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Case Report

Oral Corticosteroids for Teprotumumab-Related Hearing Loss: A Case Report

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Abstract
Teprotumumab is a novel insulin-like growth factor-1 receptor inhibitor approved for the treatment of thyroid eye disease, but growing reports of hearing loss require further investigation. To date, an effective protocol for managing hearing loss in this setting has not been determined. Here, we present the first report of the resolution of teprotumumab-related hearing loss with prompt oral prednisone. A 70-year-old woman on teprotumumab experienced sudden hearing loss and tinnitus after her first infusion. An audiogram demonstrated a mild down-sloping to moderately severe mixed conductive and sensorineural hearing loss that was promptly treated with prednisone 60 mg for 6 days with a 1-week gradual taper. An audiogram 3 weeks later demonstrated return of hearing to normal thresholds, and the whole teprotumumab treatment course was completed without further issue. This case highlights the importance of audiometric monitoring, prompt identification of hearing symptoms, and the potential for oral steroids to reverse teprotumumab-related hearing loss.

Introduction

Teprotumumab is a monoclonal antibody that inhibits the insulin-like growth factor-1 receptor (IGF-1R), a receptor implicated in the characteristic orbital inflammatory changes

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seen in thyroid eye disease (TED) [1]. The US Food and Drug Administration approved teprotumumab as the first targeted treatment for TED in January of 2020, and adoption of the drug continues to increase, given the positive results demonstrated in two randomized clinical trials [2, 3]. These trials reported hearing loss in 10% of patients on teprotumumab, with most cases thought to be mild-to-moderate and reversible after treatment cessation [4]. However, subsequent retrospective studies and case reports have suggested that the incidence and severity of hearing loss in teprotumumab patients may have been underestimated [5–9]. The incidence of subjective otologic symptoms, including hearing loss, has been reported to be up to 81.5%, and several case reports have suggested long-term moderate or severe sensorineural hearing loss (SNHL) that has persisted after discontinuation of the drug [5–10].

The relationship between teprotumumab and SNHL is presumably due to the drug's molecular mechanism as the IGF-1R is expressed in the cochlea on outer hair cells, and its pathway has been demonstrated to be important for both hearing development and SNHL in older adults [9, 11]. IGF-1 has been shown to be protective against cochlear damage from aminoglycoside antibiotics, excessive noise, and ischemic injury in animal models [12–15]. Conductive hearing loss has also been linked to teprotumumab; this is possibly due to IGF-1R blockade causing nasopharyngeal fat pad atrophy, similar to what is seen with orbital fat, leading to eustachian tube dysfunction [3, 9].

There are currently no proven treatments for teprotumumab-related hearing loss; such patients are typically monitored closely and may warrant discontinuation of therapy if hearing loss is severe or persists. In this case report, we present the resolution of teprotumumab-related hearing loss with oral prednisone within 2 days of the hearing loss onset. This resulted in rapid resolution of subjective symptoms and improvement in pure tone audiometry thresholds. The patient proceeded to complete the full teprotumumab course of 8 infusions without further hearing complaints. The collection and evaluation of patient data for this report is compliant with HIPAA and adhere to the ethical principles outlined in the Declaration of Helsinki. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529422).

Case Report

A 70-year-old woman with TED presented with worsening double vision on inferior gaze for 6 months. She had been diagnosed with Graves' hyperthyroidism 1 year prior, with an elevated thyroid-stimulating immunoglobulin level, and was treated with methimazole therapy with subsequent normalization of her thyroid function tests. She also presented with bilateral epiphora, chemosis, and upper and lower lid edema. She was diagnosed with active TED and treated with a 2-week course of oral prednisone with a small initial subjective benefit but a recurrence and worsening of symptoms a few months later. Her TED clinical activity score gradually worsened from 1 to 4, and she experienced particular distress due to progressing strabismus that significantly affected her quality of life. Given her recurrent and worsening symptoms after oral steroids, and after a thorough discussion of the treatment options that included IV steroids, orbital radiation, and biologics, the patient was started on teprotumumab therapy.

Ten days after receiving her first teprotumumab infusion (10 mg/kg over 90 min), the patient experienced hearing loss in her right ear, as well as loss of taste. She had no history of hearing problems, use of ototoxic medications, or exposure to loud noise. Prompt audiogram testing, within 2 days of the hearing loss onset, demonstrated a mild down-sloping to

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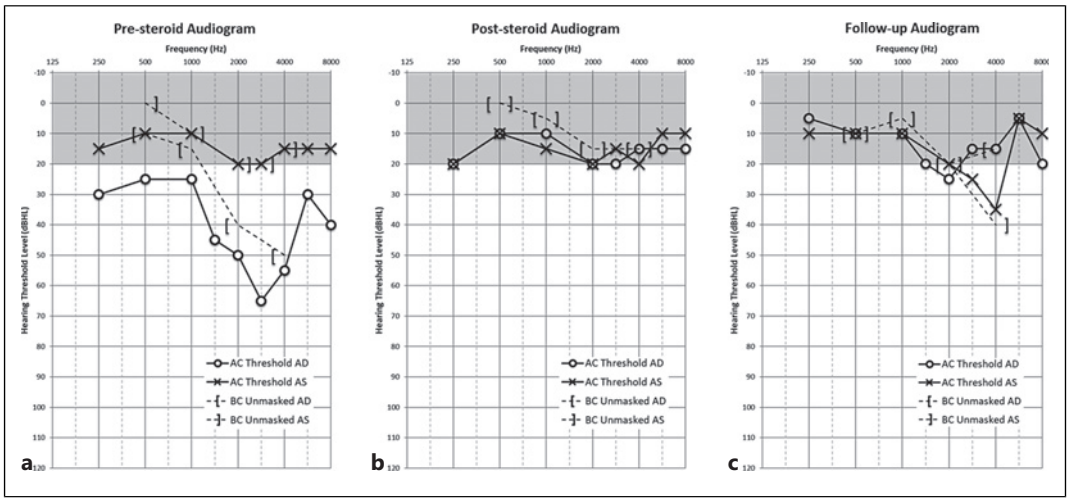

Fig. 1. a Audiogram before steroid treatment for hearing loss, post 1 dose of teprotumumab. Right ear shows mild sloping to moderately severe SNHL and conductive hearing loss. Left ear hearing is normal. **b** Audiogram 2 weeks after steroid treatment for hearing loss. Hearing on both sides is normal. **c** Audiogram at 90-week follow-up, post 8 doses of teprotumumab. Hearing remains normal on the right ear, and there is evidence of mild SNHL at 4 kHz rising back to normal in the left ear. AC, air conduction; BC, bone conduction; AD, right ear, AS, left ear.

moderately severe mixed conductive and SNHL with a pure tone average of 33 dB HL (the conductive component was minimal and ranged from 10 to 15 dB). Hearing was normal in the left ear (Fig. 1a). She was treated with oral prednisone 60 mg for 6 days with a 1 week gradual taper, in line with dosing guidelines for the treatment of sudden SNHL [16]. The patient reported improvement of her hearing symptoms 2 days after starting prednisone, and an audiogram obtained 2 weeks after initiation of prednisone demonstrated a pure tone average improvement of 20 dB HL in her right ear, which brought her to a normal level that was symmetric with her left ear (Fig. 1b). Additionally, the word recognition score improved from 92% at 70 dB before steroid therapy to a normal value of 100% at 55 dB in the right ear.

The patient completed a total of 4 teprotumumab infusions, on schedule and without delay, before treatment was paused due to a manufacturer shortage secondary to US government orders to prioritize COVID-19 vaccine production. After 3 months, she resumed teprotumumab and completed the full course of 8 infusions. She experienced improvement of her TED clinical activity score from 4 to 0 and a large subjective improvement in diplopia. She still had a mild persistent diplopia, thought to be fibrotic in nature, which is now being treated with prisms. The patient reported some residual taste changes that have not yet resolved but did not have any further hearing symptoms during or after the treatment course at 90-week follow-up. She was concurrently followed by endocrinology and remained euthyroid with medical treatment of her hyperthyroidism. A repeat audiogram performed at 90-week follow-up demonstrated normal hearing in the prior symptomatic right ear and new mild SNHL in the left ear at 4 kHz that trends back to normal at higher frequencies. Word recognition was 100% bilaterally.

Discussion

This is the first report of a patient with teprotumumab-related hearing loss that resolved after treatment with oral steroids, as supported by audiometric data. Steroid therapy is the

current mainstay of therapy for sudden idiopathic SNHL, although there is no consensus on effectiveness due to conflicting data from small randomized controlled trials [17]. Additionally, intratympanic dexamethasone injections have been shown to be effective in mitigating cisplatin- and aminoglycoside-induced ototoxicity. Such treatment is justified in these instances because the mechanism of ototoxicity is thought to involve the generation of reactive oxygen species, leading to an inflammatory response in the cochlea [18]. With teprotumumab, the role of steroids has been doubted, given that IGF-1R promotes inflammation in normal physiology, and thus, its inhibition is unlikely to increase cochlear inflammation [8, 19]. Therefore, the seemingly paradoxical mechanism behind the efficacy of prompt steroid therapy for teprotumumab-related hearing loss warrants further investigation.

Two prior cases in the literature report patients with teprotumumab-related hearing loss in which oral steroids were tried but were ultimately ineffective. Belinsky et al. [9] described a 68-year-old woman who noticed muffled hearing after her third teprotumumab infusion, treated with oral steroid pulse therapy after her fourth infusion, but had persistent mild-to-moderately severe down-sloping SNHL bilaterally measured on audiograms obtained 1 month after her fifth infusion and 3 months after her 8th infusion. Highland et al. [7] reported a 61-year-old woman who experienced bilateral hearing loss and tinnitus after her fifth infusion. She was started on a 2-week oral steroid taper after her 7th infusion with deferral of the final infusion due to hearing loss, but with no appreciable changes between her audiograms obtained after her 7th infusion and 4 months after treatment cessation.

Our case differs from the above cases in that oral steroid therapy was initiated within 2 days of the hearing loss onset, compared to a time course of several weeks after the symptom onset in prior cases [7, 9]. In idiopathic sudden SNHL, early time to treatment with steroids has been linearly correlated with improved outcomes, and the same principle may hold true for teprotumumab-related hearing loss [20]. A weakness of our study is that we cannot conclusively establish whether the patient's hearing loss was teprotumumab-related, coincidental, or preexisting. Our patient had normal hearing prior to teprotumumab initiation, no recent infectious symptoms, no exposure to other ototoxic medications, no other attributable causes of hearing loss, and normalization of audiogram values after steroid therapy, all of which argue against the hearing loss being preexisting. The temporal relationship with teprotumumab therapy supports that her hearing loss was most likely teprotumumab-related, and the timeframe of the symptom onset is consistent with those of other ototoxic drugs, which are most commonly reported to be a couple of days to a couple of weeks [21]. The unilateral nature of hearing loss may be due to prompt treatment, halting a progression to bilateral deficits, although cases of unilateral drug-induced ototoxicity have been reported in the literature [22, 23]. It is interesting to note that the patient did not have further hearing symptoms despite continuing teprotumumab therapy at subsequently higher dosages as per standard treatment protocol. This may be possibly related to an ongoing protective effect of steroids, a clue to the mechanism of action of steroids in this instance. Repeat audiogram testing almost 2 years later showed maintenance of normal hearing in the right ear, and the patient remains asymptomatic.

At our institution, out of 27 patients on teprotumumab, 81% developed hearing dysfunction symptoms and 55% of those patients had persistence of symptoms at an average of 36 weeks follow-up, leading to the recommendation to obtain audiograms for all patients starting teprotumumab at baseline, if hearing symptoms develop, and after completion of therapy [10]. While our patient unfortunately did not receive baseline testing, baseline audiograms are crucial for guiding hearing loss management. Without baseline testing, it is challenging to determine whether the hearing loss is teprotumumab-related or preexisting, the severity of hearing loss, if teprotumumab therapy should be held, or if hearing loss therapy

should be implemented. The authors believe that effective management of teprotumumab-related hearing loss centers around timely identification of hearing symptoms, guidelines for audiometric testing, and close collaboration with ENT colleagues. Furthermore, patient education of this potential side effect prior to starting treatment is paramount for identifying hearing issues early, especially in areas without easy access to audiologic testing. Once hearing changes are noted, prompt oral prednisone burst therapy should be considered, preferably within a few days, as an option to potentially mitigate a major side effect of teprotumumab. Further studies and case reports of similar steroid treatment can clarify its efficacy for teprotumumab-related hearing loss and inform treatment guidelines.

Statement of Ethics

Written informed consent was obtained for publication of the details of this medical case and any accompanying images from the patient described in this paper. Ethics approval was not required, given that this is a case report, not research, and does not contain any personal health information. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

Author A.K. is a prior consultant for Horizon Therapeutics.

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Author Contributions

Tracy J. Lu wrote this manuscript and conducted the relevant literature search associated with it. Linus Amarikwa assisted with edits and figures. Bryan J. Winn, Michelle Inserra, and Chrysoula Dosiou offered expert opinion and edits. Andrea L. Kossler is the senior author who advised and oversaw this case and manuscript.

Data Availability Statement

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

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