



Allergic myocardial infarction following recombinant human insulin

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ABSTRACT

Background: Allergic myocardial infarction is a rare clinical entity.

Objectives: Although a few number of case reports with severe anaphylactic reactions to recombinant human insulin have been reported, allergic myocardial infarction, known as Kounis Syndrome, has not been reported before.

Methods: Herein, we report a 57-year-old woman with myocardial infarction, referred for urticarial rash, chest pain, and palpitations developed after the first subcutaneous dose of recombinant human insulin.

Results: The patient treated with antihistamines and steroids and discharged from hospital in a good condition.

Conclusions: Physicians should be aware of allergic myocardial infarction. The diagnosis of Kounis Syndrome should be entertained when allergic symptoms, electrocardiographic changes, and high cardiac enzymes accompany acute-onset chest pain. All patients admitted to the emergency department with chest pain and ST elevation on electrocardiography should be asked about allergic insults.

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Introduction

Insulin allergy is a rare complication of insulin treatment, and the frequency of insulin allergy has been decreased with the use of recombinant human insulin.¹ Allergic reactions to human insulin include immediate type IgE-mediated reactions (type I), immune complex type which is characterized with localized Arthus reaction and/or generalized serum sickness (type III) and delayed-type hypersensitivity reactions (type IV).¹ In most cases, allergic reactions appear a few minutes after injection, and are restricted to the skin.¹ These reactions are often self-limited after discontinuation of therapy.¹ However, local forms can progress to severe and systemic symptoms (i.e., coughing, shortness of breath, wheezing, abdominal pain, nausea, vomiting and diarrhea) and potentially life-threatening reactions such as anaphylaxis.^{2–4}

Allergic angina and allergic myocardial infarction, currently known as Kounis syndrome, is defined as acute coronary syndrome caused by an allergic reaction or a strong immune reaction to a drug or other substance.⁵ Kounis syndrome is caused by

inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, and a variety of cytokines and chemokines released, during mast cell degranulation.⁵ Kounis syndrome has been linked with several diseases (bronchial asthma, urticaria, food allergy), environmental exposures (viper, wasp or bee venoms) and a variety of drugs used widely in daily clinical practice, such as antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, nonsteroidal anti-inflammatory drugs and others.⁵ However, Kounis Syndrome secondary to insulin has not been reported before. Herein, we report the first case of Kounis Syndrome after subcutaneous dose of recombinant human insulin.

Case report

A 57-year-old woman with no history of atopy, presented to our ED with urticarial rash on her face, precordial pain, and palpitations 5 minutes after the first subcutaneous injection of 10 IU recombinant human insulin. The patient and her family denied any history of asthma, or known history of drug or food allergy. The patient had never experienced a severe allergic reaction in the past.

The medical history of the patient revealed that she had a history of hypertension, hyperlipidemia, and type 2 diabetes for the past 10 years and started to insulin therapy on the day of the

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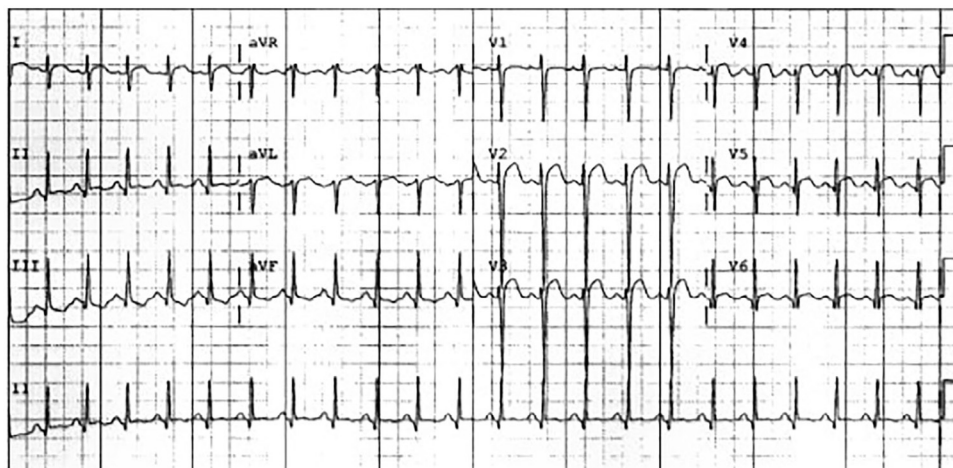


Fig. 1. Electrocardiogram demonstrating ST elevations in precordial leads in V1–V5.

ED presentation. The patient was treated with 1,000 mg twice a day for the control of hyperglycemia, which she took for 8 years. Other concomitant medications prescribed were; atorvastatin 10 mg daily, and ramipril 2.5 mg daily, tablet. Due to inadequate control of plasma glucose levels, fasting 305 mg/dL (normal 80–110 mg/dL) and postprandial 396 mg/dL (normal up to 140 mg/dL), she was advised to take subcutaneous injections of short-acting insulin morning, afternoon and before dinner and long-acting insulin at bedtime. Upon ED arrival, vital signs were as follows: temperature 37.2 °C, heart rate 102 beats per minute, blood pressure 150/70 mm Hg, respiratory rate 28 breaths per minute, and pulse oximetry 96% on room air. She had significant obesity (88 kg, BMI of 38.6). The blood glucose level in the ED was 115 mg/d L and the patient had no signs of hypoglycemia. On examination, she was noted to be in mild respiratory distress and urticarial rash on her face. There was no significant tongue swelling, edema of the uvula, or stridor. Cardiorespiratory exam was significant for tachycardia, tachypnea and expiratory wheezing. She had no history of coronary artery disease, or smoking. Her electrocardiogram showed ST segment elevations in leads V1–V5 (Fig 1). Transthoracic echocardiography, performed in the emergency department, revealed anterior wall hypokinesia with a left ventricular ejection fraction of 54%. Coronary angiography performed to exclude coronary artery disease, and revealed no sign of coronary atherosclerosis (Fig 2). Troponin-I estimated 4 hours

after admission was 7.4 ng/mL (reference: 0–0.1 ng/mL) and rose to 82 ng/mL. Creatine kinase-myocardial band (CK-MB) fraction estimated 4 hours after admission was 62 U/L (reference: 0–25 U/L) and rose to 102 U/L on the second day. Total immunoglobulin E estimated on arrival was 454 IU/mL (reference: 0–100), and serum tryptase was 44.5 mg/L (reference: 5.6–13.5 mg/L). The patient was diagnosed to have Kounis Syndrome type I variant, secondary subcutaneous recombinant human insulin injection. She was treated with aspirin, oral antihistamines (diphenhydramine 25 mg three times a day) and 8 mg of prednisolone every 6 hours for 5 days. Four days later, the repeated cardiac markers were within normal limits, with resolution of electrocardiographic abnormalities and anterior wall motion echocardiographic changes with a left ventricular ejection fraction of 62%. Intradermal skin testing by an allergist demonstrated positive reactions (wheal and flare) reactions to all insulin preparations tested. Skin prick testing for the compounds with the insulin allergy kit was negative. Insulin was discontinued and oral hypoglycaemic agents resumed in combination with intensified lifestyle management including diabetes self-management education, and support, medical nutrition therapy, physical activity, and psychosocial care. The patient was discharged from hospital in a good condition. There has been significant weight loss (79 kg, BMI of 34.6), and improvement in glycaemic control with no further allergic reactions at a 2-week follow-up visit.

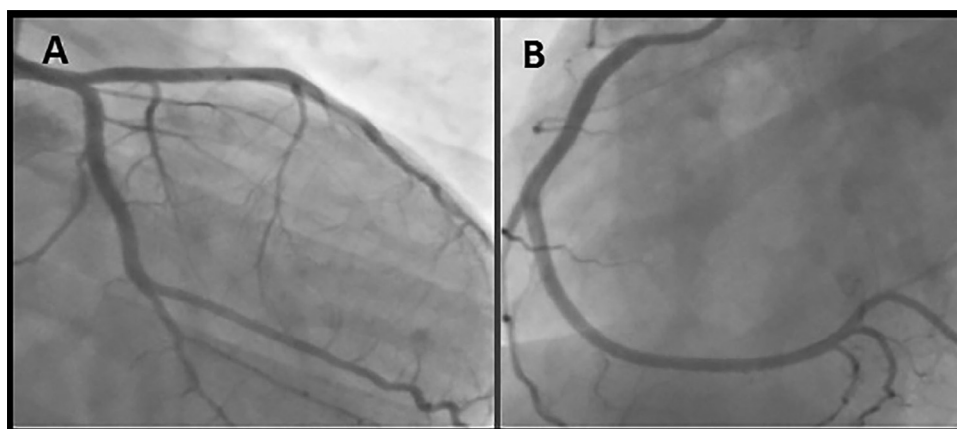


Fig. 2. Her left (A) and right coronary arteries (B) were normal in coronary angiography.

Discussion

To the best of our knowledge, this is the first case of Kounis Syndrome following the injection of subcutaneous recombinant human insulin. Kounis syndrome is a hypersensitivity coronary disorder induced by various types of exposures, drugs, conditions and stents.⁵

The diagnosis of Kounis Syndrome is based on clinical symptoms and signs as well as on laboratory, electrocardiographic, echocardiographic, and angiographic evidence. Careful review of clinical history, including medications and allergies, is always imperative. Cardiac symptoms include chest pain, palpitations and shortness of breath. Allergic manifestations such as skin rash, hives, and wheezes often happen. Cardiac troponin I or T, as well as cardiac enzymes (creatinine kinase, CK-MB) are important to diagnose the myocardium injury associated with the allergic insult. ECG usually shows ischemia with ST elevation myocardial infarction. Echocardiogram can also show regional wall motion abnormalities in the distribution of the affected artery. Kounis Syndrome has three variants; type 1 – coronary vasospasm; type 2 – coronary thrombosis; type IIIa: stent thrombosis due to allergy and type IIIb: stent restenosis due to allergy.⁶ The manifestations of Kounis Syndrome at initial presentation are broad and number of etiologic factors are continuously increasing but, allergic myocardial infarction due to insulin has not been reported before.

Insulin allergy is rare especially in patients with type 2 diabetes and its prevalence has been reduced after the introduction of new insulin analogs. However, it is still a major problem of management of diabetic patients and no effective strategy has yet been established.¹ Allergic reactions due to insulin can be type I or immunoglobulin E (IgE) mediated, type III or Arthus and type IV or delayed-type hypersensitivity reactions.¹ Allergy to insulin is usually occur immediately following the injection of insulin and in most cases, allergic reactions are restricted to the skin such as, induration, pruritus, and burning sensation. These skin reactions are often self-limited under continuation of therapy. However, systemic, potentially life-threatening reactions, such as urticaria, or anaphylaxis, have also been reported.^{2–4} Allergic reactions secondary to insulin can have many causes such as insulin molecule itself, or insulin contains additives such as cresol, phenol, and protamine that they may have allergic effects.¹

The first step should be the confirmation of the insulin allergy with the proper tests in patients present with cutaneous reactions to insulin injections. Diagnosis of type I reactions is based on clinical history, supported by specific skin tests, serologic tests, or both.⁷ Current guidelines for the management of anaphylaxis should be followed up for the treatment of allergic reactions.⁸ Airway, breathing, circulation, and level of consciousness should be immediately assessed. Patient should be placed in the recumbent position, and the lower extremities should be elevated. Oxygen should be administered to all patients with anaphylaxis who have prolonged reactions, have pre-existing hypoxemia or myocardial dysfunction. One to 2 L of normal saline should be administered to adults at a rate of 5 to 10 mL/kg in the first 5 minutes. Aqueous epinephrine in 1:1000 dilution (1 mg/mL), 0.2 to 0.5 mL (0.01 mg/

kg in children, maximum 0.3-mg dosage) should be administered intramuscularly or subcutaneously every 5 minutes, as necessary, used to control symptoms, and increase blood pressure.⁸ Initial management of insulin allergy includes the use of antihistamines, and switching to a different insulin preparation. In more severe allergic reactions, more than one antihistamine drug may be combined. Systemic steroid therapy may also be required. In patients with type 2 diabetes, discontinuation of insulin can be considered with a switch to oral hypoglycaemic agents and/or glucagon-like peptide 1 agonists. However, it is not possible to discontinue insulin in people with type 1 diabetes.

Our patient suffered a life-threatening systemic reaction and had positive cutaneous tests to all commercially available insulins. Therefore, we decided treat our patient with oral hypoglycaemic agents in combination with intensified lifestyle management. Although our strategy to avoid insulin and rely on oral antihyperglycemics seemed to be successful strategy in this patient, management strategies included use of insulin desensitization protocols, antihistamines, steroids, immunosuppressant/immunomodulator therapies, conversion to noninsulin therapies, and pancreas transplantation.⁹

Based on the clinical, laboratory, and electrocardiographic findings, the diagnosis of type I variant of Kounis Syndrome induced by insulin was made in our patient. The differential diagnosis of our patient may include insulin overdose, hypersensitivity myocarditis, Takotsubo cardiomyopathy, sepsis, status asthmaticus, panic attack, hypertensive emergency/urgency, Prinzmetal's angina, cocaine/amphetamine use, pheochromocytoma, etc. This case highlights the fact that physicians should be aware of allergic myocardial infarction. The diagnosis of this unique disease should be entertained when allergic symptoms, electrocardiographic changes, and high cardiac enzymes accompany acute-onset chest pain. All patients admitted to the emergency department with chest pain and ST elevation on electrocardiography should be asked about allergic insults.

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