CASE REPORT

Black bone disease in a healing fracture

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SUMMARY

Black bone disease refers to the hyperpigmentation of bone secondary to prolonged usage of minocycline. We present a report of a 34-year-old man who underwent femoral shaft fracture fixation complicated by deep infection requiring debridement. The implants were removed 10 months later after long-term treatment with minocycline and fracture union. A refracture of the femoral shaft occurred 2 days after implant removal and repeat fixation was required. Intraoperatively, abundant heavily pigmented and dark brown bone callus was noted over the old fracture site. There was no evidence of other bony pathology and the appearance was consistent with minocycline-associated pigmentation. As far as we are aware, this is the first case of black bone disease affecting callus within the interval period of bone healing. We also discuss the relevant literature on black bone disease to bring light on this rare entity that is an unwelcomed surprise to operating orthopaedic surgeons.

BACKGROUND

Well-documented side effects of minocycline include pigmentation of the skin, teeth, nails and soft tissues. These are externally visible and therefore easily noted and investigated. Few case reports in the orthopaedic literature have documented the presence of bone pigmentation during routine orthopaedic surgery. This hyperpigmentation in bone as a result of minocycline therapy is referred to as 'black bone disease', which, despite its intimidating name, has not been known to disrupt bone healing and implant incorporation. Nonetheless, this finding is usually a cause of alarm for an unsuspecting surgeon who may confuse it with more sinister pathology. We aim to remind readers in the orthopaedic community of this rare entity and also to add to the literature; as far as we are aware, this is the first report to show interval development of pigmented callus from underlying normal bone as a result of minocycline exposure.

CASE PRESENTATION

A 34-year-old man presented with a closed fracture of the left femoral shaft as a result of a road traffic accident. He had no medical conditions and was a non-smoker. There was no history of fragility fractures. Open reduction and internal fixation with femoral plating was performed. This was complicated by fever and haematoma formation adjacent to the inferior part of the implant. The haematoma was explored and washed out and causative muscular bleeders were ligated. Cultures of the haematoma yielded growth of the bacteria *Elizabethkingia meningoseptica*. Clinically, the haematoma was in

the muscular plane and not in contact with the fracture site, but an infectious diseases consult was sought and the patient was initiated on minocycline based on sensitivities. The patient's wounds healed well and he was discharged with long-term minocycline 100 mg twice daily. This was implemented to prevent the possible risk of deep infection or osteomyelitis development given the proximity of the infection to the implant. Removal of implants at the earliest possibility was also recommended in order to discontinue minocycline. Treatment continued for the subsequent 10 months by which point the patient had already been ambulating pain-free, and there was deemed to be adequate union on interval radiographs. Planned removal of the femoral plating and screws was then carried out.

Intraoperative findings during implant removal were significant for a hyperpigmented brown-black callus over the exposed anterior and lateral aspects of the old fracture site. No other abnormalities were noted. The patient recovered well postoperatively, was able to ambulate on the ward and had no other symptoms. Minocycline was intended to be continued for an additional 2 weeks.

Unfortunately, 2 days after discharge, the patient represented with left thigh pain associated with a loud crack while walking leisurely. Radiological investigations showed a displaced left femoral shaft fracture at the old fracture site (figure 1).

Open reduction and internal fixation with intramedullary nailing was therefore planned. To aid reduction, the fracture site was opened and wide exposure was achieved. Intraoperative findings were of a fracture through bone that was encased in brownish-black callus (figure 2). Minocycline was discontinued on the second day postoperatively; the patient recovered well and was discharged on the seventh day.

Figure 1 X-rays showing anteroposterior and lateral views of the patient's left femur with a fracture through the bone, and the abundant callus.

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Figure 2 Intraoperative photograph of the patient's left femur showing the pigmented callus, and the underlying normal bone and fractured site.

INVESTIGATIONS

During the initial implant removal, bone was sampled from screw tracts and sent for cultures. They yielded no microbial growth and, reassuringly, no chronic osteomyelitis had developed.

During the intramedullary nailing procedure after refracture, the fracture site was opened and explored. Cultures were obtained from the fracture site and again no organisms were found.

Histopathological analysis of the pigmented callus showed bone and cartilaginous tissue with fibrosis (figure 3). Metal deposits, granulomas, suppuration, malignancy and sequestrae were not noted. Notably, there were tiny specks of brown pigment material deposited throughout the fibrous tissue (figure 4). Perls stain and Fontana stain were negative, excluding haemosiderin and melanin in the pigmentation. The histopathological features were those of callus formation, and with close clinical correlation, the brownish pigment identified represented minocycline pigmentation.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses for bone pigmentation include but are not limited to ochronosis (from the rare metabolic disorder of

Figure 3 Photomicrograph of the callus tissue showing the typical features of fracture healing, comprising bone formation and fibrous tissue (H&E, original magnification $\times 100$).

alkaptonuria), metallosis from implants, infective changes or malignancy. Our patient had no known medical conditions, was not on regular medication and was fit and well before he presented to us.

Since the initial surgery exposed the femur and no pigmentation was seen, the main differentials relevant to development of pigmentation in this case would include the interval development of infection and possibly metallosis.

Regarding infection—there was no implant loosening, no macroscopic inflammatory soft tissue changes or bony pathology and no microbiological or histological evidence of infection. Throughout the patient's follow-up, inflammatory markers of white cell count, C reactive protein and erythrocyte sedimentation rate had fallen since initial infection, also suggestive of appropriate infection control. The plate and screws on removal were intact with no metallic debris in soft tissue or on bone macroscopically and histologically. The circumferential pigmentation of the new bone (as opposed to pigmentation along the surfaces exposed to the metalwork) also makes a diagnosis of metallosis less likely. Histopathological stains also ruled out melanin and iron in the pigmentation.

TREATMENT

OUTCOME AND FOLLOW-UP

Six months from intramedullary nailing of the femur, our patient is mobilising independently with no significant discomfort and is satisfied with the outcome. There is no plan for implant removal.

DISCUSSION

Minocycline is a semisynthetic tetracycline analogue that has been in use for approximately five decades.

It is commonly used in the treatment of skin infections, acne vulgaris and rheumatoid arthritis, due to its strong antimicrobial and anti-inflammatory properties. Tetracycline has the ability to bind to calcium in mineralising bone and produces yellow fluorescence in UV light, while darker pigmentation ensues on tetracycline oxidation (on exposure to light) and binding to ferric iron.^{1–3} Minocycline staining mechanisms differ from those of tetracycline and minocycline is responsible for staining of other tissues including skin, nails, teeth, sclera, bones, thyroid and breast milk.⁴

Figure 4 High magnification view of the callus showing presence of brownish pigment, either lying loosely in the fibrous tissue (arrowheads) or within histiocytes (arrows) (H&E, original magnification $\times 400$).

Minocycline is a weaker chelator of calcium than are tetracyclines, and there are various theories on how minocycline causes pigmentation, but the exact mechanism is unconfirmed. Detailed discussion of this is beyond the scope of our report, but theories include the ability for minocycline to form an insoluble polymer with iron, and the contention that because minocycline binds to plasma proteins and is well distributed in collagen rich tissues (such as bone), subsequent oxidation produces a pigmented biproduct.^{1–4} Minocycline pigmentation of teeth, unlike that caused by tetracyclines, does not clinically fluoresce in UV light but can fluoresce if treated in an acid medium.^{1–3 5}

Cumulative dose dependence on staining likelihood is evident but varies with tissue type. For example, skin pigmentation in areas of scarring and inflammation do not seem to be dose dependent.⁴ At a dose of 100–200 mg, there is a 10% risk of intraoral bone pigmentation in patients taking minocycline for 1 year, and 20% after 4 years.⁶ Soft tissue pigmentation also increases risk from 0.4% at 100 mg a day for a minimum of 8 months to 4% at 200 mg a day.⁷ It is suggested that soft tissue pigmentation does not occur until cumulative minocycline amounts of 70–100 mg have been taken.⁴ There is no consensus on cumulative dosing for development of pigmentation in skeletal bones.

Although intraoral alveolar bone pigmentation by minocycline is well documented,⁵ it is reported infrequently in the orthopaedic literature. Whereas dental pigmentation becomes obvious to the patient and can be easily inspected, the discovery of pigmented skeletal bones is incidental during surgical exposure/autopsy. We were able to find 16 reports of minocycline bone pigmentation in the orthopaedic literature. Sites reported include the knee joint surfaces,^{8–11} hip joint,⁸ ankle joint,⁸ femur,¹² hip joint surfaces,¹³ clavicle,¹⁴ acromion,¹⁵ metacarpals,¹⁶ metatarsals,^{17 18} iliac crest^{15 19} and spine.¹⁹

These authors have reported a variety of bone pigmentations: usually black,^{11 15 16 18 19} but also blue-green,^{9 17} violet-black,¹⁰ or brown.^{8 13} For simplification, any minocycline-related pigmentation is referred to as black bone disease. Such black bone encountered surgically for arthroplasty or deformity correction was noted to be of normal integrity with no consequences of implant loosening or non-union of fixation on follow-up.^{8 16–18} Concerned surgeons often sent off black bone for histological analysis, which revealed normal bone without any neoplastic or osteomyelitis pathology.^{8 10 13 15 17 18} UV light fluorescence was demonstrated on the specimens in some studies^{9 13 15} but was negative in others.¹⁰ These authors did not describe if their slide specimens were prepared in an acid or alkaline medium—these may each produce a difference in fluorescence demonstration. There is more literature on minocycline-induced skin pigmentation than the few documented cases of minocycline-induced bone pigmentation. Histological analyses of pigmented skin have shown presence of pigment granules in the dermis, or within dermal macrophages or even via increased melanin production.^{1 4 20} In all cases that we could find of black bone disease in the literature, none demonstrated histological evidence of pigment that is so evident macroscopically. Fluorescence in UV light may have helped provide useful information but this is not available in our pathology department. The role of histology is currently more valuable in ruling out sinister causes and actually confirms minocycline-related deposition. Minocycline-induced black bone becomes a diagnosis of exclusion with a supportive history of prolonged minocycline usage.

Another point of discussion is whether minocycline could affect bone healing. Scientific research on tetracyclines has been

carried out in-vitro and in animal models to show their effects on bone metabolism. These include parathyroid hormone inhibition,²¹ induction of osteoclast apoptosis,^{22 23} and inhibiting osteoclast function and differentiation,^{22–24} all resulting in reducing bone resorption.

Experiments specific to minocycline showed reduced osteoclastogenesis in mouse bone marrow,²⁵ suggesting a role in treatment of pathologically accelerated bone resorption. With minocycline alone, through stimulation of bone formation and some reduction in absorption, bone mineral density could be maintained in rats without ovaries.²⁶ In a study on rats, dogs and monkeys treated with minocycline, black discolouration of the thyroid, and yellowing of femurs and skull without detrimental effects on bone growth, were observed.²⁷ Finally, in vitro study of minocycline on human bone marrow showed that normal levels of minocycline (equivalent of 200 mg of daily treatment in adults) increased osteoblastic proliferation with resultant increased bone matrix production. Higher levels of minocycline, however, impaired osteoblastic proliferation.²⁸

Clinical encounters of black bone disease have not shown pathological weakening of bone, and three cases had undergone corrective osteotomy and fixation with adequate healing on follow-up.^{16–18} The authors did not subsequently report on removal of metalwork. There is little clinical or experimental information on the effect of minocycline on fracture healing and whether minocycline may indeed hinder or delay the strengthening or remodelling processes essential for robust healing. With regard to why our patient suffered a refracture after implant removal, we are unable to definitively attribute the cause of refracture to minocycline use as it can be argued that implant removal was performed before adequate consolidation. Removal of metalwork is not a routine orthopaedic procedure unless there are patient-specific indications. It is established that early implant removal has a higher risk of refracture than implants removed after 12 months.²⁹ However, in the literature regarding the femur, refractures following plate removal after complete union have been shown to occur even as late as 18 months from fixation.³⁰ On the other hand, several cases of implant removal within 12 months of femur fixation and as early as 6 months postfixation have yielded no refracture complications in adult populations.³¹

Our decision to remove the implants early took patient factors into consideration. Our patient was able to ambulate fully weight bearing and pain free for several months with no fracture site tenderness, and union had been achieved, based on plain radiographs. He was increasing his day to day activities and, as he travelled abroad for work regularly, there were concerns for remaining compliant to antibiotics. There were limited options for treatment with oral antibiotics in this case and our patient did complain of diarrhoea on and off. After discussion of options, he was also keen to reduce the risk of infection recurrence and opted for early implant removal and discontinuation of long-term antibiotics. Intraoperatively, the callus was hard and there was no obvious evidence of non-union when the implants were removed as the fracture site was bridged with callus and this callus was only debrided as much as required to enable removal of the implants. However, clearly, the new bone had not consolidated to adequate strength for routine activity, or there was an element of hyper trophic non-union. As no CT scanning was carried out, we cannot exclude the latter. Nonetheless, we do not suggest in this report that minocycline pigmentation has any role to play in early refracture.

Black bone disease is usually noted during elective orthopaedic surgery as generalised staining of the exposed bone and

can cause concern for other sinister pathology. In our case, it was only the new bone formation that had acquired pigmentation through minocycline use during the fracture healing phase. The underlying bone on callus removal had not pigmented, with the implication that areas of active bone formation are affected early. Tetracycline fixation in bone has a predilection for bone closely related to vascular supply, and to bone that has active growth and mineralisation; this includes callus formation at a fracture site.³² This may well apply to minocycline, as minocycline is known to cause early pigmentation of skin with active inflammation.⁴

Unlike other reported cases, we have the advantage of having plated on normal bone, where, after re-exposure 10 months later, interval pigmentation development was found. The main differential diagnosis of concern was infection, but the bone consistency, clinically and after laboratory assessment, ruled this out. We were able to demonstrate pigmentation microscopically, which has not previously been reported in black bone disease. We would like to raise awareness of black bone disease, in the orthopaedic community, as an important differential for bone pigmentation and, as far as we are aware, this is the first reported case in orthopaedics of black bone disease affecting a fracture callus. Histological examination of black bone disease has not been extensively researched, unlike in cases of soft tissue. All the more reason for orthopaedic surgeons to become more familiar with the literature review we have presented with our case. We also believe there is an avenue for further experimental work on possible detrimental effects of minocycline on fracture healing.

Learning points

- ▶ Awareness of black bone disease is important given the widespread use of minocycline in the treatment of many diseases.
- ▶ Regions of active bone metabolism such as fractures are likely to be affected with pigmentation of the callus earlier than normal bone.
- ▶ Histological evidence of minocycline on routine H&E staining may indeed be noted at high magnification as free pigment or within histiocytes.
- ▶ The current study is unable to answer questions regarding whether the use of minocycline could affect fracture healing, and establishes a foundation for further experimental and clinical research.

Contributors All the authors were involved in case write up and literature review, with varying involvement in acquiring and editing the figures and images used in this report. During the revisions, each author was involved in review and final proofreading of the manuscript before submission.

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