CASE REPORT

Kounis syndrome

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Kounis syndrome is characterised by a group of symptoms that manifest as unstable vasospastic or non-vasospastic angina secondary to a hypersensitivity reaction. It was first described by Kounis and Zavras in 1991 as the concurrence of an allergic response with an anaphylactoid or anaphylactic reaction and coronary artery spasm or even myocardial infarction. Since then, this condition has evolved to include a number of mast cell activation disorders associated with acute coronary syndrome. There are many triggering factors, including reactions to multiple medications, exposure to radiological contrast media, poison ivy, bee stings, shellfish and coronary stents. In addition to coronary arterial involvement, Kounis syndrome comprises other arterial systems with similar physiologies, such as mesenteric and cerebral circulation resulting in ischaemia/infarction of the vital organs. The incidence of this condition is difficult to establish owing to the number of potential instigating factors and its relatively infrequent documentation in the literature.

We report the case of an HIV-negative 39-year-old man with no coronary risk factors or family history of premature coronary artery disease, who developed Kounis syndrome after the administration of fluoroquinolone for dysuria. However, to the best of our knowledge, no data on the incidence and prevalence of Kounis syndrome in South Africa have ever been reported in the literature. The recent understanding of Kounis syndrome has led to the condition being classified into three syndrome variants.

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Kounis syndrome is characterised by a group of symptoms that manifest as unstable vasospastic or non-vasospastic angina secondary to a hypersensitivity reaction.[1] It was first described by Kounis and Zavras in 1991[2] as the concurrence of an allergic response with an anaphylactoid or anaphylactic reaction and coronary artery spasm or even myocardial infarction. Since then, this condition has evolved to include a number of mast cell activation disorders associated with acute coronary syndrome. There are many triggering factors, including reactions to multiple medications (non-steroidal anti-inflammatory drugs, antibiotics and anti-neoplastic agents), exposure to radiological contrast media, poison ivy, bee stings, shellfish and coronary stents. In addition to coronary arterial involvement, Kounis syndrome comprises other arterial systems with similar physiologies, such as mesenteric and cerebral circulation resulting in ischaemia/infarction of the vital organs.[3,4] The incidence of Kounis syndrome is difficult to establish owing to the number of potential instigating factors and its relatively infrequent documentation in the literature. It remains unclear whether the reported lower rates of the condition are the direct result of underdiagnosis.

We report the case of an HIV-negative 39-year-old man with no coronary risk factors or family history of premature coronary artery disease, who developed Kounis syndrome after the administration of fluoroquinolone for dysuria. However, to the best of our knowledge, no data on the incidence and prevalence of Kounis syndrome in South Africa (SA) have ever been reported in the literature. The recent understanding of Kounis syndrome has led to the classification of this condition into three syndrome variants.[2]

Case report

Our patient was a 39-year-old man with excellent baseline health. His history is significant because of exercise-induced asthma in childhood and an allergic reaction to cefixime in 2008 that responded well to antistamine and corticosteroids. In 2009 he was administered ciprofloxacin, with no untoward reaction. He was well until February 2015, when he developed dysuria and was administered ciprofloxacin. The patient developed a red pruritic rash 15 minutes after ingestion of the drug, which was followed by swelling of his hands, feet and scrotum. Four hours later, he developed retrosternal chest pain, radiating to both shoulders, rated 8/10, which persisted for about 10 minutes, with diaphoresis and nausea. The following morning he presented at the emergency centre, and developed a second episode of typical chest pain. The ECG (Fig. 1) showed ST segment

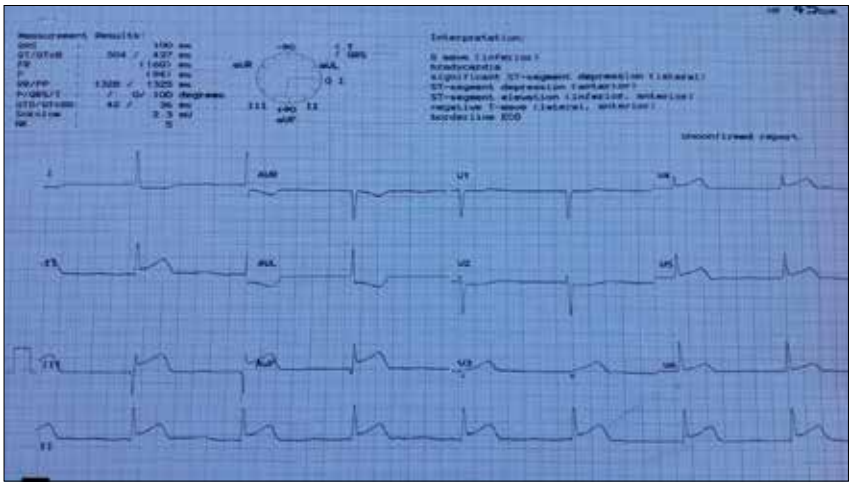

Fig. 1. ECG demonstrating inferior and posterolateral ST elevation.

elevation in the inferior leads, and a diagnosis of acute coronary syndrome with inferior, postero-lateral myocardial infarction was made. He was thrombolysed with tenecteplase, with no resolution of ST segment elevation 1 hour post lysis. The patient was referred to our division for rescue percutaneous coronary intervention (PCI) after stat doses of aspirin, clopidogrel and atenolol. On arrival, on re-taking the history, allergic myocardial infarction was considered a likely diagnosis and blood was sent for determination of troponin, tryptase, and IgE (Table 1).

The clinical examination was unremarkable: the patient was normotensive, with a blood pressure of 120/70 mmHg, tachycardia of 108 beats/minute, and tachypnoea of 22 breaths/minute. Cardiovascular examination revealed a loud S1 and no murmurs. Prednisone 1 mg/kg/day, diphenhydramine 50 mg, ranitidine 150 mg and amlodipine 10 mg were administered orally, with resolution of pain and ECG changes. Administration of aspirin, clopidogrel and a beta-blocker was discontinued. Cardiac catheterisation and a coronary angiogram were performed within 24 hours and showed unobstructed coronary arteries (Figs 2 and 3). On receipt of the blood results, allergologists were consulted. The patient was discharged 3 days later with no resurgence of symptoms; also not at 3 months' follow-up.

Table 1. Results of investigations

Investigation	Result
Full blood count	Haemoglobin 13.3 g/dL; white cell count 8.34 × 10^9/L; platelet count 276 × 10^9/L; eosinophils 0.017 × 10^9/L (0.3%)
Urea and electrolytes	Na 143 mmol/L; K 4.6 mmol/L; urea 3.6 mmol/L; creatinine 77 µmol/L
Total IgE	43 kU/L
Thyroid-stimulating hormone	0.36 mIU/L
Antinuclear antibodies	0.1 ratio – negative
Mast cell tryptase	2.5 µg/L
HIV	Negative
Lipid profile	Total cholesterol 2.8 mmol/L; triglyceride 0.9 mmol/L; high-density lipoprotein 1 mmol/L; low-density lipoprotein 1.3 mmol/L
Troponin T	1 001 ng/L
Diverse cast ciprofloxacin	Positive

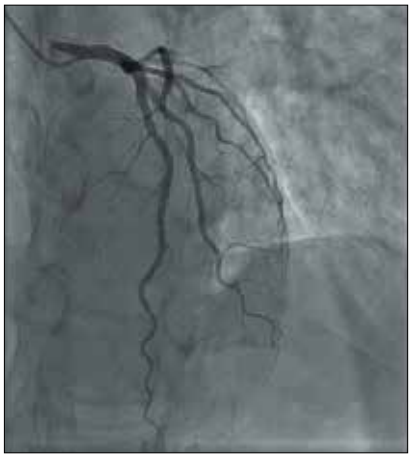

Fig. 2. Unobstructed left coronary artery.

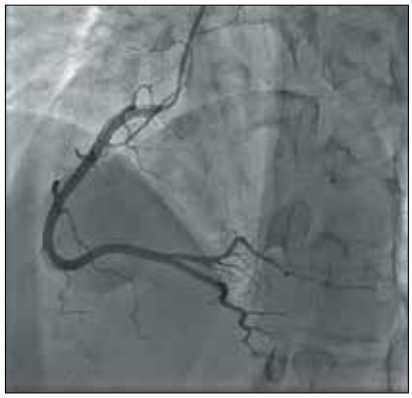

Fig. 3. Unobstructed right coronary artery.

Discussion

Kounis syndrome was described in 1991 as the concurrence of acute coronary events with an allergic or a hypersensitivity response and an anaphylactic or anaphylactoid reaction.[2] Several possible causes of Kounis syndrome have been reported.[1,5,6] The condition has three variants,[1] i.e. type 1 – coronary spasm; type 2 – coronary thrombosis; and type 3 – drug-eluting stent thrombosis. It is important to distinguish the type, as it has management implications. The syndrome is caused by inflammatory mediators released mainly from activated mast cells and via bidirectional stimuli macrophages and T-lymphocytes.[1] As activated mast cells abound at the areas of plaque erosion or rupture in patients suffering from acute myocardial infarction, a common pathway between allergic and non-allergic coronary events seems to exist.[1,7]

- **Type 1 variant** includes patients with normal coronary arteries without predisposing factors for coronary artery disease, in whom the acute release of inflammatory mediators can induce either coronary artery spasm without an increase in cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins.[1]
- **Type 2 variant** includes patients with culprit, but quiescent, pre-existing atheromatous lesions, in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or plaque erosion or rupture manifesting as acute myocardial infarction.[1]
- **Type 3 variant** includes patients with coronary thrombosis (including stent thrombosis), in whom aspirated thrombus specimens stained with haematoxylin-eosin and Giemsa demonstrate the presence of eosinophils and mast cells, respectively.[1]

Histamine released by degranulation of mast cells can also be measured within 5 - 10 minutes, but remains elevated for only 30 - 60 minutes and therefore has very limited value. To date, serum tryptase has been identified as a reliable marker of an anaphylactic reaction. Review of the literature has suggested that serum tryptase may be considered as a new marker of the instability of atheromatous plaque with regard to the existence of mastocytes in heart tissue. Regardless of documented laboratory evidence of anaphylaxis, a diagnosis can still be made based on the clinical presentation and treatment carried out accordingly.[5]

Treatment depends on the syndrome variant:

- **Type 1 variant:** treatment of the allergic event alone may abolish type 1 variant. Administer corticosteroids, antihistamines, vasodilators (e.g. nitrates), and calcium channel blockers.[3,8]
- **Type 2 variant:** apply the acute coronary event protocol and administer corticosteroids, antihistamines, vasodilators (e.g. nitrates), and calcium channel blockers when appropriate.
- **Type 3 variant:** the use of mast cell stabilisers in association with steroids and antihistamines is recommended. Harvesting of the intrastent thrombus together with histological examination of

aspirated material and staining for eosinophils and mast cells should be undertaken.

When allergic symptoms are present after stent implantation, desensitisation measures should be applied; if these fail, the stent should be extracted.

Conclusion

There is a paucity of data on the incidence and prevalence of Kounis syndrome in SA; nonetheless, it is important to be aware of the entity. There are no treatment guidelines for patients with this syndrome, and most of the treatment information has been gathered from individual case reports or case series. A diagnosis of Kounis syndrome should be considered in young, healthy patients with no atherosclerotic risk factors when they develop an acute coronary syndrome (especially inferior myocardial infarction) after administration of a potentially allergic agent. These patients need treatment with steroids, antihistamines, fluid resuscitation, possibly adrenaline, oxygen, and antithrombotic agents before transfer to a cardiac catheterisation laboratory. An allergy work-up should include the assessment of allergies to food, insect bites and other environmental agents. Skin tests and food challenges may be useful in identifying the culprit agent.

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