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Case report

Diffuse skin hyperpigmentation associated with chronic minocycline use in a patient with prosthetic joint infection

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ABSTRACT

Cutaneous hyperpigmentation is a recognized adverse effect of chronic minocycline use occurring in up to 50% of patients. In this report we present a rare case of extensive skin hyperpigmentation involving both lower extremities in a patient receiving long term minocycline. The patient was receiving minocycline as suppression for chronic prosthetic joint infection. Risk factors associated with minocycline-induced cutaneous pigmentation (MICH) will be reviewed.

Introduction

Cutaneous hyperpigmentation is a recognized adverse effect of chronic minocycline use occurring in up to 50% of patients [1,2]. In a recent study performed at the Mayo Clinic, 54% of 291 patients receiving long-term minocycline suppression for orthopedic infections developed some degree of hyperpigmentation after a mean follow-up of 4.8 years [1]. In this cohort, the mean duration of minocycline therapy before the onset of hyperpigmentation was 1.5 years. Factors associated with minocycline-induced cutaneous hyperpigmentation (MICH) include a history of vitamin D deficiency, presence of a shoulder prosthesis, noncirrhotic liver pathology, and use of a concurrent medication (e.g., calcium channel blocker) also known to cause hyperpigmentation [1]. MICH is not associated with adverse clinical effects, and it is mostly cosmetic in nature [2]. It typically involves the lower extremity, and is usually limited and localized. We herein present a rare case of extensive skin hyperpigmentation involving both lower extremities in a patient receiving long term minocycline. Risk factors associated with MICH will be reviewed.

Case report

In June 2016, a 76-year-old male with a past medical history significant for nephrolithiasis and diverticulitis, presented to the authors' institution with extensive hyperpigmentation involving both lower extremities. The patient had an extensive orthopedic and orthopedic infectious disease history. He underwent a left total knee arthroplasty in 1988 at an outside institution and underwent revision surgery in 1992. In 2001, he underwent a second revision for fractured patella that was complicated by an infection with a coagulase-negative *Staphylococcus*. He received six weeks of treatment with parenteral vancomycin followed by oral trimethoprim-sulfamethoxazole. Because of increasing knee pain, in March 2005, the prosthesis was explanted. Operative cultures from the knee grew *Enterococcus* sp., *Prevotella* sp, viridans group *Streptococcus,* as well as *Candida parapsilosis*. After completing antimicrobial treatment with vancomycin, ertapenem and fluconazole, he underwent reimplantation using a rotating hinged knee arthroplasty in September 2005 (Fig. 1). Unfortunately, operative cultures were positive for coagulase-negative *Staphylococcus*. Since that time, the patient was maintained on oral minocycline chronic suppression. In 2010, he sustained a periprosthetic fractures that required open reduction and internal fixation.

His left knee has been clinically quiescent and stable for a number of years. He uses a brace as well as a cane to ambulate. At a follow-up in February 2012, it was noted that he had slight discoloration in the lower extremities. When he was seen again in June 2016, there was extensive blue-gray pigmentation in both cheeks and in the lower extremities (Fig. 2), as well as sub-ungual blue-gray pigmentation in both hands (Fig. 3).

Discussion

There are three types of pigmentation patterns that can result from taking minocycline for long periods of time [3]. Type I is a

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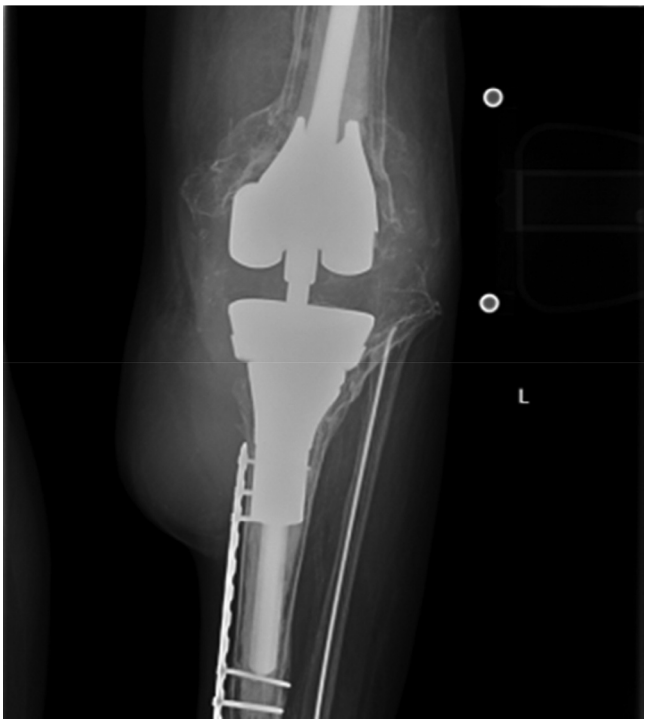

Fig. 1. Roentgenogram of the left knee revealing a hinged knee with plate and screws in the tibia as well as intramedullary rod in the fibula.

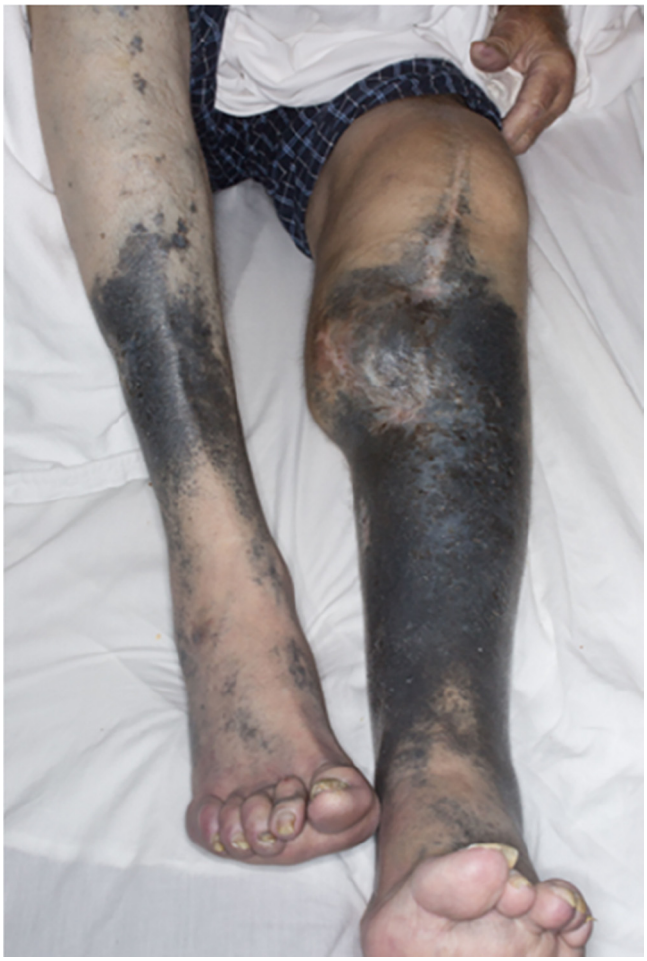

Fig. 2. Bilateral lower extremities showing diffuse blue-gray skin hyperpigmentation; a healed incision is noted over the left knee.

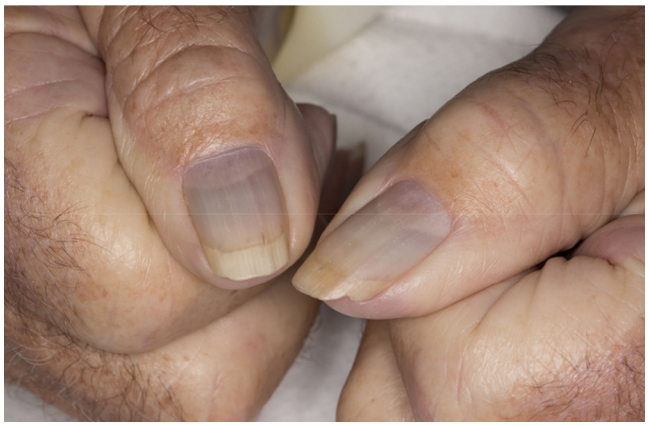

Fig. 3. Sub-ungual hyperpigmentation.

blue-gray pigmentation occurring around areas that were previously inflamed. Type II has the same appearance as Type I and covers areas of normal skin such as the anterior shins, arms, and ankles. Type III is a muddy brown pigmentation usually occurring on areas of the skin that are exposed to the sun. The blue-gray pigmentation is due to the deposition of iron within the dermal macrophages. The diffuse hyperpigmentation seen in the patient presented in this case report includes both Types I and II. Blue-gray pigmentation is clearly seen around the scar on the left knee from his knee replacement surgery (Type I). Hyperpigmentation is also distinctly seen on the shins of both legs and around the ankles of the patient (Type II).

Hyperpigmentation is predominantly seen with minocycline and less likely to occur with other tetracyclines such as doxycycline [4]. Minocycline is five times more lipophilic than doxycycline; hence, central nervous system adverse events are more common with minocycline. Doxycycline may be associated with more gastrointestinal upset and photosensitivity than minocycline [4,5].

Although doxycycline may have a higher incidence of gastrointestinal upset and photosensitivity, minocycline has an increased likelihood of severe and permanent cosmetic adverse events and central nervous system adverse events. In the study of orthopedic patients on long-term minocycline suppression, cutaneous hyperpigmentation occurred in 54% of patients [1]. Furthermore, hyperpigmentation can persist in at least 24% even with medication discontinuation [1]. These side effects are an addition to gastrointestinal adverse effects that can also occur with minocycline. In the absence of data to show that minocycline is superior to doxycycline for long-term suppression of infections including orthopedic infections, the authors propose that doxycycline be looked upon favorably when chronic use is indicated.

Conflict of interest

No relevant COI to disclose.

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