

Case report

Kounis syndrome uncovers severe coronary disease: an unusual case of acute coronary syndrome secondary to allergic coronary vasospasm

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SUMMARY

Acute coronary syndrome occurring during the course of a type I hypersensitivity reaction constitutes Kounis syndrome. We report a case of a 64-year-old man who presented with a non-ST elevation myocardial infarction and peripheral blood eosinophilia. He had rhinitis and constitutional symptoms for several days prior to presentation. Blood investigations revealed moderate eosinophilia and elevated IgE levels. A cardiac MRI showed generalised oedema with a subtle wall motion abnormality in basal inferior/inferolateral wall, and subendocardial high signal on late gadolinium enhancement suggesting a localised myocardial infarction. A coronary angiogram then revealed triple vessel disease. A diagnosis of Kounis syndrome was made. Within days of starting appropriate treatment, the patient's eosinophil count returned to normal with improvement of clinical picture.

BACKGROUND

Kounis syndrome is a coincidental occurrence, first described in the 1950s, of an acute coronary syndrome, manifested as vasospastic angina or ST-elevation myocardial infarction/non-ST-elevation myocardial infarction, with allergic reactions (reactions hypersensitivity, anaphylaxis or anaphylactoid reaction) due to coronary artery spasm secondary to inflammatory mediator release following an allergic insult.¹²

CASE PRESENTATION

A 64-year-old retired man with a known history of diabetes mellitus type II, hypertension, allergic rhinitis, dyslipidaemia and gout, presented to the Accident and Emergency department with symptom of an episode of retrosternal pleuritic chest pain with associated with shortness of breath and a dry cough, not productive of sputum. The pain lasted approximately 15 min, and was non-radiating. He is a retired manual labourer with a good exercise tolerance and had not experienced angina before. The patient also reported a 2-day history of fever associated with coryzal symptoms of sneezing, rhinorrhoea and congestion, anorexia, fatigue, chills and rigours.

Regular medications consisted of metformin, tamsulosin, allopurinol and simvastatin. He denied any food or drug allergies. He was an ex-smoker with a 15 pack-year history and his family history

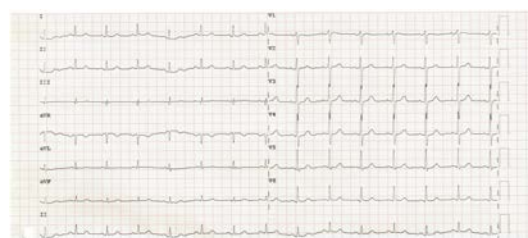


Figure 1 Admitting ECG showing normal sinus rhythm.

was unremarkable. He denied any recent travel history with no animal exposure.

On admission, the patient was haemodynamically stable with a documented low-grade fever at casuality. The patient was noted to have left basal inspiratory coarse crepitations, not cleared on coughing. Other systems were unremarkable and no rashes or lymphadenopathy was noted. We proceeded with preliminary investigations to elucidate the underlying cause of this man's symptomatology.

INVESTIGATIONS

His initial ECG showed normal sinus rhythm (figure 1). On admission, his eosinophil count was high-normal at $0.52 \times 10^9/L$; however, this subsequently peaked to $7.02 \times 10^9/L$ (41.7%) on peripheral blood smear (table 1). Janus kinase 2, B-cell lymphoma-2 and galactomannan levels were negative. Inflammatory makers were also raised with a C-reactive protein of 318 (ref: 0–5) and erythrocyte sedimentation rate of 58 mm/hour. The initial high-sensitivity troponin T was negative (table 2). A quantitative D-dimer was elevated, 1079 ng/mL, thus a CT pulmonary angiogram was performed showing no evidence of pulmonary thromboembolic disease. Extensive autoimmune and infectious screen testing (bacterial, fungi, parasitic and retroviral) were negative. The patient had significantly elevated measurements of non-specific total IgE levels, 7770 IU/mL, confirming hypersensitivity.

A repeat ECG showed new onset T wave inversion in precordial chest leads V3–V6 (figure 2) and subsequent high-sensitivity troponin T were raised (table 2). A bedside transthoracic echocardiogram showed normal left ventricular function with no apical obliteration or fibrosis suggestive of an eosinophilic myocarditis. Cardiac magnetic resonance (CMR) imaging was performed showing generalised oedema with a subtle wall motion abnormality in



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Table 1 Eosinophil counts during the course of admission

Admission day	1	2	4	6	8	10	12	13	24	47	68
WCC*	25.22	26.04	24.05	19.91	18.69	18.49	16.85	13.37	7.91	7.59	6.55
Eosinophils (%) (absolute count*)	2.06 (0.52)	3.38 (0.88)	12.52 (3.01)	28.13 (5.60)	36.33 (6.79)	37.80 (6.99)	41.66 (7.02)	42.41 (5.67)	8.85 (0.70)	5.27 (0.40)	3.21 (0.21)
Neutrophils (%) (absolute count*)	86.00 (21.7)	83.18 (21.66)	69.27 (16.66)	46.16 (9.19)	43.66 (8.16)	37.43 (6.92)	34.54 (5.82)	30.22 (4.04)	48.55 (3.84)	51.91 (3.94)	55.27 (3.62)

*Units $\times 10^9/L$.

WCC, white cell count.

Table 2 High sensitivity troponin T during the course of admission

Admission day	1	1	5	5	7	11
Troponin T (ng/L)	8	5	130	128	123	11

basal inferior/inferolateral wall, and subendocardial high signal on late gadolinium enhancement; images were suggestive of a possible localised myocardial infarction (figure 3). No diagnostic features typical of hypereosinophilic myocarditis were noted.

A coronary angiogram revealed significant lesions in the mid to distal left anterior descending (LAD) artery, in the mid to distal left circumflex (LCx) artery beyond a large obtuse marginal artery (figure 4) and in the mid-right coronary artery (mid-RCA). The RCA stenosis was heavily calcified and subtotally occluded (figure 5). Ad-hoc percutaneous coronary intervention to LAD and LCx was performed successfully. Rotablation was successfully performed to the RCA lesion at a later date.

DIFFERENTIAL DIAGNOSIS

Based on the symptomatology and clinical investigations, the initial differential was broad (table 3).

Radiological findings were not pathognomonic of eosinophilic pneumonia and thus Loeffler disease was unlikely. Allopurinol was started several months prior presentation, thus drug-induced eosinophilia and drug reaction with eosinophilia and systemic symptoms syndrome were excluded. There were no features on CMR to indicate eosinophilic myocarditis and hypereosinophilic syndrome was unlikely as eosinophilia was not present for more than 6 months.

Eosinophilic coronary periarteritis is a very rare localised vasculitis of unknown aetiology and pathogenesis. It is characterised by vasospastic angina, usually occurring in the evening to early morning, resulting in sudden cardiac death, and is almost exclusively diagnosed at autopsy. Eosinophilic coronary periarteritis is frequently accompanied by spontaneous coronary arterial dissection in the affected wall, largely described in young women. Histologically, eosinophilic inflammation is limited to the coronary adventitia and periadventitial soft tissue.³ This diagnosis is difficult to exclude outside of autopsy but some features of our case makes eosinophilic coronary periarteritis unlikely. On coronary angiography, there was no evidence of aneurysmal changes or spontaneous coronary arterial dissection in the affected wall. Our patient also had pre-existing triple vessel coronary artery disease and CMR imaging did not show any evidence of underlying periarteritis.

A diagnosis of allergic angina, also known as Kounis syndrome, was made based on the occurrence of signs and symptoms of a

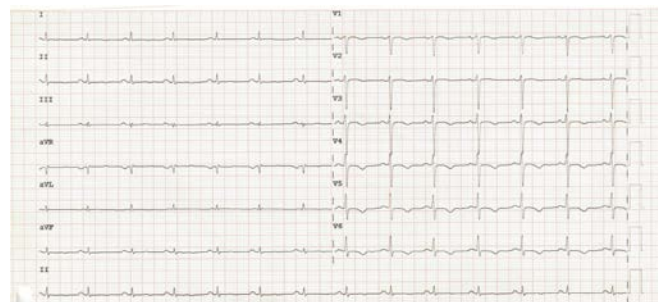
**Figure 2** A repeat ECG showing new onset T wave inversion in precordial chest leads V3–V6.

Table 3 Differential diagnosis of eosinophilia

Secondary eosinophilia	Infection
Allergic disorders	Seasonal allergic disorders (rhinitis syndromes/hayfever)
Eosinophilic myocarditis secondary to hypereosinophilic syndrome	
Acute coronary syndrome	Kounis syndrome Eosinophilic coronary periarteritis Coronary artery dissection Coronary vasospasm Plaque rupture/erosion

systemic allergic reaction with associated clinical, laboratory and ECG findings of acute ischaemic changes.

TREATMENT

The patient was administered levofloxacin in conjunction with anti-histamines. Anti-ischaemic treatment including dual anti-platelet agents (aspirin and clopidogrel), nitrates, statin, as well as angiotensin-converting enzyme inhibitor were initiated after the coronary angiogram.

OUTCOME AND FOLLOW-UP

The patient was followed up at respiratory clinic within 1 month from discharge with repeat IgE levels (3700 Im/mL). The precipitating aeroallergen was not isolated. The patient remained well, symptom free.

DISCUSSION

There are three recognised variants of Kounis syndrome: type I with normal coronary arteries, type II with pre-existing coronary atheromatous disease and type III with late coronary stent thrombosis. The underlying pathophysiological mechanism of Kounis syndrome involves release of inflammatory cytokines through mast cell activation, which leads to coronary artery vasospasm and/or atheromatous plaque erosion or rupture.^{1,2}

In T-helper (Th)2-type driven inflammatory response, the allergen causes high-affinity IgE receptor FcεRI cross-linking on tissue mast cells and basophils leading to a cascade of intracellular events precipitating IgE-driven cell activation and degranulation. (Th)2 cells release numerous cytokines and proinflammatory mediators evoking a strong IgE response. The number of eosinophils increase due to two main reasons: an early-phase response secondary to mast cell degranulation and a

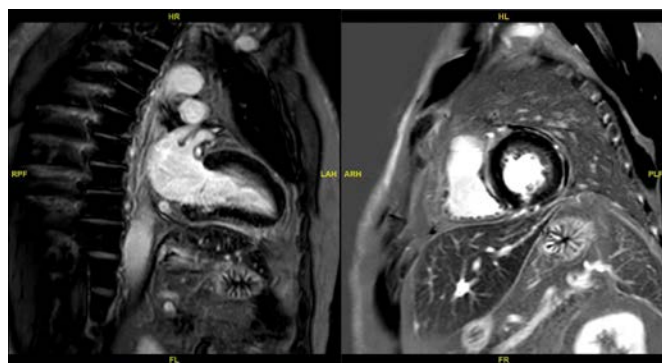


Figure 3 Subtle subendocardial high signal intensity on late gadolinium enhancement suggestive of a possible localised myocardial infarction. Patient orientation vectors - RPF: Right, Posterior, Foot; LAH: Left, Anterior, Head; PLF: Posterior, Left, Foot; ARH: Anterior, Right, Head; FR: Foot, Right; FL: Foot, Left; HR: Head, Right; HL: Head, Left.

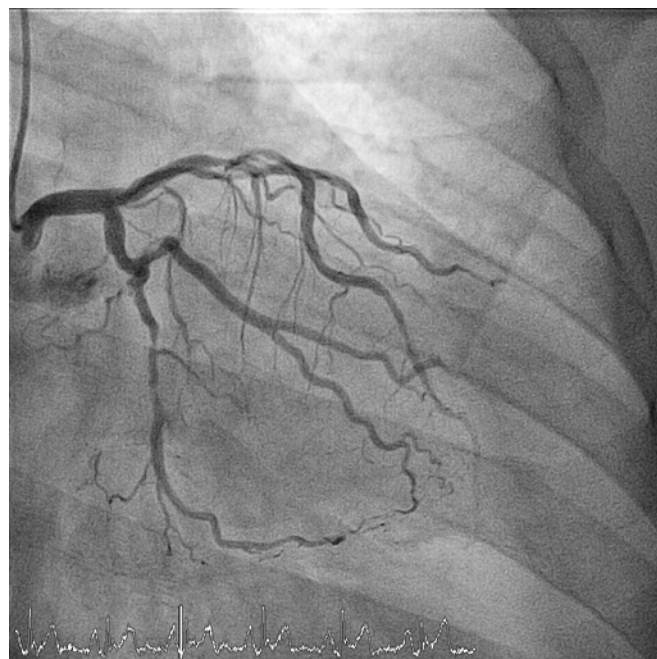


Figure 4 Image showing significant stenosis in mid to distal left anterior descending artery and in the mid to distal left circumflex artery beyond a large obtuse marginal artery.

late-phase response, which occurs after cell recruitment from the circulation.⁴ Mast cells are not only linked to allergy and asthma, but have been shown to contribute to the pathogenesis of atherosclerosis by atherosclerotic plaque progression and destabilisation.^{2,5} This mechanism links a hypersensitivity reaction with raised IgE and eosinophilia with vasospasm and/or atheromatous plaque erosion or rupture. In patients with pre-existing coronary atheromatous disease, that is, type II variant, an acute release of inflammatory mediators results in either coronary vasospasm with normal cardiac biomarker levels or coronary vasospasm

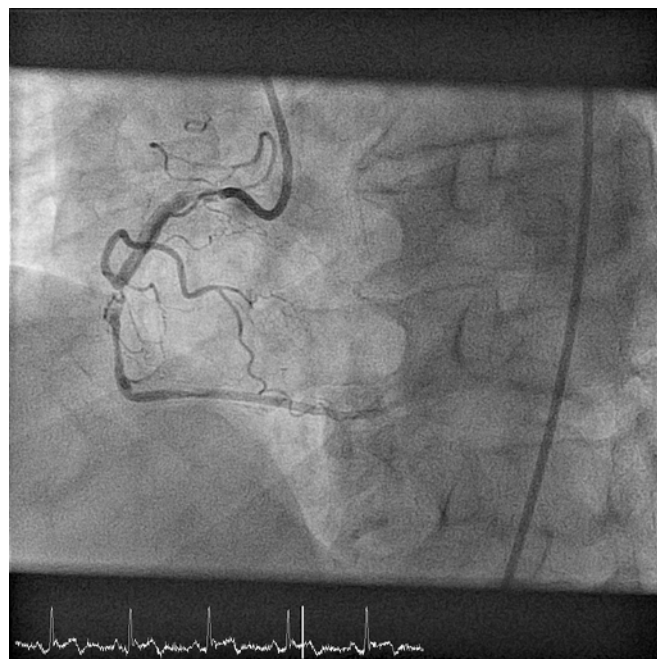


Figure 5 Imaging showing a heavily calcified and subtotally occluded right coronary artery, with poor flow distally.

Rare disease

with plaque rupture or erosion resulting in an acute myocardial infarction.⁶ The latter was the case in our patient, as troponin levels increased and imaging was suggestive of an acute myocardial infarction.

Multiple causes of Kounis syndrome have been described in the literature, including environmental exposure (insect stings, venom poisoning, latex exposure, plants such as stinging nettle), drug exposure (antibiotics, analgesics, non-steroidal anti-inflammatory drugs, contrast media and corticosteroids) and various diseases (angioedema, asthma, exercise-related anaphylaxis, food allergy, Churg-Strauss syndrome).^{1 2 6}

The underlying cause of eosinophilia was not elucidated in our patient; a thorough infectious (fungi, parasitic and retroviral), vasculitic, allergic and neoplastic screen did not yield any positive results. As the patient had significantly elevated total IgE, peripheral eosinophilia and a history of allergic rhinitis, hypersensitivity was considered a plausible cause for eosinophilia. Our patient's coronary angiogram also showed diffuse atheromatous disease and thus was diagnosed with type II variant Kounis syndrome.

Treatment of Kounis syndrome is threefold; treating the allergic reaction, avoidance of the precipitating offending allergen as well as medical and/or interventional treatment for Acute Coronary Syndrome. The role of corticosteroids, epinephrine and antihistamines for the treatment of allergic reactions is well known, and are continued until therapeutic effect is achieved. Although epinephrine is the mainstay of treatment in acute anaphylactic reactions, it is advised to use epinephrine cautiously as it has been shown to potentially aggravate ischaemia by inducing massive mast-cell degranulation and aggravate allergic reaction thus. Other medications which are

commonly used in the setting of acute coronary syndrome, such as beta-blockers and morphine, worsen coronary vasospasm. Beta-blockers worsen coronary vasospasm due to unopposed α -adrenergic action when used in conjunction with epinephrine and opiates worsen coronary vasospasm as they are potent mast cell activators.^{1 6-8}

All variants of Kounis syndrome respond well to vasodilators, such as nitrates, and calcium channel blockers as they are the mainstay of treatment of coronary vasospasm. Type II and type III variants require coronary intervention to manage acute plaque rupture and thrombus formation.¹⁻³ Unfortunately, in our patient we could not isolate the allergic component. Desensitisation measures should be employed if possible, to prevent further episodes of allergic hyper-responsiveness in the future.

Contributors LC: cared for patient; conception and design; interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article. KG: conception and design; interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article. CZ: cared for patient; critical revision of the article for important intellectual content; final approval of the article. KC: cared for patient; interpretation of the data; critical revision of the article for important intellectual content; final approval of the article.

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REFERENCES

- 1 Kounis NG. Coronary hypersensitivity disorder: the Kounis syndrome. *Clin Ther* 2013;35:563–71.
- 2 Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7–14.
- 3 Kajihara H, Tachiyama Y, Hirose T, et al. Eosinophilic coronary periarteritis (vasospastic angina and sudden death), a new type of coronary arteritis: report of seven autopsy cases and a review of the literature. *Virchows Arch* 2013;462:239–48.
- 4 Conti L, Gatt K, Zammit C, et al. Comparison of aeroallergen sensitization patterns in the United States and Europe. *Ital J Med* 2019;13:225–33.
- 5 Sun J, Sukhova GK, Wolters PJ, et al. Mast cells promote atherosclerosis by releasing proinflammatory cytokines. *Nat Med* 2007;13:719–24.
- 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.
- 7 Gunawardena MDVM, Weerasinghe A, Herath J, et al. Myocardial infarction associated with eosinophilia and plasma extravasation at multiple sites. A variant of Kounis syndrome. *Case Reports* 2015;2015:pii: bcr2014207987.
- 8 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.

Learning points

- Kounis syndrome is an acute coronary syndrome secondary to and underlying allergic reaction.
- Cardiac magnetic resonance with myocardial stress-perfusion imaging is an excellent imaging modality for assessing myocardial ischaemia, viability and function.
- It is best to avoid beta-blockers and opioids in the management of ACS in Kounis syndrome as it worsens coronary vasospasm and prognosis.
- Greater awareness of this condition will allow for an earlier diagnosis with adequate and appropriate treatment to improve prognostic outcomes.

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