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Reversible Ototoxicity: A Rare Adverse Reaction of Liposomal Amphotericin-B Used for the Treatment of Antimony-Resistant Visceral Leishmaniasis in an Elderly Male

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ABSTRACT: Amphotericin-B, a broad spectrum antifungal agent, has been known to cause adverse effects such as nephrotoxicity and infusion-related side effects such as fever, chills, rigor, and arthralgias. However, ototoxicity as an adverse effect of Amphotericin-B has not yet been reported in medical literature. We here report a case of a reversible form of ototoxicity induced by liposomal Amphotericin-B (L-AmB).

KEY WORDS: liposomal Amphotericin-B, ototoxicity

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Introduction

Ototoxicity leading to sensorineural deafness is mainly due to medication and toxin induced. Common ototoxic drugs include antibiotics like aminoglycosides,[1] loop diuretics[2] such as furosemide, platinum-based chemotherapy agents[3] such as cisplatin, and a number of non-steroidal anti-inflammatory drugs.[4] Nephrotoxicity has frequently been reported as an adverse effect of Amphotericin-B, but its ototoxic effect has not been reported so far. We report a case of resistant visceral leishmaniasis in an elderly male, who developed a reversible form of ototoxicity after treatment with liposomal Amphotericin-B (L-AmB). In our opinion, it is probably the first case to have this rare adverse effect.

Case history. A 65-year-old male patient from the endemic zone of visceral leishmaniasis in Bihar, India, was admitted to the geriatric medicine ward with complaints of high-grade fever (measured as high as up to 104 °F) with chills and rigor for about four months. One month before the present hospitalization, he had been evaluated by a physician in his locality and diagnosed with leishmaniasis by card test. He was treated with miltefosine and sodium stibogluconate for an optimum period of time with no subsidence in his fever. The patient was then referred to our center.

On examination, his vitals were stable except for a fever of 102 °F. He was pale with no icterus. There was no localized/generalized lymphadenopathy or enlargement of the thyroid. Comprehensive geriatric assessment (CGA) revealed no obvious geriatric syndromes. As a part of CGA, baseline hearing and vision of the patient were normal. There was no discharge from any of the ears. Abdominal examination revealed massive, firm, and non-tender splenomegaly with soft, non-tender hepatomegaly with a span of 16 and 14 cm, respectively. Respiratory system, cardiovascular system, nervous system, and musculo-skeletal system revealed no abnormality on examination. A provisional diagnosis of visceral leishmaniasis was made.

Ultrasonography of the abdomen revealed splenomegaly of 20 cm with portal vein diameter of 15 mm and hydronephrosis of the right-sided kidney with calculus of size 8 mm in the renal pelvis. Non-contrast computed tomography of the abdomen revealed right kidney of size 11.7 cm with hydronephrosis, with normal ureter, and a calculus measuring 1 cm in the right renal pelvis. A cortical cyst measuring 2.6 × 1.7 cm was also seen near the lower pole of the right kidney (Bosnaik grade 2). Left kidney measured 9.7 cm and was displaced anteromedially by the massively enlarged spleen.

Enzyme-linked immunosorbent essay (ELISA)-based Immunoglobulin-G (IgG) level against kala-azar was 5.7 units (significant: 1–15 units). Bone-marrow aspiration revealed cellular marrow with normal marrow elements, mild prominence of plasma cells, and presence of *Leishmania donovani* amatigotes.

Based on the bone-marrow aspirate findings, the diagnosis was confirmed as visceral leishmaniasis probably resistant to sodium stibogluconate and miltefosine. As the patient was immune-competent (non-reactive for HIV1 and HIV2, no history of immunosuppressive medications, and no other co-morbidities like diabetes mellitus), he was treated with L-AmB in a renal modified dose of 150 mg per day (3 mg/kg). The treatment regimen followed in this patient was L-AmB 3–5 mg/kg/day for first five days then repetition of the same dose (3 mg/kg) on the 14th and the 21st day of initial treatment.

On the fifth day of treatment with L-AmB, the patient complained of slight loss of hearing in both ears. As per the treatment protocols, L-AmB was discontinued. But the patient's hearing loss gradually progressed and around the 10th day of initiation of treatment, hearing was completely lost in bilateral ears in this patient.

Urgent otorhinolaryngology consultation was carried out on the very first day of hearing impairment, and audiometry was planned. Otoscopic examination revealed no abnormality except for the presence of soft wax in the right external ear, which was cleaned in the same sitting. Pure tone audiometry (PTA) done on the seventh day of starting treatment revealed bilateral sensorineural deafness of profound grade (Table 2). In the presence of no other obvious local or systemic causes of new onset of deafness, his medication chart was thoroughly reviewed to ascertain the drug-induced cause of sensorineural deafness. He did not receive any documented ototoxic medications in recent past or during the present admission. Therefore, it was assumed that his deafness was medication induced; probably L-AmB, the only medication which he received just before the hearing loss.

Patient was started on oral prednisone 30 mg/day. Days 14 and 21 of L-AmB therapy for kala-azar was deferred. After one week of starting prednisone, there was progressive recovery in the hearing of the patient. A repeat PTA examination revealed bilateral sensorineural hearing loss of moderate grade. There was improvement in air conduction (AC) and bone conduction (BC) in both ears (Table 2). Oral prednisone was gradually tapered over a period of four weeks. Patient became afebrile and symptomatically better despite incomplete regimen of L-AmB. The patient was discharged home and followed up after four weeks with another PTA by the otolaryngologist. This time, he had normal hearing both clinically and audiometrically (Table 2).

Table 1. Laboratory findings of the patient after hospitalization.

S.N	LABORATORY PARAMETER	OBSERVED VALUE	REFERENCE RANGE
1.	Hemoglobin	5.3 g/dl	12–16 g/dl
2.	Total leukocyte count	4000 cells/mm^3 (Neutrophil: 56%, Lymphocyte: 27%)	4000–11000/mm^3
3.	Platelet count	70,000 cells/mm^3	250,000–400,000/mm^3
4.	Erythrocytic sedimentation rate	103 mm in 1st hour	0–30 in 1st hour
5.	Blood urea	83 mg/dl	15–40 mg/dl
6.	Serum creatinine	3.0 mg/dl	0.2–1.2 mg/dl
7.	Serum albumin	2.4 g/dl	4.0–5.5 g/dl
8.	Serum globulin	6.2 g/dl	3.8–4.0 g/dl
9.	Serum Alanine transaminase	42 IU/L	5–40 IU/L
10.	Aspartate transaminase	25 IU/L	5–35 IU/L
11.	Alkaline phosphatase	837 IU/L	20–140 IU/L
12.	Peripheral smear	Normocytic, normochromic morphology	-

Discussion

Clinical recognition of ototoxicity came to medical limelight with the discovery of streptomycin in 1944.[5] Since then, a number of pharmacologic agents have been incriminated to cause ototoxicity, mostly irreversible. The list of ototoxic drugs includes aminoglycosides, other antibiotics, platinum-based anti-neoplastic agents, salicylates,[6] quinine,[7] and loop diuretics.

Few experimental and hypothetical explanations on the patho-biochemical basis of drug-induced ototoxicity have been available in medical literature. The mechanism of irreversible ototoxicity has been attributed to destruction of outer hair cells in the organ of Corti, predominantly at the basal turn of the cochlea.[8] Similarly, reversible ototoxicity induced by some aminoglycosides, loop diuretics, and salicylates has been linked mainly to involvement of stria vascularis of the inner ear, which becomes edematous and can cause changes in the ionic gradients between the perilymph and endolymph by inhibiting adenylate cyclase and G-proteins.[9]

In our case, the incriminated ototoxic drug was Amphotericin-B, a broad spectrum antifungal, which has been documented to be very effective in the treatment of antimony-resistant visceral

Table 2. PTA on 7th, 14th, and 30th day of initiation of L-AmB treatment.

DAY	FREQUENCY	RIGHT (AC/BC)*	LEFT (AC/BC)*	COMMENT
7th	250	80/80 db	No response	Profound Sensori-neural hearing loss
	500	85/85 db	60/60 db	
	1000	90/90 db	75/75 db	
	2000	110/100 db	No response	
	4000	No response	No response	
14th	250	80/60 db	45/30 db	Moderate to severe Sensori-neural hearing loss
	500	75/60 db	65/45 db	
	1000	75/60 db	50/55 db	
	2000	65/55 db	50/55 db	
	4000	75/65 db	55/65 db	
30th	250	40/30 db	30/25 db	Mild Hearing loss (subjectively normal)
	500	40/40 db	30/20 db	
	1000	40/40 db	35/25 db	
	2000	30/30 db	20/30 db	
	4000	30/25 db	25/25 db	

Abbreviations: *AC, air conduction; BC, bone conduction.

leishmaniasis. Drugs like paramomycin used in the treatment of leishmaniasis can cause reversible ototoxicity, but there are no reports of Amphotericin-B causing so. In a randomized controlled trial conducted by Sundar et al, 501 patients of visceral leishmaniasis were treated with paramomysin and 165 patients with Amphotericin-B. Among them, seven patients in the paromomycin arm developed reversible ototoxicity; none of the 165 patients in the Amphotericin-B arm developed it.[10]

Though the therapeutic efficacy of all three lipid formulations of Amphotericin-B (Amphotericin-B lipid complex, L-AmB, and Amphotericin-B colloidal dispersion) are almost the same, the adverse effects such as dose-related nephrotoxicity and other infusion-related reactions vary from one to another.[11] The least side effects have been seen with L-AmB. Infusion-related toxicities associated with Amphotericin-B include fever, chills, rigors, arthralgias, nausea, vomiting, and headaches.[12] Amphotericin-B-induced nephrotoxicity leading to acute renal dysfunction has been generally attributed to two main causes.[13] First, the dose-related rapid vasoconstriction of the afferent renal arterioles causes a decrease in renal blood flow, leading to suppression of glomerular filtration rate. Second, Amphotericin-B forms pores in tubular membranes and changes the dynamics of the ion-transport system, enhancing tubular dysfunction.

Ototoxicity as an adverse effect of Amphotericin-B has been scarcely reported in the literature. Rafael et al mention hearing loss as one of the neurotoxic potentials of intravenous use of Amphotericin-B.[13] Reports mentioning "ototoxicity" as an adverse effect of Amphotericin-B irrespective of its formulations used, has not yet been documented.

However, there is evidence about inner ear tissues being immunologically, biochemically, and functionally related to kidney tissues.[14–17] It is likely that medications affecting renal tubular ion-transport system may also alter ionic homeostasis of the inner ear causing functional problems like hearing loss, which is reversible and dose dependant.[15,18] Similar mechanism has also been illustrated to be involved in reversible form of ototoxicity induced by few medications as mentioned above.

Impaired renal function may allow excessive or persistently high plasma (and perilymph–endolymph) concentrations to develop, thus increasing the risks for ototoxicity. As our patient had an underlying mild renal impairment, he probably underwent a similar patho-biochemical process with Amphotericin-B infusion leading to ototoxicity. The gradual progression of hearing loss leading to complete deafness may be due to cumulative dose-related effects of Amphotericin-B in a setting of existing mild renal impairment. Subjective improvement of hearing along with improvement in PTA after the discontinuation of drug indicates that the patient had reversible form of ototoxicity. From this, we can infer that there is definitely a cause and effect relationship between L-AmB and ototoxicity. However, we cannot explain or authenticate the role of steroid (prednisolone) in reversing the hearing impairment in this case.

Conclusion

This is the first reported case to show that Amphotericin-B, even its lipid formulation (L-AmB), can cause a reversible form of ototoxicity in certain vulnerable patients, especially in the elderly and those with renal impairment. Therefore, physicians should exercise discernment and awareness of this disabling adverse effect, when treating patients with Amphotericin-B.

Author Contributions

Conceived and designed the experiments: PCD. Analyzed the data: RK, KS. Wrote the first draft of the manuscript:

PCD. Contributed to the writing of the manuscript: RK, KS, ABD. Agree with manuscript results and conclusions: ABD, KS. Jointly developed the structure and arguments for the paper: PCD, RK. Made critical revisions and approved final version: PCD, ABD. All authors reviewed and approved of the final manuscript.

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