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CLINICAL RECORD

Rusty green stained temporal bone associated with exposure to tetracycline: an unusual presentation of black bone disease

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Abstract

Objective: To review the phenomenon and implications of temporal bone and craniofacial bone staining in the context of prolonged exposure to tetracycline antibiotic.

Methods: Case report and literature review.

Results: A 52-year-old male with a 5-year history of tetracycline use presented to undergo tympanomastoidectomy and was found to have an unusual rusty green pigmentation of the entire aspect of the exposed temporal bone. A literature review revealed more than 20 cases of tetracycline-induced pigmentation of intraoral maxillary and mandibular bone, and 2 prior cases involving the cranial bones.

Conclusion: Tissue and organ pigmentation is an unexpected and unfavourable consequence of the use of tetracyclines, particularly minocycline. Tetracycline is contraindicated in children because of the risk for dysosteogenesis and enamel hypoplasia. In adults, although the unusual staining may present as an unexpected dilemma upon surgical exposure, current research shows no significant clinical consequences for this type of pigmentation.

Key words: Anti-Bacterial Agents; Bone Diseases; Minocycline; Pigmentation Disorders; Temporal Bone; Tetracycline

Introduction

The tetracycline family of antibiotics was first introduced in 1947, with the second-generation derivative, minocycline, coming into use in 1967. As a result of its great lipid solubility, complete absorption, high antimicrobial activity, marginal phototoxicity and strong anti-inflammatory properties, minocycline has been used broadly for the treatment of acne vulgaris, acne rosacea, respiratory diseases, infections and rheumatoid arthritis.[1–6]

The use of tetracycline antibiotics has been associated with the unfavourable adverse outcome of pigmentation.[1,7] Pigmentation may be observed in the teeth, mucosa, skin, nails, eyes, cardiac valves and coronary vessels,[8] thyroid, and bones. Discolouration and staining of bone due to prolonged use of tetracycline antibiotics is referred to as 'black bone disease'. Black bone disease most often results from the prolonged use of the minocycline derivative of the tetracycline family. The disease is most common at cumulative doses greater than 100 g administered for a duration of more than four years.[1]

Here we report an original case of pigmentation of temporal bone that was discovered in a 52-year-old male patient who had used tetracycline as a teenager for acne vulgaris. We also provide a summary of our literature review on 'tetracycline induced pigmentation', which involved an exhaustive search of terms relating to tetracycline-induced pigmentation, including 'staining', 'minocycline' and 'antibiotic'. Also included were pertinent references of articles identified in the primary search. We identified 26 relevant articles, of which 17 were specific case reports.

Case report

A 52-year-old male with a history of chronic right ear infections and tympanic membrane perforation presented to undergo revision tympanomastoidectomy. Upon surgical exposure, the temporal bone did not appear white, as one would expect of cranial bones. Instead, it was found to be pigmented, having an unusual rusty green colour (Figures 1 and 2).

The patient's history was significant for tetracycline use from the ages of 14 to 19 years to treat acne vulgaris. His medical history was also notable for a prior cholesteatoma in the right ear, which was treated via tympanomastoidectomy when he was 14 years old. According to the patient's records, there were no observable discolourations of the underlying temporal bone at that time, prior to initiation of the tetracycline antibiotic. The patient did have a history of stained impacted molars upon extraction during his college years. He did not use any other medications and had no other underlying medical problems. Interestingly, the patient has a twin brother who also used tetracycline for acne vulgaris from the ages of 14 to 19 years, and who had also been told by the dentist that his extracted molars appeared unusually stained and discoloured.

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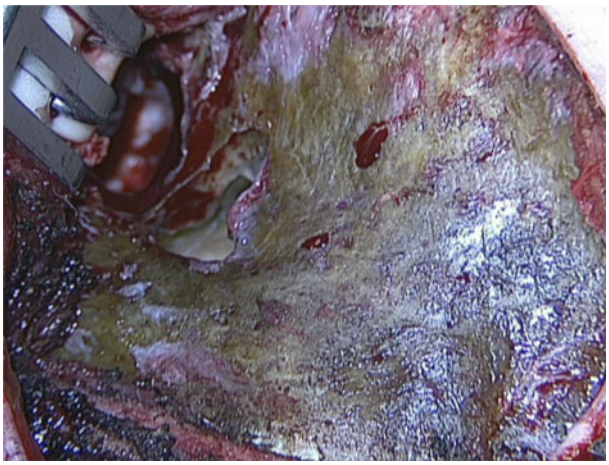

FIG. 1
Stained temporal bone discovered in the patient upon tympanomastoidectomy (magnified ×10).

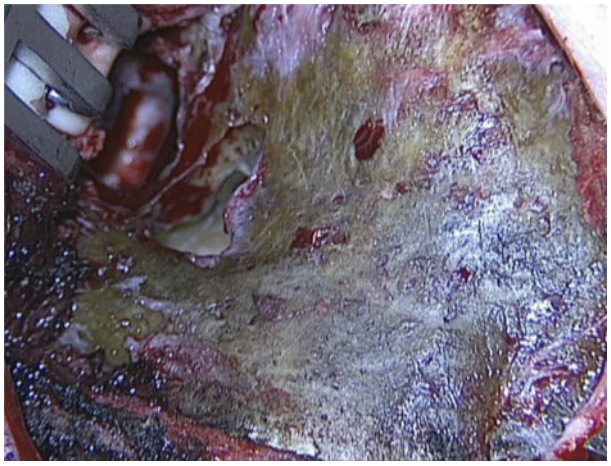

FIG. 2
Further examination of stained temporal bone in the patient (magnified ×10).

The temporal bone staining (black bone disease) in our presented patient was attributed to the use of tetracycline for acne vulgaris as a teenager. Black bone disease has been associated with multiple causes; tetracycline use is one possible cause that has gained more attention in recent years.

Discussion

While serving many useful purposes, the tetracycline family of antibiotics, particularly minocycline, may also come with the unappealing side effect of tissue staining. Tissue staining is rare and difficult to diagnose; its occurrence has been linked to ochronosis secondary to alkaptonuria, metabolic bone diseases, metal deposits, sequestrum, metastatic disease and high-dose levodopa therapy, in addition to minocycline use.[9–11] Such staining is most common with very long-term antibiotic use and large doses greater than 100 g.

Minocycline, a derivative of tetracycline, is used for both its antibiotic and anti-inflammatory properties, and often requires long-term use for such conditions as acne, rheumatoid arthritis and rosacea.[11–14] Like other tetracyclines, minocycline is rapidly and permanently absorbed into bone, but it is also more lipophilic, and has a greater distribution and half-life.[2,5]

There are multiple theories as to the mechanism of minocycline-induced pigmentation; however, the true mechanism of the staining is not completely understood. It is thought to be caused by the black degradation and oxidation products of minocycline, and their unique structures that allow binding and tissue pigmentation. Oxidised minocycline has the ability to bind ferric iron, among other constituents, which can then deposit into developing teeth, cartilage and bone.[15] As stated by Sánchez *et al.*: 'The permanent discolouration it causes has been noted to vary from yellow or grey to brown, depending on the dose or the type of drug received in relation to the recipient's body weight'.[15] In addition, the degradation products iron, melanin and calcium have been shown to be constituents of the pigment.[1,15–19]

In a typical situation, after absorption, minocycline gets bound to plasma proteins and circulates through various tissues. It binds to those tissues that have an especially strong affinity to it, like bone, collagenous tissues, dental pulp and dentin. Through non-specific and non-enzymatic reactions, minocycline slowly takes on the form of the coloured product; it may take several weeks to as much as two years for the pigmentation to appear in tissues.[1,3,10,20]

Based on a review of the literature, we were able to find over 20 reported cases of intraoral bone and mucosal staining; these cases of dental and intraoral mucosal staining composed the vast majority of reported cases involving tetracycline-induced discolouration. In addition, we found two cases involving cranial bones,[21,22] and eight cases that involved pigmentation in tissues in extracranial sites such as heart valves, bones and joints in the shoulders, hands, legs, knees and feet, as well as cutaneous pigmentation.[9,11,16,17,19,23,24] Although rare, it is important to be aware of the possibility of diffuse tissue staining throughout the body.

- **Tetracycline antibiotics (minocycline in particular) are associated with tissue staining and pigmentation, especially with long-term or high-dose use**
- **Staining is most commonly observed in teeth and oral mucosal tissue**
- **Rare cases of pigmentation in body tissues below the neck (skin, heart valves and bones) have also been reported**
- **Long-term minocycline ingestion has been associated with black thyroid pigmentation, also known as black thyroid disease**
- **Bone and tissue pigmentation in the context of tetracycline has not been associated with negative clinical consequences in adult patients**
- **However, minocycline use has been associated with dysosteogenesis and enamel hypoplasia in children**

Awareness of black thyroid disease is important. Over 60 cases of black thyroid pigmentation as a result of minocycline ingestion for weeks to years have been reported.[25] Black thyroid disease is specifically distinguished by the melanin-like pigmentation and bleaching with potassium permanganate, and lack of autoimmune fluorescence, iron

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deposits or lipfuscin.[26] Although the pigment accumulation mechanism has not been fully elucidated, most associate it with minocycline's ability to competitively inhibit thyroid peroxidase in active thyroid tissue.[26]

It is important for physicians to recognise the association of tissue staining with the prolonged use of tetracycline antibiotics, and to decide whether continued antibiotic use is still warranted. In most reported cases, minocycline-induced staining of bone was reversible after discontinuing use, although tooth pigmentation was permanent.[6,15,16] Unusual pigmentation may be discovered intra-operatively as an unexpected and surprising finding.

Although grossly unappealing, bone pigmentation has not been specifically reported to have any negative clinical consequences for the adult patient.[10,11] In children, however, minocycline use has been associated with dysosteogenesis and enamel hypoplasia, and for this reason tetracycline is contraindicated in children.[1,15,16]

Conclusion

Tetracycline antibiotics are used broadly for the treatment of acne, infections and arthritis. An unexpected and unfavourable consequence of long-term, high-dose tetracycline use, particularly minocycline, is pigmentation and staining of various organs and tissues, known as black bone disease. This may present unexpectedly upon surgical exposure. However, physicians should be able to recognise the staining in the context of a proper history and examination, and understand that the current research shows no clinical or physiological consequences of this type of pigmentation for the patient.

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