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Minocycline-induced black bone disease with synovial pigmentation in a patient undergoing revision anterior cruciate ligament surgery: A case report

Harmen D. Vermeijden^a, Jelle P. van der List^b, Yao-Tseng Chen^c, Gregory S. DiFelice^{a,*}

^a Orthopaedic Trauma Service, Department of Orthopaedic Surgery, Hospital for Special Surgery, NewYork-Presbyterian, Weill Medical College of Cornell University, New York, NY, United States

^b Amsterdam UMC, University of Amsterdam Department of Orthopaedic Surgery, Amsterdam, the Netherlands

^c Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, NY, United States

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ABSTRACT

INTRODUCTION: Long-term use of minocycline at high doses is associated with hyperpigmentation with multiple sites of involvement. While the cutaneous organs and the oral cavity are most commonly affected, bone discoloration is a rare entity.

CASE PRESENTATION: A 19-year-old male patient with a history of acne vulgaris and intermittent treatment with high dose minocycline for three years presented with recurrent anterior cruciate ligament (ACL) tear. During arthroscopic surgery, however, hyperpigmentation of the femur and synovium was observed. Abnormal tissue was biopsied and confirmed through histopathological examination to contain melanin-related minocycline pigmentation. Revision surgery was re-scheduled with no intraoperative complications and excellent long-term clinical outcomes.

CLINICAL DISCUSSION: There are several possible causes of hyperpigmentation, including hemosiderin deposition, infection, aseptic necrosis, demineralization, and metastatic disease. Black bone disease, caused by minocycline-induced hyperpigmentation, is rare. While the appearance is grossly abnormal in black bone disease, there has been no evidence suggesting that tissue integrity is compromised.

CONCLUSION: This case confirms that hyperpigmentation does not affect bone integrity and that surgical procedures can be performed safely. Knowing the adverse effects of minocycline administration could reduce inappropriate postponement of surgical procedures, thereby saving time and resources.

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1. Introduction

Minocycline is a broad-spectrum antibiotic agent routinely used as systemic therapy for acne vulgaris, rosacea, and rheumatoid arthritis, due to its potent antimicrobial and anti-inflammatory effects [1,2]. Long-term use (>1 year) of minocycline at high doses (>100 mg/day) is associated with hyperpigmentation with multiple sites of involvement. [3]. While the cutaneous organs and the oral cavity are most commonly affected, bone discoloration is a rare entity [4]. Although we are aware of approximately 20 reported cases involving minocycline-induced bone discoloration observed during open surgical procedures [5], the literature regarding arthroscopically identified hyperpigmentation is scarce [6].

We present a case of a 19-year-old male with a 3-year history of minocycline use for treatment of acne vulgaris who was found

to have hyperpigmentation of the femur and the synovial membrane of the knee joint observed during anterior cruciate ligament (ACL) revision surgery. The patient was treated in a private practice setting by the senior author (GSD), who is a fellow-ship trained orthopaedic surgeon with >20 years of experience in ligament knee surgery. This case report has been reported in line with the SCARE 2020 criteria [7].

2. Presentation of case

A 17-year-old male patient presented in 2012 in clinic following self-referral for clinical evaluation after a torsional trauma of the left knee while playing high school football. His medical history was notable for acne vulgaris, treated with an oral dose of minocycline at 105 mg daily for 11 months before his initial injury. No other relevant drug, family, and psychosocial history were notable. The patient presented with moderate pain and ambulation with antalgia to the left. Physical examination revealed mild effusion on the left knee, a grade IB Lachman, and tenderness to the medial and lateral joint line; he was otherwise ligamentous stable and neu-

* Corresponding author at: Hospital for Special Surgery, 535 E., 70th Street, New York, NY, 10021, United States.

E-mail address: difeliceg@hss.edu (G.S. DiFelice).

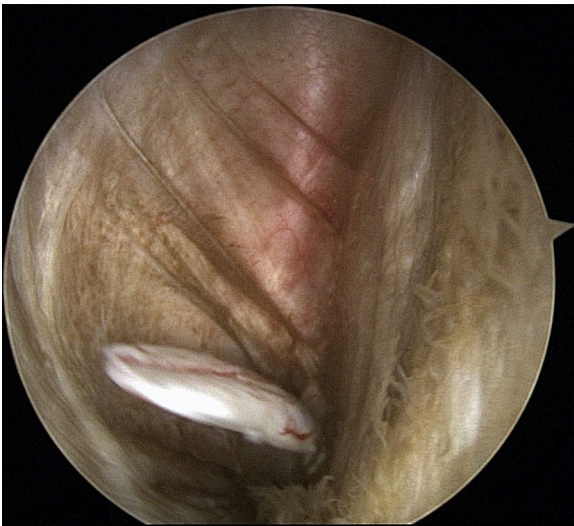


Fig. 1. Arthroscopic view of the left knee with extensive minocycline-induced brown synovitis.

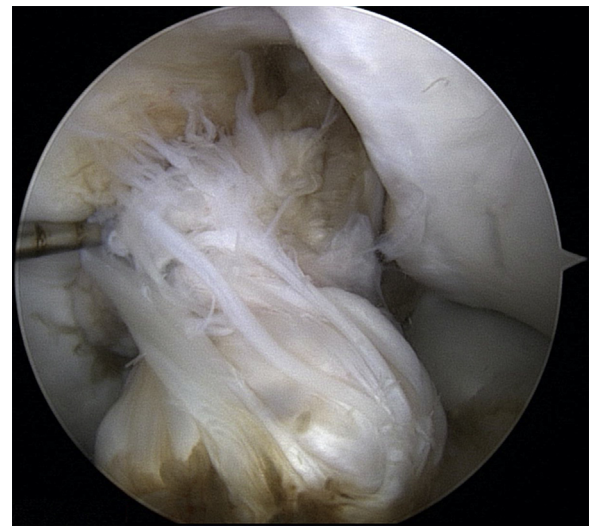


Fig. 2. Arthroscopic view of the left knee shows a torn ACL reconstruction with brown synovitis at its tibial footprint.

rovascularly intact distally. On magnetic resonance imaging (MRI), an ACL and lateral meniscal tear were confirmed. A bone-patellar tendon-bone (BPTB) allograft reconstruction and a partial lateral meniscectomy were recommended, and the operation was completed with no complications. In addition, no abnormal bony tissue was observed.

Early in 2014, the patient sustained a second sport-related injury to his affected knee. MRI revealed a torn ACL graft and a medial meniscus tear of the posterior horn. The patient was scheduled to undergo ACL revision surgery using an allograft Achilles tendon and medial meniscal repair of the left knee.

During surgery, an extensive dark brown synovitis was seen throughout the joint directly after introducing the arthroscope into the left knee joint. The patellofemoral joint and medial compartment had mild chondromalacia. The ACL graft was noted to be torn, and a soft tissue notchplasty was subsequently performed. In addition, there was a significant encroaching osteophyte from the lateral condyle for which a bony notchplasty was performed. On inspection, however, the cortical bone showed abnormal tissue with severe brown-black hyperpigmentation. The gross appearance was significantly more profound in color than the standard hemosiderin that would be seen after hemarthrosis (Figs. 1–3); therefore, a debridement and extensive synovectomy with biopsies were performed and sent for cultures.

Histopathological examination showed both the cortical bone and synovial lining contained abundant pigment-laden macrophages. The nature of the pigments was investigated with iron stain and Fontana-Masson stain (for melanin). These stains showed the presence of hemosiderin, a typical finding arising from old hemorrhage. In addition, a fine, granular pigmentation that stained black was also observed with Fontana-Masson staining (Fig. 4). These finely granular pigments also stained positive with iron stain, indicating the pigment as minocycline-related type 2 pigmentation. No additional osseous pathologies were found on histopathological examination and cultures revealed no infection.

The ACL reconstruction was re-scheduled one month later, without any complications. Post-operatively, early mobilization and passive range of motion (ROM) exercises were allowed within the first days after surgery. Formal physical therapy was then continued as per guidance of his physical therapist. At the latest follow-up, six-year out of surgery, he continued to do well with a negative Lachman and full range of motion (ROM) on physical exam.



Fig. 3. Arthroscopic view of the left knee is showing a large osteophyte of the lateral femoral condyle with brown-black discoloration.

3. Discussion

There are several possible causes of hyperpigmentation, including hemosiderin deposition, infection, aseptic necrosis, demineralization, and metastatic disease [5]. Although hyperpigmentation is an extensively reported adverse effect of minocycline therapy in the oromaxillofacial region, bone discoloration remains a rare entity. Nevertheless, it remains important to consider hyperpigmentation secondary to the chronic use of minocycline, especially in patients with a long-term history of use of the agent.

Minocycline is a semi-synthetic tetracycline derivative first synthesized in 1972 and routinely used for the treatment of acne vulgaris [8]. The broad-spectrum antibiotic agent is a lipid-soluble and long-acting drug that exerts its antimicrobial effect by interfering with protein synthesis of both gram-positive and gram-negative bacteria [9]. Furthermore, it is mostly protein-bound and, therefore, widely distributed in the body. Due to its lipophilicity, minocycline can penetrate tissues readily. Given these characteristics, minocycline agents are commonly used in the long-term treatment for rheumatoid arthritis, rosacea, and acne [10].

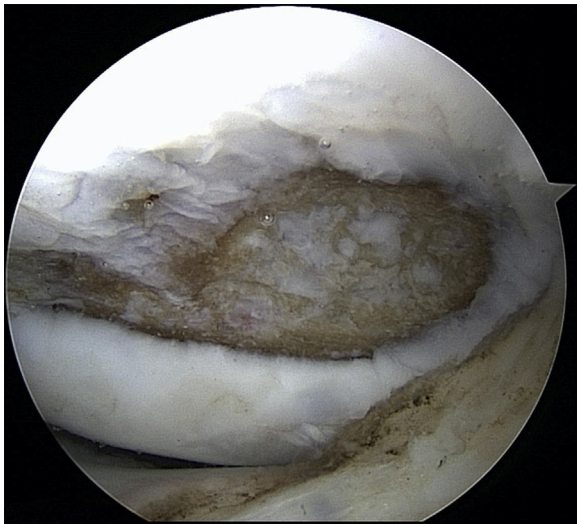


Fig. 4. High magnification view of Fontana-Masson (melanin) stain shows two types of pigments in the bone biopsy, including golden-brown hemosiderin pigment (in its natural color, negative for Fontana-Masson stain) and the minocycline-related type-2 melanin-like pigment, positive stained as fine black granular pigment.

One of the well-documented adverse effects of chronic minocycline use at high dosage is discoloration and hyperpigmentation, including the skin, teeth, nails, and bones [11]. Other reported adverse events of minocycline include but are not limited to photosensitivity, digestive disorders, and teratogenicity [5]. The most common staining location is the oral cavity, with a reported incidence of 3–6% in patients with long-term treatment be adversely affected [6]. This benign discoloration in bones is caused by chelation of the antibiotic with calcium ions or short polypeptides and can be positively identified as a tetracycline-related compound by use of Wood's lamp [12]. As a result, depositions of tetracyclines and its derivatives may incidentally lead to black bone discoloration, commonly referred to as 'black bone disease.' Although hyperpigmentation of bones is thought to be permanent, Cornejo et al. recently reported that minor longevity improvements could be expected after discontinuation of the medication [1].

While the presentation is grossly abnormal in black bone disease, there has been no evidence suggesting that tissue integrity is compromised [4]. However, it should be noted that the potential long-term adverse effects of minocycline-induced discoloration on bone metabolism remain unknown. Nevertheless, grey, brown, or black hyperpigmented bone and the synovial membrane with unknown etiology can raise the specter of indolent infection and question tissue integrity [13]. Therefore, even experienced orthopedic surgeons may be reluctant to continue with the intended procedure and may lead to postponing the surgery. Although the concept of bone discoloration is not new, no arthroscopically identified minocycline-induced black bone disease of the knee joint has been reported on in the current literature; all the cases were encountered during open surgical procedures [5]. Furthermore, in cases where there was bony involvement of the knee joint, it was noted that the synovial soft tissue maintained a normal appearance [4,12,14,15]. As demonstrated in the current case, however, both the bones as well as the surrounding synovial soft tissue could be affected by hyperpigmentation cause by long-term minocycline administration.

4. Conclusion

In the presented case, hyperpigmentation affecting the bones and synovial lining of the knee joint is reported. During the

ACL revision surgery, no structural bone damage was observed, while the long-term clinical outcomes were noted to be excellent. Therefore, this case confirms that hyperpigmentation does not affect bone integrity and that surgical procedures can be performed safely. Nevertheless, further investigation, using biopsies, is advised when no apparent underlying cause for bone hyperpigmentation is presented. Given these findings, the orthopaedic community needs to be aware of this iatrogenic hyperpigmentation phenomenon. Knowing the adverse effects of minocycline administration could reduce inappropriate postponement of surgical procedures, thereby saving time and resources.

Declaration of Competing Interest

GSD declares that he is a paid consultant and receives grants from Arthrex (Naples, FL, USA).

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Ethical approval

The paper is a case report, and therefore does not require ethics approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. Furthermore, there is no identifying characteristic.

Author contribution

HDV: data analysis or interpretation, and writing the paper.
 JPL: study concept and writing the paper.
 YTC: data collection.
 GSD: study concept or design.

Registration of research studies

Not applicable.

Guarantor

Gregory S. DiFelice.

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