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Case Report

Hearing Loss in a Patient with Waldenstrom Macroglobulinemia Receiving Bortezomib

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Abstract
Introduction: We present a case report of hearing loss in a patient with Waldenstrom macroglobulinemia (WM) receiving treatment with bortezomib. ***Case Presentation:*** Our patient developed sudden bilateral sensorineural hearing loss after receiving three doses of bortezomib. His hearing loss was irreversible and resulted in a cochlear implant. ***Conclusion:*** Hearing loss secondary to bortezomib is a known, but very rare, side effect. Hearing loss secondary to WM is also rare and has been described in case reports.

Introduction

Waldenstrom macroglobulinemia (WM) is a B-cell lymphoproliferative disorder characterized by an IgM monoclonal gammopathy. The IgM monoclonal protein may lead to symptoms of hyperviscosity and peripheral neuropathy. Additionally, infiltration of bone marrow and other tissues may lead to cytopenias, lymphadenopathy, and hepatosplenomegaly. Bortezomib is a proteasome inhibitor which is frequently used to treat various hematologic malignancies including WM, multiple myeloma (MM), and mantle cell lymphoma. Well-known complications of bortezomib include peripheral neuropathy and thrombocytopenia. A lesser known and rarely reported complication is hearing loss. We present a potential case of this rare complication.

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Case Report

A 67-year-old male with a history of atrial fibrillation hypertension, benign prostate hyperplasia, and hemorrhoids status post-banding presented to clinic for evaluation of pancytopenia and weight loss. His medications at the time of presentation were amlodipine, digoxin, metoprolol, warfarin, simvastatin, and terazosin. On presentation, he reported a 20-pound weight loss over the past year. He denied any symptoms of hyperviscosity or any other complaints. Recent CBC showed white blood cell count 3.1, platelet count 107,000, and hemoglobin 7.7 with rouleaux formations, so a serum protein electrophoresis with immunofixation was sent, which revealed a 6.2 g/dL monoclonal IgM Kappa band in the gamma region. On immunoglobulin testing, IgM was found to be 7,890 mg/dL. A bone marrow biopsy was performed, which revealed findings consistent with lymphoplasmacytic lymphoma.

Treatment of WM was planned with bortezomib, dexamethasone, and rituximab. To prevent IgM "flare," cycle one was given with bortezomib only. He received the first three doses without any dose-limiting toxicities. Prior to the scheduled fourth dose, he was thrombocytopenic, so this dose was held. After his third dose of bortezomib, he reported tinnitus followed by sudden left ear hearing loss. One day later, he awoke with hearing loss in the right ear as well and presented to the ED. He denied any recent or history of trauma to his head. Imaging with an MRI head and CT head were performed, which were found to be unremarkable. An audiogram was performed which revealed right ear profound sensorineural hearing loss at 250–500 Hz and no responses at limits of equipment 1,000–8,000 Hz. The left ear was noted to have moderate to severe sensorineural hearing loss at 250–500 Hz and no responses at limits of equipment 1,000–8,000 Hz. Of note, he did report that he underwent a free hearing screen roughly 3 years prior and was told that "he needed a hearing aid in the right ear but that the left ear was okay." ENT was consulted, and he was started on a steroid taper at the time. He reported negligible subjective improvement of hearing with the steroid taper. Repeat audiogram testing later that month found similar profound hearing loss. For his persistent hearing loss, he was initially provided with bilateral hearing aids. With the hearing aids he reported some improvement in hearing in his left ear but continued to report deafness in his right ear. Despite the improvement noted with the hearing aids, he still had profound speech understanding difficulty, so he opted for a cochlear implant. Roughly a year after his initial presentation for hearing loss, he underwent a right cochlear implant. With the cochlear implant, he reported significant improvement in his hearing so that he could now have a conversation over the phone.

Discussion

WM was considered as a possible cause of the patient's hearing loss. Sensorineural hearing loss secondary to WM is rare and has been described in fewer than ten case reports [1–6]. In these cases, the hearing loss is typically sudden (unilateral or bilateral). The etiology of hearing loss secondary to WM is still not fully understood. The first case reports of hearing loss secondary to WM proposed a hemorrhagic etiology, but later reports have attributed hyperviscosity, leading to thrombus formation as a more likely etiology [2]. In our patient's case, viscosity had decreased from 9.1 cP at the start of therapy to 4.1 cP on presentation to the ED. Although the serum viscosity remained elevated and serum viscosity measurements do not always directly correlate with hyperviscosity symptoms, it was thought to be less likely that the patient's hearing loss

was secondary to WM as the measured viscosity had significantly improved with treatment. IgM level had also improved from 8,970 mg/dL at the start of therapy to 6,010 mg/dL on the day of presentation to the ED. Additionally, he received bortezomib alone during cycle one to prevent IgM "flare" and increased risk of hyperviscosity. It is of note that many patients with hearing loss secondary to WM have had hearing loss reversed with treatment of their underlying WM. In a case series by Wells et al. [4], 3 of the four patients had reversal of their hearing loss with treatment of WM. Additionally, Syms et al. [3] reported a case where a patient's hearing significantly improved with seven cycles of fludarabine and normalization of serum viscosity. As previously noted, the hearing loss of our patient did not improve with treatment of WM and normalization of serum viscosity.

The patient's medication list was reviewed for a possible etiology of his hearing loss. The only new medications that the patient had received recently were allopurinol, acyclovir, and bortezomib. Allopurinol and acyclovir have not been previously associated with hearing loss. He did not have any known occupational or recreational chronic exposure to loud noises. On review of the literature, it appears that there have only been three case reports of hearing loss attributed to bortezomib (Table 1). In 2005, Engelhardt et al. [7] reported the first case of bortezomib-induced severe bilateral sensorineural hearing loss in a patient with MM. The patient initially reported hearing loss after the third cycle, and the dose of bortezomib was reduced for the fourth cycle. Despite the dose reduction, the hearing loss continued to worsen, so bortezomib was discontinued after the fourth dose. In 2008, hearing loss was again reported after bortezomib use by Chim et al. [8] In this case the patient received two cycles of bortezomib for treatment of IgA MM before reporting left ear hearing loss. Audiogram confirmed left ear sensorineural hearing loss. Bortezomib was thus discontinued, and the patient died 8 months later from complications related to MM. No improvement in hearing was noted prior to the patient's death. Hearing loss secondary to bortezomib was again described in 2016 by Anoop et al. [9] In this case, the patient received three doses of bortezomib along with thalidomide and dexamethasone for induction of IgG lambda MM before reporting bilateral hearing loss. Bortezomib was discontinued and hearing loss persisted but did not worsen.

The mechanism by which bortezomib causes hearing loss has not been fully elucidated. Other chemotherapies which cause peripheral neuropathy, such as platinum-based chemotherapies, are well known to also cause hearing loss. A recent study of MM patients receiving bortezomib found that there was an association between patients who reported peripheral neuropathy and auditory issues [10]. Of note, our patient did not have any previous history of peripheral neuropathy or develop neuropathy after receiving bortezomib. He also did not have a history of diabetes. Previous case reports of hearing loss secondary to bortezomib did not note if peripheral neuropathy was associated with the hearing loss. Lee et al. [11] studied the mechanism by which bortezomib can lead to hearing loss. In their research, rat auditory cells were treated with bortezomib, MG132 (another proteasome inhibitor), or a control medium (DMEM). Destruction of most stereocilia bundles of hair cells was found in cells treated with a proteasome inhibitor. They also found that proteasome inhibitors affected the function of peroxisomes by decreasing both peroxisomal protein expression and the number of peroxisomes. Congenital dysfunction of peroxisomes is well known to cause sensorineural hearing loss. In light of these findings, the researchers proposed that the mechanism by which bortezomib causes hearing loss is through a pathway of peroxisome dysfunction, leading to an accumulation of reactive oxygen species. In the case of our patient, his hearing improved with cochlear implant as expected in hearing loss secondary to stereocilia destruction.

Table 1. Reported cases of bortezomib-induced hearing loss

Author, year	Underlying malignancy	Bilateral versus unilateral hearing loss	Amount of bortezomib received prior to hearing loss
Engelhardt et al. [7], 2005	MM	Bilateral	3 cycles
Chim and Wong [8], 2008	MM	Unilateral	2 cycles
Anoop et al. [9], 2018	MM	Bilateral	3 doses
Our case, 2023	WM	Bilateral	3 doses

Conclusions

Hearing loss secondary to bortezomib is a very rare side effect. To our knowledge, this is potentially only the fourth time that this finding has been described. Hearing loss secondary to WM cannot be ruled out in this case but is less likely given that the patient's hyperviscosity was improving with treatment and the hearing loss proved to be irreversible. All cases of hearing loss attributed to bortezomib have proven to be irreversible. Duration of bortezomib treatment prior to development of hearing loss is variable with 2 patients developing deafness after multiple cycles and our patient and 1 other patient reporting deafness after only three doses. This rare side effect has only been reported previously in patients with MM. Although hearing loss from bortezomib is a very rare side effect, given that the handful of reported cases were associated with irreversible hearing loss, any reported changes in hearing by the patient should be promptly evaluated and reduction or discontinuation of the therapy should be considered. 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/10.1159/000539453).

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jack Fitzsimons, MD, wrote the initial manuscript. Edits and recommended changes were provided by Kathleen Phelan, MD, and Asha Dhanarajan, MD.

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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