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Case Report

A variant of Kounis syndrome due to diclofenac sodium

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ABSTRACT

Kounis syndrome is an acute coronary syndrome of varying degrees induced by allergic or anaphylactic reaction leading to coronary vasospasm or atheromatous plaque erosion or rupture or global myocardial hypoperfusion occurring as a result of systemic vasodilation and decreased venous return in context of anaphylaxis. We reported a case of 33-year-old female who presented to emergency department in an irritable state with complaints of nausea, vomiting, abdominal pain, breathlessness and generalized itching which developed secondary to administration of diclofenac injection by intra muscular (IM) route. On evaluation, echocardiography revealed global LV systolic dysfunction. The patient was successfully treated with continuous noradrenaline infusion, fluid resuscitation and other supportive measures with repeat echocardiography revealing normal LV systolic function.

Keywords: Drug induced coronary vasospasm, Anaphylaxis, Kounis syndrome

INTRODUCTION

Kounis syndrome is defined as the concurrence of acute coronary syndromes including coronary spasm, acute myocardial infarction, and stent thrombosis, with conditions associated with mast-cell and platelet activation and involving interrelated and interacting inflammatory cells, such as macrophages and T-lymphocytes, in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults. This syndrome is caused by inflammatory mediators such as histamine, platelet-activating factor, arachidonic acid products, neutral proteases and a variety of cytokines and chemokines released during the allergic activation process.[1]Three variants of Kounis syndrome have been described: The type I variant (coronary spasm), which seems to represent a manifestation of endothelial dysfunction or microvascular angina, includes patients with normal or nearly 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 increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. The type II variant that includes patients with culprit but quiescent pre-existing atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction. The type III variant that includes patients with coronary artery stent thrombosis in whom aspirated thrombus specimens stained with hematoxylin-eosin and Giemsa demonstrate the presence of eosinophils and mast cells, respectively.[2] The main inflammatory cells that are involved in the development of Kounis syndrome are mast cells that interact with macrophages and T-lymphocytes via multidirectional stimuli. A subset of platelets receptors are also involved in the activation cascade.[3,4] During allergy, hypersensitivity, or anaphylaxis degranulation of mast cells takes place and a variety of stored and newly formed inflammatory mediators are released locally and in

the systemic circulation. These include: biogenic amines such as histamine, chemokines, enzymes such as the neutral proteases chymase, tryptase, cathepsin-D, peptides, proteoglycanes, cytokines, growth factors and arachidonic acid products such as leukotrienes, thromboxane, prostacyclin, PAF and tumor necrosis factor-α (TNF-α).Tryptase exerts a dual action on the coagulation cascade with both thrombotic and fibrinolytic properties.[5] Furthermore, chymase and cathepsin-D can act as converting enzymes and convert angiotensin I to angiotensin II, which is a major vasoconstricting substance.[6] Leukotrienes are also powerful vasoconstrictors and their biosynthesis is enhanced in the acute phase of unstable angina.[7,8] Thromboxane is a potent mediator of platelet aggregation with vasoconstricting properties and PAF, in myocardial ischemia, acts as proadhesive signalling molecule via activation of leukocytes and platelets to release leukotrienes or as a direct vasoconstrictor.[9-11] All these pre-formed and newly synthesized inflammatory mediators released locally and pouring into systemic circulation can cause either coronary artery spasm which could progress to acute myocardial damage or immediate coronary thrombosis which constitute the main clinical manifestations of Kounis syndrome.

We reported a case of a 33-year-old female diagnosed to have severe left ventricular systolic dysfunction which occurred secondary to diclofenac sodium IM administration with normal ECG findings. Prompt and timely management with inotropes, antihistamines, steroids and fluid resuscitation encouraged successful treatment.

CASE REPORT

A 33-year-old female had a history of fever five days back for two days before she visited us, for which she has been treated with antipyretics in an outside hospital which got resolved, but she had persistent body pain since then for which she was given intramuscular diclofenac sodium in a nearby hospital. Following administration, after 15 minutes she became restless, irritable, confused and was shifted to emergency ward of our hospital. She reported complaints of generalized itching, nausea, vomiting, abdominal pain, breathlessness and urge to urinate and defaecate. There was no previous history of allergy.

On examination, patient was confused, irritable with the GCS of 14/15 (E4 V4 M6). Her pulse rate was 116 beats per minute, blood pressure was unrecordable, respiratory rate - 36 cycles per minute, SpO_2- 98%. General examination revealed urticaria over trunk, face and both upper and lower limbs. Her extremities are cold and clammy. On systemic examination, auscultation of the chest revealed basal crepitations over bilateral infrascapular area. Her blood reports revealed Hb- 15.8 g/dl, total leukocyte count- 12490 cells/µl, platelet- 3.62 cells/µl, ESR- 7 mm/hr, CRP- 7.4 mg/l, HbA1c- 5.8%, serum procalcitonin- 0.3 (<0.5 ng/ml), serum IgE-1350 (150-300 U/ml), troponin I- 2.0 (<0.94 ng/ml), CKMB-21.0 (2-10 U/l) and BNP- 12,000 (<100 pg/ml). Renal function test, liver function test, electrolytes, serum amylase, serum lipase, serum calcium, serum magnesium and urine routine were within normal limits. Her HIV I, II, HBsAg/anti HCV antibody were negative. Her blood and urine culture turned out to be negative. Her initial ECG was normal (Figure 1). Her initial ABG revealed Ph- 7.375, PCO_2- 22.7 mmHg, PO_2- 59 mmHg, lactate- 5.0 mmol/l, bicarbonate- 13.0 mmol/l suggesting respiratory alkalosis with normal anion gap metabolic acidosis. Chest X-ray revealed increased bronchovascular markings in bilateral lower zones of the lung field suggesting pulmonary odema (Figure 2). Echocardiography revealed global hypokinesia with severe LV systolic dysfunction (ejection fraction 25%) with normal chamber dimensions and structurally normal valves.

In the emergency department she was treated for anaphylaxis with injection adrenaline 0.5 cc IM stat followed by next dose of IM adrenaline 0.5 cc after 10 min, IV chlorpheniramine maleate 2 cc, injection hydrocortisone 100 mg IV, intravenous normal saline rapid bolus of 1.5 l and supplemental oxygen at 10 l/min via face mask. Despite 1.5 l fluid bolus her blood pressure was unrecordable, following which she has been started on IV noradrenaline infusion at 12 µg/min and she has been transferred to Intensive care unit for further management. In view of raised cardiac biomarkers and with echocardiography revealing severe LV systolic dysfunction, emergent coronary angiography was done which revealed normal coronary vessels. With continuous inotrope support and other supportive measures, her blood pressure was recordable- 130/80 mmHg, rash started to disappear and she improved symptomatically. Her serial ECG's were normal. Noradrenaline infusion has been tapered accordingly and on day 4 of her stay in hospital, she was inotrope free and was symptomatically better. Repeat echocardiography on day 5 revealed normal LV systolic function with ejection fraction 68% and no regional wall motion abnormality. Blood parameters like serum IgE, troponin I, CKMB and BNP were in reducing trend. On day 6 patient was symptom free and was discharged. After one month, she was doing significantly better on proper evaluation and her blood parameters were found to be within normal limits with repeat echocardiography revealing normal LV systolic function with ejection fraction of 68%.

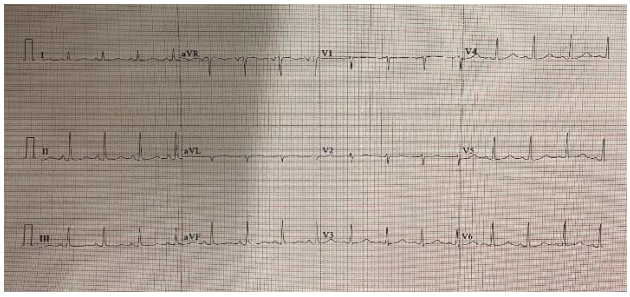

Figure 1: ECG showing normal sinus rhythm.

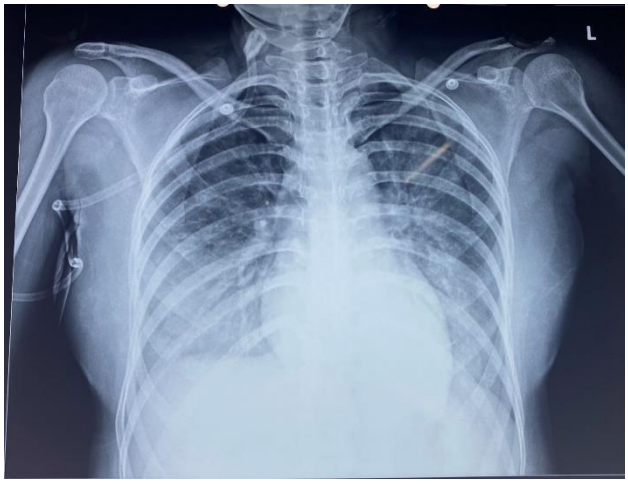

Figure 2: Chest X-ray showing increased broncho-vascular markings in bilateral lower zone region.

DISCUSSION

As far as Kounis syndrome is concerned, it is infrequently reported in the literature and recognized in clinical practice. This is due to missed, unrecognized and/or undiagnosed cases. Furthermore, there is paucity of large prospective trials, determining its prevalence and exact incidence.

However, in the only prospective study undertaken so far, it was found that between of 1,38,911 patients who were admitted to the hospital's emergency department during 1 year, 793 presented with complaints of allergy. Between them, 769 were admitted with urticaria and 24 with angioneurotic edema. The incidence of allergy admissions during 1 year was 5.7 per 1000 patients. The incidence of Kounis syndrome at the emergency department in that year among all admissions and allergy patients was 19.4 per 100 000 (27/138,911) and 3.4% (27/793), respectively.[12]

Majdi omri et al published two case reports of kounis syndrome where the first case occurred secondary to IV amoxicillin intake showing ECG findings of ST segment elevation in the inferior wall and the second case occurred secondary to herbal plant ingestion showing ECG findings of ST segment elevation in anterior wall.[13] Haoyuy et al published a case report of Kounis syndrome developed secondary to intramuscular injection of anisodamine (atropine derivative) where the patient has ECG findings of ST segment elevation in lead II, III and avF.[14] But in our case, ECG was normal revealing an atypical presentation of kounis syndrome. There was another case report published by Tiwari et al where kounis syndrome developed secondary to administration of intramuscular diclofenac injection.[15] David et al published a case report where myocardial infarction developed secondary to oral aspirin intake.[16]

NSAIDs are one of the most commonly implicated drugs causing anaphylaxis and Kounis syndrome.[17] Because of wide usage of NSAIDs, knowledge of this syndrome holds a special importance for physician, anaesthetist and general practitioners. As observed in our case, the patient reported symptoms of anaphylaxis after administration of intramuscular diclofenac sodium for pain relief, with echocardiography revealing severe LV systolic dysfunction with normal ECG and cardiac biomarkers being elevated, hence the diagnosis of variant of Kounis syndrome was made. In most of the cases published, ECG shows evidence of myocardial infarction or ischemia. ECG can be normal as in our case. Diagnosis of Kounis syndrome requires attention to both cardiac and anaphylactic pathophysiology. Key aspect of managing anaphylaxis and ACS are critical in treating Kounis syndrome.

CONCLUSION

In conclusion, even in individuals with normal coronary arteries, ACS may develop as a result of vasospasm secondary to allergic reaction and anaphylaxis especially after drug use (oral, IV and IM). Physicians dealing with cardiovascular disease should be familiar with the new information about the diagnosis and treatment of KS. We recommend that ECG be done in all patients developing hypersensitivity reactions.

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