

Minocycline-Induced Hyperpigmentation in Patients With Pemphigus and Pemphigoid

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Background: Immunosuppressive medications typically used to treat the immunobullous disorders pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid can have serious adverse effects. The tetracycline family of antibiotic drugs has been shown to be effective in the treatment of these conditions with a more favorable side effect profile. Minocycline hydrochloride use has been associated with various forms of hyperpigmentation, and its incidence is well reported in acne vulgaris and rheumatoid arthritis. We examined a series of 9 patients treated with minocycline for pemphigus or pemphigoid, most of whom have developed cutaneous hyperpigmentation.

Observations: Seven of 9 patients treated with minocycline, 50 mg daily (1 patient) or 100 mg twice daily (8 patients), for pemphigus vulgaris, pemphigus foliaceus, or bullous pemphigoid developed hyperpigmentation, which necessitated discontinuing therapy. Five of these patients had experienced notable clinical improvement of their immunobullous disease with minocycline

therapy. The average duration of treatment was 8.2 months (range, 1-25 months). The second most common adverse effect in our group was oral candidiasis, which occurred in 2 patients.

Conclusions: We found a favorable response to minocycline therapy in 5 of 9 patients. However, 7 patients developed localized hyperpigmentation as early as 1 month after starting medication use. This incidence of minocycline-induced hyperpigmentation is significantly higher in immunobullous disease than in acne vulgaris or rheumatoid arthritis. This increased incidence may be related to an increase in pigment deposition complexed with collagen during the remodeling process, subclinical inflammation, or glucocorticosteroid-induced skin fragility. The hyperpigmentation process was reversible, as most of our patients had fading of their pigmentation after minocycline cessation.

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USE OF minocycline, a semi-synthetic derivative of tetracycline,¹ can induce tissue pigmentation in a variety of organs, including skin,²⁻⁴ teeth,^{5,6} bone,^{7,8} thyroid,^{9,10} and sclera.¹¹ In patients with acne treated with minocycline, the incidence of cutaneous hyperpigmentation is uncommon, ranging from 2.4% to 14.8%.^{4,12} The incidence of alveolar oral pigmentation has been reported⁸ to be as high as 20% after 4 years of minocycline therapy. Hyperpigmentation after treatment of rheumatoid arthritis occurred in 2.75% of patients in one series.¹³ There is limited information regarding the incidence of hyperpigmentation in patients with immunobullous disorders treated with minocycline (**Table 1**). We report a series of 9 consecutive patients with pemphigus or pemphigoid treated with minocycline, 7 of whom developed minocycline-induced hyperpigmentation.

RESULTS

Nine patients, 5 women and 4 men, with PV, PF, or BP had been or were currently being treated with minocycline for their immunobullous disease. Their ages ranged from 19 to 79 years, with a mean age of 53 years. Six patients had PV, 2 had BP, and 1 had PF. Six patients had a favorable response to minocycline treatment, with 3 having a marked response (**Table 2**). Seven patients developed localized minocycline-induced hyperpigmentation (**Table 3**). One patient developed subungual pigmentation (**Figure 1**, C) and another (patient 3) developed pigmentation on the dorsum of his hands and forearms. One patient with early pigmentation on the legs had a prominent perifollicular pigment distribution (not shown).

Hematoxylin-eosin-stained sections (patient 2) showed numerous pig-

PATIENTS AND METHODS

PATIENTS

Analysis of all patients with immunobullous disorders treated with minocycline in our office between January 1, 1997, and December 31, 1999, was conducted. The diagnosis of pemphigus vulgaris (PV), pemphigus foliaceus (PF), or bullous pemphigoid (BP) was made on the basis of clinical findings, diagnostic histopathologic analysis, and direct immunofluorescence testing.¹⁷ Response to treatment was based on clinical improvement and/or a reduction in immunosuppressive drug use (**Table 2**). The diagnosis of minocycline-induced hyperpigmentation was made on clinical grounds.

HISTOLOGICAL ANALYSIS OF CUTANEOUS PIGMENTATION

Skin biopsy specimens were taken from the lower anterior leg of patient 2 (a site of minocycline-induced hyperpigmentation), fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin-eosin. In addition, staining for iron (Perls Prussian blue stain) and melanin (Masson-Fontana ammoniacal silver stain) with and without bleach was performed.

STATISTICAL ANALYSIS

Using spreadsheet software (Excel; Microsoft, Redmond, Wash), a single-sample binomial analysis was conducted on our patient population using the highest previously reported⁸ incidence of minocycline-induced hyperpigmentation of 20%.

ment-laden macrophages in the dermis and in the subcutaneous fat (**Figure 2**, A and B). In addition, pigment was observed extracellularly on collagen bundles and in adipocytes (Figure 2, B). The pigment was distributed evenly throughout the dermis and subcutis and did not seem to be localized around the eccrine glands or blood vessels. Strong staining was revealed for iron and melanin within the macrophages and extracellularly, as confirmed by hydrogen peroxide.

The incidence of minocycline-induced hyperpigmentation in this cohort of 9 patients was significantly higher than the highest reported⁸ incidence of minocycline-induced hyperpigmentation in patients with acne vulgaris (approximately 20%) ($P < .01$). We found no predilection for age, sex, or diagnosis. Pigmentation was observed after an average duration of therapy of 8.2 months (range, 1-25 months); however, by the time of examination, most patients reported a gradual history of discoloration, which was difficult to quantify temporally. At the time of cutaneous pigmentation development, the mean cumulative dose of minocycline being used was 47 g (range, 8-147 g). In patients who developed pigmentation, minocycline treatment was discontinued. A gradual fading of hyperpigmentation was observed in

all 7 patients during follow-up (4-11 months) after cessation of minocycline use (Figure 1, A and B).

In addition to skin and mucous membrane pigmentation, 2 patients developed oral candidiasis during minocycline treatment. This superficial fungal infection responded well to topical nystatin therapy, and it was not a dose-limiting toxic effect.

COMMENT

Minocycline is most commonly used to treat refractory acne vulgaris. In addition to their antimicrobial properties, tetracyclines have been found to have antichemotactic^{18,19} and collagenase inhibitory²⁰ activities. After treatment with minocycline, keratinocytes demonstrate a clear increase in interleukin 1 α activity and a decrease in tumor necrosis factor α production at protein and messenger RNA levels.²¹ This might decrease the extent and duration of the inflammatory stage in damaged follicular epithelium and inhibit granuloma formation. It has been postulated²² that the ability of minocycline to inhibit neutrophil and eosinophil chemotaxis could downgrade the afferent and efferent limbs of humoral immune response.

Because of these anti-inflammatory properties, long-term use of tetracyclines, as a corticosteroid-sparing agent, often combined with niacinamide, has expanded to include rheumatoid arthritis¹³ and immunobullous diseases.^{18,19,23-26} In PV and BP, most authors^{16,18,19,23-26} report efficacy at least equal to that of previous immunosuppressive therapies, and some suggest use of tetracyclines as a first-line agent in light of their favorable side effect profile. Although most studies focus on the efficacy and adverse effects of tetracycline therapy, minocycline has been used often as an initial agent¹⁶ or as an alternative if tetracycline adverse effects develop.^{14,15}

Observations that our patients with immunobullous disease had a significantly higher incidence of minocycline-induced hyperpigmentation suggests that this phenomenon in PV and BP is more common than in acne vulgaris or rheumatoid arthritis. There have been several long-term studies^{4,8,12} regarding hyperpigmentation in patients with acne vulgaris treated with minocycline. Therefore, it seems unlikely that the incidence in this population is underestimated because of underreporting.

In immunobullous diseases, autoantibody deposition in the epidermis or the basement membrane zone results in complement activation, which in turn results in chemotactic factors, leukocyte migration into the skin, and production of other mediators of inflammation.^{17,27} However, the immunobullous disorders, which include PV, PF, and BP, are systemic autoimmune diseases, which are frequently accompanied by circulating autoantibodies. It is possible that subclinical areas of skin or mucous membrane damage secondary to immunoglobulin and complement activity would facilitate an increased deposition of minocycline in immunobullous disorders.

Cutaneous minocycline hyperpigmentation has been observed to have 3 distinct morphologic characteriza-

Table 1. Studies of Minocycline-Induced Hyperpigmentation in Immunobullous Disorders*

Study	Patients, %	Diagnosis	Age, y/Sex	Dose, ≈g	Color and Location
Altman et al ¹⁴	100 (2/2)	BP	90/F	16	Gray-black pigmented coalescent macules on the anterior surfaces of lower legs in areas of previous bullae
Reiche et al ¹⁵	50 (4/8)†	BP	74/F	46	Blue-black macules on the anterior surfaces of legs in areas of previous blistering
		CP	71/F	NR	Lower legs
		CP	62/F	NR	NR
		CP	71/F	NR	NR
Gaspar et al ¹⁶	10 (1/10)	CP	71/NR	9	Slate gray pigmentation of lower legs
		NR	NR	NR	NR

*BP indicates bullous pemphigoid; CP, cicatricial pemphigoid; and NR, not reported.

†The fourth patient was described separately but was included in the original study.²⁷

Table 2. Patients Treated With Minocycline for Pemphigus or Pemphigoid*

Patient No.	Age, y/ Sex	Diagnosis	Date of Diagnosis, mo/y	Laboratory Study Results	Previous or Current Immunosuppressive Drug Therapy	Treatment Period (Minocycline, 100 mg BID)	Response to Minocycline Therapy†
1	48/M	PV	3/98	Bx+, DIF+	Prednisone, chlorambucil (for CLL)	11/2/98-8/99	Partial
2	68/F	BP	8/98	Bx+, DIF+	Niacin, 0.05% chlobetasol cream	8/98-2/5/99	Partial
3	79/M	BP	1984	Bx+, DIF+	Prednisone, erythromycin, methotrexate, dapsone, niacinamide, azathioprine	8/16/99-9/20/99	None
4	67/F	PV	7/92	Bx+, DIF+, IIF+	Prednisone, cyclophosphamide, intralesional triamcinolone, erythromycin	2/99-3/15/99	None
5	65/F	PV	3/84	Bx+, DIF+, IIF+	Prednisone, azathioprine, oral gold, cyclophosphamide, intralesional triamcinolone acetonide (3 mg/mL)	2/1/99-present	Marked
6	48/F	PV	1993	Bx+, DIF+, IIF+	Prednisone, azathioprine, tetracycline, clobetasol propionate, intralesional triamcinolone acetonide (3 mg/mL)	7/98-7/26/99	Marked
7	19/F	PV	6/98	Bx+, DIF+	Prednisone	8/20-10/98‡, 10/14-11/98	None
8	33/M	PV	3/95	Bx+, DIF+, IIF+	Prednisone, azathioprine, tetracycline, clobetasol propionate	7/97-8/97‡, 8/97-8/99	Marked
9	49/M	PF	Unknown	Bx+, DIF+	Prednisone, dapsone, clobetasol, propionate	3/99-present	Partial

*BID indicates twice daily; PV, pemphigus vulgaris; BP, bullous pemphigoid; PF, pemphigus foliaceus; formalin-fixed, paraffin-embedded, hematoxylin-eosin-stained skin biopsy specimens (Bx); DIF, direct immunofluorescence; IIF, indirect immunofluorescence; plus sign, positive; and CLL, chronic lymphocytic leukemia.

†Marked response indicates a decreased requirement for immunosuppressive medications and/or diminution of clinical symptoms; partial response, some decreased requirement for immunosuppressive agents and/or minimal decrease in clinical symptoms.

‡Fifty milligrams twice daily.

Table 3. Patients Who Developed Minocycline-Induced Hyperpigmentation

Patient No.	Duration of Therapy, mo	Cumulative Dose, ≈g	Inflammatory Areas During Disease Course	Sites of Pigmentation*				
				Legs	Arms	Mouth	Nails	Other†
1	9	54	Dorsum of tongue/buccal mucosa	++	-	-	++	-
2‡	6	30	Face, lower legs, arms	+++	++	-	-	-
3	1	6	Face, back, arms, inguinal	-	+	-	-	+
4	1.5	8	Erosions of gingiva, nasal mucosa, buccal mucosa, esophagus, lip	-	-	++	-	-
6	12	72	Erosions of tongue, buccal mucosa, gums, posterior palate, nares	+	-	+	-	-
7	3	12	Erosions of oral mucosa, forehead, cheeks, chin, back, chest, abdomen	-	-	+	-	+
8	25	147	Buccal mucosa gums at base of teeth, scalp	++	-	+	-	-

*Investigators' subjective assessment of severity of pigmentation: - indicates no pigmentation; +, mild hyperpigmentation (pale gray); ++, moderate hyperpigmentation (slate gray); and +++, severe hyperpigmentation (black).

†Other sites of pigmentation were the dorsum of the hands and forearms (patient 3) and the back (patient 7).

‡Patient also taking imipramine, which has been reported to cause hyperpigmentation; however, her lesions were clinically and histologically consistent with minocycline-induced hyperpigmentation.

tions: a diffuse blue-gray pigmentation involving normal skin, a localized blue-gray or black pigmentation at sites of previous inflammation or trauma,^{2-4,28} and a diffuse muddy brown hyperpigmentation involving the entire body.²⁻⁴ Our patients developed 2 types of minocy-

cline-induced hyperpigmentation: the postinflammatory type at sites of previous lesions and the diffuse blue-gray pigmentation in other skin areas (Table 3).

With the exception of the series presented by Gaspar et al,¹⁶ results of other studies of minocycline-



Figure 1. Clinical features of minocycline-induced hyperpigmentation. A, Typical pretibial pigmentation in patient 2 that developed during 7 months of minocycline therapy for bullous pemphigoid. B, Gradual resolution of pigmentation during 7 months in the same patient after discontinuing minocycline therapy. C, Subungual pigmentation in patient 1. D, Mucosal pigmentation along the alveolar ridge of the maxilla in patient 4 after approximately 6 weeks of minocycline therapy.

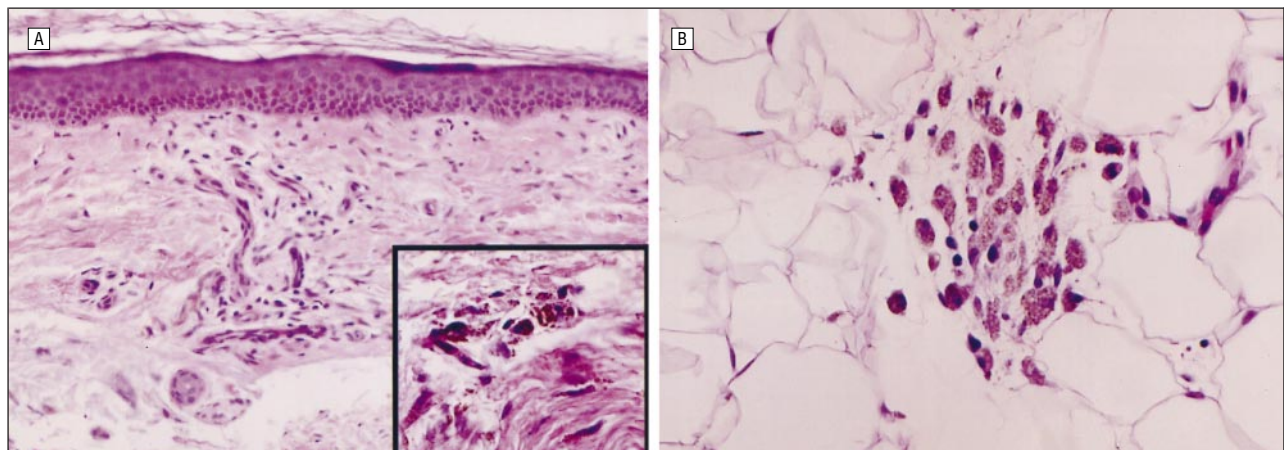


Figure 2. Histological analysis of minocycline-induced hyperpigmentation. A, Hematoxylin-eosin–stained skin biopsy specimen from the pretibia of patient 2, revealing pigment-laden macrophages in the dermis (magnification $\times 10$; inset, magnification $\times 40$); B, Pigment-laden macrophages in an adipocyte (magnification $\times 40$).

induced pigmentation in immunobullous disease are consistent with our findings (Table 1). Patients in the series by Gaspar et al¹⁶ and Reiche et al¹⁵ were receiving 100 mg of minocycline daily, and our patients and those in the series by Altman et al¹⁴ were receiving 100 mg twice daily. Reports of pigmentation location in these series were confined to the pretibial areas. We found that other areas of pigmentation, including the oral cavity, arms, and

subungual area, are less likely to be appreciated unless specifically examined for this phenomenon.

Minocycline is a yellow crystalline material that turns black on oxidation.³ Pigment formation probably occurs through polymerization in a process analogous to melanogenesis from dopa.¹⁰ Ultraviolet light has the ability to convert minocycline to a dark pigment *in vitro*⁵; however, none of our patients developed pigmentation

in sun-exposed skin. Most authors believe that the pigment complex is unique in each subtype. Electron paramagnetic resonance spectroscopy on thyroid pigment revealed it to be a unique melaninlike compound bound tightly to iron.¹⁰ This finding is supported by previous x-ray energy spectroscopic findings²⁸ in a patient with localized blue-gray pigmentation of the forearms. Minocycline, in contrast to the other tetracyclines, chelates less with calcium but forms insoluble complexes with iron. Diverse light microscopic findings might be explained by the chelation of the unique melaninlike pigment to iron, hemosiderin, or ferritin and complexed with various proteins.^{3,10,29}

Minocycline is lipid soluble, thus facilitating intestinal absorption, resulting in a lower incidence of gastrointestinal tract adverse effects than tetracycline, and increased penetration into body tissues, including skin.^{1,30,31} In vitro protein binding studies have shown minocycline to bind collagen. Collagen-rich areas such as scars, bone, and dental pulp may act as reservoirs for minocycline before its transformation into a pigment.^{5,32} This collagen-minocycline binding may help explain the distribution of pigment in vivo. Pigment location varies by subtype but has been found in cells of the epidermis, upper dermis, subcutis, and macrophages and in association with collagen bundles.^{25,33}

In patient 2, histological analysis revealed diffuse pigment distributed in the macrophages as well as extracellularly. The pigment consisted of iron and melanin and thus resembled the staining pattern described in diffuse ("muddy") brown minocycline-induced pigmentation. Many of our patients with anterior shin pigmentation recalled a previous trauma to their leg. Nearly all of our patients had previously taken systemic corticosteroids for their immunobullous disorder, predisposing them to easy bruising. Ecchymotic areas consist of iron-containing hemosiderin and melanin. The source for iron and melanin in minocycline pigmentation may be via tissue injury, with inflammation-induced melanin incontinence and extravasated red blood cells from capillary fragility.

Minocycline has been shown to inhibit thyroidal peroxidase, allowing a local buildup of hydrogen peroxide¹⁰ and presumably an accelerated oxidation of minocycline. Whether a similar reaction occurs in the skin has yet to be shown. This effect was inhibited by vitamin C in vivo, possibly through its antioxidant qualities.⁵ Similarly, receiving high doses of ascorbic acid (75 mg/kg per day) prevented development of thyroidal pigmentation in rats.³² We found no correlation in our patients between use of ascorbic acid (60-100 mg/d) and development of pigmentation. However, this dose is 1% to 2% of the protective dose used in rats.³²

In conclusion, we found a favorable response to minocycline therapy in patients with immunobullous disorders. However, 7 of 9 patients developed localized hyperpigmentation as early as 1 month after starting medication use. The incidence of this adverse effect was significantly higher than has been reported in patients with acne vulgaris or rheumatoid arthritis. The higher incidence in immunobullous disease may be related to a variety of factors, including increased pigment deposi-

tion complexed with collagen and other proteins during the remodeling response of pemphigus and pemphigoid, subclinical inflammation, or increased skin fragility due to concurrent systemic corticosteroid use. After discontinuing minocycline therapy, our patients experienced gradual fading of their skin discoloration. Patients with pemphigus or pemphigoid should be advised that hyperpigmentation can be a common adverse effect of minocycline therapy, regardless of treatment duration. However, they can be reassured that this drug-induced hyperpigmentation is reversible, in most cases, and is less troublesome than many of the adverse effects of long-term corticosteroid therapy.

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News and Notes

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