Minocycline-Induced Skin Pigmentation: An Update

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SUMMARY Minocycline is a commonly used antibiotic for long-term treatment of acne vulgaris. A well-documented and cosmetically displeasing side effect is skin pigmentation. Three distinct types occur: Type I, blue-black/grey pigment on the face in areas of scarring or inflammation associated with acne; type II, blue-grey pigment on normal skin on the shins and forearms; type III, diffuse muddy-brown discoloration in areas of sun exposure. Types I and II stain for iron and melanin extracellularly and within macrophages in the dermis. Type III shows nonspecific increased melanin in basal keratinocytes and dermal melanophages staining for melanin only. The etiology of this pigmentation is unknown, but may be related to polymerized reactive metabolites, insoluble chelation products, and lengthy treatment durations of minocycline compared to other tetracyclines. Types I and II tend to resolve slowly over time, whereas type III persists indefinitely. Treatment involves early recognition, discontinuation of the drug, sun protection, and laser for persistent pigmentation.

KEY WORDS: minocycline, blue-grey pigmentation, muddy brown pigmentation, quinine iminium ion, acne, hyperpigmentaton, rosacea, adverse drug reaction

INTRODUCTION

Minocycline is a second-generation tetracycline antibiotic in widespread use for the treatment of acne vulgaris and rosacea. Although minocycline is highly effective, a cosmetically concerning and well-documented side effect is minocycline-induced pigmentation noted to occur in the skin, subcutaneous fat, nails, teeth, gingivae, oral mucosa, lips, conjunctiva, sclera as well as various internal structures throughout the body (1-5). Minocycline is also associated with serious, albeit rare, immune-mediated hypersensitivity syndromes such as drug reaction with eosinophilia and systemic symptoms, serum sickness-like re-

actions, drug-induced lupus erythematosus, and vasculitis (6-8). These adverse effects, including skin pigmentation, occur at a much higher rate with minocycline than with other tetracyclines (8).

Three types of minocycline-induced skin pigmentation may be evident. Type I, the most common kind, consists of blue-black macules in areas of scarring or inflammation. These macules usually occur on the face and are associated with acne (Fig. 1). Type II consists of well-circumscribed blue-grey pigmentation in previously normal skin on the shins and forearms. The least common kind is type III, which is composed of a diffuse muddy

brown discoloration accentuated in sun-exposed skin (9,10). Recently, two cases of well-circumscribed blue-grey pigmentation within acne scars on the back have been described (11), probably representing a variant of the type 1 pattern.

The incidence of cutaneous pigmentation due to minocycline ranges from 2.4% to 14.8%, based on longitudinal studies (12-14). Type I pigmentation appears not to be correlated with treatment duration or cumulative dose, as it may take only a few weeks to several years for pigmentation to develop (11,13). On the other hand, types II and III are associated with long-term administration ranging from 6 months to 4 years with cumulative doses in excess of 70 to 100 grams (10,12,15-17).

HISTOPATHOLOGY

The exact composition of the pigment remains unknown and may vary depending on the type of pigmentation involved. The possible components documented include melanin, calcium, iron, lipofuscin, and minocycline breakdown products (18). The pigment in types I and II are characteristically positive for Perls' iron and Fontana-Masson stains. In type III, changes are nonspecific, consisting of increased melanin in basal keratinocytes and melanin-only staining dermal melanophages (19).

Recently described cases have expanded the above dermatopathologic findings. The previously mentioned two cases of blue-grey pigmentation within acne scars on the back exhibited similar histology to types I and II; however, they stained positive for melanin but not iron. Interestingly, calcium was present initially, but absent after 43 months (11). Another case presenting clinically with type II pigmentation was found to have deposits confined entirely to the subcutis, staining positive for melanin only (2). Pigmentation involving the dermis and subcutis may occur. Four cases exhibited brown/black granules staining positive for melanin and iron in macrophages clustered around vessels, eccrine coils, fat septae, and between lipocytes in the reticular dermis (19). Round, flocculent, gray-green globules were found in the subcutis staining brown (rather than the normal black) for melanin and negative for iron. These findings probably represent occasional extensions of types I and II into the subcutis, easily missed due to shallow biopsy techniques (19). Involvement of the subcutis is not surprising, considering that minocycline is a highly lipophilic molecule (20).

Figure 1. A 35-year-old woman with blue-grey pigmentation of facial acne scars after 3 years of minocycline use.

PATHOGENESIS

The mechanism of minocycline-induced pigmentation remains unknown; however, several theories have been proposed. Based on ultra-structural and x-ray microanalyses, siderosis has been implicated in the pathogenesis of skin pigmentation induced by minocycline (21). Siderosis might result from microhemorrhage secondary to cutaneous trauma (11). Minocycline was identified in pigmented skin and found to correspond to clumps of granular deposits in the dermis using fluorescence microscopy and high-performance liquid chromatography. This finding lends support to the concept that the pigment may consist of insoluble complexes of minocycline or a derivative chelated with iron (22).

Another mechanism suggests that, due to its unique chemistry, minocycline may potentially form reactive metabolites. Although tetracyclines share the basic four-ring structure, a unique dimethamino group at position 7 enables the formation of reactive metabolites of minocycline. In particular, a quinone iminium ion, along with other reactive species, may polymerize to form a black pigment and contribute to the formation of autoantibodies involved in idiosyncratic reactions of minocycline (23-25).

The influence of inflammation on pigmentation is unclear. Cases of acute onset diffuse skin pigmentation secondary to minocycline treatment of superficial cutaneous infections associated with atopic dermatitis have been reported (26). Total exposure to minocycline was relatively brief, ranging from 3 to 28 days. It is theorized that strong inflammatory processes might damage elastic fibrils, thereby compromising lymphatic function in the dermis. This, in turn, could cause delayed clearance of minocycline complexes and result in an accelerated, intense pigmentation (26).

The higher frequency of skin pigmentation caused by minocycline rather than other tetracyclines may be a function of treatment length and cumulative dose. Minocycline is more commonly used in long-term therapeutic regimens for acne vulgaris, whereas tetracycline and doxycycline are more often employed for acute infections requiring relatively shorter lengths of treatment (24).

TREATMENT

Resolution of skin pigmentation after stopping minocycline depends on the type of pigmentation. For types I and II, one can anticipate slow spontaneous clearing upon withdrawal, which may require several months to a year to resolve. In contrast, the diffuse muddy-brown discoloration seen in type III may persist indefinitely (10,11). Patients taking minocycline for over a year should be screened and routinely monitored for the development of pigmentation (17). Cutaneous pigmentation may be exacerbated by sunlight, suggesting that photo-protective measures, including the use of a high SPF sunscreen, should be implemented (14). Precaution should be taken with co-administered estrogen preparations, amitriptyline, and phenothiazines, as they may potentiate pigmentation (13,27).

Several pigment-specific lasers have been shown to significantly improve all types of minocycline-induced skin pigmentation. Specifically, Q-switched ruby, neodymium YAG, and alexandrite lasers, and more recently, fractional photothermolysis, have all been successful (16,18,28,29). The mechanism for laser-mediated resolution is not completely understood, but may involve mobilizing and clearing pigment complexes trapped within the dermis, while allowing deposition of healthy new collagen (16). The usefulness of laser therapy in subcutaneous pigmentation is unknown, but may be limited by the depth of pigmentation (2).

CONCLUSION

Minocycline-induced skin pigmentation continues to be a potentially disfiguring side effect of an otherwise highly effective acne and rosacea treatment. Questions regarding the underlying pathophysiology remain despite significant advances. Greater awareness of this potentially reversible side effect will allow for earlier recognition and discontinuation of the drug before significant cosmetic harm can occur.

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