Case Report

Exogenous recombinant human insulin-induced severe hypersensitivity reaction precipitating hyperglycemic crisis: A clinical conundrum

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Abstract

Hypersensitivity reactions against exogenous insulin are a rare clinical entity after the advent of recombinant human insulin; however, there are still case reports wherein patients develop hypersensitivity reactions against insulin. We present the case of a type 1 diabetes mellitus patient who developed type 1 hypersensitivity reaction against subcutaneous insulin. He had recurrent episodes of diabetic ketoacidosis after developing hypersensitivity reactions against insulin, requiring multiple hospital admissions. When he presented to us, he was on both insulin infusion and subcutaneous insulin, requiring a daily insulin dose of about 800 units and having severe insulin hypersensitivity reactions and hyperglycemia. He had multiple subcutaneous erythematous nodules at the insulin injection sites, however, had no evidence of systemic allergy. Investigations revealed eosinophilic leukocytosis, and high IgE levels and skin biopsy showing evidence of insulin hypersensitivity. He was desensitized to insulin according to Heinzerling *et al.* insulin desensitization protocol and subsequently with immunomodulation therapy using steroids (pulse methylprednisolone) and mycophenolate mofetil as well as by installation of insulin pump.

Keywords: Desensitization protocol, immunomodulation, insulin hypersensitivity, insulin pump

Introduction

After the introduction of recombinant human insulin, hypersensitivity reactions toward insulin, though rarely reported, can prove to be a clinical challenge.[1] Here, we present the case [reported after due clearance from the Institutional Ethics Committee (IRB No: 27719)] of a patient with type 1 diabetes mellitus, who developed allergy to exogenous insulin and was managed with immunomodulation therapy and insulin pump installation.

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Mr. S. F., a 37-year-old gentleman and a known patient of type 1 diabetes mellitus since 2 years, presented to our hospital with very high insulin requirements and history of allergic reactions induced by subcutaneous exogenous insulin, which was noticed by the patient since last 3 months. On presentation to our hospital, he was on intravenous regular insulin infusion and subcutaneous regular human insulin injections with a cumulative insulin daily requirement of 800 units/day. At the time of presentation, his blood glucose levels were 495 mg/dL, urine ketones test showed 4 + ketones, and arterial blood gas analysis showed a pH of 7.10 (normal 7.38–7.42) with bicarbonate levels of 12 mmol/L (normal 22–24 mmol/L), suggesting moderate diabetic ketoacidosis (DKA).

He was diagnosed with type 1 diabetes mellitus at the age of 35 years and was initiated on basal bolus regimen of

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thrice-daily injection Aspart (Novorapid) and bedtime injection Glargine (Lantus) which he continued for 1 year with an insulin requirement of about 70 units/day. For convenience, this was changed to subcutaneous premixed insulin twice daily in a dose of 36 units before breakfast and 24 units before dinner (injection Novomix 30/70, injection Aspart and Apart Protamine in the ratio of 30:70). After 3 months, allergic reactions were noted toward injection Novomix, which manifested as subcutaneous nodules and erythema at the sites of insulin injection over the anterior abdomen and the thighs, with associated itching without any other systemic complaints. Subsequently, thrice-daily subcutaneous injection Aspart (Novarapid), requiring more than 200 units/day, and twice-daily Glargine (Lantus), requiring more than 100 units/day, were restarted in place of premixed insulin, but the allergic reactions persisted with multiple episodes of DKA over the next 6 months. His insulin requirements exceeded 800 units/day requiring continuous insulin infusion, prior to referring to our hospital. On examination, his BMI was 14.8 kg/m^2 with no peripheral signs of insulin resistance. There were multiple subcutaneous nodules with induration and surrounding erythema at sites of insulin injection over the anterior abdominal wall and the anterior aspect of the thighs without any signs of localized infection or systemic illness.

Investigations revealed leukocytosis of 13,700/mm^3 (normal 4000–11,000/mm^3), eosinophilia (9%), and positive GAD antibodies [>2000 U/mL (normal <5 U/mL)] with normal liver, renal, and thyroid function tests. Serum IgE levels were high [333 U/mL (normal 5–100 U/mL)] while other autoimmune markers were negative. Patch test revealed allergy toward all the insulin preparations, including newer insulin analogues. He also underwent a skin biopsy from the allergic nodules, which showed deep dermal perivascular, periadnexal, and lobular panniculitic polyclonal plasma cell-rich infiltrate [Figure 1(a)] with evidence of small vessel vasculitis and superficial mild dermal mucin deposits [Figure 1(b)].

Analyzing the clinical and biochemical findings, this patient was diagnosed to have hypersensitivity to exogenous recombinant human insulin preparations with uncontrolled hyperglycemia. Initially, he was started on Glulisine insulin infusion (as it has least additives) along with antihistamines (fexofenadine 180 mg/day) with which his insulin allergy subsided but his insulin requirements exceeded 400 units/day. However, he experienced a recurrence of insulin allergy when concomitant subcutaneous insulin therapy was started.

Subsequently, he received the Heinzerling protocol of insulin desensitization[2] followed by pulse doses of intravenous methylprednisolone (1 g/day for 3 consecutive days) and subsequent oral mycophenolate mofetil [500 mg twice daily increased to 1 g twice daily] which was maintained.

In order to avoid exposure to high doses of insulin at a single point of time and optimize his insulin requirement, patient was initiated on an insulin pump delivering Glulisine, with which his insulin requirements stabilized (70 units/day) and no further hypersensitivity reactions occurred till discharge. Outpatient review after 3 months revealed him to be symptom-free and was continued on oral mycophenolate mofetil (2 g/day) and injection Glulisine through insulin pump.

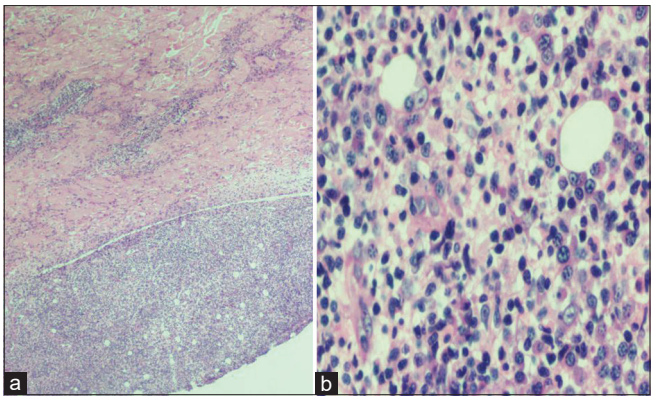

Figure 1: (a) Skin biopsy from the allergic nodules showing deep dermal perivascular, periadnexal and lobular panniculitic polyclonal plasma cell-rich infiltrate; and (b) skin biopsy of allergic nodule showing evidence of small vessel vasculitis and superficial mild dermal mucin d**eposits**
Picture courtesy: Dr.Meera Thomas & Dr. Jeseena Samuel, Dept. of pathology, CMC Vellore.

Discussion

Type 1 diabetes mellitus has shown an increasing trend since the early 2000s,[3,4] with an annual incidence of 2.8% in 1990–1999,[5] to about 3.4% in the 2000–2009 period.[6] The only treatment currently available for it is injectable insulin and can often prove to be a challenging condition to treat in a primary health-care setup because of the frequent fluctuations in blood glucose levels and increased propensity for uncontrolled hyperglycemia to develop into DKA. A number of coexisting conditions, including insulin allergy, can aggravate the risk for DKA in type 1 diabetes mellitus and a thorough knowledge of these factors is essential for the primary care physician to avoid the fatal consequences of DKA in them.

The clinical presentations of insulin allergy can vary from local erythema and swelling at the injection site to generalized reactions like urticaria and angioedema, rarely anaphylaxis and shock.[7] Insulin allergy can be type 1 or IgE-mediated reactions (commonest), type 3 or immune complex-mediated (Arthus reaction-localized or serum sickness-generalized) or delayed-type hypersensitivity reactions[8] with leukocytoclastic vasculitis allergy that can be toward insulin per se or toward the additives like zinc, protamine, latex, or cresol. Subcutaneous injections compared to intravenous route[9] and dose of subcutaneous insulin administered at a given time are determinants of insulin allergy, the latter reason explaining the benefit of insulin infusion in treatment of insulin allergy.[10] The diagnostic algorithm includes

eosinophil counts, intradermal skin testing, quantification of insulin-specific serum IgG and IgE, analysis time-dependent binding/dissociation curves of insulin-neutralizing antibodies in an ex vivo/in vitro assay[11,12], and skin biopsies from sites of hypersensitivity.

The management consists of anti-histaminics, switching of insulin preparations[13] and Heinzerling's desensitization protocol with gradual titration of the subcutaneous doses of insulin to the desired doses over a period of 2 days.[1] The initial dose of insulin used for desensitization is 0.00001 units, with progressive increase in the doses by 10-fold till 1 unit, and subsequent increase to 2, 4, 8, 12, 16, and 20 units. The last dose of insulin is repeated if allergy develops, till the allergic reaction settles, and then dose escalation is made to higher dose or the dose is halved if systemic reaction occurs. Our patient received this protocol over 48 h with concomitant tight glycemic control. Anecdotal reports of refractory cases describe the use of glucocorticoids, mycophenolate mofetil, azathioprine, methotrexate, or even rituximab or omalizumab[14] while pancreatic transplantation has been employed in life-threatening insulin allergy.[15]

Conclusion

As the incidence of type 1 diabetes mellitus is increasing globally, the primary care physicians shall be treating more number of cases of type 1 diabetes mellitus, and there is an increasing chance of seeing the complications of insulin therapy including the allergic reactions to insulin. It is very important to diagnose insulin allergy earlier, as there is a wide spectrum of signs and symptoms with which it can present. Insulin allergy should be a differential in any patient with diabetes mellitus with hyperglycemia despite being on high doses of insulin. As we have detailed in our manuscript, prompt diagnosis and earlier interventions shall keep the patient in euglycemia in a cost-effective manner. A thorough clinical evaluation, meticulous investigations, and multimodal therapy help in tackling this intriguing medical scenario.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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