Minocycline-induced Black Bone Disease Encountered During Total Knee Arthroplasty

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Abstract

Finding discolored bone intraoperatively can be confusing and concerning to orthopedic surgeons. Multiple causes of pigmented bone exist, including ochronosis, metabolic bone diseases, metal deposits, sequestrum, metastatic disease, and minocycline use. Bone quality is an important consideration in intraoperative decision making with respect to components and fixation options in total joint arthroplasty. Abnormal bone encountered in routine arthroplasty can raise concerns over the integrity and healing potential of the bone when the etiology is uncertain.

Minocycline is a drug routinely used for the treatment of acne, rosacea, and rheumatoid arthritis. Pigmentation is a commonly recognized adverse reaction associated with most of the drugs in the tetracycline family, affecting the skin, nails, teeth, oral mucosa, bones in the oral cavity, ocular structures, cartilage, thyroid, and other visceral structures.

This article describes a case of pigmented bone secondary to minocycline use in a 55-year-old woman undergoing total knee arthroplasty. This entity has rarely been documented in the orthopedic literature; however, orthopedic surgeons should be aware of this side effect secondary to the widespread use of minocycline. Questions concerning the effect of minocycline on bone metabolism and structural integrity have yet to be fully answered, but an understanding and recognition of the entity will help guide surgeons with intraoperative decision making.

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Figure: Intraoperative photographs during primary total knee arthroplasty showing violet-black discoloration of the distal femur and proximal tibia after patellar eversion (A) and subchondral bone involvement of abnormal pigmentation after standard femoral cuts and provisional tibial eminence cut (B).
Bone quality is an important intraoperative consideration with respect to components and fixation options in total knee arthroplasty (TKA). Abnormal bone encountered in routine TKA can raise concern over the integrity and healing potential of the bone when the etiology is uncertain. This article describes a case of violet-black bone discoloration encountered during TKA in a woman with a >10-year history of minocycline use for the treatment of rosacea. Although several cases of minocycline-induced bone pigmentation have been reported in the dental and oromaxillofacial surgical literature, it has rarely appeared in orthopedic publications. The patient provided informed verbal and written consent for data concerning her case to be reported.

**CASE REPORT**

A 55-year-old woman presented with a >1-year history of left knee pain. Her medical history was remarkable for hypertension, hypothyroidism, gastroesophageal reflux, seasonal allergies, depression, and rosacea. Her surgical history was significant for a right total hip arthroplasty and bilateral knee arthroscopies. Her medication profile included escitalopram, fexofenadine, lansoprazole,levothyroxine, metoclopramide, trazodone, and minocycline, the latter of which was prescribed for rosacea.

On physical examination, she was able to independently ambulate with a mild antalgic gait secondary to left knee pain. Her left knee had a mild effusion but no skin lesions. The patient had tenderness to palpation at the medial and lateral joint lines, with no significant varus or valgus deformity. No significant ligamentous laxity existed. Left knee range of motion (ROM) was 5° to 120°, with positive patellofemoral crepitus. Left lower-extremity neurologic and vascular examinations were within normal limits. Standard radiographs revealed degenerative changes in all 3 compartments.

The patient failed multiple conservative treatment modalities over the past year, including physical therapy, bracing, and oral nonsteroidal anti-inflammatory drugs. In addition, left knee arthroscopy 6 months previously had revealed tricompartmental grade III to IV chondromalacia and a degenerative lateral meniscal tear (Figure 1). No bony or soft tissue discoloration existed. In the interim between arthroscopy and presentation, she had also completed a 3-injection course of viscosupplementation, with transient relief. Despite these measures, the pain was compromising her ability to rest and perform activities of daily living. After appropriate medical and dental clearance, she was scheduled for TKA.

On making a midvastus medial parapatellar approach, the knee fluid was a normal color and consistency. With eversion of the patella, all exposed bone surfaces in the 3 knee compartments were discolored, with violet to black pigmentation. After standard tibial and femoral cuts were made, further examination revealed that the pigmentation was prevalent in the layer of subchondral bone diffusely (Figure 2). No discoloration of the periartricular soft tissues or remaining cartilage existed. Bone and soft tissue specimens were sent for histologic examination.

A TKA was performed, with the decision to fix the femoral and tibial components with cement due to concerns over the bone quality affecting growth potential. The patella was not resurfaced per the preference of the attending surgeon. Histologic bone examination confirmed evidence of osteoarthritis without inflammatory process or other significant pathologic change. Calcified and decalcified specimens exhibited no fluorescence.

Postoperative chart review and discussions with the patient revealed that she had been taking 100 mg of minocycline per day for >10 years for the treatment of rosacea. Closer physical examination revealed a subtle blue hue to her sclera but no other cutaneous pigmentionations. Prior arthroscopy revealed a subtle dark hue. The postoperative hospital course was uneventful and she was progressing well, with excellent joint stability, pain relief, and ROM from 0° to 110°, at 3-month follow-up. Radiographs revealed proper component alignment and no evidence of component loosening.

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**Figure 1:** Intraoperative arthroscopic image of the left knee showing grade III to IV chondromalacia changes but no discoloration.

**Figure 2:** Intraoperative photographs of during primary total knee arthroplasty showing violet-black discoloration of the distal femur and proximal tibia after patellar eversion (A) and subchondral bone involvement of abnorom pigmentation after standard femoral cuts and provisional tibial eminence cut (B).
Discussion

The finding of discolored bone intraoperatively is confusing and concerning to orthopedic surgeons. Multiple causes of pigmented bone should be considered, including ochronosis, metabolic bone diseases, metal deposits, sequestrum, metastatic disease, and minocycline use. Minocycline is a commonly used drug for the treatment of acne, rosacea, and rheumatoid arthritis. Minocycline is a synthetic derivative of tetracycline that was introduced in 1967. Pigmentation is a commonly recognized adverse reaction associated with most of the drugs in the tetracycline family, affecting the skin, nails, teeth, oral mucosa, bones (primarily in the oral cavity), ocular structures, cartilage, thyroid, and other visceral structures. However, minocycline is the derivative that is most often associated with pigmentation. The ability of tetracycline and its derivatives to chelate calcium ions allows incorporation into normal bone. Minocycline that is deposited is typically black or blue-black and represents a degradation product or a drug complex and resembles hemosiderin. Bone pigmentation is typically a result of long-term use at doses >100 g. If pigmentation exists, the antibiotic should be discontinued.

Pigmented bone has been well documented in the dental and oromaxillofacial surgical literature, affecting the mandible and the alveolar bone of the maxilla. However, documentation in the orthopedic literature is sparse, consisting of case reports of discolored bone reported during elective surgery. Case reports have described blue-green bone found during TKA, green bone found at the clavicle during cyst removal, black vertebrae found during partial hemi-laminectomy, and black bone found on the acromion during subacromial decompression. All patients had been previously treated with minocycline.

Diagnosis, prevalence, and changes in bone metabolism are issues with minocycline-pigmented bone that should raise concern in orthopedic surgeons. Tetracycline and tetracycline compounds deposited in bone fluoresce under ultraviolet light, which allows tetracycline and derivatives to be used in orthopedic research to evaluate bone formation. Tetracycline-labeled bone will fluoresce under ultraviolet light, and minocycline, as a derivative, should as well. However, minocycline-stained bone exhibits no fluorescence under ultraviolet light.

Therefore, to appropriately make this diagnosis, an extensive review of the patient’s medical history is recommended, noting current or prior use of tetracyclines or derivatives. A meticulous physical examination should also be performed, looking for other signs of pigmentation, most notably the skin, nails, eyes, and oral mucosa. Intraoperatively, pigmented bone should be sent for histologic evaluation and fluorescence testing.

Bone pigmentation in the oral cavity has been proposed to affect 10% of patients taking minocycline for >1 year and increase to 20% after 4 years. The orthopedic literature is limited on the prevalence of bone pigmentation and minocycline use. Further research and documentation is needed.

The effects of minocycline on human bone quality, structure, and function are unknown. Several animal models have evaluated minocycline and bone interactions. Williams et al reported that minocycline reduced bone resorption and stimulated bone formation in a rat model. Holmes et al supported this finding in a rabbit model, showing the inhibition of bone resorption. This area of study would benefit from further investigation and research in human bone.

Conclusion

This article describes a case of pigmented bone secondary to minocycline use. Orthopedic surgeons should be aware of this complication secondary to the widespread use of minocycline for the treatment of acne, rosacea, and rheumatoid arthritis. Questions remain concerning minocycline and bone metabolism, but an understanding and recognition of this entity will help guide surgeons intraoperatively.

References