Angina following anaphylaxis: Kounis syndrome or adrenaline effect?

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We have read with interest a report published in Malaysian Family Physician[1] on a 23-year-old Malay atopic patient with a known allergy (angioedema) to metoclopramide, tramadol, aspirin, and CT contrast media who was stung by an insect and developed throat tightness, vomiting, and a swollen uvula. As he was being treated with intramuscular tetanus toxoid, intravenous hydrocortisone, intravenous chlorpheniramine, and 0.5mg (1:1000) of intramuscular adrenaline for anaphylactic shock, he presented, within minutes, with a sudden escalation of drowsiness, worsening throat tightness and chest pain so excruciating on his left side that he fainted. The patient's electrocardiograms and cardiac enzymes were normal, however, and he regained consciousness with a high oxygen flow of 15 liters per minute. The following day, the patient was discharged in good condition. This report raises the issue of whether the excruciating chest pain was the result of the intramuscular adrenalin administration or of a Kounis Type I syndrome manifestation.

This atopic patient had a previous history of allergic reactions, such as angioedema, in response to several agents. Atopy refers to an inherited predisposition to produce immunoglobulin E antibodies in response to small amounts of common environmental exposures, including pollens, house dust mites, and food allergens, which can act as haptens, attaching to serum proteins.[2] In a recent study on atopy, it was found that the risk of anaphylaxis was independent of the type of causative drug, whereas atopy had a direct effect on the anaphylactic risk.[3] The patient was stung by an insect in his backyard and subsequently received intramuscular tetanus toxoid, intravenous hydrocortisone, and intravenous chlorpheniramine, followed by intravenous adrenaline. Any of these 4 drugs or the insect sting itself could have acted as allergens, causing the anaphylactic shock and/or Kounis syndrome.[4,5,6,7]

Paradoxically adrenaline, the drug that is life-saving in anaphylaxis, can by itself induce anaphylaxis. Indeed, every commercially available preparation of adrenaline contains sodium metabisulfite as a preservative, according to Drug Facts and Comparisons (a standard pharmacy reference published by Wolters Kluwer and updated monthly). Sodium metabisulfite is commonly used as an antioxidant in the food and pharmaceutical industries. Anaphylactic shock has been reported during the administration of epidural anesthesia for caesarian sections, in which the culprit was metabisulfite, an additive agent of local anesthetics containing adrenaline.[8] This situation poses a therapeutic dilemma in sulfite-sensitive patients who suffer from anaphylactic shock. Physicians dealing with anaphylactic shock should be aware of this association. Fortunately, free sulfite adrenaline is currently commercially available for administration to sulfite-sensitive patients (American Regent Inc, USA).[9] In this situation, a possible alternative is glucagon, which has been used successfully for treatment of anaphylaxis in patients taking β-blockers.[10]

Exogenous adrenaline administration is a life-saving procedure and, according to international guidelines, it should be injected intramuscularly at a dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution,[11] to a maximum dose of 0.5mg in adults.[12] For IV administration, appropriately diluted solutions (1:10 000 [0.1mg/mL] or 1:100 000 [0.01mg/mL]), may contribute to coronary spasm.

Adrenaline actions include the following:

1. Peripheral vasoconstriction via α1 receptors[13]
2. Increasing both the rate and force of cardiac contractions via β1 receptors[14]
3. Reversing bronchoconstriction and reducing the release of inflammatory mediators via β2 receptors [15]
4. Promoting platelet activation via specific receptors found on the platelet surface[16]
5. Inducing platelet aggregation by increasing platelet production of thromboxane B2[17]
6. Heightening platelet sensitivity to adenosine diphosphate[18]
7. Promoting thrombin-induced binding of platelets to fibrinogen.[19]

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Actions 4–7, therefore, aggravate myocardial ischemia, prolong QTc intervals, and induce coronary vasospasm and arrhythmias. Elderly patients, especially those with histories of hypertension and coronary artery disease, are prone to these side effects. Both α- (α1- and α2-) and β1-adrenergic receptors are present in the coronary arteries but with different distributions. The large coronary arteries are equipped mainly with α receptors, which mediate contraction.

In the present case, the patient's heart rate was 94 beats per minute (bpm) before adrenaline administration, which reduced it to 82 bpm. Therefore, adrenaline appears less likely to be the cause of the patient's excruciating chest pain in the absence of the above symptoms, such as tachycardia, which are typically induced by adrenaline. However, without coronary angiography or any evidence of left ventricular dysfunction, it is impossible to explain which came first—the egg or the chicken.

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