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Case Report

Rituximab Therapy for Insulin Allergy in Type-1 Diabetes Mellitus

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ABSTRACT

Background/Objective: Allergic reactions to insulin have decreased significantly since the introduction of human insulin preparation, but up to 2.4% of insulin-treated patients can still be affected. Rituximab is a monoclonal antibody against the surface antigen CD20 on B lymphocytes, and it is largely used to treat lymphoproliferative and rheumatological conditions. In a very few published case reports, rituximab has been used as an investigational drug to treat severe insulin allergy refractory to conventional therapy. Here, we present an unusual case of a 40-year-old woman with T1DM and severe insulin allergy that was successfully treated with rituximab.

Case Report: The patient was diagnosed with T1DM at age 37. Three years later, skin reactions developed at insulin administration sites. These consisted of pruritic and painful erythema and wheals that appeared within 1 to 4 h of insulin administration, followed by induration, subcutaneous nodules, and surrounding lipodystrophy that lasted several days with spontaneous resolution in 1 to 2 weeks. Extensive immunologic evaluation suggested the reaction was related to insulin allergy. Skin biopsy revealed sublobular panniculitis. After failed conventional treatment with antihistamines, glucocorticoid, and various insulins, rituximab infusion as an investigational approach was initiated. This was very successful, leading to prolonged remission of her insulin allergy.

Discussion: First-line management of insulin allergy should focus on second-generation antihistamines and switching insulin preparation. In refractory cases, systemic immunotherapy with rituximab can be a viable option.

Conclusion: Practitioners should be aware that in patients with insulin allergy who fail conventional treatment, immunotherapy with rituximab can be a viable option.

Introduction

Prior to the 1970s, animal-sourced insulin preparations frequently caused skin reactions. With improved purification techniques and the advent of human insulin, the reported allergic reactions decreased significantly. However, up to 2.4% of insulin-treated patients can still be affected, with varied presentations from immediate type-1 IgE-mediated reactions to delayed type-3 immune complex-mediated and type-4 IgG-mediated reactions.[1] Interestingly, less than one-third of these reported events are related to the insulin molecules, with the remainder attributed to the noninsulin components such as zinc, protamine, and metacresol in the preservatives. In particular, type-4 reactions seem to occur with the noninsulin components, whereas the type-1 reactions seem to occur with both insulin and noninsulin elements.[2]

In many mild cases, conservative therapies can be effective at managing symptoms. However, more severe cases may require insulin desensitization to relieve allergic reactions.[3] Alternatively, systemic immunosuppression can be pursued. Rituximab is a monoclonal antibody against the surface antigen CD20 on B lymphocytes, and it is largely used to treat lymphoproliferative

Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis; GLP1-RA, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; SGLT2i, sodium-glucose cotransporter 2 inhibitors; T1DM, Type-1 diabetes mellitus; T2DM, type-2 diabetes mellitus.

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and rheumatologic conditions. In this case, we describe a young female with type-1 diabetes mellitus (T1DM) who experienced severe insulin allergy and was successfully treated with rituximab.

Case Report

A 40-year-old Caucasian female presented for care of T1DM. She was diagnosed with T1DM at age 37 with a presentation of diabetic ketoacidosis (DKA) and a hemoglobin A1c (HbA1c) of 9.3%. At that time, her C-peptide was 0.8 ng/mL (reference interval, 1.1-4.4 ng/mL), and Glutamic Acid Decarboxylase antibodies were positive at 10.4 U/mL (reference interval, 0-5 U/mL). Her body mass index (BMI) was 28 kg/m^2. She was initially treated with multiple daily injections of insulin glargine and aspart and was switched to pod insulin pump therapy 6 months later with an HbA1c range of 5.7% to 7.4%. Two years later, she experienced skin reactions at the pod insertion site, with pruritic and painful erythema and wheals that developed within 1 to 4 h of pod placement, followed by induration, subcutaneous nodules, and surrounding lipodystrophy that lasted several days with spontaneous resolution in 1 to 2 weeks (Fig. 1). Barrier adhesives, topical and oral antihistamines, and topical glucocorticoids were ineffective. She denied other past medical history except for nonspecific rash to sulfonamide antibiotic. She was not on any medications besides insulin. Pertinent family history included a maternal grandmother with type-2 diabetes mellitus (T2DM) and no known dermatologic or rheumatologic conditions.

Over the next 12 months, the patient was treated with insulin aspart, lispro, regular, and glulisine with similar skin reactions despite using syringe and pen injectors. Inhaled human insulin was implemented but discontinued due to cough. Her HbA1c remained in a range of 5.9% to 6.8% during this time, as the patient was motivated, able to self-titrate insulin, and used a Do-It-Yourself automated insulin delivery system with Pod pump and Continuous Glucose Monitoring.[4] She was then referred to a drug allergy clinic, where subsequent testing included a positive immediate intradermal insulin lispro test and negative metacresol skin test. Serum human insulin-specific IgG antibody testing was positive at 156 mg/L (reference interval, <20 mg/L), but IgE antibody testing was negative at <0.1 U/mL (reference interval, <0.1 U/mL). Skin punch biopsy revealed sublobular panniculitis (Fig. 2).

The patient was empirically treated with metformin, dapagliflozin, and liraglutide to reduce insulin needs with minimal improvement in skin reaction. Her insulin requirement decreased from an average of 60 units/d to 50 units/d, and she lost 12 pounds in 4 months. HbA1c remained in a range of 5.8% to 6.8%. Given the patient's long history of insulin pump use with continuous subcutaneous insulin infusion, it was felt that a desensitization approach would have been less effective than reported in literature, so an investigational approach with rituximab was considered. She was treated with weekly intravenous rituximab infusion at a dose of 375 mg/m^2 of body-surface area for 4 weeks. This dosing strategy was chosen as it had been previously empirically used for the treatment of insulin allergy.[5] The patient was premedicated with diphenhydramine and acetaminophen to reduce potential infusion-related reactions and closely monitored during and after rituximab infusion. She tolerated the treatment well, and her skin reactions improved significantly. Repeat serum human insulin-specific antibody testing 2 weeks after her fourth dose of rituximab revealed a lower level of IgG (122 mg/L) and undetectable IgE (<0.1 U/mL) antibodies. The effect of this first round of rituximab lasted 18 months until the injection site reactions recurred. A deeper punch biopsy of skin and subcutis was again consistent with sublobular panniculitis. She was treated with a second round of rituximab infusion using the same protocol, which again resulted in drastic improvement of her skin reactions. The effect of this treatment has been much more prolonged, with no recurrent skin reactions up to 4 years afterward.

Highlights

- Insulin allergy should have a thorough workup including serological and dermatological testing.
- Initial treatment consists of antihistamines, topical glucocorticoids, and changing insulin.
- Rituximab can be beneficial without systemic glucocorticoids when conventional therapy fails.

Clinical Relevance

Some providers may use systemic glucocorticoids for severe insulin allergy, but these can add difficulty in treating patients who are insulin-dependent. Cases such as this may bring attention to B lymphocyte-specific immunosuppression as a second-line therapy for patients with severe insulin allergy who are refractory to conventional therapies.

Discussion

Insulin allergy in insulin-dependent patients understandably creates a difficult clinical conundrum. In consideration of insulin allergy testing, intradermal skin testing has higher sensitivity compared to skin prick testing, but both should be interpreted in association with the clinical symptoms, as up to 40% of asymptomatic patients with diabetes may have a positive skin test or insulin-specific IgE antibodies, and false-positive skin test results have been noted in 28% of patients with low insulin-specific IgE titers.[6]

First-line management of insulin allergy includes using second-generation antihistamines and switching insulin preparation or administration method. In non–insulin-dependent patients, an attempt should be made to switch from insulin to noninsulin agents if good glycemic control can be achieved. Glucagon-like peptide-1 receptor agonists (GLP1-RA) have been used with efficacy in switching patients with type-2 diabetes mellitus (T2DM)

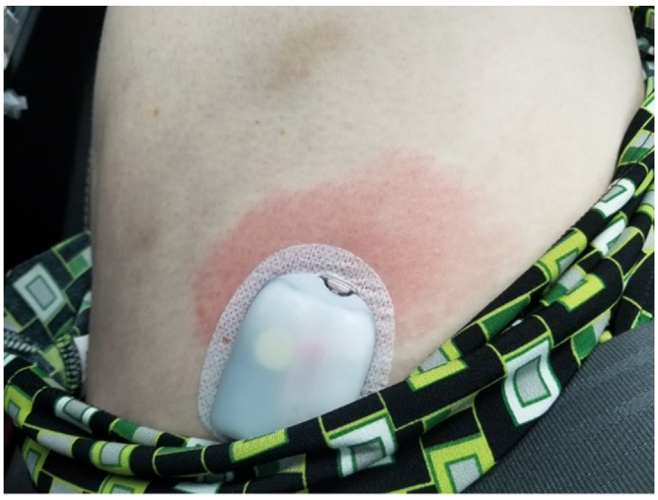

Fig. 1. Photos of the patient's skin rash with erythema, followed by nodules and induration at the insulin delivery sites.

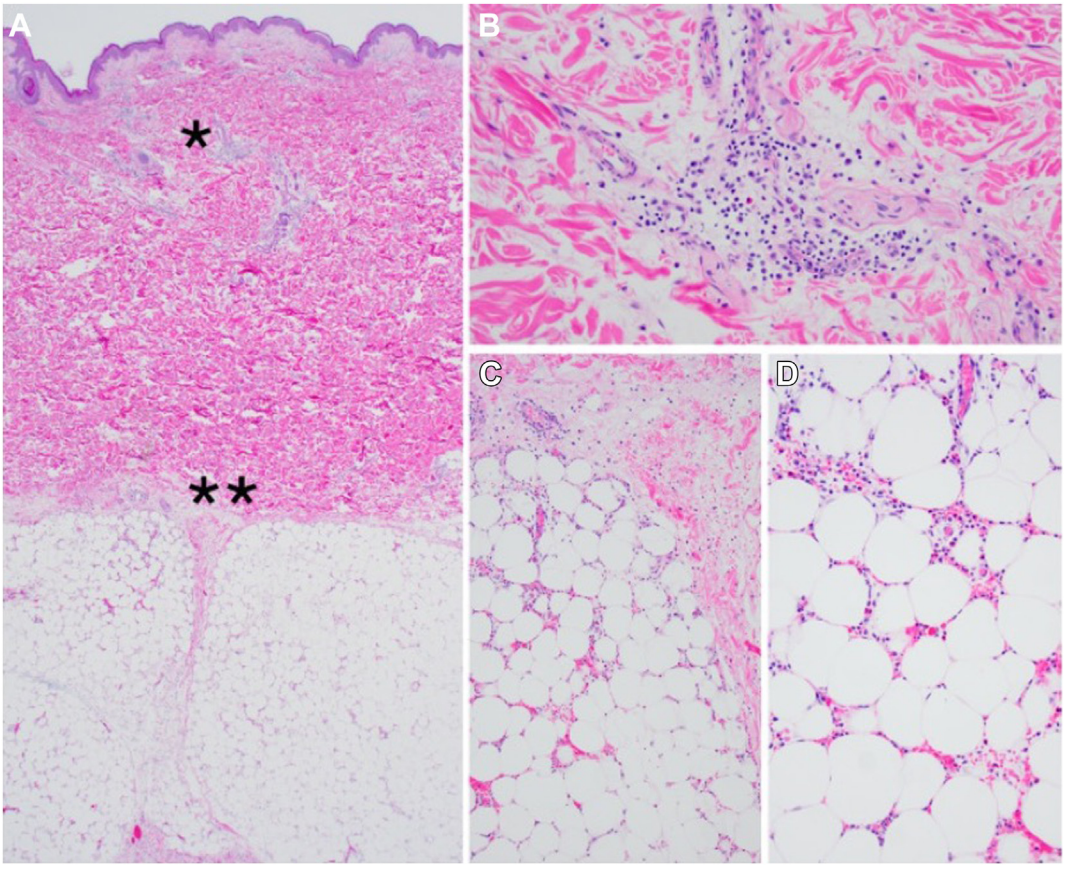

Fig. 2. *A*, Panel of micrographs from a Hematoxylin and Eosin (H&E)-stained slide from a skin and subcutis punch biopsy. Low-power (20×) view of the superficial and deep perivascular lymphoid inflammation with scattered eosinophils (asterisk) in addition to the mild mixed septal and lobular eosinophilic panniculitis (double asterisk). *B*, Medium-power (200×) view of the superficial and deep perivascular lymphoid infiltrate with scattered eosinophils along with dermal edema. *C* and *D*, Medium-power pictures (100×, *C* and 200×, *D*) of the mixed septal and lobular panniculitis with numerous eosinophils and scattered neutrophils, compatible with eosinophilic panniculitis.

and insulin allergy off insulin, but data are lacking in patients with T1DM.[7] Metformin, GLP1-RA, and sodium-glucose cotransporter 2 inhibitors (SGLT2i) are approved for use in patients with T2DM but have been used off-label in selected patients with T1DM for improving insulin sensitivity and reducing insulin requirements.[8,9] Due to this, we empirically used these agents in our patient, with close monitoring for potential side effects of gastrointestinal disturbance and DKA. For insulin dependent patients who fail first-line treatment of insulin allergy, tolerance induction can be pursued, and there are many case reports of successful treatment of insulin allergy with subcutaneous insulin desensitization infusion protocols.[10,11] Glucocorticoids in small doses have been shown to be effective in reducing local reactions during the desensitization phase, and gradual discontinuation was able to be achieved over a few months.[12] Due to the high risk of increasing insulin requirements and other side effects, systemic glucocorticoids are not recommended outside of the desensitization window.

When the above measures are insufficient, systemic immunotherapy can be a viable option. There have been rare case reports of using rituximab in patients with insulin allergy.[13] There have also been case reports of treating refractory insulin allergy with omalizumab, an anti-IgE monoclonal antibody.[14] In cases where serum IgE levels were too high for omalizumab use, rituximab has been given as initial therapy to deplete B lymphocytes and lower IgE levels, followed by mycophenolate mofetil and omalizumab treatment.[5] Rituximab monotherapy may also be considered when IgE levels are not elevated, as in our case. For both agents, there is no standardized protocol for administration given the rarity of the condition and lack of large data regarding their use. Our patient had been on long-term continuous subcutaneous insulin infusion therapy via insulin pump, so we felt an insulin desensitization approach would have been less effective than reported in the literature and made the decision to pursue rituximab treatment. Pancreas or islet cell transplantation can be considered if these measures fail but should be a last resort due to the risk of surgery and long-term complications.[15]

Our patient's insulin hypersensitivity reaction was more consistent with the delayed type-3 reaction (immune complex-mediated), as it developed 1 h or later after insulin administration with pruritic and painful rash, induration, and subcutaneous nodules. Her serum insulin-specific antibodies were negative for IgE but positive for IgG, which is also consistent with this form of hypersensitivity. Her prolonged response to the second round of rituximab is surprising, particularly without the need of introducing mycophenolate mofetil or another T lymphocyte inhibitor and warrants further study with long-term follow up. It is possible that her prolonged insulin pump infusion therapy played a role in desensitization, leading to long-term spontaneous remission years after rituximab treatment.

Conclusion

Insulin allergy is rare, and management can be very challenging, especially in insulin-dependent patients refractory to conventional treatment. Suspected patients with insulin allergy should have a thorough evaluation including skin allergy testing, serum insulin-

specific antibody assessment, skin biopsy, and exclusion of other skin disorders. Initial treatment approaches include switching insulin and its administration technique, antihistamines, short-term glucocorticoids, or even insulin desensitization in severe cases. However, systemic immunotherapy can also be a viable option. Our patient with T1DM and severe insulin allergy failed conventional treatment but was successfully treated with 2 rounds of rituximab infusion, with an effective and prolonged response. This adds to the small but growing body of literature supporting these novel therapies, but more research is needed to explore the mechanism of action and establish standard treatment protocols with the goal to achieve long term remission.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Aberumand B, Jeimy S. The complexities of insulin allergy: a case and approach. *Allergy Asthma Clin Immunol*. 2021;17:79.
2. Ghazavi MK, Johnston GA. Insulin allergy. *Clin Dermatol*. 2011;29:300–305.
3. Jacquier J, Chik CL, Senior PA. A practical, clinical approach to the assessment and management of suspected insulin allergy. *Diabet Med*. 2013;30:977–985.
4. Weedman BJ. You built a what?! Do-it-yourself automated insulin delivery systems. *AADE Pract*. 2019;7(5):24–31.
5. Yong PF, Malik R, Arif S, et al. Rituximab and omalizumab in severe, refractory insulin allergy. *N Engl J Med*. 2009;360(10):L1045–L1047.
6. Raap U, Liekenbröcker T, Kapp A, Wedi B. Delayed-type hypersensitivity to protamine as a complication of insulin therapy. *Contact Dermatitis*. 2008;53(1):57–58.
7. Matsumoto Y, Yamada H, Funazaki S, Suzuki D, Kakei M, Hara K. Effect of liraglutide on type B insulin resistance syndrome and insulin allergy in type 2 diabetes: a case report. *Diabetes Ther*. 2017;8:1191–1194.
8. Beysel S, Unsal IO, Kizilgul M, Caliskan M, Ucan B, Cakal E. The effects of metformin in type 1 diabetes mellitus. *BMC Endocr Disord*. 2018;18:1.
9. Edwards K, Li X, Lingvay I. Clinical and safety outcomes with GLP-1 receptor agonists and SGLT2 inhibitors in type 1 diabetes: a real-world study. *J Clin Endocrinol Metab*. 2023;108(4):920–930.
10. Tian K, Lee HY, Lim HB, et al. Rapid desensitization for insulin allergy in type 1 diabetes using an insulin pump: a case report and literature review. *AACE Clin Case Rep*. 2021;7:346–349.
11. Yuan T, Zhao W, Wang L, Dong Y, Li N. Continuous subcutaneous insulin infusion as an effective method of desensitization therapy for diabetic patients with insulin allergy: a 4-year single-center experience. *Clin Ther*. 2016;38(11):2489–2494.
12. Grant W, DeShazo RD, Frentz J. Use of low-dose continuous corticosteroid infusion to facilitate insulin pump use in local insulin hypersensitivity. *Diabetes Care*. 1986;9(3):318–319.
13. Harvey JN, Cronin M, Arkwright P. Insulin hypersensitivity in type 1 diabetes: investigation and treatment with immunodepletion. *Pract Diabetes*. 2020;37(2):59–61.
14. Mishra S, Connors L, Tugwell B. Role of omalizumab in insulin hypersensitivity: a case report and review of the literature. *Diabet Med*. 2018;35(5):663–666.
15. Leonet J, Malaise J, Squifflet JP. Refractory insulin allergy: pancreas transplantation or immunosuppressive therapy alone? *Transplant Int*. 2010;23(7):e39–e40.