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Case Report

Long-Term Follow-Up of a Case of Severe Hyperglycemia Requiring Hospitalization after Third Dose of Teprotumumab: A Case Report

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Keywords
Hyperglycemia · Teprotumumab · Glucose monitoring · Adverse effects · Case report

Abstract
Introduction: In 2020, teprotumumab became the first FDA-approved treatment for thyroid eye disease (TED). In clinical trials, hyperglycemia had been described as mild and controlled with medication. We present a case that occurred in 2020 of a 67-year-old male with TED and pre-existing glucose intolerance, who was hospitalized with severe hyperglycemia (1,059 mg/dL) after three doses of teprotumumab. ***Case Presentation:*** This patient's HbA1c was in the pre-diabetic range (6.3%) 6 months prior to initiating teprotumumab. After three doses, the patient was hospitalized with hyperosmolar hyperglycemic nonketotic syndrome and an HbA1c of 11.7%. He was diagnosed with type 2 diabetes mellitus and treated with insulin aspart mixed 70/30. He remained on this regimen for 14 months with an A1c of 6.0%. He then self-discontinued the insulin, with an A1c 4 months later measuring 5.5%. The patient's latest HbA1c approximately two and a half years after hospitalization was 6.1% on no medications. ***Conclusion:*** It appears that teprotumumab was a trigger for this transient case of diabetes, and detecting those that have underlying glucose intolerance ahead of time is important. We recommend blood glucose levels for patients with pre-diabetes prior to and ideally in the first few days after each infusion, to help determine patients at a greater risk for adverse hyperglycemic outcomes. A glucometer

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may be valuable for patients to self-monitor while on teprotumumab. If fasting blood glucose is ≥126 mg/dL or non-fasting glucose is >200 mg/dL, patients should be referred for further diabetes assessment and possible treatment initiation.

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Introduction

Thyroid eye disease (TED) is characterized by an expansion and inflammation of the extraocular muscles and periocular soft tissues which, in severe cases, can lead to sight-threatening corneal ulceration or optic neuropathy [1]. The pathogenesis is secondary to the autoimmune targeting of orbital fibroblasts, which increases expression of both thyrotropin receptor and insulin-like growth factor 1 receptor (IGF-1R), leading to increased glycosaminoglycan and hyaluronic acid production [2]. Teprotumumab, a human monoclonal antibody IGF-1R antagonist, became the first US Food and Drug Administration (FDA)-approved treatment for TED in 2020 [3, 4]. While clinical trials had reported on the expected side effect of hyperglycemia in an IGF-1R antagonist, these episodes were described as mild without requiring hospitalization [5–8]. We present a case that occurred in 2020, when teprotumumab was first FDA approved, of a 67-year-old male with undiagnosed pre-diabetes who developed severe hyperglycemia requiring hospitalization as a side effect of teprotumumab. Longer term follow-up showed that approximately a year after his hospitalization, he self-discontinued his medication with his HbA1c subsequently returning to baseline. Written informed consent was obtained from the patient, with the report maintaining HIPAA compliance and adhering to the ethical principles outlined in the Declaration of Helsinki. The CARE Checklist has been completed by the authors, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536153).

Case Presentation

The patient is a 67-year-old male with a history of hypertension, hyperlipidemia, chronic hepatitis B, and chronic obstructive pulmonary disease secondary to remote smoking. After presenting to an outside hospital with conjunctivitis, elevated intraocular pressure, and hyperthyroidism, he was referred to our clinic and diagnosed with TED. His clinical activity score was 4 in the right eye and 5 in the left eye, with exophthalmometry of 19 OD and 21 OS (Fig. 1a). He was also diagnosed with anterior uveitis secondary to herpes simplex virus and noted to be hepatitis B positive.

He initially received treatment for his uveitis and hepatitis B since his proptosis was not severe at this initial appointment. However, due to his persistent uveitis and gradually worsening proptosis, he developed a perforated corneal ulcer in the left eye requiring an urgent penetrating keratoplasty and, when deemed safe, an orbital decompression. The patient later developed a corneal ulcer in the right eye and was scheduled for an orbital decompression. However, with the onset of the COVID-19 pandemic, all non-elective cases were canceled, delaying his surgery. While waiting for surgery, he received multiple temporary tarsorrhaphy procedures and initiated teprotumumab. His BMI was low, approximately 16 kg/m^2 at baseline. He was not suspected to be diabetic at that time, and because original guidelines did not recommend any labaratory tests except for pregnancy prior to

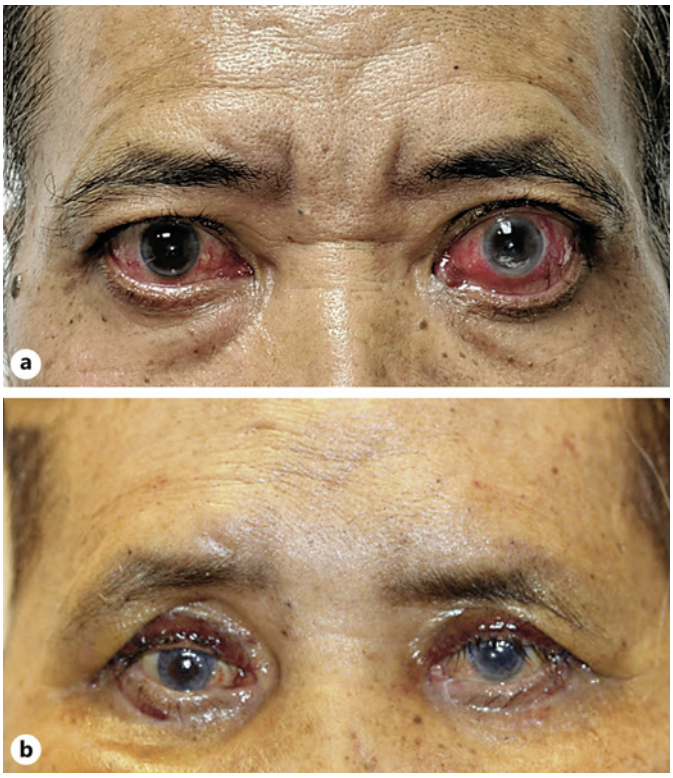

Fig. 1. Patient at initial presentation with a clinical activity score (CAS) of 4 in the right eye (**a**) and 5 in the left eye (**b**). Patient after both orbital decompressions (postoperative month 5 and month 10, respectively), 4 months after three doses of teprotumumab.

teprotumumab initiation, none were performed. An HbA1c, measured 6 months prior during his initial admission at the outside hospital, was later found to be 6.3%.

The patient received his first dose of teprotumumab partially alleviating his symptoms. Three weeks later, he received his scheduled 3-wall decompression in the right eye. One day after his surgery, a comprehensive metabolic panel reported a non-fasting blood sugar of 263 mg/dL. This was thought to be due to perioperative conditions, including perioperative steroids. He did not receive any follow-up treatment for his blood sugar elevation. A few days after his surgery, he received his second infusion and 3 weeks later, his third infusion.

Soon after his third dose of teprotumumab, the patient experienced vomiting and low appetite for 1 week. In the ED, he was found to have a blood urea nitrogen of 70, creatinine of 2.4, and blood glucose level of 1,059 with no ketonuria. His HbA1c at the time of presentation was 11.7%. He was admitted to the hospital with a diagnosis of hyperosmolar hyperglycemic nonketotic syndrome and transferred to the ICU on an insulin drip at 4 units/h. Upon discharge, he was diagnosed with type 2 diabetes mellitus, started on glimepiride, insulin glargine 15 units, and set up with regular endocrine follow-up. His teprotumumab was discontinued.

At his first follow-up appointment after hospitalization, glimepiride and insulin glargine were discontinued and insulin aspart mixed 70/30 with meals was started (20 units in the morning and 15 units in the afternoon) to improve blood glucose levels, which were in the 250s. Given his known autoimmune thyroid disease, workup was done to assess for autoimmune-mediated diabetes. The insulin autoantibody and anti-glutamic acid decarboxylase 65 antibody were

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negative, with detectable C-peptide of 3.1 ng/mL, suggesting medication-induced versus type 2 diabetes mellitus. Nine months after hospitalization, his insulin regimen was decreased to 15 units in the morning and 10 units in the afternoon with an A1c of 6.0%. He self-discontinued insulin approximately a year after hospitalization. An A1c performed on no insulin medication was 5.5%. At his latest follow-up, approximately two and a half years after his hospitalization, the patient had an A1c of 6.1% on no diabetes medication. The patient received a bilateral upper eyelid retraction repair and lower eyelid ectropion repair for his residual exposure keratopathy approximately 6 months after his hospitalization (Fig. 1b).

Discussion

This case describes a patient with pre-existing glucose intolerance who developed hyperglycemic nonketotic syndrome after three doses of teprotumumab. This patient had a unique treatment course given his past medical history and the timing of his TED with the COVID-19 pandemic. Due to his underlying hepatitis B infection, our patient was not considered a good candidate for high-dose IV steroids or tocilizumab. While orbital decompressions are normally performed during the chronic stable phase of TED [9], due to the severity of the exposure keratopathy in the right eye, our patient required a more urgent decompression. Lastly, while scheduled for an orbital decompression, the onset of the COVID-19 pandemic placed a hold on performing any non-emergent cases. Therefore, teprotumumab was thought of as a good treatment substitution.

Teprotumumab functions as an IGF-1R antagonist to block IGF-1R overactivation and signaling from orbital fibroblasts. Growth hormone stimulates insulin-like growth factor production in the liver, which subsequently increases liver gluconeogenesis and glucose production [10]. IGF-1, in turn, acts as an inhibitor of growth hormone secretion by the pituitary gland [10]. However, with teprotumumab blocking the receptor of IGF-1, there is an upregulation of growth hormone production, which leads to the increased glucose production and subsequent hyperglycemia [10, 11].

Initial clinical trials monitored hyperglycemia episodes and reported them as being mild or moderate, with no cases of hyperosmolar hyperglycemic syndrome or diabetic ketoacidosis [7, 10, 12]. However, initial trials did show a difference in hyperglycemia severity and proportion between individuals with no pre-existing glucose tolerance and individuals with diabetes [5]. Non-diabetic patients were reported to develop mild hyperglycemia, while diabetic patients experienced a more moderate elevation (160–500 mg/dL) in their blood glucose [12]. Also, 4.1% (3/74) of patients with no pre-existing diabetes reported hyperglycemia compared to 50% (5/10) of patients with pre-existing diabetes [5, 7, 10, 12]. Our patient's baseline impaired glucose tolerance may partially explain the severity of hyperglycemic reaction. Additionally, his underlying hepatitis B infection, which has been correlated with impaired glucose tolerance, may have further exacerbated his glucose intolerance, especially if it was a chronic infection [13, 14].

Evaluating long-term outcomes, 11 patients developed 12 hyperglycemia events from teprotumumab [7, 10, 12, 15]. Seven of these events were resolved during treatment, two resolved after the last dose (1 after 3 weeks, the other after 6.3 months), and three were ongoing as of the data cutoff [7, 10, 12, 15]. Out of 7 patients with pre-existing diabetes, 5 had since resolved their hyperglycemia, though no time points were reported, and 2 patients (in OPTIC-X) had persistent type 2 diabetes at least 36 weeks after the first dose [7, 10, 12, 15]. Our patient was found to be euglycemic off insulin therapy 18 months (approximately 72 weeks) after stopping teprotumumab. His baseline A1c of 6.3% was pre-diabetic, and his most recent A1c was 6.0%. In the context of this report and the broader literature, it appears that

teprotumumab may trigger diabetes temporarily rather than causing a natural progression of diabetes. Therefore, if teprotumumab is discontinued or completed, hyperglycemia may self-resolve over the course of several months.

Hyperglycemia is also a common side effect of corticosteroids, which was previously the standard of care for TED [5, 16]. The European Group on Graves' Orbitopathy (EUGOGO) protocol recommended treatment for moderate-to-severe and active TED with IV methylprednisolone 500 mg weekly for 6 weeks, followed by 250 mg for 6 weeks (total 4.5 g) [17, 18]. A meta-analysis conducted in 2014 showed that glucocorticoid-induced hyperglycemia occurred at a rate of 32.3% [19]. Another study reporting on adverse effects of patients on a cumulative dose of 7.5 g of IV methylprednisolone reported 1 patient, out of 171 total, who had pre-existing DM and stopped treatment due to severe hyperglycemia [20]. Therefore, patients should be counseled and monitored appropriately if they are started on steroids or teprotumumab.

Our case is the first reported case of an individual developing severe hyperglycemia with plasma gluocse levels above 1,000 mg/dL requiring hospitalization from teprotumumab. At the time of our patient's course in mid-2020, there were no reported cases of severe hyperglycemia requiring hospitalization in the clinical trials or in the broader literature. Shah and Charitou [21] detail a similar case of a pre-diabetic individual with hyperglycemic hyperosmolar nonketotic syndrome 3 weeks after her first dose of teprotumumab. Our report further supports the severity of hyperglycemia that can occur from teprotumumab. Additionally, it shows that not only diabetic patients, but all patients with evidence of impaired glucose tolerance should undergo closer supervision while on teprotumumab treatment. Finally, our report illustrates that hyperglycemia may also self-resolve after discontinuation of teprotumumab.

The FDA does not currently require the collection of blood glucose levels during teprotumumab administration for TED [4]. Guidance from a panel of experts involved in the phase 2 and 3 trials recommended a baseline fasting blood glucose, HbA1c, LFTs, CBC, and EKG for all patients, and for patients with diabetes, a fasting blood glucose after each of the first two infusions, twice daily self-monitoring, plus co-management with an endocrinologist [22]. Based on our report, for patients with pre-diabetes as determined by baseline HbA1c or fasting sugars, we recommend plasma fasting blood glucose levels prior to and ideally first few days after each infusion to monitor patients for adverse hyperglycemic outcomes. A glucometer would be valuable to monitor patients' fingerstick blood glucose levels while on teprotumumab or a continuous glucose monitor which can be an affordable option and may have better compliance. If the fasting blood glucose is ≥126 mg/dL or non-fasting glucose is >200 mg/dL, patients may need to be referred for further diabetes assessment and possible diabetes treatment initiation. We also recommend eliciting a family history of type 2 diabetes for patients who are considering teprotumumab, since they are predisposed to have pre-diabetic states such as impaired fasting glucose or impaired glucose tolerance. Patients with chronic hepatitis infection should also be monitored carefully on the medication given the potential for pre-existing glucose intolerance. Lastly, patients with autoimmune thyroid disease (e.g., Graves' disease or Hashimoto thyroiditis) are also at greater risk for associated autoimmune (i.e., type 1) diabetes; hence, diabetic ketoacidosis may be a potential severe adverse outcome.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

Dr. Zhang-Nunes is a consultant and a PI for a clinical trial site of Horizon Therapeutics, a company that makes teprotumumab. She is also a PI on a site for Viridian Pharmaceuticals and a co-PI for Immunovant Pharmaceuticals, which are testing other drugs for thyroid eye disease. She is also a previous consultant for Tarsus Pharmaceuticals, Sciton, Inc., and previously for Bruder.

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Author Contributions

P.M., T.A., V.L., M.L., and A.N. were responsible for acquisition of data for the work, drafting the manuscript, and editing the manuscript to its final version, and are in agreement to be accountable for all aspects of the work. S.Z.-N. was responsible for the conception and acquisition of data for the work, drafting the manuscript, and editing the manuscript to its final version, and is in agreement to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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