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CASE REPORT

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# Ambulatory intravenous insulin and islet cell transplantation to treat severe type III insulin hypersensitivity in a patient with type 1 diabetes mellitus

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**Abstract**

Allogenic pancreatic islet cell transplantation is an appropriate treatment option to consider in the management of refractory cases of severe hypersensitivity to insulin in patients with type 1 diabetes mellitus.

**KEYWORDS**

allergy and immunology, endocrinology and metabolic disorders, transplant surgery

## 1 | INTRODUCTION

Insulin hypersensitivity reactions are relatively uncommon in current diabetes management, and most cases can be resolved through the implementation of simple management strategies. In rare cases where these interventions are unsuccessful, allogenic pancreatic islet cell transplantation should be considered a viable alternate treatment option.

Herein, we report a case of severe, type 3 hypersensitivity (T3HS) to subcutaneous insulin in a woman with type 1 diabetes (T1DM) that proved refractory to standard management. Ultimately, control was achieved using ambulatory intravenous insulin (IVI) infusion followed by allogenic pancreatic islet of Langerhans cell transplantation (ICT), the first reported the use of both approaches in this setting.

## 2 | CASE

A 35-year-old lady with long-standing T1DM reported a five-year history of increasingly severe, local reactions at subcutaneous insulin administration sites, characterized by painful and pruritic subdermal nodules up to several centimeter diameter. Lesions were raised, indurated and mildly erythematous, with a well-defined border (Figure 1A,B), developing within 30 minutes to 4 hours after insulin administration and resolving over weeks. There were no systemic symptoms.

Punch biopsy demonstrated a deep dermal abscess, accompanied by a mixed lobular panniculitis. Insulin IgG antibodies were significantly elevated (140.8 U/mL; reference 0.0-0.5 U/mL). The clinical and histologic features were most suggestive of T3HS with Arthus reaction. Symptoms necessitated change in continuous subcutaneous insulin infusion

(CSCII) cannula site 3-4 times daily and corresponded with a rise in HbA1c (Figure 1C) and recurrent hospitalizations for diabetic ketoacidosis. Subjectively, the patient reported substantial distress, sleep disturbance, and deterioration in quality of life.

Trials of all commercially available insulin preparations, use of oral antihistamines, and topical betamethasone were unsuccessful in achieving symptom control. Other strategies, including use of nafamostat, intramuscular insulin administration (painful muscular site reaction), oral prednisolone, co-administration of hydrocortisone and insulin via CSCII pump, and azathioprine were also ineffective. Desensitization using subcutaneous aspart over 2 days according to the Heinzerling protocol[1] failed, with recurrence of hypersensitivity on escalation to therapeutic doses.

Intravenous insulin was tolerated without hypersensitivity development during hospitalizations, ultimately prompting a trial of ambulatory IVI by portable infusion pump (Sapphire®, ICU Medical) via a peripherally inserted central cannula. Following education, the patient managed independently in the community with no observed reaction, nor other serious adverse events. After several months of IVI, hypersensitivity still recurred on retrial of subcutaneous administration.

Islet of Langerhans cell transplantation was undertaken 8 months later per the Australian Islet Consortium,[2] due to safety concerns with indefinite IVI use and absence of viable alternative strategies. Two separate islet infusions were administered via percutaneous portal vein puncture at 5-month intervals. Standard immunosuppression was administered (tacrolimus 0.1 mg/kg bid, mycophenolate mofetil 500 mg bd, plus induction with antithymocyte globulin 3 mg/kg for 5 days, and etanercept IV 50 mg at transplant and 25 mg days 3, 7, and 10). Following the first infusion (9218 IEQ/kg), a significant reduction in total insulin daily dose (75-16 units/d) and HbA1c (Figure 1C) was observed and subcutaneous insulin tolerance was restored. Insulin independence

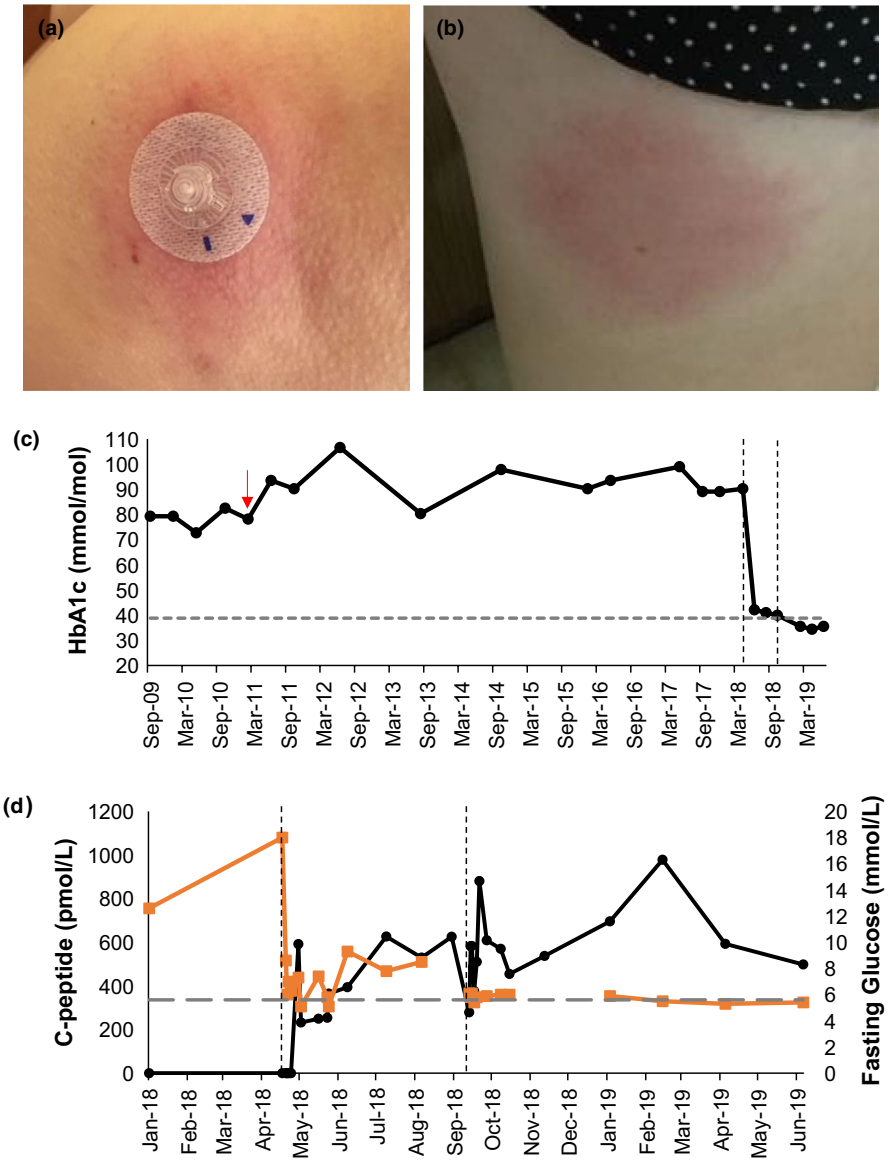


**FIGURE 1** A, Acute subdermal nodule appearance underlying a site of insulin administration via pump, with cannula in situ. B, Large nodule involving the posterolateral thigh. C, Patient's glycated hemoglobin (HbA1c) trend over time from prior to hypersensitivity onset to present. Red arrow indicates the approximate onset of hypersensitivity. Vertical interrupted lines indicate the timing of islet cell infusions. The HbA1c assay upper limit of normal (ULN) is indicated by the horizontal dashed line. D, Change in serum c-peptide (●) and fasting blood glucose (■) over time. Vertical interrupted lines indicate the timing of islet cell infusions. The upper limit of the normal (ULN) for fasting glucose is indicated by the horizontal dashed line

was achieved after the second infusion (6179 IEQ/kg), with normalization of fasting glucose and serum c-peptide (Figure 1D). The patient reports significant improvement in well-being and quality of life, remains insulin independent with a stable HbA1c, and is yet to encounter any complications more than 15 months after ICT (pancreatic islet of Langerhans cell transplantation). Immunosuppression has been maintained with tacrolimus (target 5-8 ng/mL) and mycophenolate mofetil.

## 3 | DISCUSSION

Insulin hypersensitivity is now a relatively uncommon problem with the use of human and analogue insulin preparations, and when occurs can usually be managed by changing insulin preparation, or symptomatic treatment with antihistamines or topical glucocorticoids.[3] More severe hypersensitivity reactions may require desensitization, systemic glucocorticoids, or immunosuppression for management.[3] T3HS reactions represent only a minority of insulin hypersensitivity presentations and may arise from reaction to insulin itself, its aggregates or other incipient agents.[4]

In our patient, standard treatment measures were ineffective. Desensitization, though efficacious for IgE mediated, immediate type-1 hypersensitivity (T1HS),[3,5] has been noted to be unsuccessful in other cases of T3HS.[5,6] Oral prednisolone doses up to 40 mg daily[5] have been reported as efficacious, but the use is typically described in conjunction with other interventions, such as insulin cessation,[7] change, or use of an alternate immunosuppressant.[5] Our patient received a relatively low prednisolone dose (10 mg daily), which may explain the absence of response to glucocorticoids. Adjunctive strategies as above were nonetheless either unsuccessful or inappropriate to implement in this case, and the hyperglycemic effects of glucocorticoids remain problematic for their utility as long-term treatment. Symptom control was only achieved for our patient with immunosuppression using a multiagent regimen associated with pancreatic islet of Langerhans cell transplantation.

Intravenous insulin appears to evade induction of hypersensitivity observed with subcutaneous administration, and as such, it is recommended for use during insulin desensitization to prevent ketoacidosis.[3] The explanation for these phenomena remains unclear. IVI may help to control glycemia in difficult cases of insulin hypersensitivity, but the use is typically confined to the hospital setting, due to issues including securing intravenous access, monitoring, and safety. This can contribute to prolonged hospitalization.[5] Ambulatory IVI has been reported in a single case of T1HS to subcutaneous insulin,[8] though our patient marks the first reported use for severe T3HS. IVI use was considered justified in our patient in spite of potential risks given the absence of reasonable alternative strategies and the significant morbidity attributable to the hypersensitivity reaction. The approach avoided lengthy hospitalization and permitted the patient to continue her normal lifestyle and maintain employment.

Transplantation of the total pancreas or islets has been proposed as a last line treatment option for insulin hypersensitivity,[3] though only a single case of whole pancreas transplantation has been reported for life-threatening hypersensitivity to insulin in T1DM.[9] There have been no documented cases of pancreatic islet of Langerhans cell transplantation for this indication. ICT (pancreatic islet of Langerhans cell transplantation) can restore quality of life and metabolic control in complicated T1DM. Severe and recurrent hypoglycemia in the absence of chronic renal failure is the most common indication. Compared to pancreas transplantation, ICT (pancreatic islet of Langerhans cell transplantation) is less invasive, has lower procedure-associated morbidity and differences in glycemic outcomes in terms of insulin independence and HbA1c control, and is narrowing.[10] Though transplantation necessitates long-term immune suppression, in the setting of severe insulin hypersensitivity where this is otherwise required, ICT (pancreatic islet of Langerhans cell transplantation) offers additional benefits to counterbalance-associated risks.

## 4 | CONCLUSION

This case highlights how insulin hypersensitivity, though uncommon, can pose a significant challenge and our experience demonstrates both the feasibility of ambulatory IVI use and supports severe, refractory insulin hypersensitivity as a rare, but important indication for ICT (pancreatic islet of Langerhans cell transplantation).

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### CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

### AUTHOR CONTRIBUTIONS

BC: was involved in the patient's management and is the primary author of the manuscript draft and revisions. PTC and DT: oversaw the patient's management and revised the manuscript. TL, TR, and CD: had major roles in facilitating the islet cell transplantation and reviewed the manuscript.

## CONSENT STATEMENT

Written informed consent was obtained from the patient, including permission to publish case details and photographs

## DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

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