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Is It Kounis Syndrome? - A Case Report

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Abstract
"Kounis syndrome", otherwise known as "allergic angina" or "allergic myocardial infarction", refers to acute coronary syndrome occurring due to allergic, hypersensitivity or anaphylactoid reaction(1). It results due to activation of mast cells, leading to vasospasm of coronary artery and/or erosion or rupture of atherosclerotic plaque. Here, we present a probable case of Kounis syndrome Type 1 induced by a scorpion sting.
Keywords: *allergic myocardial infarction, scorpion sting, hypersensitivity.*

Introduction

Pfister *et al* published the first case of "allergic myocardiac infarction" in 1951: a gentleman aged 49 years old who developed anterolateral myocardial infarction along with urticaria following allergy to penicillin(2).

The term 'allergic myocardial infarction' was first used by Zosin et al in 1965(3).

In 1991, Kounis and Zavras described the clinical syndrome of "allergic angina": chest pain with clinical and biochemical findings of classical angina pectoris occurring along with allergic manifestations(1). Allergic angina progressing to acute myocardial infarction was called "allergic myocardial infarction".

In 1995, Kovanen *et al.* (4) and Constantinides(5,6) described the role of cytokine-mediated mast cell de-granulation in the pathogenesis of the condition. They identified that mast cell precursors could penetrate the open junctions between endothelial cells lining human atheromatous plaques better than the closed junctions present in the intima of normal arteries(5,6), and that proteases released on degranulation of these mast cells lead to plaque erosion/ rupture(4).

Kounis syndrome has been reported to have multiple etiologies, including

i. Environmental exposures including grass cutting, millet allergy, poison ivy, Hymenoptera, jellyfish and scorpion stings, centipede bite, viper venom, latex contact, metals;
ii. Drugs including analgesics (eg, aspirin), anesthetics (eg, propofol, isoflurane, midazolam, etomidate); antibiotics, anticoagulants, contrast media, NSAIDs, proton pump inhibitors, thrombolytics, skin disinfectants and some other drugs including protamine, iron, iodine,

allopurinol, dextran, clopidogrel, enalapril, esmolol, tetanus antitoxin;

iii. Foods including fish, shellfish, fruits, mushroom *Coprinopsis atramentaria*, canned food, vegetables, tomato salad;

iv. Conditions like angioedema, anisakiasis, bronchial asthma, Churg-Strauss syndrome, exercise-induced anaphylaxis, food allergy, hay fever, mastocytosis, scromboid syndrome, serum sickness;

v. Coronary and other stents (bare metal or drug-eluting)

Case Report

A male aged 14 years was brought to the Emergency Room approximately 2 hours following alleged history of scorpion sting on the fourth digit of his right foot.

He presented with profuse sweating, drowsiness and breathlessness. His pulse rate was 58 bpm, blood pressure 80/60 mmHg and oxygen saturation 60%. Priapism was present. JVP was normal. Respiratory system examination revealed basal crepitations in bilateral lung fields. Normal heart sounds were heard; no murmurs were present.

Chest X-ray (Figure 1) showed pulmonary oedema and ECG (Figure 2.1 and 2.2) showed ST depression in leads II, III and aVF, tall T waves in V2 to V4 chest leads and q waves in leads I and aVL, simulating anterolateral MI with reciprocal changes and no arrhythmia. Investigations also revealed a CK-MB of 91 IU/L (normal range: 5 to 25 IU/L), positive Troponin T, metabolic acidosis and hypokalemia.

Echocardiogram done (Figure 3) showed regional wall motion abnormality, severe mitral regurgitation, dilated left ventricle with poor LV systolic function (Ejection Fraction: 33%), with no significant pulmonary artery hypertension and normal pericardium.

Due to the presence of elevated CK-MB, positive Troponin T, ECG changes on anterolateral leads, regional wall motion abnormality on Echocardiogram, absence of ECG changes on all leads and normal serum potassium levels, a probable diagnosis of allergic myocardial infarction or "Type 1 Kounis syndrome" with cardiogenic pulmonary edema was made. Coronary angiogram was not done.

Patient was managed in ICU with prazosin, intravenous fluids, inotropic and ventilatory support. During hospitalisation, the patient developed ventilator-associated infection with *E. coli* for which he was managed with antibiotics.

Serial ECGs that were done showed reversion of the ST segment changes and tall T waves (Figure 2.3). Repeat echocardiograms were done 2 days and 7 days after admission which revealed mitral regurgitation and trivial triscuspid regurgitation and grade II diastolic dysfunction. It also showed increase in Ejection Fraction to 43% and 60% respectively.

CK-MB when repeated had normalized. At discharge, patient was stable and advised repeat Echocardiogram on follow-up.

Figure 1

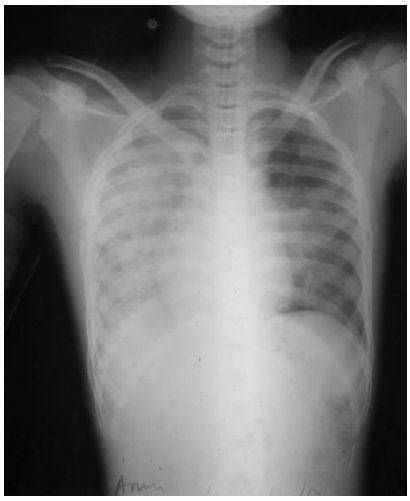


Figure 2.1 (at presentation)

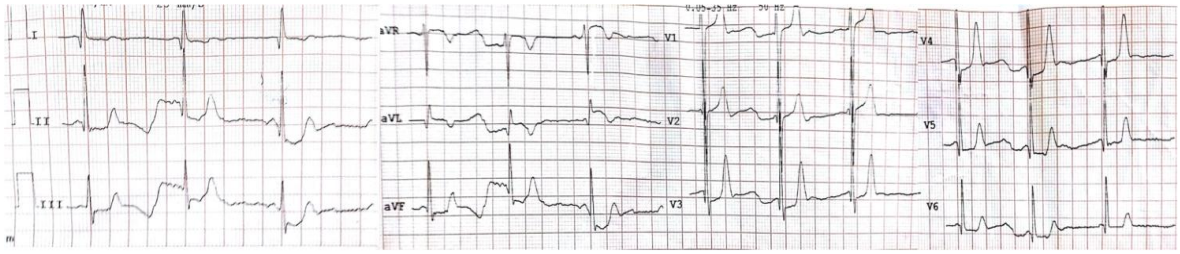


Figure 2.2 (at presentation)

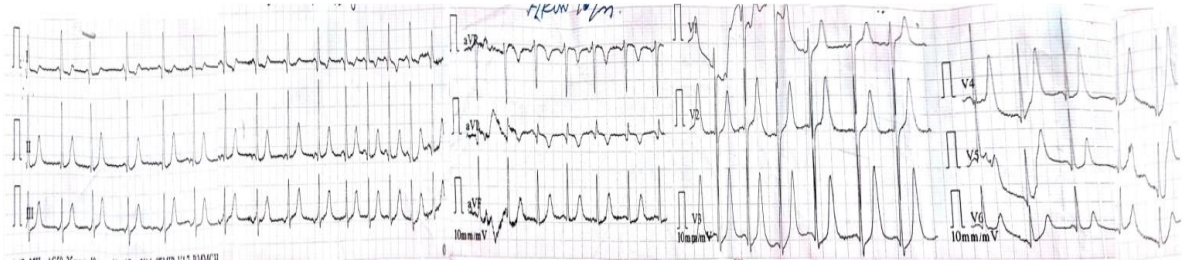


Figure 3

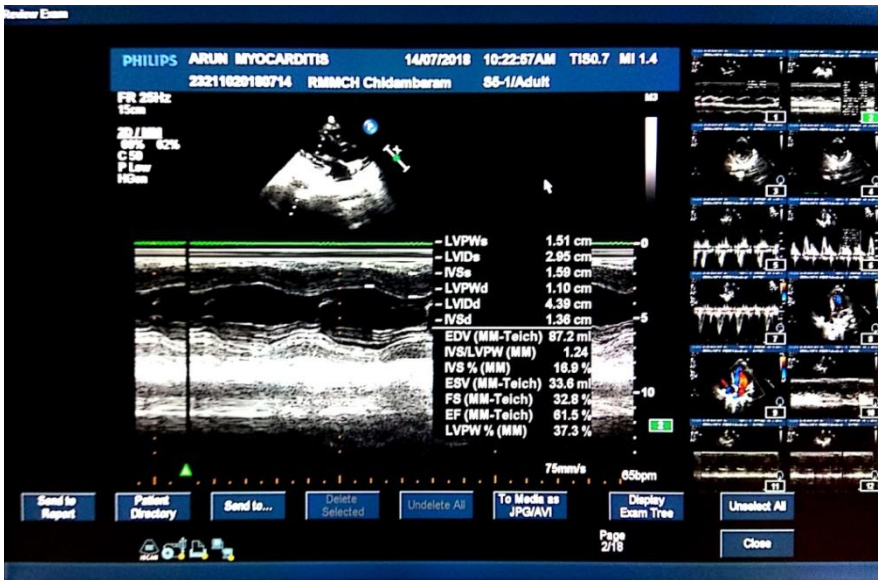
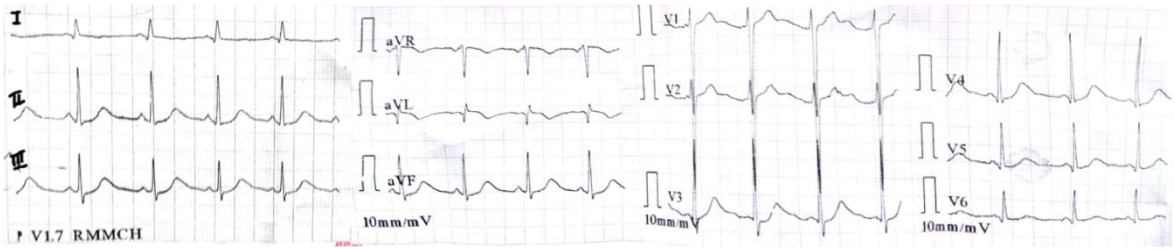


Figure 2.3



Discussion

Three types of Kounis syndrome have been reported[7]. The type I variant occurs in patients with normal coronary arteries without predisposing risk factors for coronary artery disease. It has been described as occurring due to endothelial dysfunction or microvascular angina[8]. The type II variant is found in patients with preexisting atherosclerotic disease. The allergic insult causes rupture or erosion of the plaque leading to coronary vasospasm or acute myocardial infarction[7]. The type III variant is

thrombosis of coronary arterial stent occurring due to allergic reaction, in which histological examinations would reveal eosinophils and/or mast cells[7].

The pathogenesis of Kounis syndrome is by mast cells mainly[10], which release the culprit inflammatory mediators and by a subset of platelets bearing FCγRI, FCγTII, FCεRI and FCεRII receptors [11].

1. Degranulation of mast cells occurs when specific antigens induced by the allergy react with IgE antibodies attached to mast cells and produce a significant number of bridged IgE antibodies [12].
2. Inflammatory mediators released following degranulation cause coronary vasospasm[7,9] leading to ischemia by the following mechanisms.
   i. Histamine leads to coronary vasoconstriction, produces tissue factor expression and activation of platelets.
   ii. The three neutral proteases chymase, tryptase and cathepsin D can lead to degradation of the collagen cap, thereby causing rupture or erosion of the atheromatous plaque[13]. Tryptase has properties of both thrombosis and fibrinolysis [14]. Chymase and cathepsin-D can additionally convert angiotensin I to angiotensin II which is a potent vasoconstricting substance.
   iii. Biosynthesis of leukotrienes – powerful vasoconstrictors – increases during the acute phase of unstable angina[15,16]. Thromboxane causes aggregation of platelets and vasoconstriction.
   iv. In myocardial ischemia, platelet-activating factor (PAF) activates both leukocytes and platelets, thereby leading to release of leukotrienes. It also has a direct effect on vasoconstriction [17].

The present case is, therefore, a probable case of Type I Kounis syndrome induced by scorpion sting. Cases of Kounis syndrome induced by spider bite, honeybee sting and snake bite have been reported [18 - 24].

Scorpion envenomation induces venom-specific immunoglobulin E (IgEs), and, thereby, produces mast cell-mediated histamine release leading to Type 1 hypersensitivity reaction [25].

Treatment

The mainstay in Kounis syndrome should be management of the allergic reaction.

Simultaneous stabilization of the coronary arteries with medical or interventional techniques is also required.

Treatment in scorpion sting-induced Type 1 Kounis syndrome includes:

- antivenom and dobutamine for cardiovascular effects,
- benzodiazepines for neuromuscular involvement,
- adrenaline and fluid resuscitation for anaphylaxis management,
- antihistamines and leukotriene receptor antagonists as second line treatment of anaphylaxis, and
- prazosin, a postsynaptic alpha blocker, to reduce sympathetic symptoms and also in pulmonary edema (cardiogenic) with arterial hypertension. Oral prazosin is used due to its rapid onset of action, easily availability and high effectiveness.
- Corticosteroids are to be used in interstitial pulmonary edema that is non-cardiogenic.

Type I Kounis syndrome has been reported to have good response when treated with corticosteroids and histamine (H1 or H2) receptor blockers, along with coronary vasodilators such as nitrates or calcium channel blockers.

In Type II and Type III Kounis syndrome, the same management is followed and coronary interventions may be required.

Drugs contraindicated in Kounis syndrome

i. Morphine – may exacerbate histamine release and related pathologic cascade of events;

ii. Beta-blockers – their unopposed alpha adrenergic action can worsen coronary vasospasm;
iii. Epinephrine – worsens coronary vasospasm and should, therefore, be used cautiously[7].

On identification of the allergic component, desensitization measures should be carried out in order to prevent further events in the future. Mast cell stabilizers like sodium cromoglycate, ketotifen, sodium nedocromil and iodoxamide need more exploration for their potential role in prevention.

Conclusion

The diagnosis and management of Kounis syndrome can be challenging as it requires attention to both the cardiac and anaphylactic pathophysiology concurrently. Oral prazosin may be beneficial in controlling sympathetic symptoms and pulmonary edema induced by the scorpion sting, while dobutamine, adrenaline and fluid resuscitation are also essential in the management of scorpion venom-induced anaphylaxis. The condition requires rigorous and immediate action, meticulous treatment and careful monitoring.

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