Delayed type hypersensitivity injection site reaction and tolerance induction to liraglutide for the treatment of obesity

Martina Yaneva, MD,[a] Teodora Handjieva-Darlenska, MD, PhD, DSc,[b] Jana Kazandjieva, MD, PhD, DSc,[c] and Razvigor Darlenski, MD, PhD, DSc[a,d]

Key words: adverse; allergy; GLP-1 agonist; skin test.

INTRODUCTION

Liraglutide is a glucagon-like peptide 1 receptor agonist used for the treatment of obesity, and type 2 diabetes and skin-related side effects are rarely reported. Here, we report a case of a delayed type of hypersensitivity reaction at the injection site and induction of tolerance to liraglutide.

CASE REPORT

A 39-year-old male White patient presented with obesity and a history of failure of nonpharmacologic strategies for weight reduction and was treated with liraglutide administered subcutaneously. The initial dose of liraglutide (approved for obesity treatment with a daily dose of 3 mg) 0.6 mg daily was increased weekly by 0.6 mg to the therapeutic dose of 3 mg daily. On reaching a daily dose of 1.8 mg, pruritic erythematous patches appeared on the injection sites 1 day after the medication application. The itch was negligible for the patient, and he continued the drug administration reaching 3 mg/d.

The clinical examination revealed round erythematous plaques on the abdomen at the injection sites of liraglutide (Fig 1, *A*).

The patient did not report any allergies, previous history of atopy, or concomitant disease beyond obesity, class 2 and a body mass index of 39.2 kg/m^2.

Patch test with European baseline series, propylene glycol (5% in petrolatum) (Chemotechnique Diagnostics), as well as liraglutide (6 mg/mL; aqueous solution and in petrolatum), was conducted on the back and the abdomen (on a site of receding lesion of the abdomen), but no positive reaction was noted during the readings of days 2 and 3. Skin prick test with liraglutide (6 mg/mL; aqueous solution) yielded a negative result. Intradermal test with liraglutide (6 mg/mL) diluted 1:10 in saline was negative at the 20th minute and positive at the 24-hour reading (Fig 1, *B*).

The same concentration intradermal test was performed in 5 healthy controls and all results were negative. The patient refused skin biopsy and histopathologic examination because of benign course and the complete healing of the skin lesions.

Based on the clinical presentation of the skin lesions and the tests performed, a diagnosis of delayed hypersensitivity to liraglutide was rendered. Symptomatic treatment was administered with a twice-daily application of clobetasol propionate ointment 0.05% for 2 weeks, followed by 30 days of once-daily mometasone furoate ointment 0.1% use. The patient continued his treatment with liraglutide 3 mg/daily. He was able to tolerate the drug without any skin reaction at the end of the treatment and during the 6-month follow-up.

DISCUSSION

Liraglutide is a glucagon-like peptide 1 receptor agonist used for the treatment of obesity and type 2 diabetes. Side effects are mainly from the

From the Department of Dermatology and Venereology, Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria[a]; Department of Pharmacology and Toxicology, Medical University of Sofia, Sofia, Bulgaria[b]; Department of Dermatology and Venereology, Medical University of Sofia, Sofia, Bulgaria[c]; and Section of Dermatovenereology, Trakia University, Stara Zagora, Bulgaria.[d]

Funding: None.

IRB approval status: Not applicable.

Correspondence to: Martina Yaneva, MD, Department of Dermatology and Venereology, Acibadem City Clinic Tokuda Hospital, 51B Nikola Vaptsarov blvd., 1407 Sofia, Bulgaria. E-mail: yaneva.martina@yahoo.com.

JAAD Case Reports 2023;38:100-1.

2352-5126

https://doi.org/10.1016/j.jdcr.2023.06.010

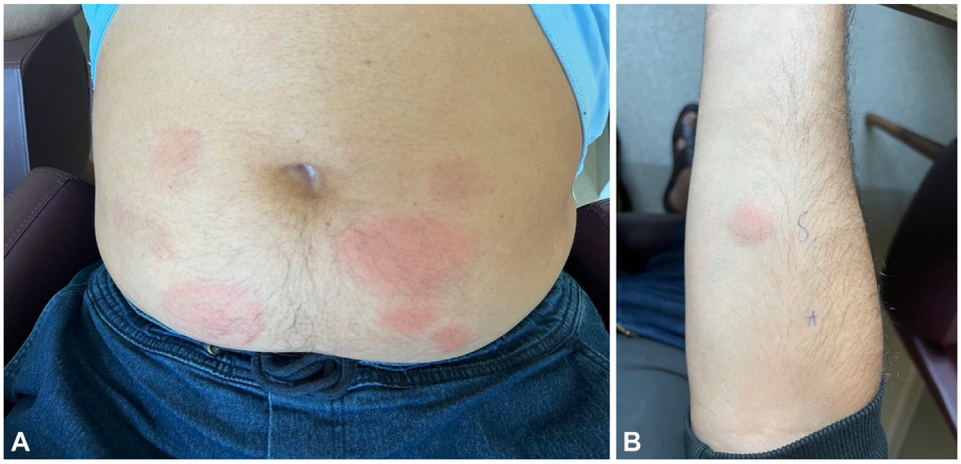

Fig 1. A, Round erythematous plaques at the injections site of liraglutide. **B,** Positive delayed reaction of the intradermal test to liraglutide.

gastrointestinal tract, and only several cases of adverse skin reactions have been reported in the literature. A vesiculo-pustular rash,[1] acute exanthematous pustulosis,[2] and generalized erythematous plaques and nodules[3] associated with liraglutide treatment have been described. Injection site reactions are listed as adverse drug reactions of liraglutide (for obesity or diabetes indications); however, the product information does not specify whether these can be delayed or immediate onset.[4] Injection site reactions include hemorrhage, deep nodular infiltrate, and pruritic erythematous macules.[5,6] Only a single case of delayed hypersensitivity to liraglutide has been published, confirmed by a skin test.[7] We would recommend intradermal test as a first-line test in the diagnosis of cases with suspected delayed liraglutide hypersensitivity.[8] The explanation for the negative patch test could be the large size of the drug molecule (3751 Da), which cannot penetrate the skin barrier permeable for molecules <500 Da.[9] On the other hand, the short contact time and the small concentration of tested drugs could result in a negative prick test. No positive prick test to liraglutide has been documented, despite the observations of such to other glucagon-like peptide 1 receptor agonists, such as exenatide and lixisenatide.[10]

Conflicts of interest

None disclosed.

REFERENCES

1. Besemer F, Verschoor AJ, Diamant M, Hoogma RP. Vesiculopustular dermatosis: an uncommon side-effect of liraglutide? *J Diabetes Complicat*. 2012;26(5):458-459. https://doi.org/10.1016/j.jdiacomp.2012.05.018
2. Cogen AL, Desai K, Elder D, Rosenbach M. Acute photodistributed exanthematous pustulosis associated with liraglutide treatment. *JAMA Dermatol*. 2019;155(10):1198-1200. https://doi.org/10.1001/jamadermatol.2019.1893
3. Bovijn L, Arianayagam S, Asher R. An unusual case of a generalised cutaneous drug reaction to liraglutide. *Eur J Dermatol*. 2019;29(6):675-677. https://doi.org/10.1684/ejd.2019.3691
4. Food and Drug Administration, ed. *Saxenda Prescribing Information*. ed2014. Food and Drug Administration; 2014.
5. Neel N, Ghobara Y, Turkmani M. Liraglutide-induced injection site reaction (case report). *J Dermatol Dermatolog Sur*. 2019;23(2):97-98. https://doi.org/10.4103/jdds.jdds_5_19
6. Jaworecka K, Pojawa-Gołąb M, Otto-Buczkowska E, Reich A. Injection site reaction during liraglutide therapy. *J Dermatol Plast Surg*. 2019;3(1):1023.
7. Carvallo A, Silva C, Gastaminza G, D'Amelio CM. Delayed hypersensitivity reaction to liraglutide: a case report. *J Investig Allergol Clin Immunol*. 2020;30(5):367-369. https://doi.org/10.18176/jiaci.0521
8. Saff RR. Skin testing as a biomarker in drug allergy. *Ann Allergy Asthma Immunol*. 2023;130(2):161-168. https://doi.org/10.1016/j.anai.2022.10.006
9. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol*. 2000;9(3):165-169. https://doi.org/10.1034/j.1600-0625.2000.009003165.x
10. Shamriz O, NaserEddin A, Mosenzon O, Sviri S, Tal Y. Allergic reaction to exenatide and lixisenatide but not to liraglutide: unveiling anaphylaxis to glucagon-like peptide 1 receptor agonists. *Diabetes Care*. 2019;42(9):e141-e142. https://doi.org/10.2337/dc19-0720