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Minocycline-associated intra-oral soft-tissue pigmentation: clinicopathologic correlations and review

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Abstract

Background: Intra-oral minocycline staining of alveolar bone and teeth is well-described in the literature. Minocycline-induced discoloration of oral soft tissues is less common and has been often attributed to staining of the underlying bone.

Aim: This report documents the clinical and histopathologic features of a case of actual oral soft tissue minocycline-induced pigmentation. The patient, a 45-year-old Caucasian female, presented with pigmentation of the gingiva, lips, and nail beds of recent onset. The past medical history revealed initiation of minocycline therapy 6 months earlier for dermatological concerns. Histopathologic examination of biopsy specimens from the gingiva and lip showed evidence of increased melanin/melanocytes in the epithelium and melanin/melanophages in the connective tissue. A working diagnosis of drug-associated pigmentation was determined and the patient discontinued immediately minocycline therapy. Nine months after cessation of minocycline the patient exhibited a marked reduction in pigmentation.

Conclusion: Systemic minocycline treatment has the potential to induce significant and esthetically objectionable discoloration of the gingiva and oral mucosa. A brief review of the literature is presented to help understand this uncommon finding that should be included in the differential diagnosis of spontaneous discoloration of intra-oral soft tissues.

Key words: minocycline; oral soft tissues; pigmentation

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First introduced in 1967, minocycline, a semi-synthetic derivative of tetracycline, is chiefly used for the treatment of acne, chronic respiratory diseases, and rheumatoid arthritis. Minocycline has both anti-inflammatory as well as antibiotic properties making it well suited for relieving symptoms in these patient populations. The drug possesses several advantages over others in its class including better absorption, increased antimicrobial activity, and little to no phototoxicity (Fendrich & Brooke 1984, Saivin & Houin 1988, Maibach 1991). Minocycline is lipid soluble and therefore can easily penetrate into body fluids, such as saliva and gingival crevicular fluid, and into various body tissues including bone and soft tissues (Saivin & Houin 1988, Siller et al. 1994). Although minocycline is considered to be safe in long-term high doses, the most frequently observed adverse reaction is cutaneous pigmentation (Goulden et al. 1996).

Minocycline-induced intra-oral staining, primarily affecting hard tissues such as teeth and alveolar bone, has been documented in both the dermatological and dental literature. Pigmentation of oral soft tissues because of minocycline use is less frequent and, in most published cases, has been associated with staining of the bone with resultant discoloration visible clinically only because of the translucency of the overlying soft tissues (Westbury & Najera 1997, Siller et al. 1994). Only a few cases with minocycline-associated pigmentation occurring within the oral soft tissues have been presented to our knowledge. The aim of this report is to demonstrate the clinical and histopathologic characteristics of a case of minocycline-induced intra-oral pigmentation with actual soft-tissue involvement.

Case Report

A 45 year-old Caucasian female patient presented at a private office after noticing the onset of pigmentation in the gingiva, lips, and skin.

The patient first noted pigmentation on the facial gingiva of tooth #11, 6 weeks prior to presentation. The pigmentation had since spread to the facial surfaces of the upper and lower gingiva and lips. The patient was also aware of the recent onset of pigmentation in the skin adjacent to the fingernails. The patient was in good general health. She reported smoking two packs of cigarettes a day for a number of years, drinking primarily water, having no unusual dietary habits, and using Listerine daily. She had been taking hydrochlorothiazide and lisinopril for 6 years for control of hypertension. She had also been taking minocycline 100 mg BID for 6 months for facial acne.

On clinical examination, the gingiva exhibited a generalized slightly enlarged appearance without edema, being otherwise normal in colour and texture. Brown pigmentation was noted especially at the gingival margin on the facial surfaces of the upper and lower anterior teeth (Fig. 1, a and b). This discoloration was also present on the mucosal surface of both lips with sharp demarcation at the transition from the labial mucosa to the vermilion border (Fig. 1c). Pigmentation of the skin adjacent to the fingernails was also evident (Fig. 1d).

Under local anaesthesia, biopsies were obtained from the facial attached gingiva between #42 and #43 and from the right side of the upper lip approximately 1 cm from the commissure. The specimens were submitted for histopathologic examination, revealing evidence of melanosis (Fig. 2). Increased melanin/melanocytes in the basal and parabasal layers of normal stratified squamous epithelium were evident. Melanin was also seen free and within melanophages in the subepithelial connective tissue.

After discontinuation of minocycline therapy, and despite the persistence of smoking, the affected areas resolved slowly over time. At approximately nine months after cessation of drug therapy, follow-up clinical examination revealed a marked reduction in pigmentation at all previously involved sites (Fig. 3 a–c).

Discussion

Minocycline-induced soft-tissue pigmentation was first described in the scientific literature in 1967 by Benitz as causing an abnormal discoloration of the thyroid gland in rats, dogs, and monkeys (Benitz et al. 1967). Subsequently, minocycline was reported to cause significant discoloration of various intra-oral and extra-oral tissues as documented in the dental and dermatological literature. Extra-oral cases of minocycline-associated pigmentation encompass a wide variety of anatomic presentations including the skin, nail beds, conjunctival cysts and sclera, atherosclerotic plaques, substantia nigra, thyroid gland, cardiac valves, bone, and breast milk (Gordon et al. 1984, Westbury & Najera 1997).

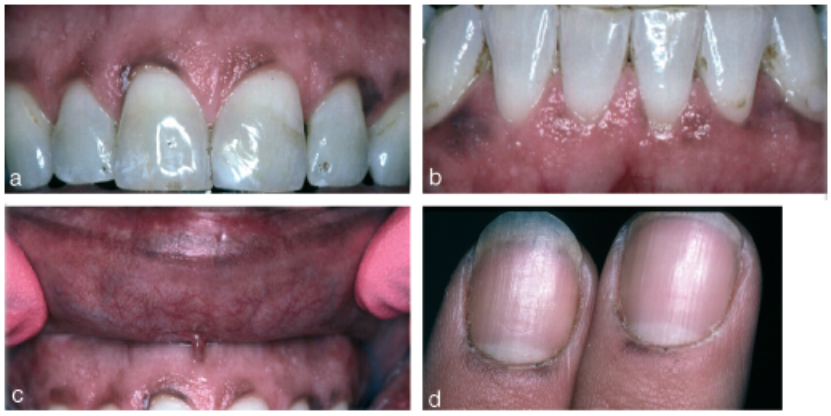

Fig. 1. Brown pigmentation is present at the maxillary (a) and mandibular (b) buccal gingival margins. Also, the upper lip (c) exhibits pigmentation at the transition from the labial mucosa to the vermilion border. Additionally, brown discoloration is present in the nail beds (d).

Intra-orally, minocycline staining was first described by Fendrich and Brooke in 1984 (Fendrich & Brooke 1984). Most intra-oral cases presented in the literature deal primarily with pigmentation of the hard tissues including alveolar bone, roots, and crowns of teeth. The most commonly affected oral anatomic site appears to be the alveolar bone, which assumes a characteristic black discoloration. Moreover, fully erupted teeth often exhibit a blue-gray appearance in the incisal three-fourths with the middle one-third being maximally involved. Roots demonstrate a green colour whereas developing roots tend to be black (Westbury & Najera 1997, Bowles 1998, Neville et al. 2002). When pigmentation of oral soft tissues is present, the distinctive blue-gray or brown appearance is usually the result of pigmented black bone showing through the thin overlying mucosa without any actual involvement of the soft-tissue itself. Only few cases of actual oral soft-tissue pigmentation have been described, involving the tongue, lips, buccal mucosa, and gingiva (Dummett & Barens 1967, Basler 1985, Berger et al. 1989, Meyerson et al. 1995, Tanzi & Hecker 2000).

The pathophysiology of minocycline staining is currently unknown. The drug, which is initially yellow in color, appears to bind to specific types of collagen where it undergoes oxidation thereby producing its distinctive black coloring (Eisen & Hakim 1998, Neville et al. 2002). Others feel that the actual tissue-staining elements could include iron, lipofuscin, melanin, neuromelanin, or minocycline degradation products (Westbury & Najera 1997). Four distinct clinical and histological patterns of minocycline-associated soft-tissue pigmentation have been described, each one associated with accumulation of different pigmentation-inducing particles (Goulden et al. 1996, Eisen & Hakim 1998). Bone pigmentation is thought to occur through ferric iron bound to the oxidized drug in developing bone, and via the accumulation of insoluble quinine from the degradation of the aromatic ring of the drug in mature bone (Kelly & Kanegis 1967, Bowles & Bokmeyer 1997, Cockings & Savage 1998). Finally, intrinsic and extrinsic theories regarding the discoloration of the dentition have been postulated (Berger et al. 1989, Bowles & Bokmeyer 1997, Westbury & Najera 1997).

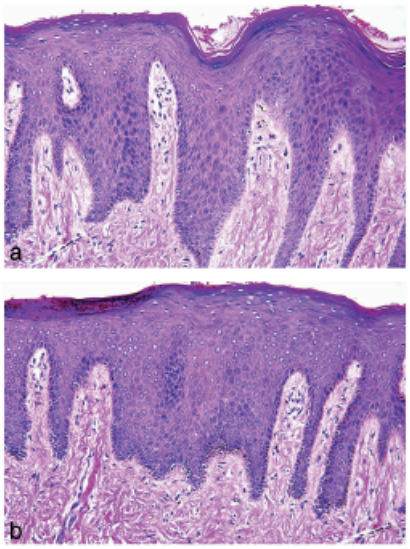

Fig. 2. Increased number of melanocytes and melanin deposition in the basal and parabasal layers of normal stratified squamous epithelium are evident. (a) Melanin is also seen free and within melanophages in the subepithelial connective tissue (b) (haematoxylin and eosin, original magnification × 200).

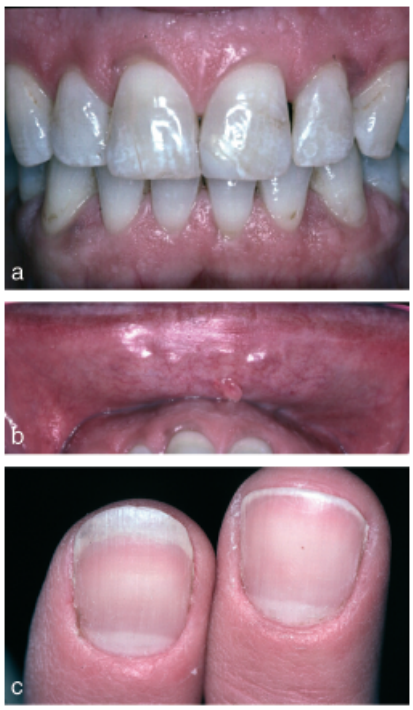

Fig. 3. Significant reduction in pigmentation of the gingiva (a), upper lip (b), and nail beds (c) is noted at nine months post-cessation of minocycline therapy.

Although once thought to be independent of dose, minocycline-induced pigmentation is now thought to be dose-dependent with a general incidence range from 0.4% to 15% in patients being treated for acne, although incidence as high as 70% in patients treated for rheumatoid arthritis has been reported (Goulden et al. 1996, Eisen & Hakim 1998, Cheek & Heymann 1999, Langevitz et al. 2000). Dental pigmentation appears to have a lower incidence, with the highest rates around 6% (Berger et al. 1989, Dwyer et al. 1993) and tends to occur after several years of therapy (Eisen & Hakim 1998). In a study exploring the dose-dependent nature of the pigmentation in a patient population of 700 individuals, patients taking higher doses (200 mg) of minocycline showed a 4% incidence in pigmentation compared with 1.1% in those taking 100/200 mg on alternating days and 0.4% in those taking 100 mg daily. Pigmentation in this population appears to have occurred after a minimum of 8 months of treatment and with a cumulative dose of 70 g (Goulden et al. 1996).

The resolution of minocycline-induced pigmentation is variable, taking months to years (Westbury & Najera 1997). Dental discoloration appears to be more tenacious with most cases failing to resolve (Cheek & Heymann 1999). Various modalities have been pursued to correct persistently pigmented areas. The treatment of minocycline-induced pigmentation with Q-switched ruby, alexandrite, and neodymium:YAG lasers has been documented (Collins & Cotterill 1996, Tsao et al. 1996, Wilde et al. 1997, Greve et al. 1998, Wood et al. 1998, Green & Friedman 2001, Friedman et al. 2002). In animal studies, ascorbic acid used in conjunction with minocycline therapy has demonstrated an inhibition of pigment deposition, most likely because of the vitamin's anti-oxidant properties (Bowles 1998).

Definitive diagnosis of minocycline-associated stain can be difficult. Clinical and histological presentations are often varied or ambiguous. Some authors have advocated the use of a Wood's lamp to fluoresce affected areas, which is useful in cases of tetracycline stain. Unfortunately, minocycline shows little to no fluorescence when examined (Oklund et al. 1981, Reid 1983, Ohaki et al. 1986, Cohen & Abrams 1989, Rosen & Hoffmann 1989). Because of a lack of diagnostic indicators, most diagnoses must be made on the basis of association and temporal events including initiation of minocycline therapy, onset of pigmentation, and resolution of discolouration after discontinuation of the drug. The differential diagnosis for pigmented oral lesions of the soft tissues includes: racial pigmentation, amalgam and non-amalgam tattoo, melanotic macule, smoker's melanosis, melanocytic nevus, oral melanoacanthoma, malignant melanoma, Kaposi sarcoma and other vascular lesions, Addison's disease, haemochromatosis, Peutz Jegher's syndrome, McCure–Albright syndrome, neurofibromatosis, heavy metal poisoning, and, of course, drug-induced pigmentation (Neville et al. 2002, Nikitakis 2003). In addition to minocycline, drugs which may be implicated in discolouration include phenolphthalein, tranquilizers, antimalarial medications, oestrogen, chemotherapeutic agents, and medications used in the treatment of AIDS (Neville et al. 2002).

In the case presented here, the clinical and histopathologic features, including a generalized, symmetrical, brown pigmentation on healthy soft-tissue and the presence of melanin microscopically, were compatible with a diagnosis of minocycline-associated soft-tissue pigmentation. However, the final diagnosis was made on the basis of the onset of the pigmentation coincident with the patient's onset of minocycline therapy for treatment of acne and the resolution of the discolouration shortly after discontinuation of the drug. The fact that the discolouration was localized to the anterior facial gingiva may be theoretically attributed to the increased exposure of this location to sunlight, which has been implicated in cases of minocycline-associated soft-tissue pigmentation. Because biopsies were only obtained from soft tissue with no exposure of the underlying bone, it is also possible that in the areas of pigmentation of the gingiva, ''black bone'' could have been viewed through the soft tissue. This theory, of course, cannot apply to the areas of lip pigmentation.

On the basis of the clinical and histopathologic features of our case, along with the smoking habit of the patient, strong consideration was given to a possible diagnosis of smoker's melanosis. This condition, which frequently affects the anterior gingiva, is often found in cigarette smokers. Histopathologic examination reveals increased melanin pigmentation in the basal layers of epithelium and free melanin in the connective tissues and melanophages, similar to the presentation in this case.

The increased melanin production is thought to serve a protective function against the harmful substances within the smoke, akin to the protective increase in melanin production observed in response to UV light (Neville et al. 2002). Despite the similarities of our case with smoker's melanosis, an association with minocycline treatment was strongly supported by the temporal events surrounding this episode of oral discoloration, i.e. onset 6 months following initiation of treatment and resolution after discontinuation of the drug. In contrast, the history of smoking in the years before the onset of pigmentation and, especially, the persistence of this habit during and after the resolution of the lesions militate against a causal role of smoking. Nonetheless, one can postulate an additive effect of the insult of tobacco smoke to the minocycline therapy to create a reactive pigmentation; however, this potential synergism has to be validated in future studies.

In conclusion, this unique case of intra-oral soft-tissue pigmentation associated with minocycline treatment exemplifies an uncommon finding that should be included in the differential diagnosis of spontaneous discoloration of oral mucosa.

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