Insulin Therapy: “When Saviour Turns Hostile”

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Abstract
Insulin is the cornerstone of type 1 diabetes mellitus (T1DM) treatment. Insulin allergy in patients with T1DM on insulin is an uncommon problem that might manifest itself as immediate or delayed symptoms after injections. We present 2 cases: the first is a 17-year-old girl who was diagnosed with T1DM at the age of 14 and has had several skin lesions at injection sites over the past 2 months that have not responded to antibiotics. The second case involves a 4-year-old boy who was diagnosed with T1DM at the age of 15 months and had non-tender, erythematous, and indurated lesions. Insulin hypersensitivity was detected in both cases, thus newer analogues were administered instead of regular and isophane insulin, and the lesions dramatically reduced.

Introduction
Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by a complete lack of insulin [1]. Because the pancreatic cells are irreversibly destroyed, lifelong insulin therapy is required to maintain sufficient metabolic regulation [2]. Insulin allergy symptoms can range from minor itchiness to life-threatening anaphylaxis [3, 4]. The prevalence of reactions with insulin therapy appears to be around 2%. Insulin therapy has been directly linked to less than a third of these reactions[5]. Hypersensitivity reactions to insulin have been divided into three groups based on the underlying pathophysiologic mechanisms. Rapid onset type I hypersensitivity is caused by immunoglobulin (Ig) E, while type III hypersensitivity caused by immune complexes (IgG and IgM) is the most prevalent, and type IV (T cell mediated) is a delayed reaction. Insulin allergy is one of many variables that contribute to poor adherence [6]. Type 1 hypersensitivity reactions are the most common among the documented cases of insulin allergy [5] Insulin allergy is one of the reasons that might lead to poor treatment adherence and sub-optimal glycaemic status.
Clinical Presentation

Case 1
At the age of 14, a 17-year-old girl born to consanguineous parents (first cousins) was diagnosed with T1DM and treated with Human Mixtard (Insulin Regular – NPH: 30/70) by a physician. She was referred to our centre 7 months after her diagnosis for treatment of severe diabetic ketoacidosis caused by 4 days of insulin omission. Her DKA was managed according to ISPAD guidelines, and once stable, she was switched over to a 1.2-unit/kg/day basal-bolus regimen (Regular Insulin and NPH). She also complained of redness at the injection site after each insulin administration. For the previous 2 months, she had developed several skin sores and open wounds on her abdomen and thighs. These lesions had previously been diagnosed as likely folliculitis by a general practitioner and treated for 10 days with oral antibiotics (amoxicillin-clavulanic acid) and local antibiotic treatment, with no improvement. Due to pain, she had started skipping the afternoon insulin dose. Further investigation revealed that the insulin storage mechanism was poor. Her insulin injection method was flawless. She had no known drug or food sensitivities.

Her vitals were stable and was moderately nourished on examination, BMI was 19.9 kg/m², weight was 47.3 kg (25–50th centile), and height was 154 cm (10–25th centile). The findings of the systemic examination were normal. Multiple tender, warm, indurated to ulcerated nodules with clear fluid discharge were found around the umbilicus and over the thighs, accompanied by hyperpigmentation and erythema (Fig. 1). Complete blood counts were found to be normal during the study. Her HbA1c was 14.4% (10.6% 3 months earlier). Total cholesterol was 202.8 mg/dL, triglycerides were 180.9 mg/dL, HDL cholesterol was 31.8 mg/dL, LDL cholesterol was 160.5 mg/dL, and VLDL cholesterol was 36.2 mg/dL. Urine microalbumin was 16.3 mg/mg of creatinine and TSH was 1.22 μIU/mL. Her retinal examination was normal. Only at the site of insulin delivery did the skin lesions appear. As a result, she was diagnosed with localized type 4 hypersensitivity and switched over to glargine instead of NPH. Mometasone ointment was prescribed for local use. A skin biopsy was recommended to rule out suppurative granuloma caused by insulin injection, but the patient did not give consent. After a month, the lesions had significantly diminished (Fig. 2), and she was transferred to insulin aspart and glargine.

Case 2
A 4-year-old boy with T1DM was diagnosed at 15 months of age and had been on basal-bolus insulin regimen with regular and NPH insulin for a year when he presented with non-tender, erythematous, indurated plaques, and clear fluid discharge from the insulin injection site (Fig. 3). His HbA1c level had risen from 9% to 11%. He began to have severe symptoms several hours after receiving subcutaneous insulin injections. The possibility of a delayed hypersensitive reaction to insulin administration was considered. Other systemic symptoms, such as fever, nausea, or anaphylactic reaction, were absent. Antihistamines and topical steroids were used to treat him. The insulin preparation was changed to a basal-bolus regimen using Lispro and Glargine. Symptoms subsided after 3 months, and glycaemic control improved with an HbA1c of 6%.
Discussion

The cases presented here show how insulin allergy can appear in a variety of ways in clinical practice. The diagnosis of insulin allergy was made based on the clinical picture and available information; however, a skin prick test or intradermal test is recommended for confirmation. Because of the practical constraints, a trial of a different insulin formulation could aid in diagnosis. Type IV hypersensitivity reactions appeared to be the cause of our cases.

Insulin allergy symptoms can appear right away or take a while to appear. Insulin hypersensitivity must be distinguished from injection site irritation. Injection site reactions can be avoided by optimizing the injection method. IgE-mediated responses occur quickly and might result in localized or systemic symptoms. They usually happen within an hour of receiving the injection [7]. Delayed reactions usually present after an hour of the injection as local eczematous or nodular skin changes which are usually not life threatening.

Because a sensitization period is required to generate insulin-specific IgE, type 1 hypersensitivity reactions to human insulin normally occur months or years after starting insulin therapy, while reactions can be observed even after the first few insulin injections [3]. IgE against insulin or other components of insulin preparations mediates type 1 hypersensitivity responses. Antigenic determinants in the recombinant proteins or the immunogenicity of one of the non-protein components can cause these reactions. Additives in insulin preparations, such as protamine, zinc, and cresol, have been shown to cause allergic responses [3]. Immediate reactions must be actively assessed and managed, as they tend to deteriorate over time.

The skin prick test is the first step in a skin test. It is carried out with the use of non-diluted insulin formulations. A wheal diameter over 3 cm is deemed positive. If the skin prick test is negative, an intradermal test can be performed, which involves applying serially increasing doses of diluted insulin solutions to the skin. The identification of specific IgE in the serum is also beneficial [8].

Suppurative granuloma (type 4 hypersensitivity) is caused by ruptured cysts/hair follicles, infections with deep mycoses, mycobacterium, and pyoderma gangrenosum. On biopsy, a suppurative granuloma has histiocytes surrounded by neutrophilic abscesses. Because the skin lesions in our patients were caused by the injection of recombinant human insulin, it is doubtful that the suppurative granuloma was caused by pyoderma granulosa or ruptured cysts. The alternative possibility is that human insulin crystals develop immunogenicity as a result of chemical changes in stored insulin, aggregation, or breakdown of administered insulin [9, 10]. Skin biopsy and immunohistochemistry staining can be used to diagnose type IV hypersensitivity reactions. Type IV hypersensitivity to insulin analogue has been treated with subcutaneous injections of dexamethasone and biphasic insulin aspart [11].

If a patient has an allergic reaction to the contents of an insulin preparation, switching to an insulin preparation that does not contain the triggering component can provide relief from symptoms [12]. Desensitization may be required for certain patients who continue to have symptoms after changing their insulin formulation. Insulin desensitization, which is normally conducted by allergy specialists, is well-tolerated and effective in a majority of patients. The use of an insulin pump is another option for people who have an essential need for insulin and who cannot be managed by switching to a different insulin composition [13].

Conclusion

In people with TIDM, insulin allergy is a difficult scenario to manage because insulin is the basis of the treatment. In the case of delayed hypersensitivity, a high level of clinical suspicion is required. Early action by the treating diabetologist, such as modifying the insulin formula-
tion, may bring relief to the patients and aid in greater adherence to medication, good glycaemic control, and the avoidance of unnecessary therapies.

**Statement of Ethics**

The research related to human use has been complied with all the relevant national regulations, institutional policies, and is in accordance with the tenets of the Helsinki Declaration. This case report does not require the approval of the Institutional Review Boards in our institute, but a written consent was obtained from the patients’ families. The patient provided written informed consent for the publication of this manuscript and any accompanying images.

**Conflicts of Interest Statement**

The authors have no conflicts of interest to declare.

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