• Letter to the Editor •

Severe nausea and vomiting after teprotumumab initiation with corticosteroid pretreatment: a case report

Justin Youn[1], *Kim Firn*[2], *Eman Hawy*[2], *Douglas Van Putten*[2]

[1]Loma Linda University School of Medicine, 11175 Campus St, Loma Linda, CA 92350, USA
[2]Loma Linda University Eye Institute, 11370 Anderson St #1800, Loma Linda, CA 92354, USA
Correspondence to: Eman Hawy. Department of Ophthalmology, Loma Linda University Eye Institute, 11370 Anderson St #1800, Loma Linda, CA 92354, USA. ehawy@llu.edu
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Dear Editor,

We present a case of severe weight loss from intractable nausea and vomiting after teprotumumab infusions pretreated with corticosteroids. Teprotumumab, a monoclonal antibody against insulin-like growth factor 1 receptor (IGF1-R), was approved in 2020 as the first and only approved medication for thyroid eye disease (TED) in the USA[1]. The main reported adverse effects are muscle spasms, rare hearing loss, and transient hyperglycemia[1]. PubMed search in August 2024 using search terms, “Teprotumumab”, “Weight Loss”, “Nausea”, and “Vomiting” revealed no similar reports.

CASE PRESENTATION

Ethical Approval The study was conducted in accordance with the principles of the Declaration of Helsinki. The informed consent was obtained from the subject.

A 70-year-old 78.8 kg [body mass index (BMI) 30.8 kg/m^2] woman with Hashimoto’s thyroiditis, Graves’ disease, primary open angle glaucoma oculus uterque (OU), hypertension, and sensorineural hearing loss was referred to oculoplastics for evaluation of TED in November 2021. She reported five years of proptosis, seven months of eyelid edema, recent lateral gaze diplopia, decreased vision, dry eyes, and eye pain. On presentation, medications included levothyroxine 75 μg/d, latanoprost 0.005% nightly in both eyes, timolol 0.5% twice daily in both eyes, cyclosporine 0.05% twice daily in both eyes, and omeprazole 20 mg/d. She was previously prescribed 10 mg oral prednisone for six months tapered to 5 mg for four months, then 2.5 mg for one week to treat Grave’s disease in October 2017. Surgical history includes thyroidectomy in April 2021 to slow disease progression, laser-assisted *in situ* keratomileusis (LASIK) OU, and cataract surgery right eye (OD). She denied using tobacco, illicit drugs, and alcohol. Visual acuity was 20/40 OU with pinhole improvement to 20/30 OD. Exophthalmometry measured 25 mm OD and 26 mm left eye (OS) at base 100 mm. Slit lamp exam was significant for 3 mm lagophthalmos OU, 1+ blepharitis OU, and lower eyelid retraction OS.

Orbital magnetic resonance imaging (MRI) demonstrated partial fatty replacement of the bilateral superior and inferior recti and mild atrophy of the bilateral lateral recti, and the patient was started on teprotumumab infusions every 3wk in March 2022 due to lagophthalmos, diplopia, and proptosis. The local infusion center protocol included pretreatment with 100 mg intravenous (IV) methylprednisolone. The teprotumumab manufacturer only recommends consideration of pretreatment if a patient experiences an infusion reaction, and pretreatment is not routine at all infusion facilities. Blood glucose checks were normal at the first and fifth infusions. She experienced no infusion reactions.

Nausea and vomiting first occurred 2.5wk after the first infusion. Over the next six months while receiving treatment, she experienced muscle spasms and episodic, intractable nausea and vomiting, leading to one emergency department visit during the infusion course and two more in the six months following treatment. She was hospitalized for these symptoms three times in the six months after treatment. Multiple antiemetics showed limited success, and tizanidine controlled muscle spasms. Her lowest recorded weight was 46.3 kg (BMI 18.1), a 41.2% decrease from baseline (Figure 1). The workup included unremarkable serum lipase and amylase, electrocardiography (EKG), chest X-ray (CXR), and computed tomography (CT) abdomen and pelvis. esophagogastroduodenoscopy (EGD) was positive for helicobacter pylori (H. pylori), but triple therapy did not resolve symptoms. Her thyroid function tests showed free T4 levels ranging from 1.31-2.61 ng/dL (baseline:1.88 ng/dL; normal: 0.80-1.50 ng/dL) without any changes or new symptoms.

Cortisol levels ranged from 14.42-35.29 μg/L (normal: 3.0-23.0 μg/L).

An ante meridiem (AM) cortisol level of 24.22 μg/L (normal: 4.0-23.0 μg/L) was obtained in April 2023. Given the unremarkable workup and history of corticosteroid use, tertiary adrenal insufficiency and corticosteroid withdrawal syndrome were considered. Referral to endocrinology was made and adrenocorticotropic hormone (ACTH) stimulation test was ordered but never obtained. A test dose of oral prednisone 5 mg daily with a 1 mg/wk taper was planned. She was on 5 mg for six weeks but was maintained at 2.5 mg daily for three weeks due to recurrence of symptoms. She then tapered to 2.5 mg every other day for three weeks before returning to 10 mg daily due to significant fatigue. She later switched to hydrocortisone 10 mg every morning and 5 mg at bedtime with daily fludrocortisone 0.05 mg due to skin thinning and for prevention of Cushing's syndrome. Endocrinology increased the morning hydrocortisone to 15 mg and stopped fludrocortisone due to hypokalemia. She has remained stable with this regimen. At one-month follow-up after corticosteroid initiation, she reported significant improvement in symptoms. She regained 21.2 kg over the following year (Figure 1) with improved symptoms. She reported sustained improvement in vision, dry eye symptoms, pain, edema, and diplopia after the course of teprotumumab infusions through her most recent ophthalmology follow-up, 1.5y after treatment initiation.

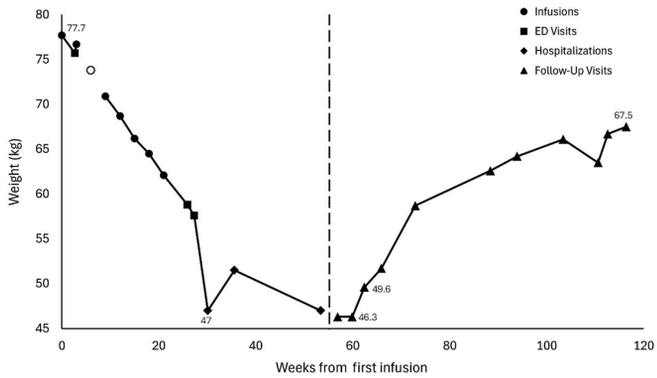

Figure 1 Weight trajectory over time during infusions, ED visits, hospitalizations, and outpatient follow-up visits The vertical dashed line indicates initiation of corticosteroids. An open circle denotes infusion #3, where weight was not recorded. ED: Emergency Department.

DISCUSSION

The patient's symptoms were initially attributed to teprotumumab treatment. Despite refractory symptoms, she agreed to continue teprotumumab given symptomatic improvement of her active TED. The persistence of symptoms months after teprotumumab completion led to an unremarkable workup for other etiologies. Cortisol levels were within normal limits. Given the incomplete diagnostic workup for adrenal insufficiency and corticosteroid withdrawal syndrome, the only evidence suggesting these etiologies remains the improvement after empiric therapy.

Without a definitive diagnosis, the adverse effect of teprotumumab remains in the differential diagnosis. The main side effects of teprotumumab include transient hyperglycemia, muscle spasms, and hearing loss. Other reported side effects include fatigue, hair loss, weight loss, nausea, diarrhea, dysgeusia, inflammatory bowel disease exacerbation, vomiting, transient cognitive changes, and infusion skin reactions[2-5]. The OPTIC trial was a randomized, double-masked, placebo-controlled, phase 3 multicenter trial investigating teprotumumab's effectiveness in TED treatment[3]. In this trial, mild nausea was observed in six patients (15%)[3]. Vomiting and significant weight loss were not reported in the trial's adverse events. Other GI side effects were observed in up to 10% of patients in this trial: diarrhea (10%), dysgeusia (10%), stomatitis (7%), and upper abdominal pain (5%). Another study found GI symptoms in 38.2% of their cohort[4]. In previous phase 1 clinical trials, teprotumumab was used in the setting of cancer treatment[5]. Reported nausea ranged from 7%-34% while vomiting ranged from 5%-21%[5]. Notably, these patients often used teprotumumab in conjunction with other chemotherapies.

Corticosteroid withdrawal syndrome typically presents after abrupt cessation of long-term use of exogenous supraphysiologic corticosteroids that suppress the hypothalamic-pituitary-adrenal (HPA) axis, but it has also been shown to occur after use of low-dose corticosteroids and after brief treatment[6]. Suppression of the adrenal response by glucocorticoids is unpredictable. Further, plasma cortisol measurements are unreliable indicators of adrenal suppression, and corticotropin-releasing hormone testing is much more reliable in detecting adrenal suppression after exogenous glucocorticoid use[7-8]. The presence of symptoms during the period in which she received pretreatment and unclear information about the temporal relation of symptoms to infusions make it difficult to determine whether symptoms were related to either corticosteroids or teprotumumab.

Although there is no suggested pathophysiology for severe, intractable nausea and vomiting caused by an IGF1-R monoclonal antibody, patient weight should be monitored, especially in the setting of corticosteroid pretreatment. Physicians should be aware of their local infusion center protocols and consider avoiding pretreatment unless patients experience a significant adverse infusion reaction. Corticosteroid use at a wide range of doses and durations is associated with adrenal suppression[6]. Furthermore, corticosteroid use may alleviate symptoms of TED, so

it is difficult to distinguish the effects of teprotumumab from those of corticosteroids when both are administered together[1]. In patients experiencing symptoms consistent with adrenal suppression after the use of corticosteroids, further management should be guided by an endocrinologist's expertise.

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