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Allergic coronary vasospasm induced by ibuprofen: a case of type I Kounis syndrome and literature review

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Case Report

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Abstract

Background

Kounis syndrome is defined as acute coronary syndrome triggered by allergic or anaphylactic reactions, and type I Kounis syndrome is characterized by coronary artery spasm without underlying atherosclerotic stenosis. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most common drug triggers, but the condition remains underrecognized due to low clinical awareness, especially in female patients without traditional cardiovascular risk factors.

Case presentation

A 44-year-old female with atopic constitution presented with persistent chest pain and generalized urticaria 30 minutes after oral administration of 0.3 g ibuprofen sustained-release capsules, accompanied by transient syncope. Electrocardiography showed horizontal ST-segment depression in leads II, III, aVF, and V4–V6. Serum total immunoglobulin E (IgE) was markedly elevated to 430.57 IU/mL, while cardiac injury biomarkers including troponin I and creatine kinase-MB remained within normal ranges. Coronary angiography revealed no organic stenosis or atherosclerotic plaques, with TIMI grade 3 flow in all coronary segments. The patient was diagnosed with type I Kounis syndrome. Symptoms resolved rapidly after treatment with cetirizine for anti-allergy and diltiazem for coronary vasodilation. No recurrence was observed during 1-year follow-up with strict avoidance of NSAIDs.

Conclusions

Type I Kounis syndrome can be easily misdiagnosed as conventional acute coronary syndrome. Clinicians should consider this diagnosis when atopic patients develop chest pain concurrent with allergic manifestations after NSAID exposure. Early combined anti-allergic and vasodilator therapy, together with long-term allergen avoidance, can achieve favorable clinical outcomes.

Background

Kounis syndrome, also known as allergic myocardial ischemia syndrome, refers to the concurrence of acute coronary syndrome (ACS) in the setting of allergic, hypersensitivity, or anaphylactic reactions[1]. The condition was first systematically described by Kounis and Zavras in 1991, and its core pathogenesis involves mast cell degranulation and release of inflammatory mediators such as histamine, tryptase, leukotrienes, and platelet-activating factor during allergic reactions, which subsequently induce coronary artery spasm, plaque erosion, or even thrombosis[2].

Based on the underlying coronary pathology, Kounis syndrome is classified into three subtypes: type I (coronary spasm without preexisting atherosclerosis), type II (plaque erosion or rupture on top of preexisting coronary artery disease), and type III (stent thrombosis or restenosis related to stent material

allergy)[3]. Type I accounts for more than 70% of all cases and predominantly occurs in younger populations without traditional cardiovascular risk factors[4].

Epidemiological data show that Kounis syndrome occurs in 1.1–3.4% of patients presenting with allergic or anaphylactic reactions[5–6]. Drugs are the most common triggering factors, among which non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and insect venoms rank highest[7]. Ibuprofen, as a widely used over-the-counter NSAID, has been increasingly reported to induce type I Kounis syndrome in recent year[8–9]. However, due to its atypical presentation and low clinical awareness, the condition is frequently missed or misdiagnosed, particularly in female patients without chest pain or traditional cardiac risk factors[10].

Herein, we report a case of ibuprofen-induced type I Kounis syndrome in a middle-aged female with atopic constitution, and review the relevant literature to summarize the diagnostic clues and management strategies from the perspective of allergology and cardiology.

Case presentation

A 44-year-old female patient presented to the emergency department with persistent chest pain and skin rash for 1 hour on April 9, 2024. The patient took 0.3 g ibuprofen sustained-release capsules for headache at 14:30 on the day of admission. Thirty minutes after ingestion, she developed progressive retrosternal chest tightness, respiratory distress, and generalized cold sweating, accompanied by scattered erythematous wheals with severe pruritus on both upper extremities. The chest tightness progressed to oppressive precordial pain without radiation. Twenty minutes after symptom onset, she experienced transient loss of consciousness for approximately 30 seconds, then regained consciousness spontaneously, but the chest pain did not fully resolve. She denied throat tightness, jaw pain, tearing back pain, or abdominal pain.

Past medical history

The patient had an atopic constitution with confirmed pollinosis and persistent allergic rhinitis, and a history of sulfonamide allergy. She had no history of hypertension, diabetes mellitus, coronary heart disease, surgery, or trauma. There was no family history of cardiovascular disease.

Physical examination on admission

Vital signs: body temperature 36.5 ℃, pulse rate 81 beats per minute, respiratory rate 18 breaths per minute, blood pressure 126/80 mmHg. The patient was conscious but in poor general condition. Scattered pale red wheals were visible on both upper extremities, with partial regression. Lung auscultation revealed clear breath sounds without rales. Cardiac examination showed normal cardiac border, regular rhythm, slightly diminished heart sounds, and no pathological murmurs in all valve

auscultation areas. The abdomen was soft and non-tender. No edema was observed in both lower extremities.

Investigations

1 Electrocardiography (ECG): The 12-lead ECG obtained immediately on admission (16:31) showed sinus rhythm with horizontal ST-segment depression > 0.05 mV in leads II, III, aVF, and V4–V6(Fig. 1), suggesting subendocardial myocardial ischemia. Twenty-four-hour Holter monitoring demonstrated persistent multi-lead ST-segment depression concordant with chest pain symptoms(Fig. 2). The ST-segment deviations completely normalized after coronary angiography(Fig. 3).

Sinus rhythm with horizontal ST-segment depression ≥ 0.05 mV in leads II, III, aVF, V4–V6, consistent with subendocardial myocardial ischemia.

Sinus rhythm with persistent ST-segment depression in multiple leads, consistent with the patient’s chest pain symptoms.

Sinus rhythm; ST segments in all leads returned to the isoelectric line without abnormal deviation.

2 Laboratory examinations: Serum total IgE was 430.57 IU/mL (reference range < 100 IU/mL). Routine blood count, liver and renal function, coagulation profile, and lipid profile were generally within normal limits. Cardiac injury biomarkers including troponin I (< 0.020 ng/mL) and creatine kinase-MB (< 1.00 ng/mL) remained within reference ranges throughout hospitalization (Table 1).

Table 1
Laboratory investigations on admission

Parameter	Observed value	Reference range
Red blood cells (10^6/μL)	4.38	3.8–5.1
Hemoglobin (g/dL)	12.3	11.5–15.0
White blood cells (/μL)	4440	3500–9500
Mean corpuscular volume (fL)	88.6	82–100
Hematocrit (%)	38.8	35–45
Platelets (10^9/L)	317	125–350
Neutrophils (%)	54.9	40–75
Lymphocytes (%)	35.7	20–50
Eosinophils (%)	2.5	0.4–8.0
Total IgE (IU/mL)	430.57	< 100
Total cholesterol (mmol/L)	5.07	2.59–6.47
Triglycerides (mmol/L)	1.53	0–1.7
High-density lipoprotein cholesterol (mmol/L)	1.18	> 1.04
Low-density lipoprotein cholesterol (mmol/L)	3.58	0–3.37
Lactate dehydrogenase (U/L)	212	120–246
Potassium (mmol/L)	4.11	3.5–5.1
Creatinine (μmol/L)	60.2	46–92
Blood urea nitrogen (mmol/L)	5.43	2.5–6.1
Prothrombin time (s)	11.5	11–13
Activated partial thromboplastin time (s)	29.6	25–38
International normalized ratio	1.07	1–1.5
Creatine kinase-MB (ng/mL)	< 1.00	≤ 5
Troponin I (ng/mL)	< 0.020	≤ 0.04

3 Imaging examinations: Transthoracic echocardiography showed normal dimensions of all cardiac chambers, coordinated wall motion in all left ventricular segments, and a left ventricular ejection fraction (LVEF) of 63%(Fig. 4). Coronary angiography revealed natural course of the left and right coronary arteries, no stenosis, no atherosclerotic plaques, and no thrombus formation, with TIMI grade 3 flow in all distal segments(Fig. 5).

Mild tricuspid regurgitation; left ventricular wall motion score: Grade I.

The left and right coronary arteries and their branches showed normal course without stenosis, atherosclerotic plaques or thrombus formation, with distal coronary blood flow classified as TIMI grade 3.

Diagnosis

Combined with the clear history of NSAID intake, synchronous onset of allergic symptoms and myocardial ischemia, markedly elevated serum total IgE, and exclusion of organic coronary stenosis by angiography, the patient was diagnosed with type I Kounis syndrome.

Differential diagnosis

Conventional acute coronary syndrome

Patients with typical ACS usually have traditional cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and smoking, and coronary angiography often reveals atherosclerotic stenosis or thrombotic occlusion. In this case, the patient had no cardiovascular risk factors, coronary angiography showed completely normal vessels, and the onset was closely related to drug intake with concurrent allergic manifestations, which did not support conventional ACS.

Variant angina (Prinzmetal angina)

Variant angina is caused by spontaneous coronary artery spasm, mostly occurring at rest without allergic triggers. In this case, coronary spasm occurred synchronously with allergic symptoms after ibuprofen administration, and total IgE was significantly elevated, supporting an allergy-mediated mechanism rather than primary vasospasm.

Takotsubo syndrome

Takotsubo syndrome typically presents with chest pain and transient left ventricular apical ballooning, often preceded by severe emotional or physical stress. The characteristic ECG finding is giant negative T waves, and left ventricular wall motion abnormalities usually extend beyond a single coronary territory[11]. In this case, echocardiography showed normal wall motion, no giant negative T waves were observed on ECG, and the symptoms were temporally related to allergic reaction, which ruled out Takotsubo syndrome.

Treatment and outcome

After diagnosis, the patient was treated with diltiazem sustained-release capsules 90 mg once daily to relieve coronary spasm and cetirizine 10 mg once daily for anti-allergy. During the initial emergency

evaluation, aspirin combined with ticagrelor was empirically administered for suspected ACS, and pantoprazole was given for gastric protection.

The wheals gradually subsided after admission, and no further chest pain episodes occurred. The patient was discharged on day 7 of hospitalization in stable condition. Echocardiography before discharge showed an LVEF of 62% with normal wall motion. At 1-year follow-up, the patient strictly avoided all NSAIDs, and experienced no recurrence of chest tightness, chest pain, or allergic attacks, with normal daily activity tolerance.

Discussion

Kounis syndrome represents an important cross-disciplinary entity connecting allergology and cardiology. Its essence is systemic allergic inflammation involving the coronary circulation. Although type I Kounis syndrome is not rare in clinical practice, its recognition rate remains low, which may lead to delayed treatment and potential life-threatening complications[12].

Pathogenesis of NSAID-induced type I Kounis syndrome

NSAIDs are the leading cause of drug-induced Kounis syndrome, accounting for more than 60% of all drug triggers, with ibuprofen, diclofenac, and flurbiprofen being the most frequently reported agents[7, 13].The pathogenesis involves two major pathways:

IgE-mediated immune pathway: Drugs act as haptens and bind to endogenous proteins to form complete antigens, triggering specific IgE-mediated degranulation of mast cells and basophils. Released histamine acts on H1 receptors on coronary smooth muscle, directly inducing vasospasm; it also damages vascular endothelium and increases vascular permeability, further aggravating myocardial ischemi[1]. In this case, the patient had an atopic constitution, rapidly developed symptoms within 30 minutes after drug intake, presented with typical urticaria, and had significantly elevated total IgE, all supporting an IgE-mediated type I hypersensitivity mechanism.

COX-inhibition non-immune pathway: Ibuprofen inhibits cyclooxygenase (COX), shifting arachidonic acid metabolism toward the lipoxygenase pathway and leading to excessive leukotriene production. Leukotrienes exert potent coronary constrictive effects, which are particularly prominent in patients with aspirin-exacerbated respiratory disease (Samter's triad), and may even trigger cardiac arrest[14–15].

Diagnostic clues from allergology perspective

The diagnosis of Kounis syndrome requires four core elements: acute allergic manifestations, acute myocardial ischemia, clear temporal association, and exclusion of other etiologies[16]. From the allergology perspective, the following points are critical for early recognition:

First, detailed history taking is the cornerstone of diagnosis. For all patients presenting with chest pain, clinicians should routinely inquire about recent medication, food intake, and insect exposure, especially NSAIDs and beta-lactam antibiotics, and screen for atopic background, which is the most important risk factor for Kounis syndrome.

Second, allergic biomarkers provide important diagnostic clues. Elevated total IgE indicates a systemic hyperallergic state, while elevated acute-phase tryptase is the gold standard for mast cell activation, with the highest positive rate when blood samples are collected within 1–2 hours of symptom onse[17]. Combined with dynamic ECG changes, these biomarkers can provide strong diagnostic evidence before coronary angiography. In this case, although the skin rash had partially regressed on admission, the markedly elevated total IgE was the key clue leading to the correct diagnosis.

Treatment strategies and long-term allergy management

For type I Kounis syndrome, the treatment principle is "rapid anti-allergy + coronary vasodilation + long-term allergen avoidance", requiring collaborative management by allergologists and cardiologists[18].

In the acute phase, second-generation non-sedating antihistamines are the first-line anti-allergic agents to block histamine effects. For severe cases, short-term glucocorticoids can be used to inhibit mast cell degranulation. Epinephrine remains the first-line rescue drug for anaphylactic shock or laryngeal edema, although it may theoretically aggravate coronary spasm in rare case[19]. For coronary vasodilation, calcium channel blockers (diltiazem, amlodipine) are first-line agents, which can effectively reverse vasospasm induced by allergic mediators, and can be combined with nitrates to enhance the vasodilatory effect[20]. Notably, beta-blockers should be avoided as they may antagonize the therapeutic effect of epinephrine and worsen coronary spasm through receptor imbalance[21].

Long-term management is the core intervention from the allergology perspective. After identifying the culprit drug, patients should strictly avoid it for life, including cross-reactive drugs with similar structures. For atopic patients requiring analgesia or antipyretics, paracetamol can be preferred, or drug desensitization can be performed under allergology evaluatio[22]. For patients with recurrent episodes, long-term oral calcium channel blockers can be prescribed to prevent coronary spasm, and underlying atopic diseases (allergic rhinitis, asthma) should be well controlled to reduce the baseline hyperallergic state.

Conclusions

Type I Kounis syndrome induced by ibuprofen is an easily overlooked cause of acute chest pain, especially in atopic populations. Clinicians should establish the diagnostic thinking of "allergy-coronary spasm", and be highly alert to Kounis syndrome when patients with atopic constitution develop chest pain accompanied by allergic manifestations after taking NSAIDs. Early recognition, combined anti-

allergic and vasodilator therapy, and standardized long-term allergen management can significantly improve patient prognosis.

Abbreviations

ACS
Acute coronary syndrome
COX
Cyclooxygenase
ECG
Electrocardiography
IgE
Immunoglobulin E
LVEF
Left ventricular ejection fraction
NSAIDs
Non-steroidal anti-inflammatory drugs

Declarations

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Ethical review and approval were not required for this case report in accordance with institutional regulations, as it does not involve any clinical trial. Written informed consent was obtained from the patient for publication of this case report and 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 that they have no competing interests.

Author Contribution

FX and QZ contributed equally to this work. FX and QZ collected the clinical data and drafted the manuscript. HP participated in data interpretation and literature review. JL and YY conceived the study, revised the manuscript critically, and gave final approval of the version to be published. All authors read and approved the final manuscript.

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Figures



Figure 1

Twelve-lead electrocardiogram obtained at initial presentation (April 9, 2024).

Sinus rhythm with horizontal ST-segment depression ≥0.05 mV in leads II, III, aVF, V4–V6, consistent with subendocardial myocardial ischemia.

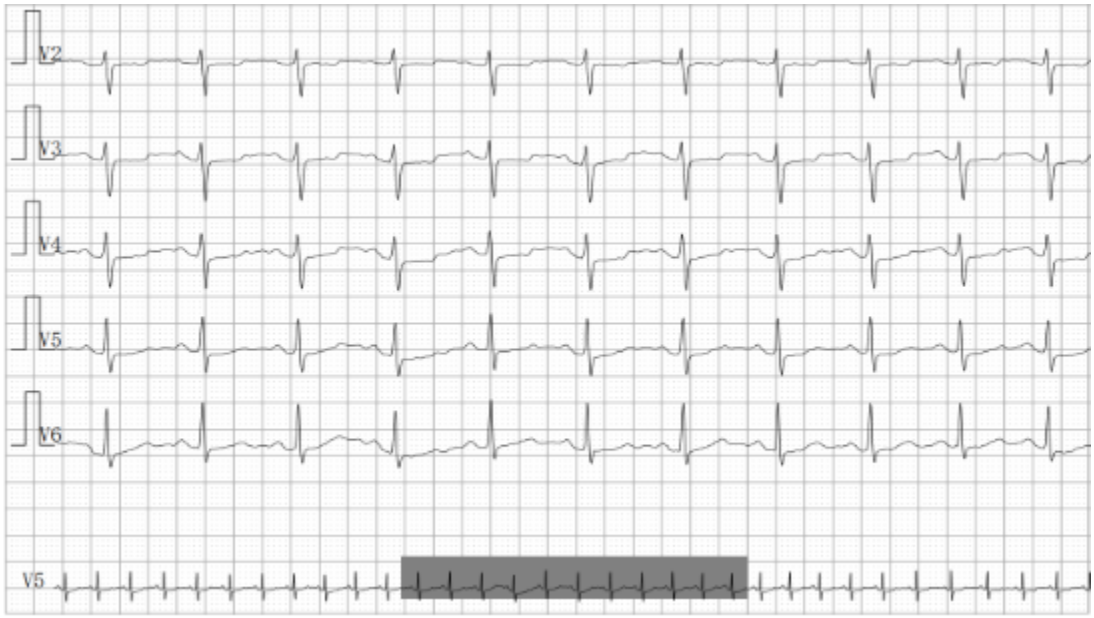


Figure 2

Screenshot of the 24-hour ambulatory electrocardiogram of the patient.

Sinus rhythm with persistent ST-segment depression in multiple leads, consistent with the patient's chest pain symptoms.

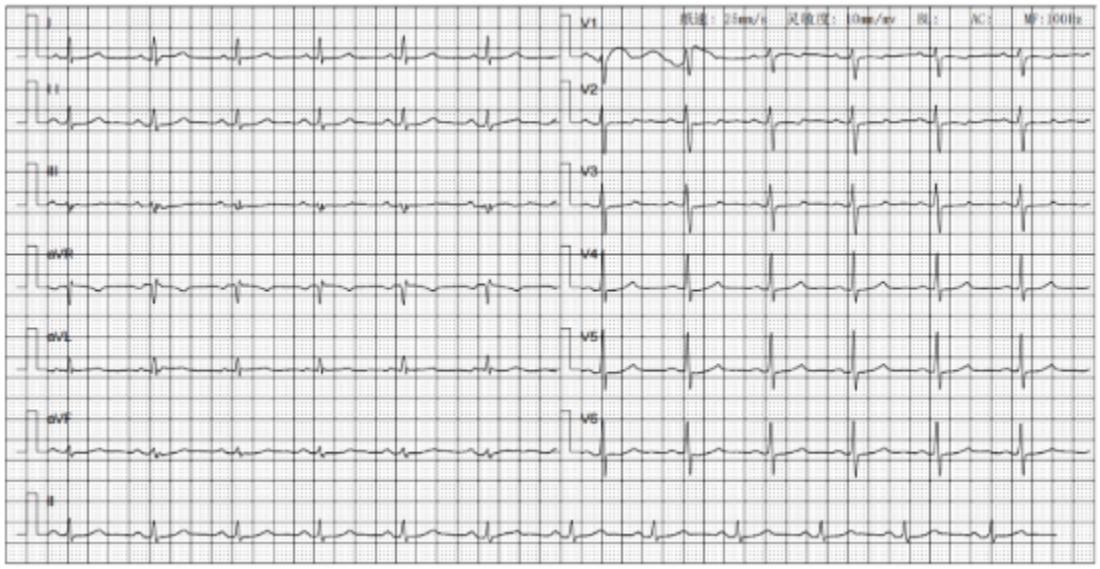


Figure 3

12-lead electrocardiogram of the patient 12 hours after coronary angiography.

Sinus rhythm; ST segments in all leads returned to the isoelectric line without abnormal deviation.

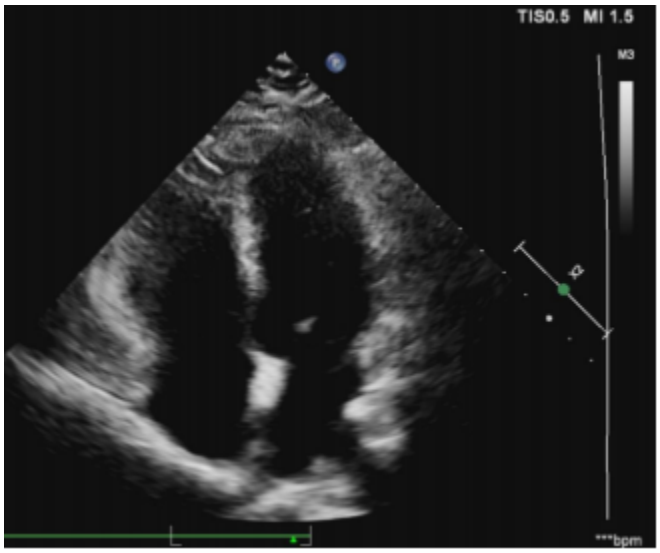


Figure 4

Coronary angiography of the patient.

Mild tricuspid regurgitation; left ventricular wall motion score: Grade I.

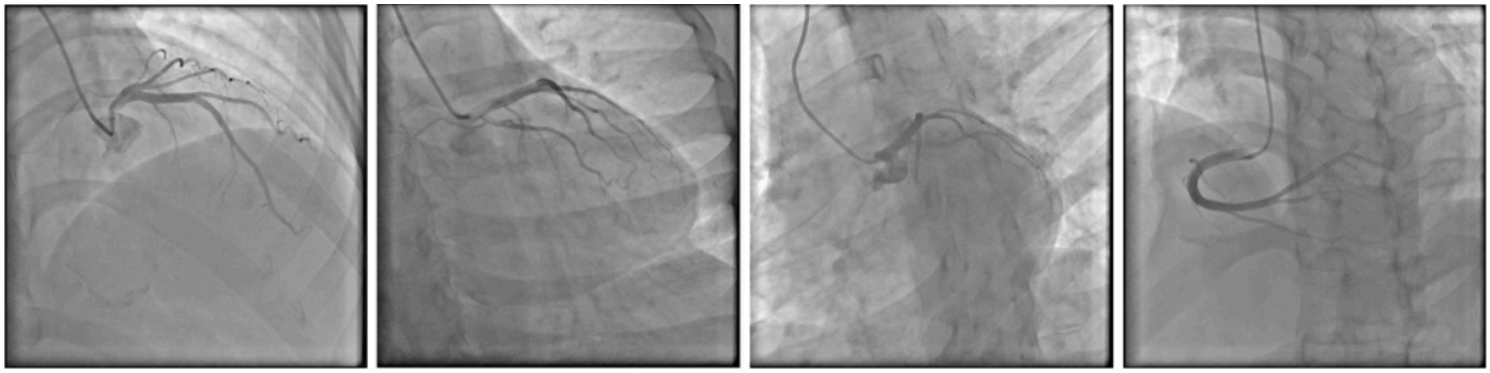


Figure 5

Coronary angiography of the patient.

The left and right coronary arteries and their branches showed normal course without stenosis, atherosclerotic plaques or thrombus formation, with distal coronary blood flow classified as TIMI grade 3.