Case Reports in Ophthalmology

Case Rep Ophthalmol 2024;15:246–249
DOI: 10.1159/000537872
Received: August 8, 2023
Accepted: February 14, 2024
Published online: March 19, 2024

Case Report

Severe Hyperglycemia with Teprotumumab for Treatment of Thyroid Eye Disease

Savannah Cottom[a] Brayden Barrientez[b] Andrew Melson[b]

[a]College of Medicine, University of Oklahoma, Norman, OK, USA; [b]Department of Ophthalmology (Dean McGee Eye Institute), University of Oklahoma, Norman, OK, USA

Keywords
Thyroid eye disease · Teprotumumab · Hyperglycemia

Abstract
Introduction: Thyroid eye disease (TED) is a rare condition involving autoimmune-mediated inflammation of the orbit and periocular structures, which can result in many debilitating symptoms. Teprotumumab, a monoclonal antibody that targets the insulin-like growth factor 1 receptor, is gaining popularity for the treatment of TED. In fact, owing to its efficacy and side effect profile, some recommend that it be considered as a first-line therapy for patients with TED. While teprotumumab is often chosen due to its efficacy and relatively favorable side effect profile compared to other treatments, there is a known risk of hyperglycemia with this mechanism of action, which is well described through clinical trials in the oncology literature. Though all cases in the clinical trial study of teprotumumab were mild, there is growing evidence that its effect on blood sugar can be more profound. ***Case Presentation:*** We present a case of a well-controlled, recently diagnosed type 2 diabetic placed on teprotumumab for treatment of TED who developed life-threatening hyperglycemia. The case report provides evidence of hyperglycemic risk, as it highlights a patient's significant increase in hemoglobin A1C to 15.4 in addition to elevated serum glucose of 954 mg/dL while receiving teprotumumab. ***Conclusion:*** This case of severe hyperglycemia accentuates the need for more diligent, if not universal, glucose monitoring during teprotumumab treatment.

Correspondence to:
Savannah Cottom, Savannah-Cottom@ouhsc.edu

Case Rep Ophthalmol 2024;15:246–249
DOI: 10.1159/000537872

Introduction

Thyroid eye disease (TED) is a complex autoimmune disease that affects the orbit and surrounding structures. Often manifesting as enlargement of the extraocular muscles and proptosis, it can affect gaze, alignment, diplopia, keratopathy and may progress to a sight-threatening and disfiguring disease [1]. Treatment of TED may involve a multidisciplinary approach including ophthalmologists, endocrinologists, radiologists, primary care physicians, and more. As knowledge of the pathogenesis of the disease progresses, more options for treatment including pharmacological, surgical, and general supportive treatments are being explored. The field of immunomodulatory agents for medical treatment of TED has expanded the options for treatment. This case describes treatment of TED with the monoclonal antibody agent teprotumumab in a patient who subsequently developed severe hyperglycemia.

Case Presentation

Our patient is a 72-year-old woman with TED who had previously been treated for restrictive strabismus 2 years prior with eye muscle surgery. She presented to clinic with recurrent diplopia, orbital pain at rest and with extraocular movements, caruncular inflammation, and conjunctival injection. A TSI was obtained and was elevated at 5.25 IU/L. A CT scan of the orbits showed enlarged extraocular muscles with sparing of the tendons. Given the patient's clinical activity score (CAS) and elevated thyroid-stimulating immunoglobulin, the various treatment options for TED were presented, and the patient elected to proceed with teprotumumab as first-line treatment.

After three uneventful infusions, the patient called in to the office, requesting that she discontinue further teprotumumab infusions due to fatigue for the past week. She was seen the same day in clinic where she reported polydipsia and polyuria, was lethargic, and had difficulty ambulating to the exam chair. A fingerstick blood glucose was checked by glucometer in the clinic and was undetectably high. Given this finding, she was urgently referred to the adjacent emergency room for further evaluation.

In the hospital, the initial blood glucose test was again above the upper reporting limit at greater than 600 mg/dL. Formal laboratory testing identified her blood glucose at 954 mg/dL. She had a beta-hydroxybutyrate of 3.78 mmol/L, a venous blood gas pH of 7.34 with an anion gap of 21, a venous blood gas bicarbonate of 24 mmol/L, and a serum osmolality of 310 mOsm/kg. These findings indicate that the patient was in a severely hyperglycemic state with mild acidosis and ketone production. The patient was admitted to the intensive care unit with careful lowering of the blood glucose levels with insulin and electrolyte monitoring. Blood glucose levels were appropriately lowered without rapid overcorrection.

During her hospitalization, a hemoglobin A1C was obtained and found to be 15.4. This value was remarkably higher than the pretreatment A1C of 6.8 just 2 months prior. As the hemoglobin A1C value is the average of blood sugar levels over 3 months, this drastic increase emphasizes how much her blood sugars had increased since starting teprotumumab. She was discharged on insulin, with close follow-up with her primary care physician and no further teprotumumab infusions. At 4-month follow-up, the patient reported that she was doing well on insulin and decreasing the dose. There were no additional adverse events reported.

Discussion

While the pathophysiology of TED is not fully understood, it is known to be mediated by fibroblast activity in the orbit, resulting in deposition of glycosaminoglycans and tissue swelling [2]. The insulin-like growth factor 1 receptor has been shown to stimulate both

fibroblasts and TSH. These studies made teprotumumab a viable target in the treatment of TED, which would eventually lead to its landmark trial.

Teprotumumab's most common side effects include muscle cramps, tinnitus, hearing impairment, alopecia, and hyperglycemia [3]. Hyperglycemia from teprotumumab has been attributed to insulin-like growth factor 1 receptor and the insulin receptor being "partially homologous," resulting in insulin resistance and increased blood glucose [4]. Alternatively, teprotumumab may cause hyperglycemia through dysregulation of growth hormone, resulting in gluconeogenesis and insulin resistance [5]. Most previously reported cases of hyperglycemia have been relatively mild. In the phase 1 trial of teprotumumab in treatment of TED, hyperglycemia was found to be less than 5%; in both cases, the hyperglycemia was mild [3]. In the phase 2 and phase 3 trials, hyperglycemia was reported at 10%, none of which resulted in the discontinuation of teprotumumab.

It stands to reason that underlying insulin resistance may make patients more susceptible to the hyperglycemic effects of teprotumumab. A recent study of 41 patients at a single academic institution found an average hemoglobin A1C increase of 0.5 at 3 months after infusion, with Asian or Hispanic ethnicity, age, and preexisting diabetes as risk factors for a worse A1C [6]. Recently, there has been a case of reported hyperglycemic, hyperosmolar state in a patient with TED after taking teprotumumab [7]. Our case report strengthens the growing evidence of hyperglycemic risk by highlighting our patient's significant increase in hemoglobin A1C in addition to elevated serum glucose levels. A limitation of this case is that it is a single case, representing the experience of 1 patient.

It is important to remember that while teprotumumab may have a higher risk profile than previously thought, the alternative treatments for TED also carry risk of significant side effects. Oral steroids have been reported to cause hyperglycemic hyperosmolar syndrome as well, with fatal cases reported in treatment of Vogt-Kayanagi-Harada syndrome and iridocyclitis, entities known well to ophthalmologists [8]. Other biologics used to treat TED can cause robust immunosuppression and susceptibility to infections.

No formal recommendations for monitoring hyperglycemia in patients receiving teprotumumab are identified on the medication label. Informal recommendations have been suggested such as checking a fasting blood glucose after each of the first two infusions, with self-monitoring at least twice a day, in patients with diagnosed diabetes [9]. Others recommend adequate blood sugar control before the start of infusion, with a hemoglobin A1C at least less than 8.5, ideally lower than 7 [4]. Interestingly, the patient detailed above qualified as well controlled, yet still went on to develop severe hyperglycemia. Perhaps future research can help elucidate which patients are at greatest risk of extreme hyperglycemia. In the meantime, we agree with more diligent, if not universal, glucose monitoring during teprotumumab treatment, given our patient's experience and the growing evidence of the effect of teprotumumab on blood glucose. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537872).

Statement of Ethics

Research ethics board approval was not required by the University of Oklahoma Institutional Review Board. Ethical approval was not required for this case report in accordance with the local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors report that there are no competing interests to declare.

Funding Sources

The authors received no financial support for the research, authorship, or publication of this manuscript.

Author Contributions

Savannah Cottom and Brayden Barrientez: manuscript design, data collection, and final approval; Andrew Melson: critical revisions and final approval.

Data Availability Statement

The authors confirm that the data supporting the findings of this case report are included within the article. Further inquiries can be directed to the corresponding author.

References

1 McAlinden C. An overview of thyroid eye disease. Eye Vis. 2014;1(1):9.
2 Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, et al. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in graves' disease. J Immunol. 2008;181(6):4397–405.
3 Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med. 2020;382(4):341–52.
4 Lee HB, Mariash CN, Yoon MK, Belinsky I, Creighton FX, Mahoney N, et al. Teprotumumab and hyperglycemia guidelines to monitor for hyperglycemia in teprotumumab. Ophthalmic Plast Reconstr Surg. 2021;37(4):393.
5 Ma H, Zhang T, Shen H, Cao H, Du J. The adverse events profile of anti-IGF-1R monoclonal antibodies in cancer therapy. Br J Clin Pharmacol. 2014;77(6):917–28.
6 Amarikwa L, Mohamed A, Kim SH, Kossler AL, Dosiou C. Teprotumumab-related hyperglycemia. J Clin Endocr. 2023;108(4):858–64.
7 Shah K, Charitou M. A novel case of hyperglycemic hyperosmolar state after the use of teprotumumab in a patient with thyroid eye disease. AACE Clin Case Rep. 2022;8(4):148–9.
8 Fujikawa LS, Meisler DM, Nozik RA. Hyperosmolar hyperglycemic nonketotic coma. A complication of short-term systemic corticosteroid use. Ophthalmology. 1983;90(10):1239–42.
9 Douglas RS, Wang Y, Dailey RA, Harris GJ, Wester ST, Schiffman JS, et al. Teprotumumab in clinical practice: recommendations and considerations from the optic trial investigators. J Neuro Ophthalmol. 2021;41(4):461–8.