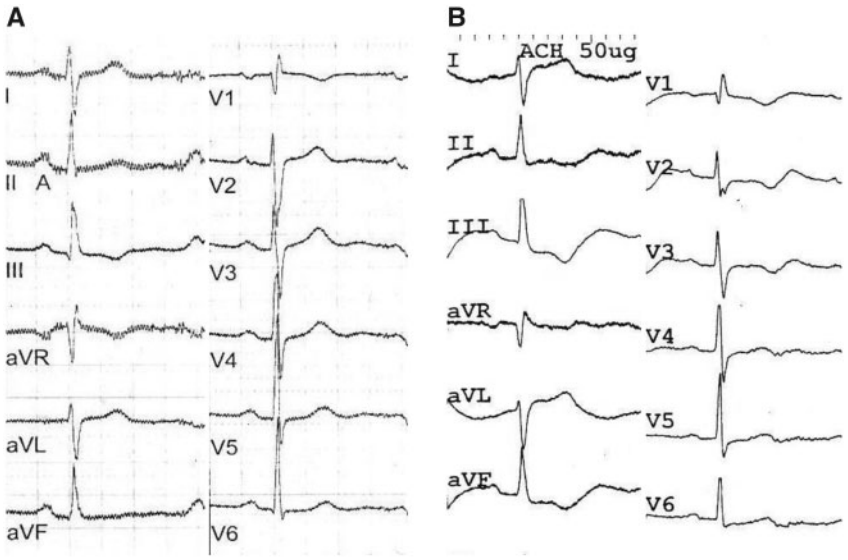

Figure 3 Electrocardiogram recorded during acetylcholine provocation test. (*A*) Baseline electrocardiogram shows no abnormality. (*B*) Electrocardiogram during coronary infusion of 50 μg acetylcholine revealed ST-segment elevation in leads I and aVL and ST-segment depression in leads II, III, aVF, and V2–V4 and T-wave inversion in leads in aVF and V2–V4.

showed that concurrent aspirin administration facilitates and enhances the allergic response during skin prick test of patients with FDEIA.[7] In this context, NSAIDs can provoke an allergic reaction or increase its severity, however, it is not certain if aspirin should be avoided for concurrent ACS. If the benefit of aspirin for ACS do not overweighs the risk of aggravating anaphylaxis, clopidogrel, and other antiplatelet agents can be an alternative option for the treatment of Kounis syndrome.[9]

Adrenaline is a vital treatment for life-threatening anaphylaxis, but administration of adrenaline in the presence of significant CAD requires a challenging decision. Alfa-adrenergic stimulation of adrenaline can induce coronary vasoconstriction accompanied by an increase of oxygen demand through beta-adrenergic stimulation, leading to aggravation of ischaemia.[10] The risk factors of adrenaline-induced coronary vasoconstriction are age, pre-existing CAD, beta-blocker treatment, and intravenous administration of high-dose adrenaline.[11] In our case, chest pain with ischaemic ECG change developed right after intramuscular administration of adrenaline, indicating that allergic vasoconstriction was exacerbated by it. A similar case was reported in a 21-year-old healthy male presenting ischaemic ECG change and myocardial injury after intramuscular injection of adrenaline for the treatment of food-induced anaphylaxis without any of the above-mentioned risk factors.[11] In our case, the patient had a 5-year history of chest tightness at night and showed a positive acetylcholine provocation test, indicating a pre-existing endothelial dysfunction, which is a predisposing factor to adrenaline-induced vasospasm.[12] Therefore, pre-existing coronary vasospastic state induced by allergic reaction and endothelial dysfunction might induce adrenaline-induced coronary vasospasm. Glucagon is thought to be a second-line treatment of refractory anaphylaxis for patients under beta-blocker therapy, exerting a positive inotropic effect on the myocardium and airway smooth muscle cell relaxation without adrenergic receptor stimulation and with possible vasodilatory effect.[13] Glucagon also inhibited the allergen-evoked histamine and other pro-inflammatory cytokine release from mast cells.[14] Theoretically, these effects are more favourable than adrenaline in the complicated situation of concurrent anaphylaxis and ACS, though its clinical benefit is not proven yet and therefore, further studies are necessary.

Conclusion

In conclusion, we experienced a case of FDEIA associated with Kounis syndrome aggravated by adrenaline and aspirin administration that proves the importance of personalized treatment. Glucagon and clopidogrel can be suitable alternatives for the treatment of Kounis syndrome; however, further research is needed.

Lead author biography

Takumi Toya was a general cardiologist at National Defense Medical College and currently working at Mayo Clinic as a visiting research fellow. Before starting the career as a general cardiologist, Takumi spent nine years for Japan Maritime Self-Defense Force.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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