REVERSIBLE SENSORINEURAL HEARING LOSS AFTER RENAL TRANSPLANT IMMUNOSUPPRESSION WITH OKT3 (MUROMONAB-CD3)

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Reversible and irreversible ototoxicity has been documented following the administration of various therapeutic agents. Reversible hearing loss is a known complication following the administration of quinine, salicylates and other nonsteroidal anti-inflammatory drugs, and erythromycin. We report a case of reversible hearing loss following OKT3 (murine monoclonal antibody CD3) administration. OKT3, a monoclonal antibody used as an immunosuppressant following cadaveric renal transplants, was associated with a transient sensorineural hearing loss that reversed following discontinuation of OKT3.

KEY WORDS — immunosuppression, OKT3, sensorineural hearing loss, transplant.

CASE REPORT

A 41-year-old man was admitted to the hospital for acute rejection of a renal transplant and started on a daily regimen of 5 mg OKT3 (murine monoclonal antibody CD3; muromonab-CD3) four times per day. His past medical history was significant for right renal agenesis and a left megaureter that necessitated a cadaveric renal transplant 1 month prior to the hearing loss. On admission, the patient had no subjective hearing loss, nor did he have a history of hearing loss, tinnitus, or vertigo. He noted difficulty hearing, poor speech discrimination, and an acute-onset, continuous, nonpulsatile tinnitus approximately 36 hours after initiating OKT3 treatment. He denied any sensation of nausea or vertigo. On physical examination, the patient was found to be afebrile, and with a regular heart rate and rhythm. A head and neck physical examination yielded unremarkable findings, without nystagmus or otologic findings. The tinnitus slowly worsened over the ensuing 3 days. An audiogram on the third day of administration of OKT3 revealed a bilateral, mildly down-sloping, sensorineural hear-

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Fig 1. Pure tone audiograms representing acute onset of sensorineural hearing loss following administration of OKT3. Accompanying tympanograms for these audiograms were normal. For air conduction, O — right ear, X — left ear, Z — contralateral acoustic reflex, I — ipsilateral acoustic reflex. For bone conduction, < — right ear, > — left ear. A) Right ear. Speech threshold 30 dB, speech discrimination 92%. B) Left ear. Speech threshold 35 dB, speech discrimination 88%.
The speech thresholds and discriminations were 15 dB and 88%, respectively. The patient's tympanograms and acoustic reflexes were normal.

The patient was treated with OKT3 for a total of 8 days, until it was felt that the OKT3 could be safely discontinued. During this time, the patient was closely observed for progression of the auditory findings, and no change was noted. The patient was discharged home on the same medications as those he had taken previously. Over the next several days his hearing slowly improved, although the tinnitus persisted. A follow-up audiogram 10 days after the discontinuation of OKT3 showed marked improvement (Fig 2): the audiograms for the right and left ears showed essentially normal hearing up to 2,000 Hz, with a downsloping, high-frequency sensorineural hearing loss. The speech thresholds and discriminations were 15 dB and 100% for the right ear and 10 dB and 96% for the left ear. He has since noted slow improvement of the tinnitus.

DISCUSSION

Reversible ototoxicity has been demonstrated after the administration of various pharmacologic agents, including salicylates and erythromycin. Salicylate-induced ototoxicity has been the most extensively studied model for reversible hearing loss, and seems to be multifactorial. While there is no obvious morphologic cochlear damage, salicylates seem to alter the electrophysiologic milieu of the outer hair cells. They also seem to exert an effect, via arachidonic acid metabolites, on cochlear blood flow.

Also to be considered in the differential diagnosis of any case of sudden hearing loss is the possibility of trauma, syphilis, a postviral syndrome, an autoimmune phenomenon, a perilymphatic fistula, or a transient ischemic event. In the case discussed above, the differential is focused and narrowed by the history antecedent to the presenting symptoms. The patient had no recent history of trauma, nor any recent history that would predispose him to developing a perilymphatic fistula. The possibility of the patient's having a postviral, an autoimmune, or an ischemic-related hearing loss remains plausible; however, the patient's lack of other symptoms suggesting a prior viral cause, the time course associating the advent of hearing loss with the administration of OKT3, and the resolution of hearing loss with cessation of OKT3 strongly point toward the role of OKT3 in this case of reversible hearing loss.

OKT3 is a murine monoclonal antibody used in the treatment of acute rejection of renal allografts. This antibody reacts with the CD3 portion of a surface molecule on thymocytes and mature human T-cells. Once bound to OKT3, the CD3+ cells are opsonized, and subsequently removed by the reticuloendothelial system. OKT3 has been found to significantly reduce the rate of renal transplant rejection; however, the use of OKT3 has been hampered by a constellation of side effects that range from pruritus, rashes, headaches, and diarrhea to hypotension, aseptic meningitis, seizures, and anaphylaxis. Reported aural side effects include auditory hallucinations and otitis media (secondary to increased vascular permeability), but there has been no documentation in the literature to date of OKT3's producing sensorineural

![Diagram of pure tone audiograms representing subsequent resolution of hearing loss 10 days after discontinuation of OKT3.](image-url)
hearing loss. The current patient had no prior history of hearing loss or other auditory complaints. He was taking furosemide as a part of the initial posttransplant regimen; however, he noted no hearing loss during the month he was on the drug prior to the hearing loss. Moreover, once the course of OKT3 had been completed, the patient continued taking the same dose of furosemide. The only variable that marked the transient loss of hearing and the advent of tinnitus was the administration of OKT3.

The pathophysiology of this case of transient sensorineural hearing loss is unknown. One possibility hinges on the association of OKT3’s so-called “first-dose” reaction with the release of several cytokines. The effect of various cytokines and neurotrophins on the organ of Corti has been well documented. Further investigations into the effects of OKT3 on the inner and outer hair cells, as well as on the spiral ganglia neurons, might be insightful. Another possible explanation for the untoward effects of OKT3 on the auditory system is suggested by the increased vascular permeability following administration of OKT3, which can predispose a patient to developing otitis media. It may well be that such vascular changes alter the environment of the inner as well as the middle ear. Whatever the exact explanation may be, the effect seems to be reversible, as discontinuation of OKT3 led to a resolution of hearing in this patient.

To date, the patient still has sensorineural hearing loss at frequencies higher than the normal spoken frequencies and some degree of tinnitus. It remains to be seen whether the effects of OKT3 are fully reversible after its discontinuation. However, it is notable that the auditory side effect that is perhaps the most severe, namely, hearing loss, is transient in nature and appears to abate after the discontinuation of OKT3.

REFERENCES