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# Audiologic Demonstration of Ototoxicity From Teprotumumab Treatment in a Patient With Thyroid Eye Disease

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**Keywords**

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Graves' ophthalmopathy, or thyroid eye disease (TED), is an autoimmune disease characterized by inflammation, fibrosis, and fat expansion of orbital tissue, leading to vision loss.[1] TED is mainly associated with Graves' disease but can also be seen in patients with Hashimoto's disease due to elevated levels of TRAb (thyroid-stimulating hormone receptor autoantibodies) and TSI (thyroid-stimulating immunoglobulins).[1] Growing research has shown that teprotumumab (Tepezza), an insulin-like growth factor I receptor (IGF-IR) inhibitor, is effective at controlling the stimulation and progression of TED. IGF-I has been known to protect inner ear hair cells from noise-induced damage, ischemia, and medication toxicity.[2,3] Therefore, inhibition of IGF-IR is a possible mechanism for teprotumumab-induced ototoxicity. Initial trials have reported the presence of otologic side effects in as many as 12.8%; however, no objective measures were used to record its extent.[4] In this case study, we report our encounter with teprotumumab-induced ototoxicity in a woman with TED who had demonstrated normal hearing on pretreatment audiogram. This study did not require an application for an exemption per the Institutional Review Board of the Office for the Protection of Research Subjects at the University of Illinois at Chicago.

## Case Report

A 57-year-old woman with a history of Hashimoto's disease presented to our clinic with hearing loss and tinnitus. Prior to presentation, the patient had developed ocular changes consistent with TED. Laboratory testing demonstrated thyroperoxidase antibodies and elevated TRAb and TSI levels, confirming the diagnosis of TED. The patient was started on teprotumumab once every 3 weeks for a total of 8 infusions. Before starting therapy, she underwent audiometric testing for intermittent bilateral tinnitus that demonstrated normal hearing bilaterally (**Figure 1**). By the second infusion, the patient developed consistent ringing in both ears. After the fifth infusion, the patient reported improvement of ocular symptoms but a decline in overall hearing. Audiometric testing at this time showed a diminished hearing when compared with baseline. Right ear results revealed normal hearing in the low

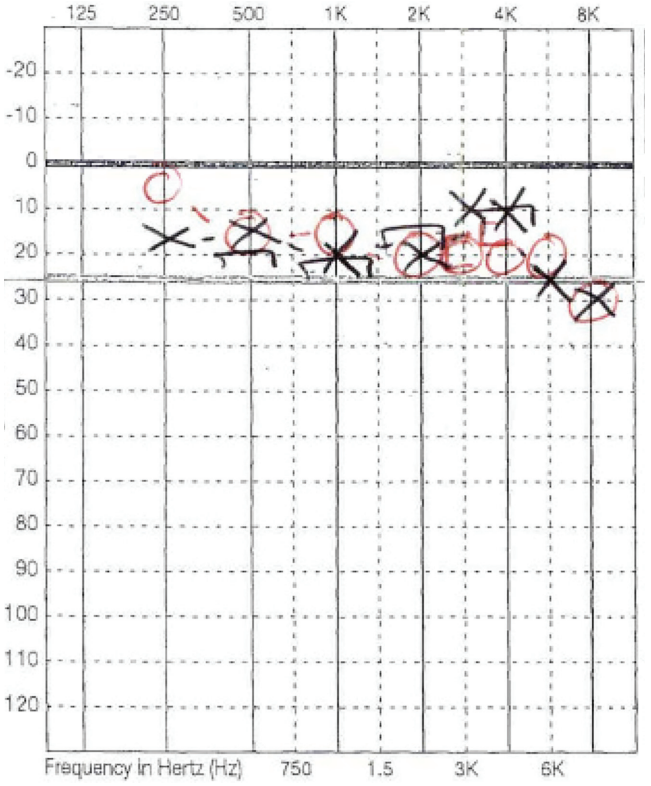


**Figure 1.** Pretreatment hearing test demonstrating normal hearing bilaterally over all frequencies.

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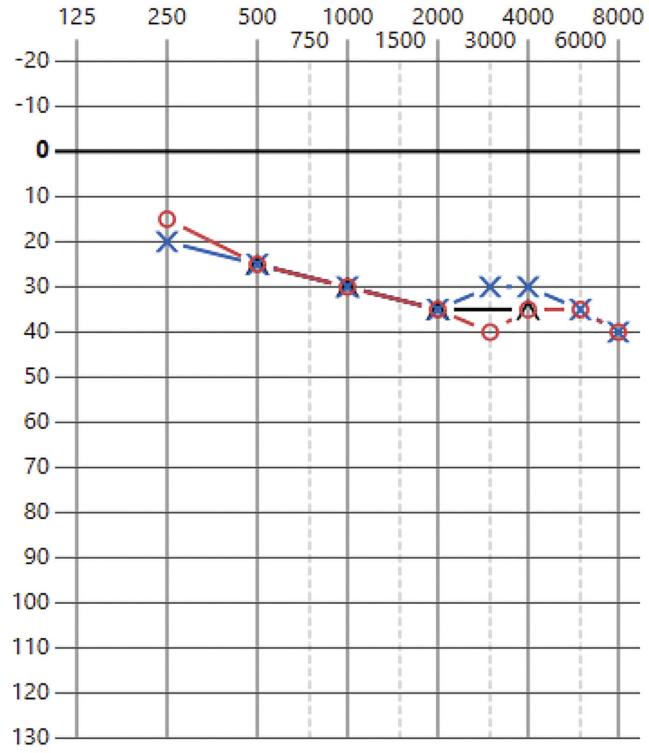


**Figure 2.** Hearing test done after the fifth infusion and onset of hearing loss demonstrating mild sensorineural hearing loss bilaterally.

frequencies, sloping to mild sensorineural hearing loss at 2000 to 8000 Hz. Left ear results revealed normal hearing in the low frequencies, sloping to mild sensorineural hearing loss from 1000 to 8000 Hz. Speech and word recognition were not affected bilaterally (**Figure 2**). The infusions were stopped, and an audiogram at 1 month revealed no improvement. At that time, otolaryngology was consulted. Her history was negative for disorders that could cause tinnitus and hearing loss, and the otoscopy finding was normal. Infusions were not resumed due to limited information on the progression and treatment of teprotumumab ototoxicity.

## Discussion

Teprotumumab has provided an improvement in TED, visual symptoms, and quality of life.[2] However, our report and others suggest an association with bilateral sensorineural hearing loss.[2,3] The tinnitus by the second infusion indicates the need for vigilant monitoring for the development of hearing loss. The development of hearing loss after the fifth infusion may indicate a cumulative dose effect as seen in other studies.[3] We were fortunate to have a normal pretreatment hearing test result, allowing us to attribute the new hearing loss to teprotumumab treatment. Unfortunately, possible reversal with steroids was not considered because of our late involvement. Otolaryngologists and endocrinologists should collaborate so that patients receive pretreatment hearing tests, monitoring, and education on reporting otologic symptoms to the clinical team. Given that IGF-I is cochlear protective and that inhibition of IGF-IR is a possible mechanism for teprotumumab-induced ototoxicity,[2,3] pharmacologic studies should be directed at identification of a cochlear protective agent that could be used in a pretreatment and preventative manner. In theory, localized transtympanic delivery of such an agent to the round window of cochlea would avoid subsequent interference of teprotumumab systemic therapy to the orbital tissue.

The exact proportion of patients treated with teprotumumab who will develop audiometrically confirmed hearing loss has not been studied in a prospective manner[4] and may be very different from the proportion who report hearing symptoms. The incidence of hearing symptoms was recently presented as 46%; however, the entire cohort did not receive audiometric testing.[5] A new prospective clinical trial should be performed with comprehensive pretreatment audiologic testing and ongoing audiologic monitoring. Although many reports of teprotumumab-induced hearing loss appear in journals related ophthalmology,[2] otolaryngologists should be aware of the growing evidence because patients may be referred to us to assess hearing loss and we may be involved in treatment.

### Author Contributions

**Wassim Najjar**, substantial contributions to conception and design, drafted the article for important intellectual content, made final approval of the version to be published, and agreed to be accountable for all aspects of the work; **Jeffrey Yu**, substantial contributions to conception and design, drafted the article for important intellectual content, made final approval of the version to be published, and agreed to be accountable for all aspects of the work.

### Disclosures

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