CASE REPORT

Myocardial infarction associated with eosinophilia and plasma extravasation at multiple sites. A variant of Kounis syndrome

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SUMMARY

Myocardial infarction occurring during the course of type I hypersensitivity constitutes Kounis syndrome. We report a case of a 38-year-old man who presented with anterior ST elevation myocardial infarction and peripheral blood eosinophilia. He had rhinitis and malaise for several days prior to presentation. There was no urticarial rash or pruritus to suggest hypersensitivity. Coronary angiogram revealed only mild plaque disease. Blood investigations revealed moderate eosinophilia and elevated IgE levels. CT of the thorax revealed fluid extravasation at multiple sites. Screening for a possible secondary cause for eosinophilia revealed hypersensitivity to multiple antigens. A diagnosis of Kounis syndrome was made. Within days of starting steroids and antihistamines, the patient's eosinophil count returned to normal with improvement of clinical picture. This case differs from classical Kounis syndrome as there was no acute allergic reaction (except atopic rhinitis). Fluid extravasation at multiple sites has not been described in previous cases.

BACKGROUND

Allergic phenomena in predisposed participants can trigger not only anginal episodes, but also acute myocardial infarction. The association between allergy and acute coronary syndrome was first reported in 1950, during an allergic reaction to penicillin.¹ Later, in 1991, Kounis and Zavras named this entity allergic angina and allergic myocardial infarction.² This condition is now recognised as 'Kounis syndrome' and has been defined as an acute coronary syndrome that manifests as unstable vasospastic or non-vasospastic angina, and even as acute myocardial infarction in the context of allergy or hypersensitivity.

There are three variants of this syndrome.^{3 4} Type I variant includes patients in whom an acute allergic reaction induces coronary artery spasm leading to acute coronary syndrome with or without troponin elevation. Type II variant includes patients with pre-existing atherosclerotic plaques in whom an acute allergic episode can induce plaque erosion or rupture manifesting as acute myocardial infarction. Type III includes patients with coronary stent thrombosis in whom aspirated thrombi stain positive for eosinophils and mast cells.

Our patient did not have a classic history of hypersensitivity. However, a history of recent

allergic rhinitis, peripheral eosinophilia and elevated IgE levels indicated presence of hypersensitivity.

CASE PRESENTATION

A 38-year-old man was admitted to the emergency treatment unit with a retrosternal tightening chest pain radiating to the jaw of 3 h duration. He had no cardiovascular risk factors. He is a carpenter with good exercise tolerance and had not experienced angina before. He had been getting very infrequent episodes of allergic rhinitis since childhood. He developed an episode of sneezing, rhinorrhoea and nasal congestion 4 days prior to admission. He had generalised myalgia and malaise since then.

On admission, the patient was haemodynamically stable. ECG showed 1–2 mm ST segment elevations in the anterior leads ([figure 1](#)). The patient initially opted for thrombolysis over percutaneous intervention and was treated with streptokinase. Post-thrombolysis ECG did not show resolution of ST segments. The patient continued to have severe chest pain despite repeated injections of morphine.

INVESTIGATIONS

The patient had elevated troponin I (12.467 ng/mL), and echocardiography showed mild anterior and apical hypokinesia (ejection fraction 50–60%), and a trivial pericardial effusion. Chest X-ray was normal on admission. Blood investigations carried out prior to and after administration of thrombolytics showed moderate eosinophilia ([table 1](#)). A coronary angiogram was performed 24 h later. The angiogram did not demonstrate any evidence of significant occlusive atherosclerotic disease suggesting successful thrombolysis or resolved vasospasms.

As the patient continued to get chest pain (with pain occasionally radiating to his back) a CT thorax was performed to exclude aortic dissection (spontaneous or catheter induced) on day 3 of hospital admission. CT excluded dissection but showed evidence of generalised fluid extravasation at different sites (fluid around ascending aorta, see [figure 2](#)), trivial pericardial effusion, bilateral pleural effusion ([figure 3](#)), bilateral lower zone consolidations, and fluid collection around both kidneys ([figure 4](#)) and gallbladder ([figure 5](#)).

Eosinophil counts continue to rise reaching a peak of 25% (absolute count 2800/Cumm) on post-myocardial infarction day 4. At this point two-dimensional ECHO showed worsening of

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Figure 1 ECG on admission.

pericardial effusion (10 mm) and clinically detectable bilateral pleural effusion. The patient did not have orthopnoea or oedema to suggest heart failure. He developed a supra ventricular tachycardia, which was managed with intravenous amiodarone.

Screening for infectious (fungi, parasitic and retroviral), autoimmune, allergic and neoplastic diseases as a possible secondary cause for eosinophilia was performed (table 2 and box 1).

The patient had significantly elevated IgE levels (>2000 I μ /mL) confirming hypersensitivity. There was no definite history of drug or food exposure to cause eosinophilia. Allergic rhinitis/atopy is a possible cause of eosinophilia. However, it is unlikely to cause moderate eosinophilia. Several careful stool and serological analyses excluded gut and tissue helminth infestations, which are common in this region.

TREATMENT

Oral methyl prednisolone 16 mg/day and oral fexofenadine 180 mg once daily were added to the standard acute coronary syndrome treatment on day 4 of postmyocardial infarction to prevent tissue damage by eosinophil and mast cell derived inflammatory mediators.

Within 2 days of starting steroids, eosinophil count returned to normal and evidence of fluid extravasation disappeared (including pericardial and pleural effusion). A diagnosis of allergic angina (Kounis syndrome) was made. The patient was discharged on steroids. His eosinophil counts were monitored on a regular basis and steroids tailed off within 1 month.

OUTCOME AND FOLLOW-UP

Six weeks after the myocardial infarction he resumed his duties as a carpenter and on the very next day his eosinophil count was raised to 16% (absolute count 1400/Cumm). There was no evidence of coronary involvement on this occasion. Occupational exposure to dust is assumed to be the trigger of eosinophilia and the patient was advised on avoiding dust exposure. He did not have further flairs of eosinophilia after changing his occupation.

The patient's serological assays revealed high IgE response to many common basic, inhaled and ingested allergens. Except for dust, we could not establish a direct temporal relationship with exposure and current presentation with other antigens. These positive results were probably due to cross reactions of antibodies. In addition, the patient's *Toxocara* antibodies (IgG) and *Aspergillus fumigatus*-specific IgE (rAsp f 1) showed positive results. However, since the patient improved without specific treatment for these conditions, parallel testing of serial samples for these infections was not performed.

DISCUSSION

Association between eosinophilia and heart disease is described in few disease entities. Endomyocardial fibrosis can result from a variety of eosinophilic syndromes including Loeffler's endocarditis (eosinophilic myocarditis). A more severe form of eosinophilic infiltration is known as acute necrotising eosinophilic cardiomyopathy, which follows a more rapidly deteriorating cardiac course with less systemic involvement. Eosinophilic

Table 1 Eosinophil counts during the cause of admission

Post-MI day	Day 0	Day 3	Day 5	Day 6	Day 7	Day 8
WCC ($10^3/\mu$ L)	11.5	12.8	11.6	10.5	20.7	20.6
Eosinophils (%) (absolute count) (μ L)	15 (1725)	27.7 (3456)	24.2 (2784)	0.9 (90)	2.3 (476)	0.3 (60)

MI, myocardial infarction; WCC, white cell count.

Figure 2 CT of the chest showing fluid extravasation around the aorta.

coronary arteritis has been noted secondary to Churg-Strauss syndrome.

Elevated eosinophil count in a patient presenting with anterior ST elevation myocardial infarction (STEMI) brought up several issues. First, it was necessary to figure out whether eosinophilia was related to the current presentation or whether it was an unrelated incidental finding. This patient had radiological and clinical evidence of fluid extravasation around multiple organs including the aorta, pericardial space, pleural space, kidneys and gallbladder, which is likely to have resulted from eosinophil-mediated tissue damage. Normalisation of eosinophil count and parallel rapid clinical response observed following administration of antihistamines and steroids further confirmed eosinophil-mediated tissue injury. The patient had no cardiovascular risk factors to account for an acute coronary syndrome. Therefore, it is highly likely that the coronary arteries also got involved in the same disease process.

Second, the clinical question of how to identify the cause of eosinophilia came up. A broad variety of infectious (fungi, parasitic and retroviral), autoimmune, allergic and neoplastic diseases are associated with increased blood and/or tissue eosinophilia. Through laboratory assays we safely excluded

Figure 3 CT of the chest showing pericardial effusion and pleural effusion.

Figure 4 CT of the chest showing fluid extravasation around the kidneys.

many infectious, vasculitic and neoplastic conditions. Since the patient had allergic rhinitis, atopy or allergy was considered a possible cause for eosinophilia. This was supported by the elevated total IgE levels in the patient's serum. Relapse of eosinophilia following occupational exposure to wooden dust particles and improvement following avoidance of exposure confirmed atopy/allergy as the triggering event of eosinophilia.

Professor Nicholas G Kounis concluded through clinical observations and laboratory studies that angina pectoris or acute myocardial infarction can be provoked by acute allergic reactions.² This phenomenon was first reported in the *American Heart Journal* in 1950 with a case of a prolonged allergic reaction to penicillin.¹ Since the description of Kounis syndrome, many case reports have been published.^{5–8}

The exact pathophysiological mechanism linking allergic event and acute coronary syndrome is still not established; however, many possible explanations have been suggested. In 1995, Kovanen *et al*⁹ examined specimens of coronary arteries from 20 patients who had died of acute myocardial infarction and found that the degree of mast cell degranulation was much higher (200 to 1 ratio) at the sites of plaque erosion or rupture than in adjacent areas or in the more distant unaffected areas. They concluded that collagen-degrading proteases from mast cells could induce plaque erosion and/or rupture. Following this clinical description, Constantinides,¹⁰ in 1995, raised the

Figure 5 CT of the chest showing fluid extravasation around the gallbladder.

Table 2 Investigations to screen for possible causes for secondary eosinophilia

Possible secondary cause	Test	Result
Gut helminthic infection	Stool for amoeba/ova/cyst	Negative
Tissue helminthic infection	Filarial antibodies (IgG/IgM)	Negative
Toxoplasma	IgG antibody level IgM antibody level	8.7 IU/mL (reactive) Reference <1.6 (non-reactive) Non-reactive
Toxocara	IgG antibody level	0.72 (positive) Reference <0.299 (negative)
Aspergillosis	<i>Aspergillus fumigatus</i> IgE (rAsp f 1) immunoglobulins	2.96 KU/L (positive)
Vasculitis (Takayasu)	Perinuclear antineutrophil cytoplasmic antibodies/Cytoplasmic antineutrophil cytoplasmic antibodies	Negative
Atopy	IgE panel for common, inhaled and food antigens	Box 1
Lymphoma	Ultra sound scan of the abdomen/lactate dehydrogenase	Negative

possibility that “even ordinary allergic reactions could promote plaque disruption”. This was based on Constantinides’s observation that circulating mast cell precursors could penetrate the open junctions between endothelial cells that line human atherosclerotic plaques in contrast to closed junctions over the normal arterial intima. In an editorial in 1998, Braunwald¹¹ noted that vasospastic angina can be induced by allergic reactions, with mediators such as histamine and leucotrienes acting on coronary vascular smooth muscle.

Mast cells have also been implicated in the pathogenesis of atherosclerosis.^{12 13} Their number in the adventitia of coronary arteries increases with the progression of atherosclerosis. Higher mast cell counts are seen in coronary arteries containing both fresh and organising thrombi, and lower counts are observed in association with fully organised thrombi. Several stimuli can activate mast cells to release a wide variety of vasoactive compounds.

Eosinophils and mast cells are both important effector cells in the late phase allergic response and they have been implicated in the pathogenesis of allergic diseases. Eosinophils are multifunctional leucocytes involved in initiation and propagation of diverse inflammatory responses, as well as modulators of innate and adaptive immunity. They normally reside in tissues and express H4 histamine receptors. These receptors facilitate eosinophil chemotaxis towards mast cells that are the major producers of histamine. In Th2-type immune response (as in the case of hypersensitivity), eosinophils are recruited into sites of inflammation where they produce an array of cytokines and lipid mediators and release toxic granule proteins.

Human eosinophil granules contain chemicals such as major basic protein, eosinophil cationic protein, eosinophil peroxidase and β -glucuronidase. These molecules themselves are highly

toxic to mammalian cells and they can also induce mast cells to degranulate.

The best known mechanisms of mast cell activation involve IgE. They bind to specific receptors on the mast cell surface, thus priming the cells to release their mediators in response to challenge with a specific antigen. The cytokines produced by Th2 cells during type 1 hypersensitivity evoke strong IgE response. This is the best explanation to link hypersensitivity, eosinophilia, elevated IgE and atherosclerotic plaque rupture in Kounis syndrome.

Intravenous morphine is a commonly prescribed medication for chest pain during myocardial infarction. However, our patient’s chest pain paradoxically worsened with repeated morphine injections. It is an interesting observation as morphine is a potent mast cell activator that can worsen the pathological mechanism of Kounis syndrome. We were not considering a diagnosis of Kounis syndrome on admission and were unaware at that point about the paradoxical harmful effect morphine could have on Kounis syndrome. Retrospectively, we feel that an alternative analgesic such as fentanyl would have been a better choice to manage the chest pain in our patient.

Although many questions about the exact pathophysiological mechanism of Kounis syndrome remain unanswered, the increasing number of cases published in the past few decades shows that this condition should be taken into consideration in the differential diagnosis of ischaemic heart disease.

However, plasma leakage at multiple sites seen in our patient is not described in previously published case reports of Kounis syndrome. In this patient, hypersensitivity was occult and was exposed while searching for a cause of eosinophilia.

Our patient presented with anterior STEMI with evidence of hypersensitivity and had normal coronary anatomy. We concluded that he had a type I variant of Kounis syndrome.

Box 1 Antigens that showed high IgE levels during screening (common basic, inhaled and ingested allergen screening).

- High allergen-specific IgE levels were noted following allergen classes. (These were immunoblot assays based on the sandwich—ELISA principal.)
 - Basic allergens—dust/insects.
 - Food allergens—potato, shrimp.
 - Inhaled allergens—mite mix, *Dermatophagoides farinae*, straw dust.

Learning points

- Kounis syndrome should be borne in mind when diagnosing patients with no cardiovascular risk factors who experience acute coronary syndrome and who have evidence of an allergy.
- An allergic event could be occult and may miss medical attention while attending to more dramatic myocardial infarction.
- Peripheral eosinophilia could be a clue to underline hypersensitivity.
- Morphine can worsen the clinical picture of Kounis syndrome through its action on mast cells.

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