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Minocycline-Induced Hyperpigmentation in a Patient with Multiple Causes of Skin Discoloration

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ABSTRACT

Minocycline-induced hyperpigmentation is a well-documented but poorly understood adverse effect of the popular tetracycline antibiotic minocycline, mainly affecting patients who use it for a prolonged duration. When patients develop dark skin lesions, the etiology may be clouded if a patient on minocycline has other risk factors. We describe a patient on suppressive minocycline therapy as well as anticoagulation and a history of chronic venous stasis who developed ecchymosis after an invasive procedure.

INTRODUCTION

Minocycline is a synthetic tetracycline derivative antibiotic, commonly prescribed for skin infections such as moderate to severe acne vulgaris and rosacea.[1] It has excellent coverage for Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA).[2] Adverse effects are uncommon and generally mild, but one of the most significant is hyperpigmentation of various tissues. Since the drug's development in the 1960s, minocycline-induced hyperpigmentation (MIH) has been reported in as varied places as sclerae, teeth, gingivae, bones, thyroid, and breast milk.[3] Though usually well-tolerated, this effect can cause significant distress in patients and their providers who are unfamiliar with it and is often permanent, though some cases may be reversible with cessation of the drug or certain therapies.[4] We report on a patient on long-term suppressive therapy with minocycline following a MRSA infection who developed not only MIH but also skin changes related to chronic venous insufficiency as well as extensive ecchymoses while on anticoagulation, complicating his clinical picture.

CASE REPORT

An 80-year-old man with a past medical history of atrial fibrillation, aortic dissection one year prior status post thoracic endovascular aortic repair, systolic heart failure, and chronic anemia and thrombocytopenia, presented to the emergency department with acute decompensated heart failure and atrial fibrillation with rapid ventricular response. He stated that his symptoms of dyspnea and lower extremity edema began a few days after a tooth extraction that had been complicated by melena and oral bleeding requiring hospitalization. He had been maintained on apixaban for years for his atrial fibrillation but was taken off all anticoagulation during this episode. Of note, platelets were 75,000 /µL, hemoglobin was 8.4 g/dL, and INR was 1.57 on admission.

He was found to have an enlarging infrarenal abdominal aortic aneurysm with intramural thrombus. During this admission, on consultation with vascular medicine specialists, he was maintained on therapeutic enoxaparin. He underwent transesophageal echocardiogram with cardioversion on hospital day 7 but quickly decompensated into cardiogenic shock. A biventricular automated implanted cardioverter-defibrillator (ICD) was placed on hospital day 13, and post-operative course was complicated by hypotension requiring initiation of pressors. Full anticoagulation was held due to formation of a hematoma on the site of his ICD pocket with extension of ecchymosis to his left chest, flank, and left upper extremity. He was discharged after 25 days in the hospital with plans to resume full oral anticoagulation after one week.

Throughout his stay, the patient was noted to have hyperpigmented skin changes on the dorsum of his hands (**Figure 1**), bilateral shins extending from his malleoli to tibial plateaus (**Fig. 2**), left flank (**Fig. 3**), left chest (**Fig. 4**), gingivae (**Fig. 5**), and sclerae (**Fig. 6**). Given his myriad risk factors, it became necessary to differentiate between new and pre-existing skin changes, complicating his clinical picture.

He had been maintained on daily prophylactic minocycline 100 mg for ten years following treatment for MRSA wound infection and bacteremia after placement of cardiothoracic stents due to a thoracic aortic aneurysm. Between 2020 and 2022, he reportedly took 50 mg daily due to confusion regarding dosing. He consistently denied gastrointestinal side effects due to

the medication. The patient had been diagnosed with venous stasis dermatitis in bilateral lower extremities, but hyperpigmentation of skin on bilateral legs is first noted in the medical record in 2022.

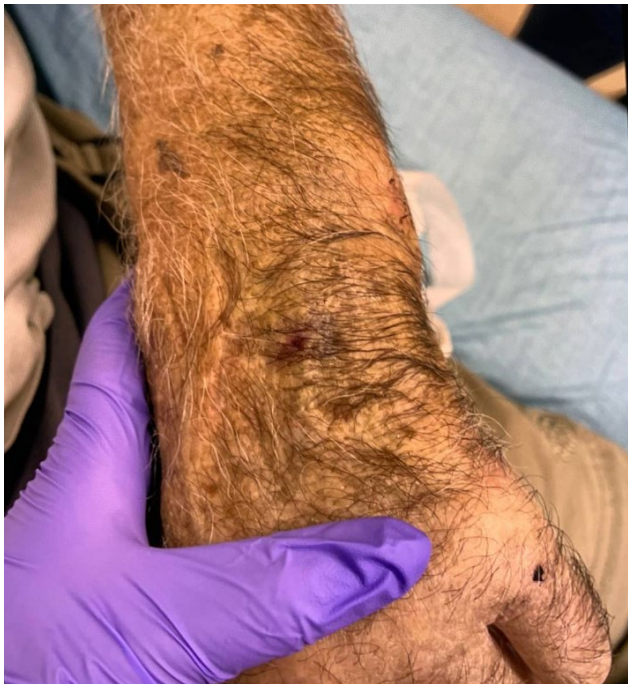

Figure 1: Dorsum of the patient's hand, demonstrating dark discoloration consistent with MIH.

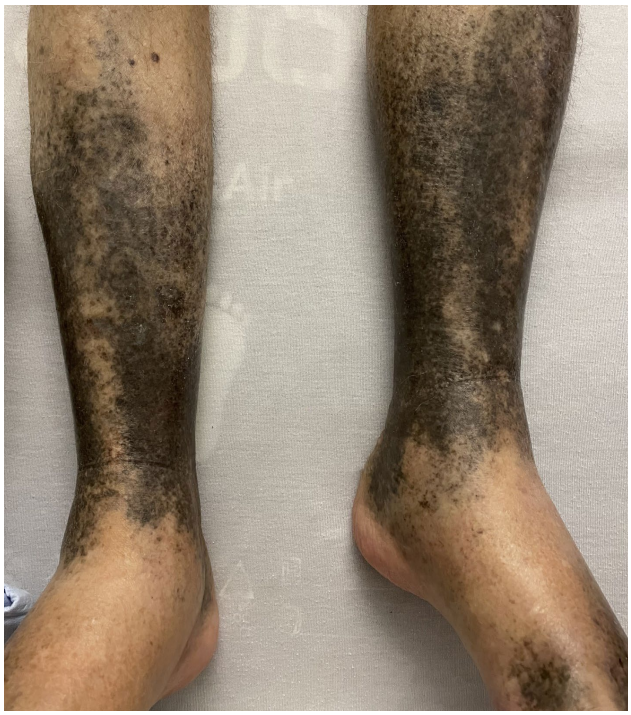

Figure 2: Dark discoloration on the patient's bilateral lower legs, consistent with MIH.

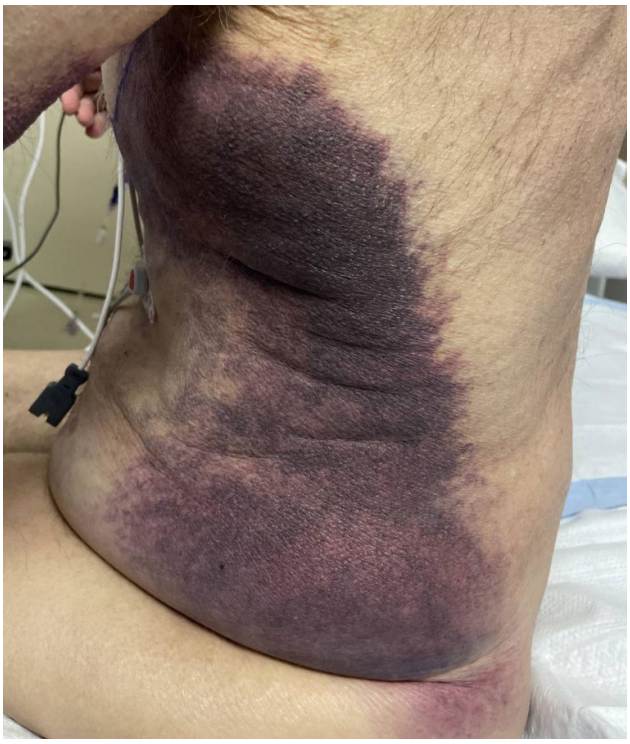

Figure 3: In this photograph of the patient's left flank, a dark purple ecchymosis is evident.

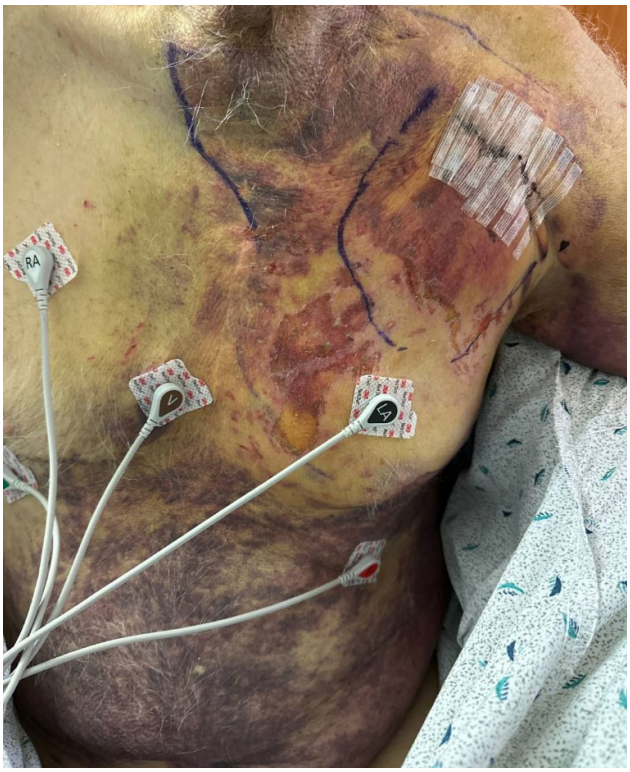

Figure 4: Hyperpigmentation of left chest and abdomen after surgery, more likely ecchymosis.

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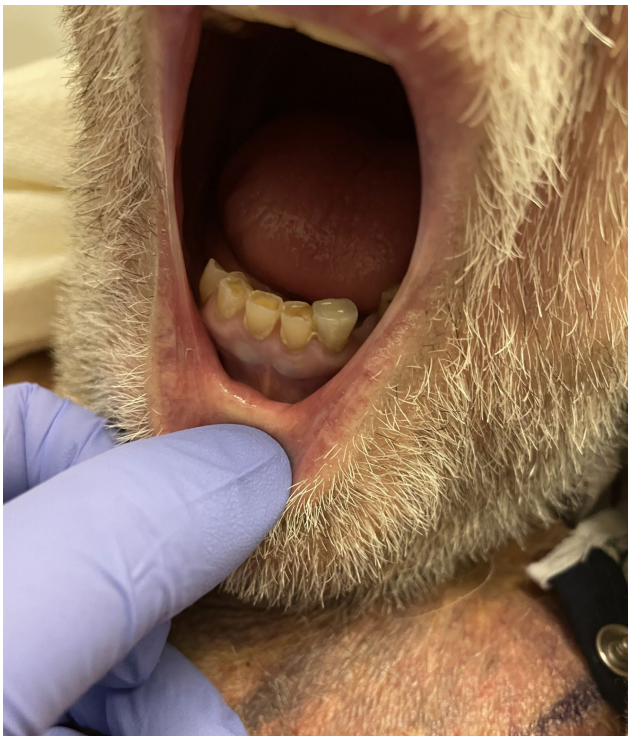

Figure 5: Bluish discoloration of the gingiva, consistent with MIH.

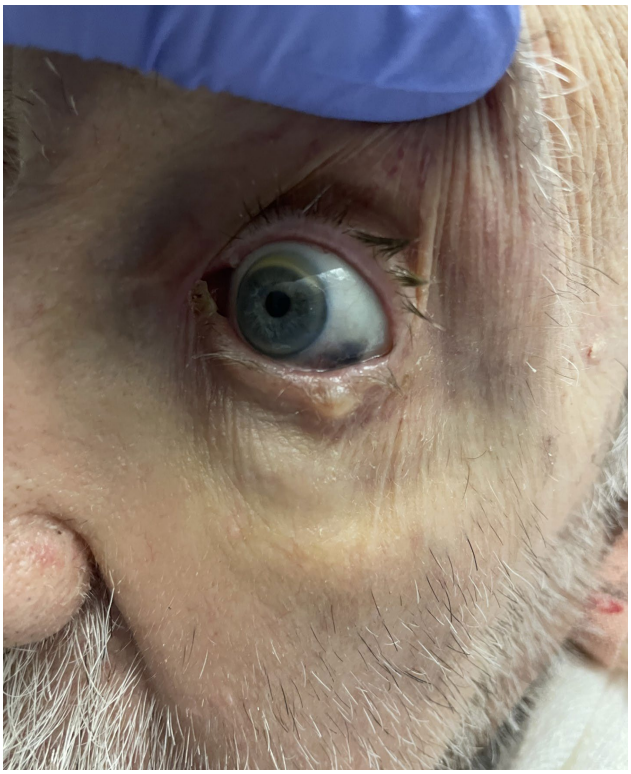

Figure 6: Patient's left eye, with notable dark discoloration of the lateral sclera representing ocular MIH

DISCUSSION

Minocycline, like other tetracyclines, is a bacteriostatic antibiotic that works by inhibiting bacterial protein synthesis.[2] Patented in 1961 and introduced for commercial use ten years later, it remains a common treatment for skin infections like acne vulgaris and rosacea due to its favorable pharmacokinetic profile.[1,3] Rare side effects include hypersensitivity syndromes such as drug reaction with eosinophilia and systemic symptoms (DRESS) and drug-induced lupus. One of the most well-reported but least understood effects is MIH, which may affect up to 15% of patients taking minocycline.[1]

MIH, if it occurs at all, tends to develop after at least three months of use of at least 70-100 mg daily, though reports of it developing decades after therapy begins are common.[5–7] Hyperpigmentation of cutaneous tissues or oral mucosae appears to be independent of dose or duration.[4] There are three commonly recognized subdivisions: type 1, which appears as blue-black macules at sites of old scarring or inflammation; type 2, which involves darkening of the skin on the forearms and lower legs; and type 3, presenting as a symmetric, brownish discoloration in a photosensitive distribution.[1] The most commonly affected tissue is skin, but MIH has been reported in the sclerae, ears, oral mucosa, teeth, nails, bones, thyroid, prostate, lymph nodes, basal ganglia, and heart valves.[3,7]

Though first documented in 1967, the mechanism behind MIH remains unclear. Types 1 and 2 appear to be associated with the breakdown of minocycline into hemosiderin, which combines with iron and deposits extracellularly as pigmented macules.[1,8] Type 2 also involves deposition of pigmented minocycline metabolites in macrophages.[9] Type 3 is due to accumulation of melanin in basal keratinocytes, though how minocycline potentiates this effect is unknown.

The inconsistent presentation and uncertain etiology of MIH makes its treatment problematic. The best management appears to be prevention; the benefits of long-term minocycline administration should be weighed against the risks of patients have significant concerns about their appearance.[7] Basic photoprotective measures like sunscreen with a high SPF may decrease the severity of the condition. MIH of the skin and oral mucosa may partially resolve with discontinuation of the offending agent, though pigmentation of other tissues tends to be permanent.[4] Specialized practices such as laser therapy and bleaching have been attempted, with varying degrees of success.[1,3]

Because of its varied appearance and unpredictable timeline, MIH causes problems in patients with other acute or chronic conditions with skin manifestations. For example, Wallace, *et al.*, describe a patient on warfarin for recurrent pulmonary emboli and atrial fibrillation, which was stopped after a minor fall when an examining practitioner observed "extensive facial bruising", presumed to be due to anticoagulation. When the patient subsequently developed another PE, further questioning revealed that the skin discoloration had preceded the fall by many months and was more likely attributable long-term minocycline use for rosacea.[5] Hints to its etiology were the photosensitive distribution of the pigmentation, as well as darkening of the sclera and proximal nail beds.

Similarly, Youssef, *et al.*, report MIH mimicking persistent ecchymosis following a traumatic injury.[3] A patient taking minocycline exhibited lasting bruising at the sight of an ankle fracture. Only after many weeks of investigation and a skin biopsy was MIH identified, and the patient was switched to doxycycline for her acne vulgaris.

In both cases, MIH mimicked other forms of skin discoloration and affected clinical decision making. Reports abound MIH being confused for shingles, bleeding diathesis, and many other inflammatory, chemical, and iatrogenic causes of hyperpigmentation.[3,10,11]

Our patient had at least three distinct causes of skin discoloration: MIH, chronic venous insufficiency, and ecchymosis following a procedure while on anticoagulation. When he developed a hematoma and extensive bruising after ICD implantation, it became necessary to differentiate which skin abnormalities were new or old. Management required careful, daily skin checks and documentation. The treatment team decided to continue minocycline for suppressive therapy, given the patient's otherwise benign side effect profile.

In this case, identification of MIH allowed his care team to treat his pressing concerns more effectively without distractors. This allowed more accurate documentation of his changing clinical picture in the medical record, helping future practitioners chart his course. It was decided to keep the patient on minocycline for the time being, given his tolerance of the medication and its efficacy.

CONCLUSION

MIH is a well-known but poorly understood adverse effect of long-term minocycline administration. Early identification and documentation of it can aid future practitioners when other forms of skin pigmentation arise.

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