

Case Report

Pan-insulin allergy and severe lipoatrophy complicating Type 2 diabetes

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Abstract

Background Insulin allergy is a rare complication of insulin use. Localized lipoatrophy is also known to occur following subcutaneous injections of insulin.

Case report A 53-year-old non-obese female patient with Type 2 diabetes displayed local allergic-type symptoms to all available insulin preparations. This was complicated by the development of severe lipoatrophy on her abdominal and thigh injection sites and subsequently resulted in suboptimal glycaemic control.

Conclusions Whilst uncommon, insulin allergy and lipoatrophy can cause major problems in diabetic management. Potential pathophysiological mechanisms and a stepwise approach to management are discussed.

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Keywords desensitization, diabetes mellitus, insulin allergy, lipoatrophy, skin-prick testing

Introduction

Insulin allergies range from localized skin reactions to systemic anaphylaxis. The reaction can be to the insulin itself or to components of the preparation, in particular zinc and protamine [1,2]. Insulin allergies were once very common: rates as high as 50–60% were reported in the 1960s. Whilst the current incidence of insulin allergies is not entirely clear, it is estimated to be less than 1–3% [3]. This dramatic fall in incidence represents the improvement in purification techniques and the move away from animal insulins to recombinant human insulins and insulin analogues. Insulin analogues in particular were heralded as a solution to insulin allergies and they were subsequently used as primary treatment [4,5]. However as the use of these analogues has increased, case reports of allergies to both short- and long-acting insulin analogues have been described [6,7]. Some cases do report patients having allergies to more than one form of insulin [8]—for example, an allergy to short and intermediate forms of insulin but not long-acting insulin [9], or positive skin-prick testing to all insulins, with the exception of insulin aspart [10]. We report an unusual case of a patient who displayed local

allergic reactions to all available preparations of insulin. This allergy was complicated by massive lipoatrophy affecting all injection sites.

Case report

A 53-year-old Indian woman developed gestational diabetes with her second pregnancy in 1990 and required subcutaneous insulin therapy with porcine insulin. Post-pregnancy she was converted to metformin and glimepiride. Her glycaemic control remained suboptimal: HbA_{1c} 9.4% (79 mmol/mol) despite maximal doses of oral hypoglycaemics, including the addition of rosiglitazone. Her BMI was 23 kg/m². She had background diabetic retinopathy. In November 2005 her HbA_{1c} was 13.5% (124 mmol/mol): she was converted to insulin therapy because of failure of oral agents. She was commenced on NovoMix® 30 (30% soluble insulin aspart and 70% protamine-crystallized insulin aspart; Novo Nordisk, Crawley, UK).

Within a few weeks she developed local reactions at the injection site. The area became intensely itchy and mildly erythematous a few minutes after the injection. Her blood sugars were erratic and she also experienced significant hypoglycaemia. As her glycaemic control remained sub-optimal, in August 2007 she was changed to a basal-bolus regime with rapid (NovoRapid®; Novo Nordisk) and long-acting insulins (Detemir—Levemir®, Novo Nordisk). She also started to develop lipoatrophy at the injection sites that

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persisted and progressed, despite rotation of injection sites. This led to profound lipoatrophy of her abdominal wall (Fig. 1).

Her injection sites were switched to the thighs where she also subsequently developed lipoatrophy (Fig. 2). Attempts at changing her insulin regime between March and September 2008 were to no avail as she continued to experience similar skin irritation and lipoatrophy with other analogue and human insulins including: Humalog® Mix 25 (25% soluble insulin lispro and 75% protamine-crystallized insulin lispro; Eli Lilly, Basingstoke, UK), insulin glargine (Lantus®; Sanofi-Aventis, Guildford, UK) and Human Mixtard® 30 (30% dissolved recombinant human insulin and 70% isophane insulin; Novo Nordisk, Crawley, UK). Each of these insulins was trialled for a few weeks individually. Her glycaemic control remained suboptimal, likely because of erratic insulin absorption.

In view of her ongoing local allergic-type symptoms, the subject was referred to a regional centre for immunological testing in December 2008. Skin-prick and intradermal testing revealed sensitivity to all available insulin preparations: insulin glargine (Lantus), insulin detemir (Levemir), human insulin (Actrapid®; Novo Nordisk, Crawley, UK), insulin aspart (NovoRapid), insulin lispro (Humalog) and Hypurin® porcine insulin (Wockhardt, Wrexham, UK). No reaction was seen with additives from the preparations.

Because of these dermatological complications and suboptimal glycaemic control, insulin was ceased in favour of the

incretin mimetic Byetta® (Exenatide; Eli Lilly, Basingstoke, UK), in conjunction with gliclazide and metformin. She initially responded well with improvement in her glycaemic control: HbA_{1c} 8.2% (66 mmol/mol). However, this effect lasted only for 6 months and in July 2009 she developed worsened primary symptoms of diabetes: weight loss of 6 kg, ketonuria and HbA_{1c} of 9.8% (84 mmol/mol). In view of these findings, it was considered that she had become insulinopaenic. As skin-prick testing had demonstrated allergy to all available insulin preparations, she was commenced on a continuous subcutaneous insulin infusion pump. Unfortunately, she did not tolerate the pump because of local site reactions and discontinued it after a week.

She was converted back to Humalog Mix 25 with meals, on a very small bolus doses, combined with gliclazide and metformin. Although she continues to experience local injection site symptoms, she has regained weight and her glycaemic control has marginally improved [HbA_{1c} 8.8% (73 mmol/mol)]. Avoidance of her abdomen as an injection site has largely resolved her abdominal lipoatrophy (Fig. 3).

Discussion

We hypothesize that our patient had two elements to her insulin allergy: the first was localized urticaria around the injection site



FIGURE 1 Severe lipoatrophy affecting the anterior abdominal wall as a result of subcutaneous insulin injections.



FIGURE 2 Lipoatrophic areas on the anterior and lateral aspects of both thighs.



FIGURE 3 Almost complete resolution of the subject's abdominal lipoatrophy is seen after the use of non-insulin therapies and use of other injection sites.

and the second was massive lipoatrophy. The localized urticaria represents a type I (immediate) hypersensitivity reaction: an immunoglobulin E (IgE)-mediated response which typically results in localized erythema around the injection site which resolves within a few hours. Occasionally, a systemic response may be triggered presenting as an anaphylactic reaction [11]. Whilst type III [12] (insulin-antibody complex formation) and type IV [13] (T-cell mediated) hypersensitivity reactions to insulin have been reported, they are less common.

Whilst anti-insulin antibody levels were not directly measured in our patient, up to 80% of patients treated with subcutaneous insulin may develop them [14,15]. Use of purified and recombinant human insulins, as well as insulin analogues, all lead to circulating insulin antibodies [16,17]. The clinical significance of these antibodies is less clear. The evidence connecting immunological responses to insulin and quality of glycaemic control, escalation of insulin dose and development of complications is weak [18]. Whilst case reports describing severe insulin resistance secondary to high antibody titres do exist [19], most studies suggest a lack of correlation between antibody levels and glucose control [18]. Indeed, both increased and decreased action of insulin has been described as a consequence of insulin antibodies [20]. As a result, our patient's local hypersensitivity reactions and positive skin-prick testing clearly demonstrate the negative consequences of the immune system's action on insulin, but we are unable to conclusively relate these phenomena with her poor glycaemic control and hypoglycaemic episodes.

Lipoatrophy describes the loss of subcutaneous adipose tissue around the sites of insulin injection and gives rise to both poor cosmesis and variable insulin absorption at that site. The profound skin changes in this patient caused significant psychological morbidity. Lipoatrophy has been reported with all preparations of insulin. It is more commonly seen in patients with Type 1 diabetes, but as demonstrated here, this is not always the case. The phenomenon is relatively poorly

understood: evidence from biopsy specimens suggests an immune-mediated process characterized by immunoglobulin deposits, eosinophilia and lymphoid activated mast cells [21–23]. It is not entirely clear how this immune reaction triggers loss of adipocytes. Some authors have suggested that the release of cytokines such as tumour necrosis factor alpha (TNF- α) may result in dedifferentiation of local adipocytes [24].

A stepwise approach to the management of insulin allergy has been described [25]. The first step is to assess injection technique and to define the patient's insulin allergy using intradermal testing. In confirmed insulin allergy, initial conservative management can entail switching to alternative insulins and dividing the doses between different injection sites. Similarly, management of lipoatrophy largely consists of rotating injection sites to allow regeneration of adipose tissue. However, insulin mixed with corticosteroids, or the topical mast inhibitor, sodium cromolyn have been tried in severe cases [23,26].

The use of the glucagon-like peptide-1 analogue, exenatide, may provide a useful tool in patients with Type 2 diabetes with insulin allergy. Indeed, whilst it provided a temporary relief in our patient, her development of insulinopaenia limited its utility. Definitive therapy can take the form of desensitization with slowly increasing doses of insulin, or continuous subcutaneous insulin infusions. Continuous subcutaneous insulin infusion involves the administration of short-acting analogues (such as insulin lispro) through an insulin pump. A number of case reports describe the successful use of both techniques [3,8,10,27]. In conjunction with definitive therapy, non-specific treatments such as anti-histamines and immunosuppressants [25] may be required. In some very severe cases of allergy, extreme measures have been resorted to, including the use of biologic agents (rituximab and omalizumab) [28] and even pancreatic transplant [29].

Conclusions

This case has highlighted a rare but important side effect of insulin therapy. Insulin allergies and severe lipoatrophy represent different aspects of malfunction in the immune system in response to exogenous insulin. They can lead to diabetic and psychological morbidity, especially when as severe and widespread as in this case. A literature review has demonstrated that a stepwise approach to the management of these allergies is required, but no clinical trials exist to guide clinicians in choosing definitive therapy for these patients.

Competing interests

Nothing to declare.

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