



# Kounis Syndrome (Allergic Angina and Allergic Myocardial Infarction) a Disease to Know: Cases Report and Literature Review

Yong-Ye Yang<sup>1</sup>, Hung-Yun Su<sup>1,5,6</sup>, Chin-Feng Hsuan<sup>2,4,7</sup>, Kuo-Hsin Lee<sup>1,3,7,\*</sup>

Kounis syndrome (KS) is a unique clinical entity that has been defined as acute coronary events resulting from coronary vasospasm, acute plaque rupture, or stent restenosis secondary to allergic or anaphylactic insults. Exposures to numerous allergens such as foods, medications, coronary stents, or environmental factors have been reported to provoke KS. Herein, we described two cases of different types of KS triggered by seafood, epinephrine, and bee sting. These cases highlight the need to not only have a high index of suspicion and early diagnoses of KS but also to be cautious in prescribing medications, particularly epinephrine, beta-blocker, morphine, and nitroglycerin, while managing both cardiac and allergic reactions, without exacerbating the patient's symptoms.

**Key words:** bee stings, epinephrine, anaphylaxis, allergic angina, kounis syndrome

## Introduction

Allergic reactions have various manifestations, ranging from simple skin reactions to life-threatening cardiovascular symptoms. During mast cell activation, inflammatory mediators are released, which can induce coronary arteries spasm and atheromatous plaque rupture.<sup>1</sup> Concurrence of acute coronary syndrome with conditions associated with mast cell activation is defined as Kounis syndrome (KS).<sup>1,2</sup> The concept was first described as

“allergic angina or allergic myocardial infarction” by Dr. Kounis and Dr. Zavras in 1991.<sup>2</sup> KS is classified into three variants: type 1 is a transient or persistent coronary spasm in patients with normal or near-normal coronary arteries without risk factors for coronary artery disease, type 2 is related to patients with pre-existing atheromatous disease, and type 3 is seen in patients with stent thrombosis.<sup>1</sup> In recent years, considerable concern has arisen over the diagnosis and treatment of KS. Herein, we reported two cases of KS triggered by seafood, epinephrine, and bee sting.

From the <sup>1</sup>Department of Emergency Medicine and <sup>2</sup>Division of Cardiology, Department of Internal Medicine, E-Da Hospital, I-Shou University; <sup>3</sup>Department of Emergency Medicine and <sup>4</sup>Division of Cardiology, Department of Internal Medicine, E-Da Dachang Hospital, I-Shou University; <sup>5</sup>School of Medicine for International Student, College of Medicine, <sup>6</sup>School of Chinese Medicine for Post Baccalaureate, College of Medicine and <sup>7</sup>School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan.

Received: September 15, 2021

Accepted: November 17, 2021

\* Address reprint request and correspondence to: Kuo-Hsin Lee, Department of Emergency Medicine, E-Da Hospital, No. 1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 824005, Taiwan

Tel: +886-7-615-0011 ext. 2987, E-mail: peter1055@gmail.com

## Case Report

### Case 1: Epinephrine-induced type I Kounis Syndrome

A 40-year-old man, a chronic smoker, presented to the emergency department (ED) with developing pruritic skin rash in extremities after eating seafood. Upon arrival to our ED, initial vital signs showed blood pressure of 89/37 mmHg, respiratory rate of 22 breaths/minute, and pulse rate of 109 beats/minute. Considering the impression of anaphylactic shock, he was resuscitated. Intravenous fluids, antihistamine, corticosteroid, and epinephrine 0.5 mg (intramuscular injection) were administered. Twenty minutes later, he experienced acute-onset chest pain accompanied with nausea, vomiting, and diaphoresis. A 12-lead electrocardiogram (ECG) revealed sinus tachycardia with ST-segment elevation in lead aVR and diffuse ST-segment depression in inferior leads and V3 – V6, which was considered left main coronary artery acute infarction (Fig. 1). The initial serum troponin level was not elevated ( $< 0.01$  g/dL). Under the suspicion of acute coronary syndrome (ACS), dual antiplatelet therapy (DAPT) with aspirin and ticagrelor was started, and 4,000 units of heparin

were administered intravenously. Surprisingly, 1 hour later, the chest pain resolved, the pruritic skin rash subsided, and ECG findings normalized (Fig. 2). Serial follow-up ECG revealed no specific changes, and no further elevation in troponin I level was noted. Therefore, epinephrine-induced coronary vasospasm was the likely cause of the myocardial ischemia, as the patient developed chest pain only after epinephrine injection. This case is referred as type I KS. The patient was discharged without recurrence of chest pain.

### Case 2: Bee sting-induced type II Kounis Syndrome

A 57-year-old man with a history of hypertension was stung by a bee on his left upper back. Acute-onset chest pain and shortness of breath developed 2 hours later. Upon arrival to our ED, his initial vital signs showed blood pressure of 84/56 mmHg, respiratory rate of 22 breaths/minute, and pulse rate of 106 beats/minute. Cold sweats and lip swelling were noted in the triage area. Physical examination revealed normal breath sounds in bilateral lung fields, and some wheals were found on the anterior abdominal wall. His ECG revealed deep T wave inversion in V2 – V5 (Fig. 3). The initial troponin I was 0.307 g/L (normal range,

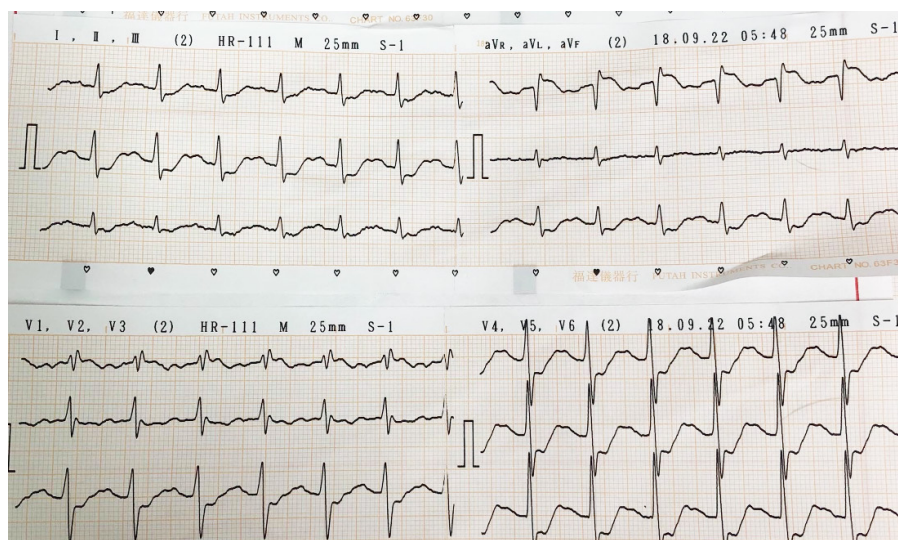


Fig. 1 EKG showing ST-segment elevation in lead aVR and diffuse ST-segment depression over II, III, aVF and V3 – V6, which is considered as acute infarction of the left main coronary artery.



< 0.01 g/L). Given the very high suspicion of ACS, he underwent coronary angiogram (CAG) the next day. CAG revealed that the proximal left anterior descending coronary artery had 90% stenosis from the ruptured ulcerative plaque (Fig. 4A). Therefore, a drug-eluting stent was implanted (Fig. 4B). His presentation and CAG findings correlated with type II acute myocardial infarction from the ruptured plaque of pre-existing atheromatous disease after a bee sting. He was discharged on DAPT with aspirin and ticagrelor.

## Discussion

The incidence rate of KS ranges from 0.002% to 3.4%.<sup>3,4</sup> In 2019, Desai et al. demonstrated that 235,420 patients were primarily hospitalized with allergy-hypersensitivity-ana-

phylactic reactions. Among them, 0.2% had an unstable angina, 0.2% had ST-segment elevation myocardial infarction (STEMI), and 0.7% had non-STEMI (NSTEMI), these patients were identified as having KS. The subsequent all-cause mortality rate was 7.0%.<sup>5</sup>

The pathophysiology of KS was described by Kounis et al. as a complex multisystem disease accompanied with allergy-hypersensitivity-anaphylaxis.<sup>6</sup> After exposure to allergens, the mast cells and lymphocytes are stimulated and released inflammatory mediators, promoting an allergic reaction through high serum levels of histamine, proteases, arachidonic acid products, and chemokines, resulting in platelet aggregation and tissue factor expression.<sup>6</sup> Proteases can activate matrix metalloproteinases that can degrade the collagen cap and induce plaque erosion and rupture.<sup>3</sup> Hista-

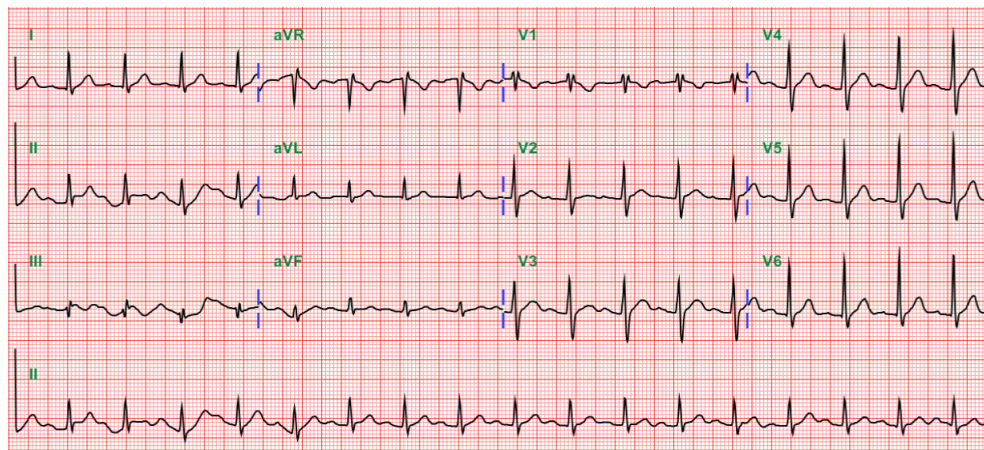


Fig. 2 EKG showing no ST-T changes, resolution of ST-segment depression as compared to initial ECG (Fig. 1).

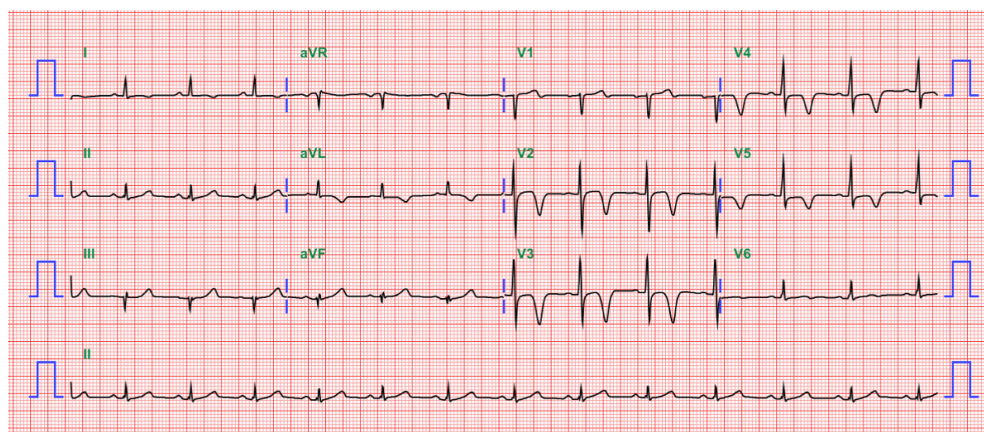
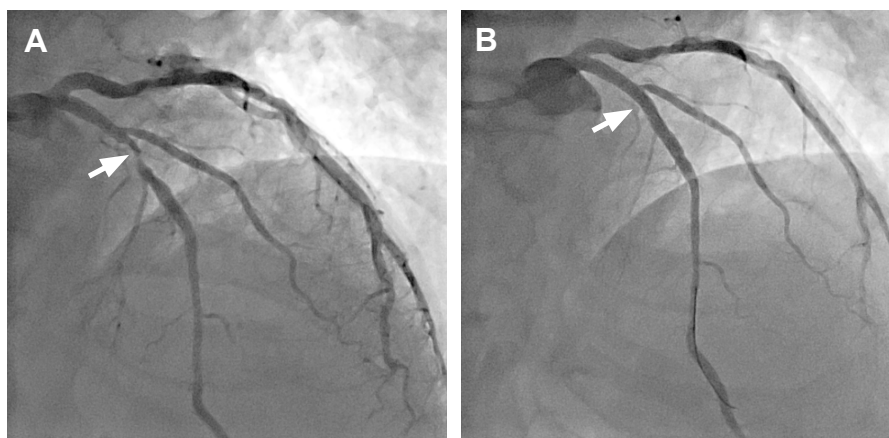


Fig. 3 EKG showing deep T wave inversion in V2 – V5 , which indicates acute ischemic in the anterior wall.



*Fig. 4 (A) Coronary angiogram the next day which revealed proximal LAD 90% stenosis, white arrow head pointed out ruptured ulcerative plaque. (B) Coronary angiogram after drug-eluting stent placement to proximal LAD, white arrow head showed increased coronary flow after percutaneous intervention.*

mines not only can provoke coronary arterial spasm but also can affect cardiac function mediated by H1 and H2 receptors found on the four cardiac chambers and coronary arteries.<sup>2</sup> Three KS variants have been identified. Type I involves coronary artery spasm caused by the acute release of inflammatory mediators in a normal or near-normal coronary artery. Type II involves coronary artery spasm or plaque erosion in an artery with pre-existing atherosclerotic disease and is caused by acute inflammatory mediators. Type III is coronary artery stent thrombosis, wherein eosinophils or mast cells are detected in the aspirated thrombus.<sup>6</sup>

The diagnosis of KS is based on clinical presentation, and the cardiac evaluation included cardiac biomarkers, ECG, echocardiography, and CAG. Akoç et al. proposed that 71.4% of the patients presented with chest pressure, 52.4% with shortness of breath, 47.6% described palpitations, and 14.3% had syncope. Examination revealed that 76.2% of the patients had hives, 47.6% had uvular edema, 24% had angioneurotic edema, and 19% had hypotension.<sup>4</sup> Furthermore, studies have reported that various drugs, foods, environmental exposures, coronary stents, and clinical conditions can provoke KS, but the most common etiology was the use of medications (81%).<sup>5</sup> Commonly used drugs such as aspirin, antihypertensives, corticosteroids,

antibiotics, and nonsteroidal antiinflammatory drugs are some of the main offenders.<sup>6</sup> The most-reported findings on the ECG of patients with KS are ST elevations in the anterior and inferior leads; however, the ECG could be normal or merely reveal nonspecific ST–T wave changes.<sup>7</sup> The serum levels of histamine, immunoglobulin E, eosinophils, and tryptase are helpful to confirm the diagnosis.<sup>6</sup>

The treatment strategy becomes challenging when anaphylaxis and ACS co-exist. Currently, in the absence of a specific treatment guideline, management is mostly based on individual case reports available in the literature, with the administration of drugs that could not exacerbate either allergic reaction or myocardial ischemia.<sup>7</sup> In patients with type I KS, cardiac manifestation can resolve after controlling allergic reaction with corticosteroid and H1 and H2 antihistamines.<sup>6</sup> Epinephrine is a life-saving medication in treating anaphylaxis presenting with respiratory and circulatory compromise, but in KS, epinephrine should be used with caution because it can worsen myocardial ischemia, prolong the QTc interval, and induce coronary vasospasm and arrhythmias.<sup>6</sup> Similar to case 1, nine cases of epinephrine-induced myocardial ischemia have been reported when treated for anaphylaxis.<sup>8</sup> Vasodilators, such as calcium channel blockers and nitrates, can abolish the vasospasm. Intravenous or sub-

lingual nitroglycerin appears reasonable and safe in patients with KS if the blood pressure is satisfactory.<sup>1</sup>

For type II KS, treatment includes an acute coronary event protocol together with corticosteroids and antihistamines. Nevertheless, aspirin should be used with caution because it inhibits cyclooxygenase, thereby stimulating the release of arachidonic acid into the leukotriene pathway.<sup>9</sup> Furthermore, beta-blockers can exaggerate coronary spasm because of the unopposed action of alpha-adrenergic receptors. Hence, epinephrine might be ineffective in patients already on beta-blockers. In such cases with anaphylaxis and hypotension, glucagon infusion can be provided, as it may increase heart rate and myocardial contractility and improve atrioventricular conduction.<sup>6</sup> Administration of opiates may be detrimental because they can induce massive mast cell degranulation and aggravate the allergic reaction. Otherwise, fentanyl and its derivatives cause slight mast cell activation and are preferable.<sup>10</sup> For type III KS, the ACS protocol accompanied with the urgent aspiration of in-stent thrombus is paramount. In addition, corticosteroids, antihistamines, and mast cell stabilizers can alleviate the allergic manifestations after stent implantation.<sup>6</sup>

In conclusion, KS is an underdiagnosed rather than a rare disease. Hence, physicians should have a high index of suspicion for KS in patients with myocardial ischemia accompanied with anaphylaxis. Furthermore, to implement rapid treatment for both conditions, specific medications, such as epinephrine, beta-blockers, morphine, and nitroglycerin, should be prescribed with caution to prevent further vasospasm and deterioration of hypotension.

### Author Contributions

Kuo-Hsin Lee conceived and designed the study, Yong-Ye Yang collected data and drafted the manuscript, Ching-Feng Hsuan performed

data analysis. Hung-Yun Su critically revised the manuscript and final approval.

### Funding

This research received no external funding.

### Institutional Review Board Statement

Not applicable.

### Informed Consent Statement

Not applicable.

### Data Availability Statement

Not applicable.

### Conflicts of Interest

The authors declare no conflict of interest.

### References

1. Kounis NG: Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med* 2016;54:1545-59. doi: 10.1515/cclm-2016-0010.
2. Kounis NG, Zavras GM: Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract* 1991;45:121-8.
3. Kounis NG, Mazarakis A, Tsigkas G, et al: Kounis syndrome: a new twist on an old disease. *Future Cardiol* 2011;7:805-24. doi: 10.2217/fca.11.63.
4. Akoz A, Tanboga H, Emet M, et al: A prospective study of kounis syndrome: clinical experience and cardiac magnetic resonance imaging findings for 21 patients. *Acta Medica Mediterranea* 2013;29:811-6.
5. Desai R, Parekh T, Patel U, et al: Epidemiology of acute coronary syndrome co-existent with allergic/hypersensitivity/anaphylactic reactions (Kounis syndrome) in the United States: a nationwide inpatient analysis. *Int J Cardiol* 2019;292:35-8. doi: 10.1016/j.ijcard.2019.06.002.
6. Kounis NG, Koniari I, Velissaris D, et al: Kounis syndrome—not a single-organ arterial disorder but a multisystem and multidisciplinary disease. *Balkan Med J* 2019;36:212-21. doi: 10.4274/balkanmedj.galenos.2019.2019.5.62.
7. Fassio F, Losappio L, Antolin-Amerigo D, et al:



- Kounis syndrome: a concise review with focus on management. *Eur J Intern Med* 2016;30:7-10. doi: 10.1016/j.ejim.2015.12.004.
8. Urushidani S, Kuriyama A: A potential association between myocardial ischemia and epinephrine for anaphylaxis. *Am J Emerg Med* 2020;38:1297.e1-e3. doi: 10.1016/j.ajem.2020.01.033.
  9. Hangouche AJE, Lamliki O, Oukerraj L, et al: Kounis syndrome induced by oral intake of aspirin: case report and literature review. *Pan Afr Med J* 2018;30:301. doi: 10.11604/pamj.2018.30.301.14948.
  10. Akgullu C, Eryilmaz U, Gungor H, et al: Myocardial infarction secondary to morphine-induced Kounis syndrome. *Herz* 2014;39:874-6. doi: 10.1007/s00059-013-3919-7.