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Case Reports and Series

Green Bone: Minocycline-Induced Discoloration of Bone Rarely Reported in Foot and Ankle

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ABSTRACT

The tetracycline antibiotics incorporate into bone similar to bisphosphonates. Tetracycline stains bone a fluorescent yellow and minocycline, more commonly used for chronic acne, stains bone dark green. Owing to its frequent use, the occurrence of green bone discoloration due to antibiotics in the tetracycline class is well understood. Its pigmentation can be seen through delicate, thin tissue as a dark blue-gray. Histologic inspection of this bone will confirm a benign condition without evidence of bone disease. Although yellow and green discoloration has been documented frequently in association with oral surgery, it has been reported less commonly in the lower extremity. Green discoloration of bone has rarely been reported in the foot and ankle. Unlike other forms of hyperpigmentation of the skin and bone, this entity is benign when resulting from tetracycline therapy. It is always prudent to have a clinical correlate for an unusual discoloration or hyperpigmentation of any tissue when it exists. In the absence of a definitive clinical correlation, a biopsy is warranted. The following case studies provide a pictoral of green bone as it was encountered in the foot and ankle of 2 young adult females undergoing surgery.

Tetracycline incorporation into bone has been described in multiple areas of the skeletal system. Including the 2 present cases, >30 case of tetracycline incorporation into bones have been reported. Most of these (23 cases) have been in the mandible or alveolar bone of the maxilla (1). One case was noted in the clavicle (2). Another report described black discoloration in the vertebrae in a patient with a 6-year history of minocycline use (3). Tetracycline incorporation has also been noted in the femur during total knee arthroplasty (1). The most recent report was of discoloration of the acromion and, after biopsy, in the iliac crest (4). Before the present report, only rare cases of bony discoloration below the knee have been reported. Whether the rarity of tetracycline-induced bone discoloration in the foot and ankle has resulted from its infrequent occurrence or underreporting is a matter of speculation. We believe discussion of the present 2 cases of green bone secondary to exposure to tetracycline drugs is important for specialists in lower extremity surgery and medicine, because it can be mistaken for other more morbid diagnoses associated with hyperpigmentation of tissue.

Tetracyclines were introduced to the medical community in 1947, and minocycline, a semisynthetic tetracycline, was introduced 20 years later (5–7). Tetracyclines have antimicrobial action by binding to the 30s subunit of bacterial ribosomes and inhibiting protein synthesis (8,9). They have antimicrobial effects against gram-positive and gram-negative bacilli, methicillin-resistant *Staphylococcus aureus*, Enterobacteriaceae, spirochetes, actinomyces, chlamydia, and rickettsia (5,7–9). Minocycline, in particular, was found to have greater antimicrobial activity than all other tetracyclines and achieves a peak serum concentration in only a few hours (6,10). In addition to antimicrobial activity, minocycline is also known to have an antiinflammatory action, which has been demonstrated by its antichemotactic and anticollagenase activity (11–14). This antiinflammatory property has led to its long-term use for rheumatoid arthritis, rosacea, and acne (1,12,15,16). Minocycline is commonly used in treating chronic acne because it is the most lipid soluble of the tetracycline class of antibiotics. In both of the present cases, the common denominator was the long-term use of minocycline.

The side effects of minocycline have been described in detail. Hyperpigmentation is the most common side effect and has been described in many areas, including the skin, oral mucosa, tongue, teeth, nails, and bones (2,6,12,17–20). Skin hyperpigmentation has been attributed to iron deposits in dermal macrophages, typically formed by minocycline degradation or iron-chelated minocycline

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(1,12,18). Other side effects of tetracycline/minocycline use include gastrointestinal irritation, nausea, vomiting, vestibular toxicity, and hepatotoxicity (7).

The first description of tetracyclines incorporating into bone was in 1957 (21). Deposition of minocycline into bones has been described secondary to chelation of minocycline with both calcium and magnesium, and it has been noted that skeletal incorporation occurs rapidly after parenteral administration (21,22). Dahners and Bos (23) proved that incorporation only occurs in live bone. They administered 100 mg of doxycycline by mouth twice daily to a patient with known chronic osteomyelitis. Months later, with bone debridement, all live bone fluoresced secondary to doxycycline incorporation, and any necrotic bone was easily identified by the nonfluorescence and debrided (23). A study by Oklund et al (5) revealed affected adult bone to be structurally sound. In the present cases, no deleterious effects were found on bone healing. Although all these cases have been in fully developed bone, problems have occurred with tetracyclines in growing bone. Studies have shown that tetracyclines cause a reversible decrease in fibular growth in premature children (24). Animal studies have shown a decrease in bone maturation in developing monkeys and inhibition of mineralization and development in chick embryos, although no deleterious effects were found in adult rats, dogs, or monkeys (25–27).

Identification of tetracyclines in bone is by high-intensity ultraviolet illumination. The first description of tetracycline fluorescence in bone was in 1958 by Milch et al (28), and the wavelength originally described was 365 nm (29). However, when affected bone has been decalcified, it will not fluoresce at any wavelength, giving more support to the incorporation being secondary to chelation with calcium (7,30). Spectrophotometry has also been used for the identification, and the peak wavelength recommended is 380 nm (7). Using a fluorescence microscope with a dark field filter, tetracycline-labeled human bone from ancient Sudanese Nubia (A.D. 350) fossils has been documented (31). This is a testament that this chemical reaction has been occurring in bone since ancient times.

Although the concept of the tetracycline drugs, specifically minocycline, causing discoloration of bone is not new, reports of such changes within the foot and ankle are rare (19,32). Hyperpigmentation of tissue secondary to minocycline can be divided into 3 clinical categories based on the pathophysiology (19): type I, dark blue-black macules in regions of depressed acne scar that are sharply demarcated; type II, circumscribed hyperpigmented macules or a more diffuse hyperpigmentation remote from the infection or inflammation and most commonly reported in the lower leg and sun-exposed regions of the skin; and type III, referred to as "muddy skin syndrome," which appears as a dark brown-gray or off-color tan, is found generalized over the body but appears lighter in non–sun-exposed areas. The pigmentation when seen on the face looks like poorly applied cosmetics or otherwise factitial. None of these 3 types of hyperpigmentation will be perceptible on plain radiographs. We present 2 such cases in which the use of minocycline was associated with discoloration of bone in the fibula and the first metatarsal bone.

Case Report

Patient 1

In May 2007 a 19-year-old female presented to the senior author's office (M.S.J.) 11 months after open reduction and internal fixation for an ankle fracture dislocation. That procedure had been uncomplicated, and she had recovered promptly, returning to all her usual daily and athletic activities as desired. The chief complaint was of a black-brown discoloration that had broken out over the region of her lateral ankle (Fig. 1). The pigmentation seemed to be darkest in the region of the fracture; however, it extended the entire length of the retained hardware. The black-brown coloration became more diffuse the further it was from the site of the hardware. The margins of the pigment were indistinct and spared the region of the cicatrix. Her skin had a normal texture and turgor otherwise, and no elevated regions, deep dermal defects, or nodular eruptions were present in the area. No evidence of skin adhesions was found, and the cicatrix was supple, without thickening or pigmentation. The ankle motion was smooth and noncrepitant, and she had no evidence of joint pain. She had a full range ankle motion that had a spongy end feel with and without knee flexion. Her muscle strength was graded as 5 of 5 for all groups about the leg and ankle, and her neurovascular status appeared within normal limits.

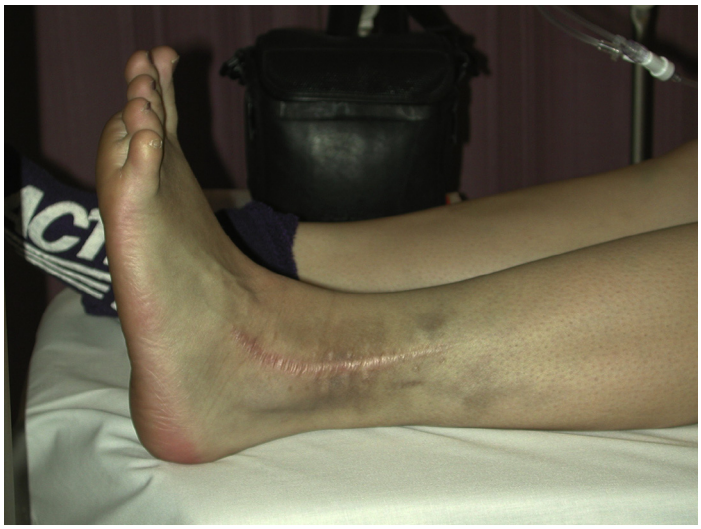

Fig. 1. Clinical photograph 11 months after treatment of the patient's ankle fracture. Note the black-gray hyperpigmentation visible throughout the lateral ankle in the region of the internal fixation devices. The pigmentation appears darkest at the area of the fracture but extends the entire length of the plate and screw fixation devices. The margins of the pigment were indistinct and spared the region of the cicatrix.

Additionally, progressive morning stiffness in the ankle had evolved over the previous few months. This correlated with the timing of the skin discoloration. She denied pain, and, despite wearing prescription orthotics regularly, the ankle stiffness had developed insidiously many months after her recovery from surgery. The stiffness had begun to interfere with her usual daily activities during the most recent weeks and had failed to respond to ibuprofen 800 mg 3 times daily. She denied any recent injury or changes in activity that could have been related to the skin condition or ankle stiffness. She had not traveled out of the country and had no other allergic reactions or incidence of infection since her surgery 11 months previously. When asked about metal allergies, she recalled that during her adolescence she had worn a copper ring for ~2 years that had left a dark brown ring around her finger once it was removed. The suspicion for a metal allergy causing a skin reaction and associated ankle stiffness was highest on the differential diagnosis list; however, the consideration for hyperpigmentation due to melanoma could not be excluded. She was otherwise healthy, and her medication history included only minocycline for chronic acne. Plain radiographs failed to reveal evidence of degenerative change, periostitis, osseous insufficiency, or fracture. Migration of the most proximal screw was noted compared with the views immediately after open reduction and internal fixation. However, it was not palpable on clinical examination (Fig. 2).

The patient requested removal of the internal fixation. She had a number of social issues that factored into her decision. She would only