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Title: Hearing loss caused by topical imiquimod for squamous cell carcinoma in situ (Bowen's disease)

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Hearing loss in association with topical imiquimod use for squamous cell carcinoma in situ (Bowen disease)

Dear Editor,

Imiquimod is a topical immunomodifying cream used in the treatment of solar (actinic) keratosis, Bowen disease, condyloma acuminata and superficial basal cell carcinomas. Imiquimod-induced vitiligo is well documented. We have noted a case of topical imiquimod possibly causing hearing loss through an effect on melanocytes.

A 78 year old woman was prescribed imiquimod cream (Aldara®) for a biopsy-proven plaque of Bowen's disease (squamous cell carcinoma in situ) on her right lower cheek.

She had a past history of left-sided Ramsay Hunt Syndrome causing partial facial paralysis and permanent profound hearing loss in her left ear. Her medical history included hypertension and medications included aspirin, atenolol, candesartan/hydrochlorothiazide, amitriptyline and lercanidipine.

The patient applied the imiquimod as prescribed, three times weekly. During the day of her sixth application (day 12), the hearing in her right ear deteriorated. Despite this, she did not experience any recognised side effects, such as cutaneous erythema or flu-like symptoms.

She applied the cream on one further occasion (day 15) and woke that night with mild vertigo and an inability to hear. At no time was depigmentation of the skin noted.

The patient consulted with her Otorhinolaryngology surgeon the next day, whom she had consulted for her Ramsey-Hunt syndrome previously. After a clinical assessment, the patient was diagnosed with severe sensori-neural hearing loss (SNHL) in her only hearing ear, on the right side. Prior to the use of the imiquimod cream she had a mild SNHL loss with a four frequency (05, 1.0, 2.0 & 4.0KHz) pure tone average (PTA) of 38dB and a speech discrimination score (SDS) of 90% (using AB words) (Figure 1). The PTA dropped to 70bB with an up-sloping pattern and the SDS to 0% after use of the cream (Figure 2).

An MRI brain was performed and excluded acoustic neuroma. While this did reveal changes of chronic microvascular ischemia, such changes were not thought to account for her SNHL.

She was treated with a reducing dose of prednisolone starting at 50mg daily over 10 days. Her hearing began to improve in the first seven days (Figure 3) and three weeks later, audiology testing revealed that her hearing had returned to its pre-morbid- level with a PTA of 40dB and SDS of 97%. Her hearing has remained at these levels since.

Imiquimod-induced vitiligo is well documented.[1] Depigmentation may be due to its ability to induce interferon (IFN) α/β, which also induces CXCL10. This pathway promotes the migration of melanocyte-specific, autoreactive T cells into the skin in vitiligo. Of note, melanocytes are also present in the inner ear including the cochlea (stria vascularis, hair cells, Reissner membrane, modiolus, osseous spiral lamina and endolymphatic sac)[2]. Proper functioning of the cochlea and sensori hair-cell survival require melanocytes and melanin. When melanocytes are lost, SNHL may result. Recent reports revealing an association between vitiligo and bilateral cochlear dysfunction supports this theory.[3] Systemic effects such as flu-like symptoms may result from topical imiquimod application. Imiquimod, therefore, could theoretically induce SNHL through the systemic effect of IFNα/β on inner ear melanocytes causing their destruction and subsequent hearing loss.

While hypertension may also adversely affect cochlear function, the temporal relationship between application of imiquimod and the acute onset of the patient's symptoms cannot be ignored. Furthermore, immunosuppression with oral prednisolone may have facilitated melanocyte recovery in the inner ear, resulting in a reversal of the hearing loss.

While a literature review failed to reveal any reports of imiquimod-induced hearing loss, a post-marketing study of Aldara® undertaken by internet site eHealthMe reported hearing loss in two people after using the cream in 2012.[4] Furthermore, hearing loss has been mentioned on various patient-related internet blogs.[5,6]

We acknowledge that SNHL may occur spontaneously and from a wide variety of possible causes[7] and that a definitive cause may not be found. Furthermore, oral corticosteroids may reverse various causes of hearing loss. While ototoxic agents usually exert a bilateral effect on the ears, the hearing loss was experienced in one ear as there was only one hearing ear in this patient.

It is important to alert clinicians to have an increased awareness of such a symptom and to report any further cases. Any symptoms of inner ear disturbance including hearing loss, tinnitus and/or dysequilibrium should prompt rapid cessation by the clinician with urgent Otorhinolaryngology referral.

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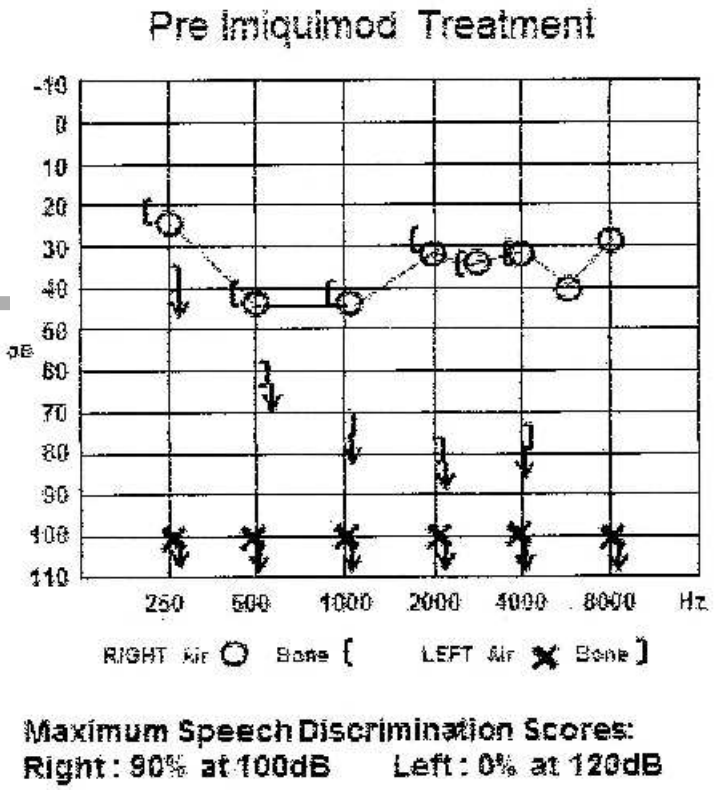

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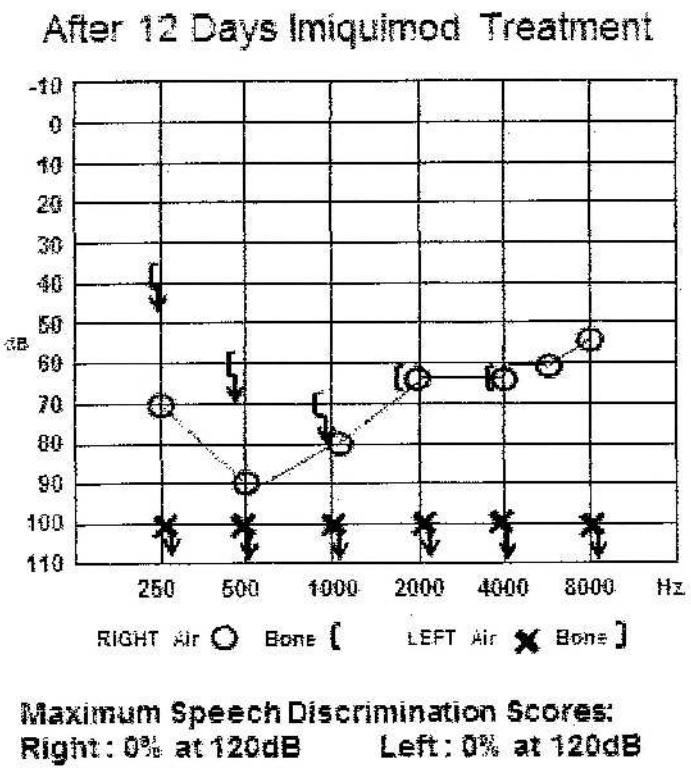

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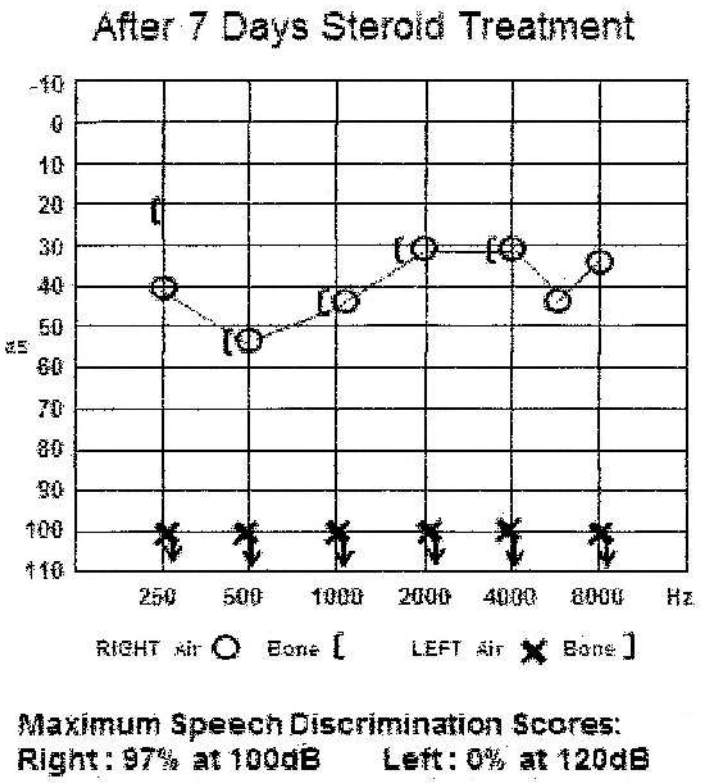

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