

CASE REPORT

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Type I Kounis syndrome in a young woman without chest pain: a case report

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Abstract

Background Kounis syndrome is defined as the concurrence of acute coronary syndromes in the setting of allergic or anaphylactic reactions. It primarily affects men aged 40–70 years and is often associated with chest pain. This syndrome is often unrecognized and undiagnosed in clinical practice due to a low level of awareness. Herein, we present a case of type I Kounis syndrome in a young woman without chest pain.

Case presentation A 28-year-old Japanese woman with a history of atopic dermatitis received a glycyrrhizin, glutathione, and neurotropin preparation (a preparation of inflamed skin extract from rabbits inoculated with vaccinia virus) at a dermatology clinic to treat pruritus caused by atopic dermatitis. Immediately after the administration, the patient developed abdominal pain and generalized body wheals. The patient was diagnosed with anaphylaxis and was transported to our hospital. She had no chest pain on arrival at our hospital; however, a 12-lead electrocardiogram showed ST elevation in leads I, aVL, V2, and V3, and an echocardiogram showed decreased wall motion in the anterior and lateral walls of the left ventricle. Sublingual nitroglycerin administration improved ST-segment elevation and left ventricular wall motion abnormalities. The patient underwent emergency coronary angiography, which revealed no significant stenosis, and was diagnosed with type I Kounis syndrome.

Conclusion Kounis syndrome without chest pain is rare in young women. Since it can be fatal in cases with severe allergic symptoms such as anaphylaxis, the possibility of concurrent acute coronary syndrome should be considered when treating systemic allergic reactions, regardless of age, sex, or the presence or absence of chest symptoms.

Keywords Allergy, Anaphylaxis, Coronary syndrome, Chest pain, Atopic dermatitis, Wheals, Case report

Background

Kounis syndrome is defined as the concurrence of acute coronary syndromes in the setting of allergic or anaphylactic reactions [1], characterized by various underlying pathological conditions that precipitate acute coronary syndrome. These conditions arise due to the release of inflammatory mediators and cytokines from mast cells during allergic reactions [2]. Kounis syndrome is classified into three types based on the underlying mechanisms: type I, acute coronary syndrome caused by spasms in coronary arteries without arteriosclerosis; type II, acute coronary syndrome due to erosion or rupture of preexisting coronary artery plaques; and type III, acute

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coronary syndrome in cases where coronary artery stents have been placed [2]. Type III is further classified into IIIa (stent thrombosis) and IIIb (stent restenosis) subtypes [3]. Although much about the pathogenesis of this syndrome remain unclear, triggers such as drugs, food, and insect bites cause mast cell degranulation and the release of inflammatory mediators such as histamine, leukotrienes, prostaglandins, and chymase. These inflammatory mediators cause coronary artery spasms and thrombosis, leading to acute coronary syndrome [1, 2, 4]. Due to a low level of awareness of this syndrome, it is often unrecognized and undiagnosed in clinical practice [5].

Kounis syndrome occurs in 1.1–3.4% of patients with allergic symptoms [6, 7]. It is more prevalent in male individuals (74.3%), with the most common age of onset ranging from 40 to 70 years (68%). Moreover, 86.8% of the patients experience chest pain [8]. This report presents a case of type I Kounis syndrome in a young woman without chest pain.

Case presentation

A 28-year-old Japanese woman presented to our hospital with headache and vomiting on November 16, 2020. She had a history of atopic dermatitis accompanied by

itching, for which she visited her family physician. Therefore, she was administered Stronger Neo-Minophagen (containing monoammonium glycyrrhizinate, glycine, aminoacetic acid, and L-cysteine hydrochloride hydrate), neurotropin (an extract from inflamed cutaneous tissue of rabbits inoculated with the vaccinia virus), and Tathion (glutathione) for atopic dermatitis intravenously. Immediately after administration, she had abdominal pain and generalized body wheals. Anaphylaxis was diagnosed, and she was treated with 0.3 mg of intramuscular epinephrine, 5 mg of intravenous d-chlorpheniramine maleate, and 80 mg of intravenous methylprednisolone. She subsequently developed headache and vomiting and was transported to our hospital. Neither chest symptoms were observed, nor was there a history of hypertension, dyslipidemia, diabetes, or smoking. Additionally, the patient had no family history of acute coronary syndrome. Although she had a history of skin and throat itching while using or consuming acetaminophen, latex, kiwis, or redfish, the patient had never experienced anaphylaxis.

Investigation

Upon arrival at the emergency department of our hospital, she presented with a Glasgow Coma Scale score of E4V5M6; body temperature, 37.2°C; blood pressure, 88/54 mmHg; pulse, 73 beats per minute (bpm); respiratory rate, 32 times per minute; and oxygen saturation, 100% (8 L/min oxygen was provided by mask). Wheezing was heard in the left anterior chest, with no heart murmur. Cold sweat on the skin and eyelid edema were observed. The wheals disappeared, and there was no skin eruption.

The table shows the laboratory data at the time of the visit. The white blood cell count was 10,160 / μ L, the creatine kinase (CK) level was 114 U/L, and the troponin I level was < 10 pg/mL (Table 1).

A 12-lead electrocardiogram on arrival showed normal sinus rhythm with a heart rate of 75 bpm; ST elevation in leads I, aVL, V2, and V3; and ST depression in leads II, III, and aVF (Fig. 1). Accordingly, 0.3 mg epinephrine was intramuscularly administered to treat anaphylactic shock (17 min after arrival), and the patient's blood pressure increased to 106/73 mmHg. An electrocardiogram obtained after intramuscular epinephrine injection showed no worsening of the ST changes (Fig. 2). Subsequently, 0.3 mg nitroglycerin was sublingually administered 55 min after arrival, and the ST changes improved (Fig. 3). A chest radiography showed sharp costophrenic angles on both sides, and no cardiomegaly or pulmonary congestion was observed. A transthoracic echocardiogram obtained upon arrival revealed a left ventricular ejection fraction of 50%, decreased wall motion in the anterior and lateral walls of the left ventricle, and absence

Table 1 Laboratory investigations on admission

Parameter	Observed value	Standard value
White blood cell count (/ μ L)	10,160	4,500–7,500
Neutrophils (%)	37.7	42–74
Lymphocytes (%)	51.2	18–50
Monocytes (%)	1.5	1–10
Hemoglobin (g/dL)	12.4	11.3–15.2
Platelet count (/ μ L)	29.5 \times 10 ⁴	13–35 \times 10 ⁴
Total protein (g/dL)	6.0	6.9–8.4
Albumin (g/dL)	3.8	3.9–5.1
Total bilirubin (mg/dL)	0.3	0.2–1.2
Aspartate aminotransferase (U/L)	21	11–30
Alanine aminotransferase (U/L)	19	4–30
Lactate dehydrogenase (U/L)	243	109–216
Creatine kinase (U/L)	114	40–150
Blood urea nitrogen (mg/dL)	9.8	8–20
Creatinine (mg/dL)	0.87	0.63–1.03
C-reactive protein (mg/dL)	0.2	\leq 0.60
Sodium (mEq/L)	143	136–148
Potassium (mEq/L)	3.0	3.6–5.0
Chloride (mEq/L)	104	98–108
Glucose (mg/dL)	149	70–109
Hemoglobin A1c (%)	5.5	5.6–5.9
Total cholesterol (mg/dL)	154	130–220
Triglyceride (mg/dL)	50	35–149
High density lipoprotein cholesterol (mg/dL)	48	40–149
Low density lipoprotein cholesterol (mg/dL)	97	70–139
Troponin I (pg/mL)	< 10	\leq 26.2
Brain natriuretic peptide (pg/mL)	< 5.8	\leq 18.4

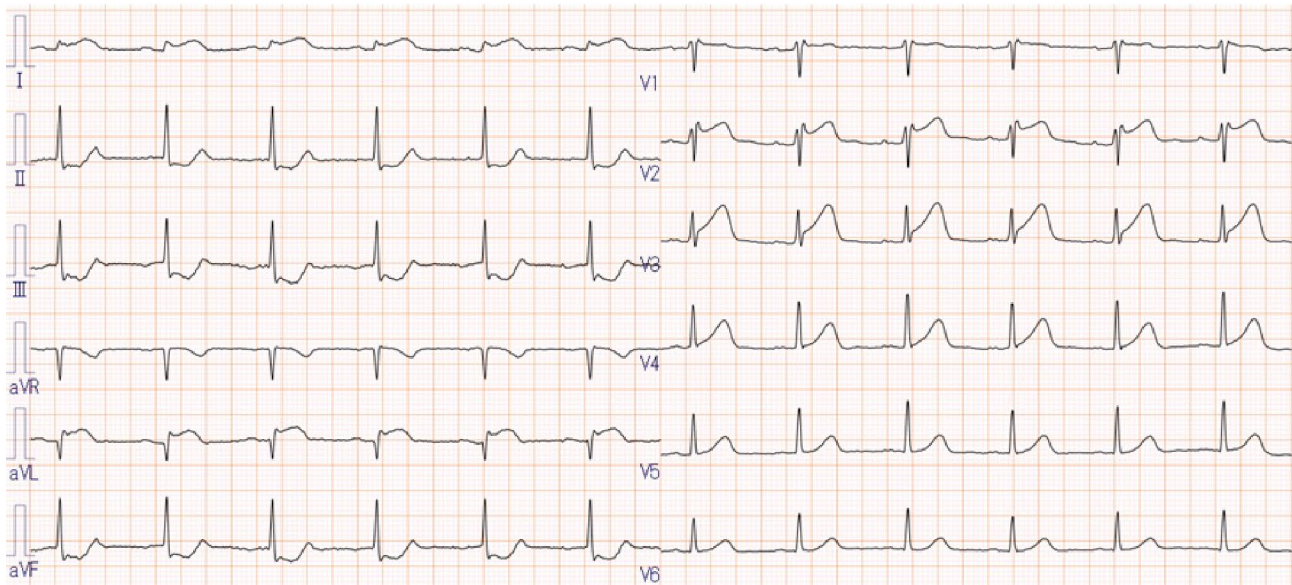


Fig. 1 A 12-lead electrocardiogram on arrival. On arrival, screening electrocardiography was performed. ST elevation is observed in leads I, aVL, V2, and V3, and ST depression is observed in leads II, III, and aVF

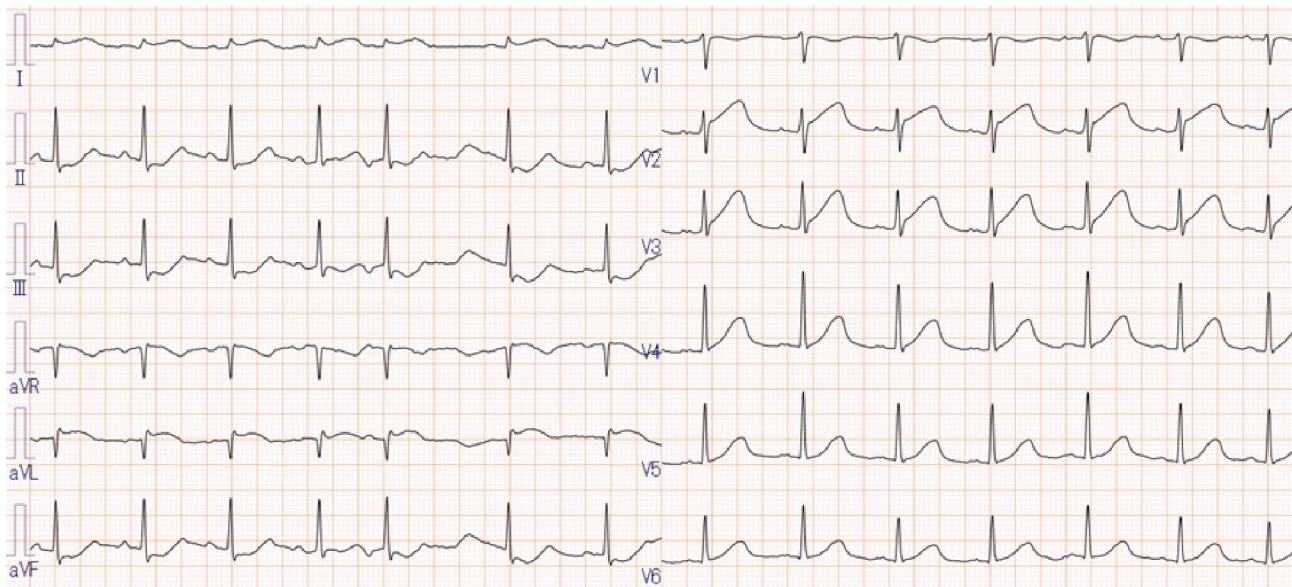


Fig. 2 A 12-lead electrocardiogram after intramuscular injection of 0.3 mg epinephrine. ST elevation is observed in leads I, aVL, V2, and V3, and ST depression is observed in leads II, III, and aVF. Compared with the 12-lead electrocardiogram on arrival (Fig. 1), no worsening of ST elevation or depression was observed

of moderate or severe valvular disease (Fig. 4). The troponin I level measured 5 min post-arrival showed no increase (<10 pg/mL); however, it increased to 688.5 pg/mL when the test was repeated 1 h and 40 min later. Coronary angiography performed 4 h after arrival showed no significant stenosis in the coronary arteries (Fig. 5). An electrocardiogram obtained at the time of coronary angiography showed that ST changes had almost normalized (Fig. 6).

Differential diagnosis

Because ST elevation improved with nitroglycerin administration, and no significant organic stenosis was observed in the coronary arteries, coronary spasms were suspected, and the patient was diagnosed with type I Kounis syndrome.

Takotsubo syndrome and coronary spasms induced by catecholamine administration were considered differential diagnoses. In this case, giant negative T waves [9], which are observed in 95% of patients with Takotsubo

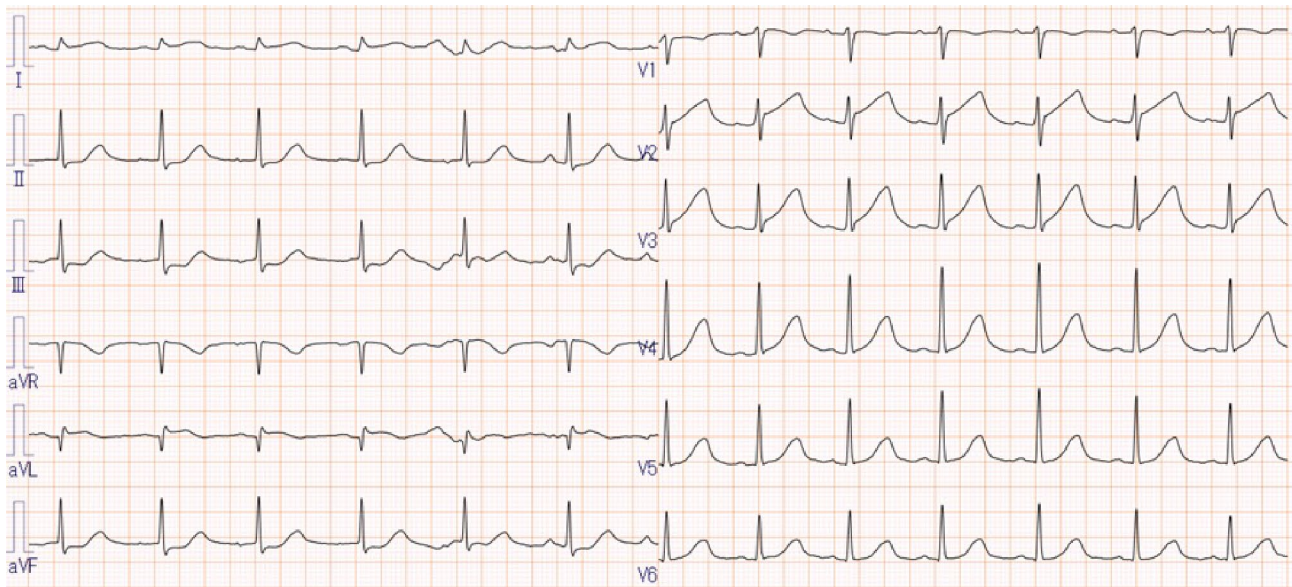


Fig. 3 A 12-lead electrocardiogram after sublingual administration of 0.3 mg nitroglycerin. ST elevation in leads I, aVL, V2, and V3 and ST depression in leads II, III, and aVF are partially improved

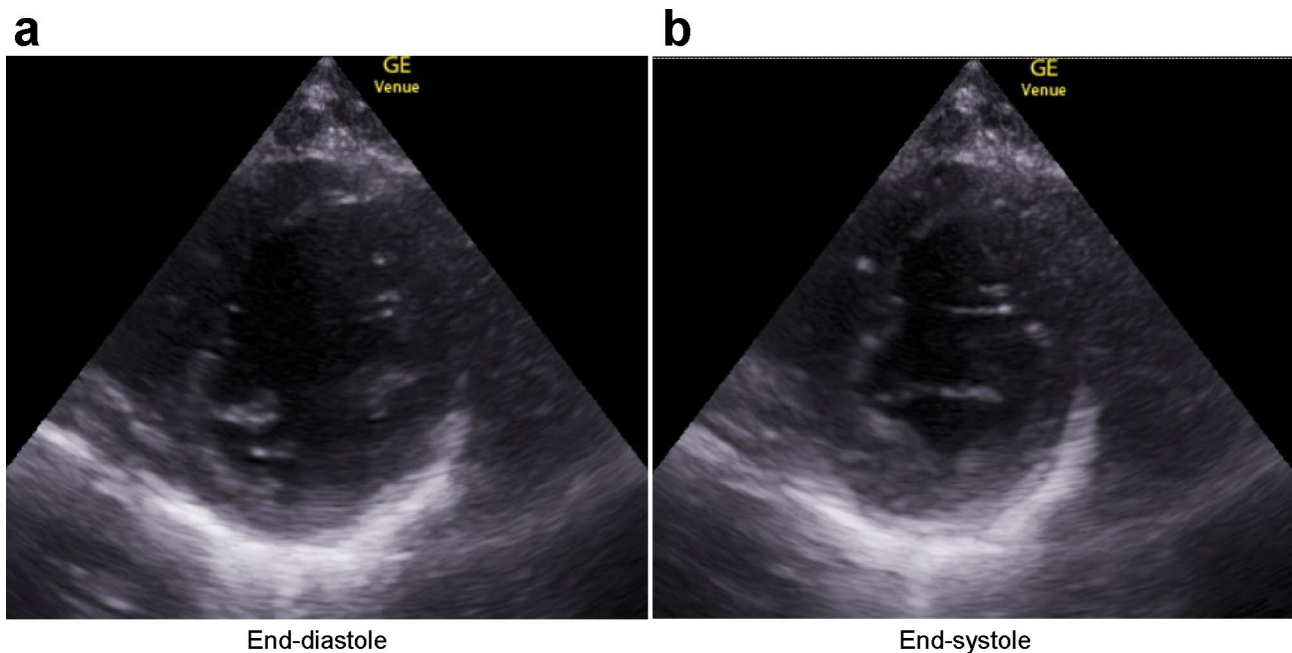


Fig. 4 A transthoracic echocardiogram in the parasternal short-axis view at papillary muscle level on admission. Decreased wall motion of the left ventricular anterior and lateral walls is observed. (a) End-diastole. (b) End-systole

syndrome, were not observed, and electrocardiogram ST changes improved immediately after the administration of a coronary artery dilator; therefore, Takotsubo syndrome was ruled out. Although epinephrine is used to treat anaphylaxis, exogenous catecholamines increase platelet aggregation and cause coronary artery spasms [10]. Paradoxically, epinephrine administration to treat anaphylaxis can lead to Kounis syndrome and worsen coronary spasms [8, 11]. Notably, coronary spasms can

be caused by the administration of low-dose epinephrine (0.1–0.5 mg) for anaphylaxis, regardless of the route of administration [12–14]. In the present case, no electrocardiograms were taken before and after epinephrine administration at the dermatology clinic; therefore, the possibility of epinephrine-induced coronary spasms cannot be excluded entirely. This patient was diagnosed with Kounis syndrome because ST changes did not worsen on the electrocardiograms taken before and after the

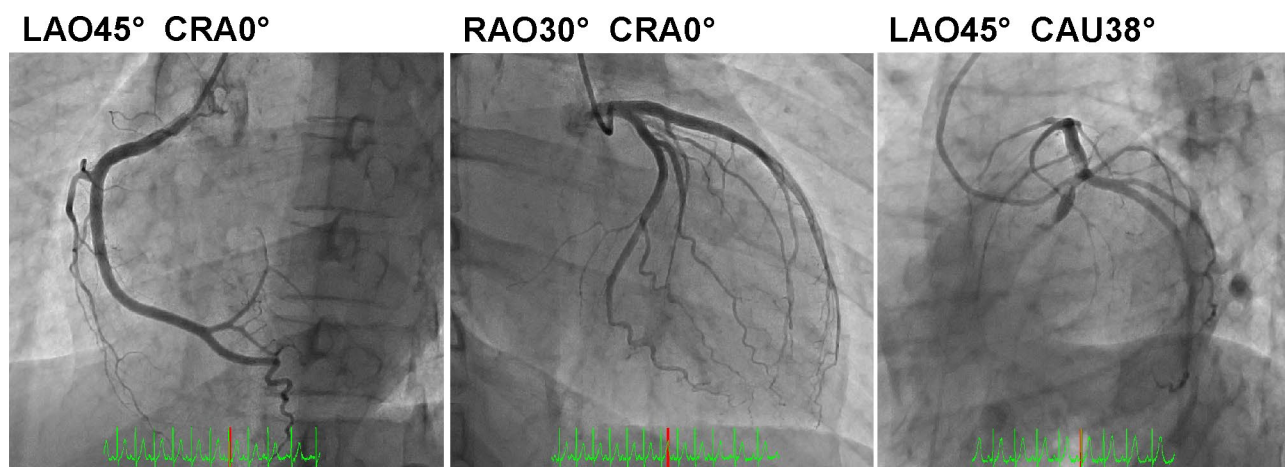


Fig. 5 Coronary angiography. No significant stenosis and thrombus formation are observed in the coronary arteries. CAU, caudal; CRA, cranial; LAO, left anterior oblique; RAO, right anterior oblique

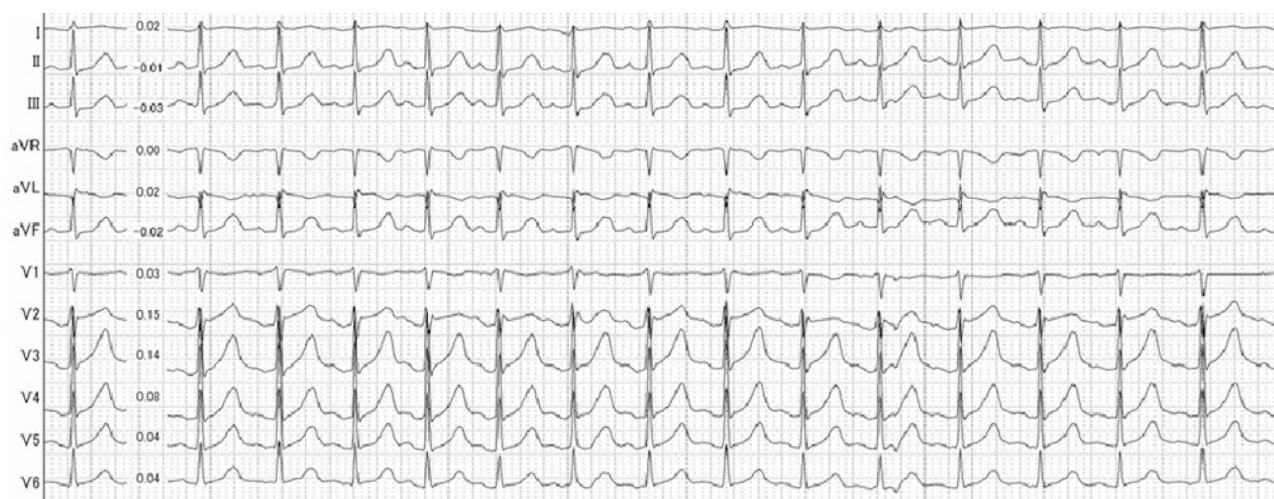


Fig. 6 A 12-lead electrocardiogram when performing coronary angiography. A 12-lead electrocardiogram was obtained upon admission to the examination room of coronary angiography. ST elevation in leads I, aVL, V2, and V3 is almost normalized

intramuscular administration of 0.3 mg epinephrine at our hospital, and she had atopic dermatitis, a chronic inflammatory disease with an increased number of active mast cells [15, 16], which is also closely related to the pathogenesis of Kounis syndrome.

Treatment

Blood tests showed that the troponin I level increased to 688.5 pg/mL 1 h 40 min after arrival, the CK level peaked at 305 U/L 24 h after arrival, and both values decreased thereafter. The patient's headache disappeared 5 h after arrival. On the second day of hospitalization, she developed redness and itching throughout the body, which was thought to be a biphasic reaction to anaphylaxis. The patient was intravenously administered 125 mg solumedrol and 20 mg famotidine, and her symptoms quickly improved. Thereafter, the patient was prescribed 240 mg/day of oral fexofenadine and topical steroid ointments.

An echocardiogram obtained on the seventh day of hospitalization showed improvement in the left ventricular wall motion abnormalities. The patient was discharged from the hospital on the ninth day of admission.

Outcome and follow-up

The use of the suspected drugs, glycyrrhizin, glutathione, and neurotrophin preparation (a preparation of inflamed skin extract from rabbits inoculated with the vaccinia virus), by the patient was prohibited. An echocardiogram obtained after discharge (21 days after admission) showed complete normalization of the left ventricular wall motion abnormalities. Treatment for atopic dermatitis was continued in the Dermatology Department of our hospital. Three years have passed since the initial diagnosis of Kounis syndrome, and no recurrence of acute coronary syndrome has been observed.

Discussion

We encountered a case of a young woman with type I Kounis syndrome without chest pain. Kounis syndrome is prevalent in 40–70-year-old male individuals and is mostly accompanied by chest pain [8]. Thus, Kounis syndrome without chest pain is rare in young women. When treating patients exhibiting severe allergic symptoms such as anaphylaxis, the possibility of concurrent acute coronary syndrome, regardless of age, sex, or the presence or absence of chest symptoms, must be considered.

There were no complaints of chest pain in the present case. Symptoms of myocardial ischemia, such as myocardial infarction, exhibit sex differences, with women reported to experience chest pain less frequently than men [17, 18]. Although many mechanisms underlying sex differences in coronary artery disease symptoms remain unknown, the female hormone estrogen has been reported to affect pain sensitivity [18–21]. Thus, one reason chest pain was not observed at the onset of Kounis syndrome in this case may be because the patient was a woman. Kounis syndrome frequently occurs in middle-aged men [8]. This is because some types of Kounis syndrome are associated with the risk of arteriosclerosis (hypertension, dyslipidemia, diabetes, and smoking, among others) [22] and coronary artery disease, which are prevalent in this patient population. Drugs are the most common cause of Kounis syndrome [23]. In a previous study, 142 of the 252 (56.3%) cases of Kounis syndrome were drug-induced [24]. In the present case of Kounis syndrome in a young woman with a low risk of arteriosclerosis, the occurrence of the syndrome could be attributed to drug use or atopic dermatitis, which are risk factors for anaphylaxis [11].

Because Kounis syndrome is often accompanied by anaphylactic symptoms [23], the more severe the allergic symptoms, the more carefully attention must be paid to its onset. Although it has been reported to occur more frequently in middle-aged men [8], in a retrospective study of 235,420 patients hospitalized for allergies or anaphylaxis based on ICD-9 codes, the incidence of Kounis syndrome was 1.1%, and the male-to-female ratio was approximately 1:1 [6]. The fact that many cases of the syndrome are overlooked in clinical practice [5] may explain the discrepancies in the results between studies. Future large-scale prospective studies are necessary to elucidate the background and characteristics of Kounis syndrome.

Among patients with allergic reactions, the in-hospital mortality rate in patients with acute coronary syndrome (Kounis syndrome) was 7.0%, which was considerably higher than that in those without acute coronary syndrome (0.4%) [6]. An increased incidence of stroke and venous thrombosis has also been observed in patients with Kounis syndrome [6]. Hence, rapid diagnosis and

appropriate treatment of this syndrome are important. In most (80%) cases, Kounis syndrome develops within 1 h of exposure to a trigger [8]. If this syndrome is suspected, 12-lead electrocardiography or transthoracic echocardiography should be performed immediately, and physicians must consider using a vasodilator or coronary angiography according to the situation. Unlike other acute coronary syndromes, Kounis syndrome requires management of the underlying allergic reaction. Intravenous corticosteroids and H1 and H2 antihistamines are typically effective. For types II and III Kounis syndrome, reperfusion therapy is required in addition to allergy treatment [4]. Because of the low awareness of Kounis syndrome [5] and as all patients in any medical department can develop this syndrome triggered by allergies, widespread awareness and knowledge of Kounis syndrome are warranted for better understanding and effective management.

Conclusion

In conclusion, although Kounis syndrome is rare in young women and may present without a chest pain, in cases of severe allergic symptoms such as anaphylaxis, it is necessary to consider the possibility of concurrent acute coronary syndrome while treating systemic allergic reactions, regardless of age, sex, or the presence or absence of chest symptoms.

Abbreviations

Bpm	Beats per minute
CK	Creatinine kinase

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Not applicable.

Author contributions

M.N. and T.H. contributed to writing the initial draft, gathering data, performing literature search, and revising the manuscript. T.K. contributed to critical revision and gave final approval. R.S. and H.N. reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical review and approval were not required for the study as per institutional requirements since the patient was not a part of any clinical trial (a clinical trial number is not applicable). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare no competing interests.

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