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Dr. Kavya. Jonnalagadda [α], Dr. Pranav. Jonnalagadda [σ] & Shreevikaa. Kannan [ρ]

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In this case report we elaborate on a case of a 32-year-old female with latent autoimmune diabetes in adults (LADA) who presented with episodes of itching and rash 20-30 minutes after injecting premixed analog insulin (Aspart and Degludec) at night for one week. During this time, her symptoms resolved with oral antihistamines and steroids. Notably, she had no prior history of allergies.

A skin prick test was done separately with Aspart and Degludec, given the suspicion of an insulin injection reaction. The test yielded an immediate positive result for Degludec. Additives such as zinc or metacresol present in Degludec are potential culprits behind the hypersensitivity reaction.

Diagnostic tests such as skin prick tests, intradermal skin tests, and serum IgE levels can confirm the diagnosis of insulin injection reactions (1). This case report highlights the importance of effectively diagnosing and managing insulin injection reactions.

Keywords: IgE-mediated, LADA, insulin injection reactions.

I. Introduction

From the introduction of human recombinant insulin preparations, insulin allergy has become rare, with a reported prevalence of approximately 2.4% (1). Insulin injection reactions can be classified as Type I or Type IV. Most reactions are immediate and mediated by IgE (1). Clinically, these reactions may manifest as swelling at the injection site, erythema, urticaria, angioedema, rhinitis, bronchospasm, or, in severe cases, anaphylaxis. (1)

Managing patients with insulin allergies, particularly those who are insulin-dependent poses significant challenges in achieving successful glycemic control. In this case report, we describe a 32-year-old female who developed an immediate allergic reaction to a premixed analog insulin preparation containing Aspart and Degludec.

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II. Case Report

A 32-year-old female with latent autoimmune diabetes in adults (LADA) was treated with multiple oral antidiabetic drugs in combination with four daily injections of recombinant human insulin. This regimen included one injection of intermediate-acting insulin at bedtime and three premeal injections of rapid-acting insulin. Despite dose adjustments based on her blood sugar levels and food intake, the patient experienced recurrent episodes of fluctuating blood glucose levels.

As a result, her treatment was modified to three injections: one premixed analog insulin injection before dinner and two injections of rapid-acting recombinant human insulin before breakfast and lunch. This adjustment successfully stabilized her blood glucose levels. However, the patient began experiencing rash and itching at the injection site 20–30 minutes after administering the dinner insulin dose. Figure 1 shows the rash that developed after injecting the night dose of insulin. Seeking dermatological consultation, she was prescribed antihistamines and steroids, which alleviated her symptoms. Other than the localized rash and itching, she had no systemic symptoms and no history of allergies.

The patient noted that these episodes consistently followed her evening insulin dose, prompting her to revisit the clinic with concern. To investigate a possible allergic reaction, a skin prick test was conducted separately with Aspart and Deglude . The test yielded an immediate positive result for Degludec, Figure 2 shows the rash that developed immediately after injecting Degludec during the skin prick test, confirming the diagnosis of Degludec-induced hypersensitivity. Figure 3 shows no rash at the site of the skin prick with insulin aspart.

Consequently, the patient was transitioned back to her prior basal-bolus insulin regimen. However, this led to spikes in her blood glucose levels. To optimize glycemic control, she was switched to three injections of rapid-acting insulin combined with a long-acting insulin (300 U Glargine). Given the synthetic nature of Glargine, there was a potential risk of an allergic reaction. Therefore, a skin prick test was performed before initiation, which showed no reactivity. The patient was subsequently started on Glargine along with rapid-acting insulin, achieving stable blood glucose levels without further hypersensitivity reactions.

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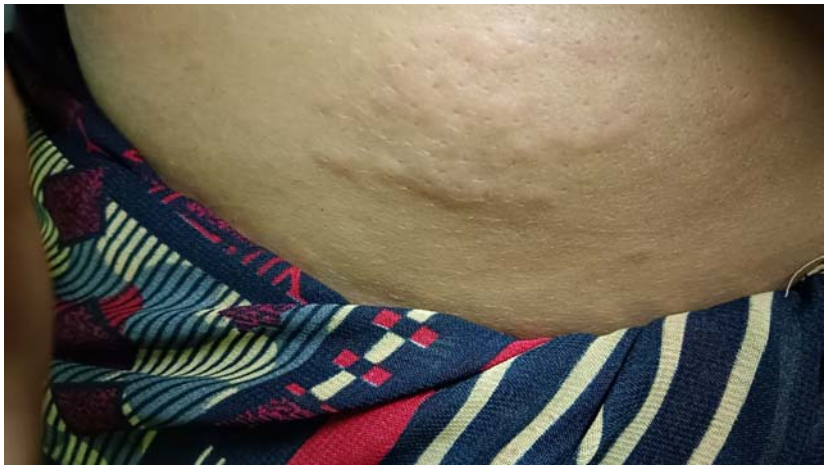

Fig. 1: Rash at the Site of Insulin Injection

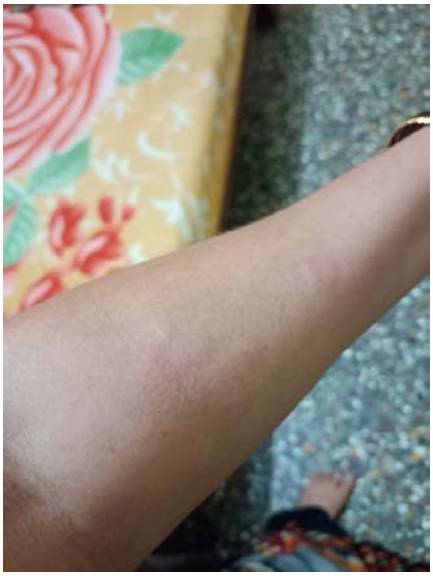

Fig 2: Skin Prick Test Showing Rash at the Site of Degludec Injection

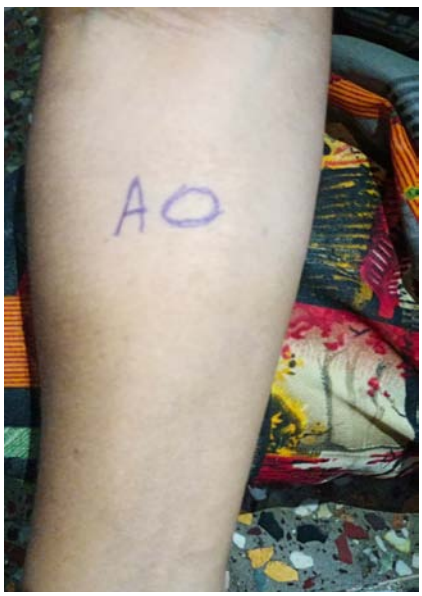

Fig 3: Skin Prick Test Was Not Showing Any Rash at the Site of Aspart Injection

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III. Discussion

The availability of recombinant human insulin and its analogs has revolutionized the treatment of diabetes, substantially decreasing immunogenicity that is linked to traditional animal-derived insulins. However, hypersensitivity remains a clinical challenge, particularly in insulin-dependent patients. This case report presents a rare instance of hypersensitivity caused by insulin degludec in a patient with latent autoimmune diabetes in adults (LADA).

IV. Trigerrs and Pathogenesis

Hypersensitivity reactions to insulin can be classified into two major categories: Type I and Type IV. Type I reactions are immediate and mediated by IgE, typically involving mast cells. Symptoms of Type I reactions include urticaria, pruritus, angioedema, and, in severe cases, systemic anaphylaxis. In contrast, Type IV reactions are delayed and T-cell-mediated. These reactions develop more gradually, usually presenting as localized erythema or induration, appearing several hours to days after insulin injection. (2)(3).

Type I hypersensitivity reaction is well demonstrated in this case by the rapid onset of symptoms (particularly, a rash and itching within 20 to 30 minutes of the injection) and positive results of the skin prick test for degludec. This type of hypersensitivity can be caused by the insulin molecule itself or additives like zinc, protamine, or metacresol. Degludec contains additives like metacresol and zinc, two common allergens that can cause allergic reactions (4).

V. Diagnostic Approach

The diagnosis of insulin hypersensitivity requires a detailed evaluation. The history and physical examination should be detailed to identify potential triggers, such as latex contamination of syringes or concurrent allergens. When diagnosing allergic reactions, skin tests-skin prick and intradermal tests-are the most appropriate methods (1). In this case, a skin prick test confirmed the immediate allergy to degludec. Measuring serum levels of IgE that are specific to insulin or its parts may also assist in making a diagnosis, but their practical use is limited (4).

VI. Management Approach

"Managing insulin hypersensitivity in insulin-dependent patients is particularly challenging, as discontinuation of insulin therapy is not an option. The primary objective is to maintain glycemic control while minimizing allergic reactions."

1. *Switching Insulin Formulations*

Rapid-acting insulin and glargine (300 U) were added to our patient's basal-bolus insulin regimen. Before starting glargine, a skin prick test was conducted to ensure its safety. Hypersensitivity is frequently resolved by switching insulin formulations with different excipients or by utilizing a different administration method (3).

2. *Desensitization Protocols*

Desensitization involves administering increasing dosages of the inciting insulin to produce immune tolerance. Although it works well in resistant cases, it is laborious and needs to be carried out under strict supervision in a hospital setting (1)(5).

3. *Adjunctive Therapies*

Acute allergic reactions can be alleviated by treating symptoms with corticosteroids and antihistamines. (1)(3). In our patient antihistamines adequately controlled the symptoms during hypersensitivity episodes.

4. *Alternatives*

Non-insulin therapies such as SGLT2 inhibitors or GLP-1 receptor agonists may reduce insulin needs and, hence, the risk of hypersensitivity reactions. Sometimes, hypersensitivity reactions may even be prevented by Continuous Subcutaneous Insulin Infusion (CSII) using an insulin pump (6). For patients with severe, recurrent allergic reactions, omalizumab can be considered, particularly after reducing IgE levels with B-cell-depleting monoclonal antibody Rituximab. When insulin allergies are more severe and unresponsive to these treatment options, the remaining therapeutic options are islet cell transplantation and pancreatic transplantation (1). Figure 4, gives a rough idea about evaluation of insulin allergy and its treatment (1).

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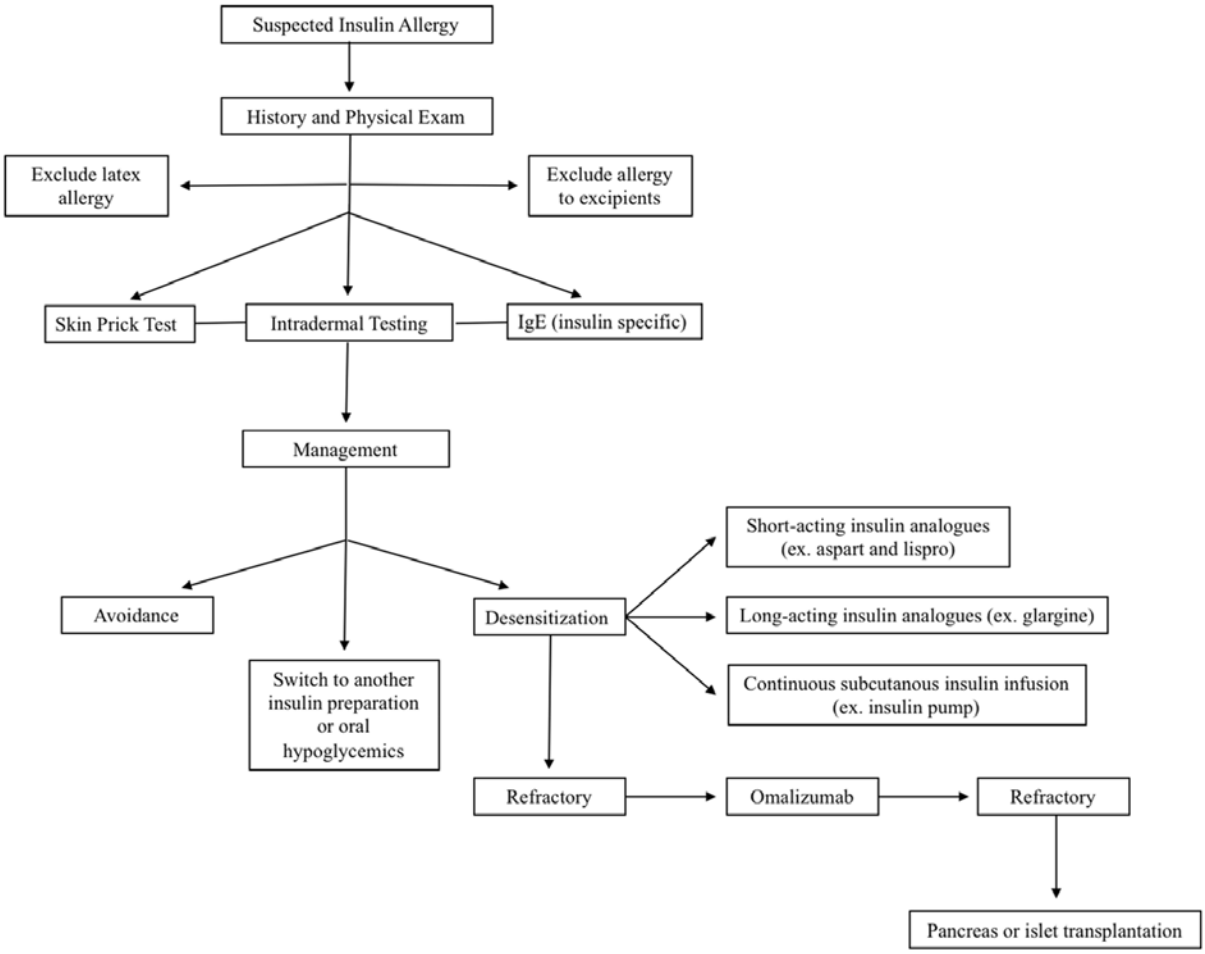

Fig 4: Flow Chart Showing the Evaluation and Treatment of Insulin Allergy (Sourced From Reference 1)

VII. Conclusion

This case underscores the importance of promptly recognizing and managing hypersensitivity reactions in insulin-treated patients. Although rare, such reactions can significantly perturb glycemic control and impair quality of life. A structured diagnostic approach-one that includes a thorough investigation of potential allergens, confirmatory skin tests, knowledge of alternative insulin formulations and adjunctive therapies will help clinician handle these challenges effectively.

Future Perspectives:

Further research is essential to deepen our understanding of the immunological mechanisms underlying insulin hypersensitivity, paving the way for the development of more targeted and specific insulin formulations. Investigating genetic predispositions, particularly those associated with human leukocyte antigen (HLA) variants, may offer valuable insights into individual susceptibility to hypersensitivity reactions. Additionally, advancements in the design of hypoallergenic insulin formulations-through techniques such as protein engineering or alternative delivery systems-hold significant promise for reducing the incidence of adverse reactions. Such progress could lead to improved clinical outcomes, enhanced patient adherence, and a better quality of life for those affected by insulin hypersensitivity.

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