

the lower, just above the ankles. On the soles, there were a few small bullous lesions (see Figures. 1 and 2).

Initial investigations only showed eosinophilia and a creatinine clearance of 35 ml/minute. Rest of the immunological workup, including anti DNA, ANA, and complements C3 and C4, were within normal limits.

The differential diagnosis that was considered initially was allergic reaction to aspirin, allopurinol, or hydralazine. Keeping this in mind, the first step was to withdraw all these drugs. Due to the polymorphic nature of the lesions, specially, vasculitic lesions autoimmune pathology was also on the list. As the patient gave history of the lesions appearing after taking insulin, allergy to insulin was a serious consideration.

All the possible inciting drugs, including aspirin, allopurinol, and hydralazine, were withdrawn. Moreover, the patient was also asked to put hold on finasteride and tamsulosin. The allergic reactions did not subside. Subsequently, insulin regimen was changed to a basal bolus combination comprising of glargine and glulisine. Unfortunately, patient reacted to this combination, hence, glargine was withdrawn first but when patient continued to have the reaction, glulisine was switched to as a part but to no avail. Even human regular insulin and lyspro were tried without any improvement. During this period, the patient was advised to be admitted for possible desensitization of insulin but the advice was not taken. As the glucose control was decompensated, in desperation gliclazide MR and vildagliptin were started and were quickly escalated to the maximum dosage. Despite this blood sugar remained high at 350–400 mg/dl. A trial of insulin

degludec (IDeg) was given after which the patient was admitted for desensitization. A small dose of four units was given which was tolerated without any undue reaction and all the skin lesions were subsided (Figures 3 and 4). The dose was later increased to 10 units which controlled the blood sugar very well along with vildagliptin for post prandial control.

Discussion

Insulin allergy is quite rare and there are no guidelines for managing these patients [1]. The clinical presentation can be very complicated as patients may be on multiple medications and there can be an overlap of multiple hypersensitivity mechanisms [1,2]. Presentation may occur several months or years after starting insulin therapy, or immediately after the first injection. Basal insulin glargine with short-acting analogues have both been utilized to treat insulin allergic patients [3–5]. This was the first strategy that was tried, unfortunately in the present case, reaction occurred to both glargine and all other available insulins. Patient was offered insulin desensitization as it is a good option for patients with multiple insulin allergies [6–8]. However, the patient refused to be admitted to the hospital. Subsequently, insulin was withdrawn, and patient was started on gliclazide MR and vildagliptin without any improvement in the blood sugar. The only insulin preparation that was remaining to be tried was IDeg. After initiating therapy with IDeg, there were no allergic reactions and the previous skin lesions subsided considerably. This may be due to the unique crystallized structure of IDeg which has the same amino acid sequence as human



Figure 1. Petechial lesions on the lower limb.



Figure 2. Vesico bullous lesions.



Figure 3. Healed lesions on the leg.



Figure 4. Healed lesion on the sole.

insulin except for the removal of threonine in the position 30 of the B chain and the attachment, via a glutamic acid linker of a 16-carbon fatty diacid (hexadecanoic diacid) to lysine in the position 29 of the B chain [9] (Figure 5). This alteration allows for the formation of multi-hexamers in subcutaneous tissues [10] which may have concealed its antigenic potentials.

To the authors' knowledge, this is the first case report that used a combination of IDeg insulin with vildagliptin a DPP4 inhibitor in a patient with type-2 diabetes with

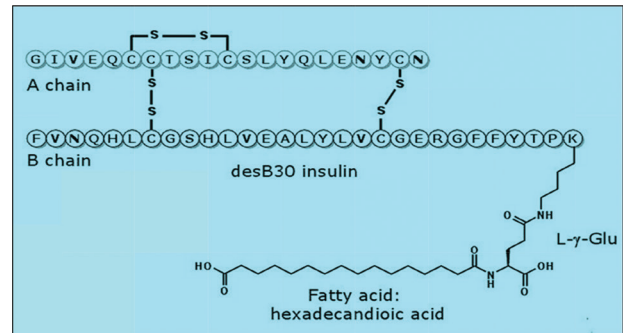


Figure 5. Molecular structure of IDeg.

decompensated glycemic control due to severe insulin hypersensitivity. This case identifies an innovative approach for managing a very difficult diabetic patient with multiple drug allergies, including most of the insulins and oral anti diabetic agents.

Acknowledgement

The authors would like to thank the support of the Medical Services, Department Armed Forces, Scientific Research Center in conducting this research.

List of Abbreviations

IDeg	degludec
ER	emergency room

Conflict of interest:

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Informed consent was obtained from the patient.

Ethical approval

Medical Services Department for Armed Forces, Scientific Research Center, Research Ethics Committee, Ref no RECT 2015, Reg No H-02-T-078, Date 11/3/2015.

Author details

Asim Hassan¹, Saud Al Sifri¹, Mohammed Bilal Jaja¹, Mohammed Motasim Ali Haj Elamin¹

1. Department of Diabetes and Endocrinology, Armed Forces Hospital AlHada, Taif, Saudi Arabia

References

- Heinzerling L, Raile K, Rochlitz H, Zuberbier T, Worm M. Insulin allergy: clinical manifestations and management strategies. *Allergy*. 2008;63(2):148–55. <https://doi.org/10.1111/j.1398-9995.2007.01567.x>
- Heinzerling L, Adkinson NF, Nathan DM, Feldweg AM. Hypersensitivity reactions to insulins. [cited 2019 Apr 3]. Available from: www.uptodate.com
- Hasani-Ranjbar S, Fazlollahi MR, Mehri A, Larijani B. Allergy to human insulin and specific immunotherapy with glargine; case report with review of literature. *Acta Diabetol*. 2012;49(1):69–73. <https://doi.org/10.1007/s00592-011-0254-4>

4. Fujikawa T, Imbe H, Date M, Go Y, Kitaoka H. Severe insulin allergy successfully treated with continuous subcutaneous insulin infusion. *Diabetes Res Clin Pract.* 2012;97(2):e31–3. <https://doi.org/10.1016/j.diabres.2012.04.027>
5. Petrovski G, Zivkovic M, Milenkovic T, Ahmeti I, Bitovska I. Successful desensitization in patient with type 2 diabetes with an insulin allergy using insulin pump and glargine. *Acta Diabetol.* 2014;51(6):1073–5. <https://doi.org/10.1007/s00592-014-0591-1>
6. Moyes V, Driver R, Croom A, Mirakian R, Chowdhury TA. Insulin allergy in a patient with type 2 diabetes successfully treated with continuous subcutaneous insulin infusion. *Diabet Med.* 2006;23(2):204–6. <https://doi.org/10.1111/j.1464-5491.2006.01811.x>
7. Radermecker RP, Scheen AJ. Allergy reactions to insulin: effects of continuous subcutaneous insulin infusion and insulin analogues. *Diabetes Metab Res Rev.* 2007;23(5):348–55. <https://doi.org/10.1002/dmrr.714>
8. Yokoyama H, Fukumoto S, Koyama H, Emoto M, Kitagawa Y, Nishizawa Y. Insulin allergy; desensitization with crystalline zinc-insulin and steroid tapering. *Diabetes Res Clin Pract.* 2003;61(3):161–6. [https://doi.org/10.1016/S0168-8227\(03\)00114-1](https://doi.org/10.1016/S0168-8227(03)00114-1)
9. Steensgaard DB, Schluckebier G, Strauss HM, Norrman M, Thomsen JK, Friderichsen AV, et al. Ligand-controlled assembly of hexamers, dihexamers, and linear multi-hexamer structures by the engineered acylated insulin degludec. *Biochemistry.* 2013;52(2):295–309. <https://doi.org/10.1021/bi3008609>
10. Nasrallah SN, Reynolds LR. Insulin degludec, the new generation basal insulin or just another basal insulin? *Clin Med Insights Endocrinol Diabetes.* 2012;5:31–7. <https://doi.org/10.4137/CMED.S9494>

Summary of the case

Patient	1	Male, 68 years
Final diagnosis	2	Insulin Allergy
Symptoms	3	Allergic reaction, maculopapular rash
Medications	4	Insulin degludec, vildagliptin
Clinical procedure	5	Insulin desensitization, oral medication
Specialty	6	Endocrinology