American Journal of Ophthalmology Case Reports 36 (2024) 102154

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Minocycline-induced retinal pigment epithelium hyperpigmentation masquerading as age-related macular degeneration: Case presentation and proposed mechanism

Michael D. Yu, Nikhil Bommakanti, Yoshihiro Yonekawa, Jose Serafin Pulido *

From the Retina Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, 19107, USA

ARTICLE INFO

Keywords:
Minocycline
Hyperpigmentation
Retina
Retinal pigment epithelium
Optical coherence tomography
Fundus autofluorescence

ABSTRACT

Purpose: We describe the case of an 80-year-old man with bilateral minocycline-induced retinal pigment epithelium (RPE) hyperpigmentation, which initially masqueraded as AMD. Secondarily, using multimodal imaging features, we propose a mechanism for the development of minocycline-induced RPE hyperpigmentation.
Observations: The patient was referred with concern for AMD given the presence of macular drusenoid deposits on optical coherence tomography. However, funduscopic evaluation showed dense granular parafoveal hyperpigmentation, with a diffuse slate-colored hyperpigmentation throughout the peripheral fundus. Short-wavelength fundus autofluorescence of the macula disclosed no irregularities (as would be expected with drusen) while on near-infrared reflectance (NIR) imaging, numerous hyperreflective foci were noted corresponding to the hyperpigmented granules observed clinically (as would instead be seen with melanin deposits). Clinical examination was notable for blue-gray hyperpigmentation of the lower and upper extremities, as well as of the face, periorbital skin, and sclera. Upon further questioning, the patient disclosed daily oral minocycline use for 15 years for acne rosacea, confirming a diagnosis of minocycline-induced hyperpigmentation of the RPE.
Conclusions: Multimodal imaging can be useful for differentiating minocycline-induced RPE hyperpigmentation from similar masquerade entities. Timely diagnosis can prevent progressive vision loss.

1. Introduction

Minocycline is a semisynthetic tetracycline-derived antibiotic with unique anti-chemotactic and collagenase-inhibitory properties. These anti-inflammatory characteristics make minocycline a valuable agent for treating chronic dermatological disease. Up to 88 % of patients on long-term minocycline develop systemic hyperpigmentation, which involves the skin, mucosa, and teeth. Ocular hyperpigmentation occurs rarely, with an estimated 2.7 % of patients developing scleral hyperpigmentation after long-term minocycline use.[1] Rarer yet are cases of ocular posterior segment involvement. To date, there are only sparse reports of minocycline-induced retinal pigment epithelium (RPE) hyperpigmentation, making this entity poorly characterized and understood.[2–5]

Herein, we describe a case of visually-significant bilateral minocycline-induced RPE hyperpigmentation, which initially masqueraded as age-related macular degeneration (AMD). Using clinical and multimodal imaging features from our case, we propose a mechanism for minocycline-induced RPE hyperpigmentation and describe a method for its differentiation from AMD, a potential masquerading diagnosis.

2. Case report

An 80-year-old man with no prior ocular history was referred for evaluation of AMD in both eyes (OU). He had endorsed worsening metamorphopsia in the right eye (OD). His medical history was notable for acne rosacea, for which he had been on oral minocycline for 15 years at an average daily dose of 200 mg.

At presentation, best-corrected visual acuity was 20/50 OD and 20/30 in the left eye (OS). Amsler grid confirmed central distortion OU. Clinical examination revealed blue-gray hyperpigmentation of the lower and upper extremities, as well as of the face, periorbital skin, and sclera (Fig. 1: A, B). The anterior segment was otherwise unremarkable. Funduscopic evaluation showed dense granular parafoveal hyperpigmentation OU (Fig. 1: C, D). There were no apparent drusen in the central

* Corresponding author. Retina Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, 19107, USA.
E-mail address: jpulido@willseye.org (J.S. Pulido).

https://doi.org/10.1016/j.ajoc.2024.102154
Received 2 May 2024; Received in revised form 5 August 2024; Accepted 21 August 2024
Available online 23 August 2024

macula. A diffuse slate-colored hyperpigmentation was noted throughout the peripheral fundus. Short-wavelength (green) fundus autofluorescence of the macula disclosed no irregularities (Fig. 1: E, F); however, on near-infrared reflectance (NIR) imaging, numerous hyperreflective foci were noted corresponding to the hyperpigmented granules observed clinically (Fig. 1: G, H).

Swept-source optical coherence tomography (SS-OCT; Carl Zeiss Meditec, Dublin, CA) over the macular hyperpigmentation revealed multiple confluent pigment epithelial detachments OU resembling soft drusen (Fig. 1: I, J). The ellipsoid zone was intact, but trace subfoveal subretinal fluid (SRF) without intraretinal fluid was noted. A trial of bevacizumab was initiated OU without interval SRF improvement, confirming the diagnosis of minocycline-induced RPE hyperpigmentation.

3. Discussion

To date, there exist only three reports of presumed minocycline-induced RPE hyperpigmentation in the literature.[2–5] There is no proposed mechanism for its involvement of the RPE and unique parafoveal distribution. However, the various mechanisms of minocycline-induced hyperpigmentation have been described in other tissues more amenable to biopsy.[6] Extrapolating from these histopathologic findings and incorporating the clinical and multimodal imaging features from our case, we put forth a unifying hypothesis for the development of minocycline-induced RPE hyperpigmentation. We also describe a method for its differentiation from a masquerading diagnosis, AMD, for which our patient was initially referred.

Minocycline is a yellow crystalline material that turns black with oxidation.[7] This process of pigment formation is thought to occur through polymerization, in a manner analogous to melanogenesis from dopa.[8] The resultant minocycline-derived pigments appear similar to melanin in most respects yet are still fundamentally unique.[7] Electron paramagnetic resonance spectroscopy has revealed it to be a unique melanin-like compound that also tightly binds to iron.[8]

Minocycline polymerization is likely catalyzed by ultraviolet light. In *vitro* experiments, ultraviolet light has the ability to convert minocycline into a dark pigment.[9] Although this has not been demonstrated *in vivo*, the propensity of minocycline hyperpigmentation to involve sun-exposed dermal surfaces, such as the forearms and face, suggests a contributory effect from ultraviolet exposure.[1] In the eyes, minocycline most commonly affects the interpalpebral sclera, which also has the highest ultraviolet exposure.[10] This may also partly explain the preferential macular involvement when posterior segment hyperpigmentation is present.

The process of minocycline-pigment polymerization incorporates true melanin pigment as well, owing to the structural similarities between melanin and minocycline-derived pigments.[8] That this minocycline-pigment complex necessarily incorporates both iron and melanin might explain the unique distribution of minocycline-induced hyperpigmentation within the fundus. Multimodal imaging in our case demonstrates an accumulation of minocycline-pigment compounds laterally within the parafoveal fundus and anteroposteriorly within the sub-RPE space. This distribution aligns with the densest concentration of melanin within the retina. Fundus reflectometry has previously shown that melanin is most concentrated in the parafoveal macula,[11] while cross-sectional histopathologic evaluation of the retina shows melanin granules to be most concentrated within the apical RPE.[12,13] In the adult fundus, iron similarly exists in the highest concentrations within the macula.[13] The high lipophilicity of minocycline, even relative to other

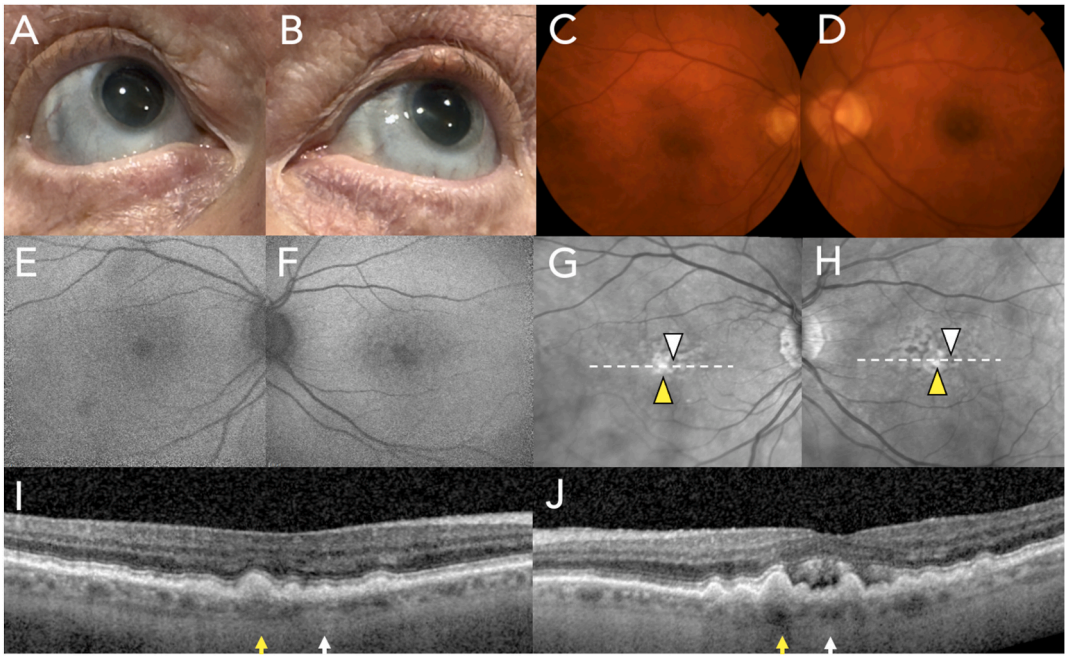

Fig. 1. Multimodal imaging of the scleral and macular hyperpigmentation. External photographs demonstrate blue-gray hyperpigmentation of the right **(A)** and left **(B)** sclerae, a common ocular manifestation of minocycline-induced hyperpigmentation. Fundus photographs highlight parafoveal slate-colored hyperpigmented deposits in the right **(C)** and left **(D)** maculae, which we presume represent minocycline-melanin complexes in the sub-retinal pigment epithelial (RPE) space. Short-wavelength autofluorescence (AF) **(right, E; left, F)** and near-infrared reflectance (nIR) **(right, G; left, H)** help confirm the composition of these sub-RPE deposits. Their diffuse hypoautofluorescent appearance on short-wavelength AF indicates a low lipofuscin content. Conversely, these nodules appear markedly hyperreflective (yellow arrowheads) on near-infrared reflectance (nIR) imaging **(right, G; left, H)**, suggesting a predominant melanin composition. The intervening bands of hyporeflectance (white arrowheads) represent RPE atrophy. Optical coherence tomography through the right **(I)** and left **(J)** maculae (dotted white lines) show near confluent drusenoid deposits, corresponding to the areas of hyperreflectance on nIR. These areas also demonstrate variable choroidal shadowing (yellow arrows) proportional to the height of the sub-RPE deposits, as high melanin concentration blocks light penetration. Focal choroidal transmission (white arrows) is seen in areas of RPE atrophy; these changes are more prominent in the right eye (**J**). Also seen is trace transudative intraretinal fluid in the right eye and subretinal fluid with shaggy photoreceptors in the left eye.

tetracyclines, allows it to penetrate and deposit in this space, where it polymerizes and binds melanin and iron.[15]

On optical coherence tomography, the lesions seen in our case resemble that of soft confluent drusen, as might be seen in AMD. In fact, the patient presented with a referring diagnosis of AMD given the presence of drusen and subretinal fluid. However, these two entities can be differentiated by leveraging their unique biochemical compositions and resultant differences on multimodal imaging. While minocycline-pigment complexes bind melanin, soft drusen are thought to comprise, at least in part, extracellular lipofuscin-containing debris. Near-infrared reflectance (nIR) imaging, with an excitation wavelength of 787 nm, is best equipped to image melanin within the RPE, while accumulation of lipofuscin and its major fluorophore A2E is best visualized with conventional fundus autofluorescence (FAF), with an excitation wavelength of 488 nm.[14,16] It follows then that minocycline-pigment complexes, with their dense melanin content, would appear most hyperreflective on nIR imaging and relatively hypofluorescent on FAF, as was indeed seen in our case. The intervening bands of hyporeflectance on nIR were presumed to correspond to areas of RPE atrophy. Additionally, while hyperpigmentation can occur in AMD, the location is usually on the inner surface of the pigment epithelium detachment or within the neurosensory retina, as opposed to in the sub-RPE space in our patient.

Despite multimodal imaging and clinical features suggestive of minocycline-induced hyperpigmentation, given the presence of subretinal fluid (SRF), and the possibility of AMD, our patient elected to undergo a trial of intravitreal anti-vascular endothelial growth factor (VEGF) treatment in both eyes. The patient demonstrated no response to intravitreal *anti*-VEGF, confirming the presumptive diagnosis of minocycline-associated hyperpigmentation of the RPE. In this case, the visually-significant SRF was thought to result from compromised RPE fluid transport mechanisms due to large minocycline-pigment complexes deposited in the sub-RPE space.

Our findings suggest that minocycline-induced RPE hyperpigmentation could be underrecognized and underdiagnosed. Posterior segment involvement is concentrated in the parafoveal macula and may resemble AMD. Unlike other systemic manifestations of minocycline-induced hyperpigmentation, RPE involvement can have functional consequences; thus, prompt diagnosis and discontinuation of minocycline can be paramount to preventing visual decline.

Patient consent

The patient(s)/patient's legal guardian consented to publication of the case in writing/orally. However, this report does not contain any personal information that could lead to the identification of the patient.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

CRediT authorship contribution statement

Michael D. Yu: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Nikhil Bommakanti:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Yoshihiro Yonekawa:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Jose Serafin Pulido:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

References

1. Hanada Y, Berbari EF, Steckelberg JM. Minocycline-induced cutaneous hyperpigmentation in an orthopedic patient population. *Open Forum Infect Dis*. 2016; 3:1–6.
2. Patel M, Wingert AM, Sridhar J. Blue sclera and retinal hyperpigmentation in a patient with long-term minocycline use. *JAMA Ophthalmol*. 2022;140(6), e221848.
3. Bradfield YS, Robert DM, Salomao DR, et al. Minocycline-induced ocular pigmentation. *Arch Ophthalmol*. 2003;121(1):144.
4. Jung JJ, Chen MH, Sorenson AL, Rofagha S. Swept-source optical coherence tomography and OCT angiography of minocycline-induced retinal and systemic hyperpigmentation. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47:356–361.
5. Baaklini C, Kesav N, Reinhart W. Minocycline-induced ocular ochronosis. *Cureus*. 2023 Aug 10;15(8), e43307.
6. Ozog DM, Gogstetter DS, Scott G, et al. Minocycline-induced hyperpigmentation in patients with pemphigus and pemphigoid. *Arch Dermatol*. 2000;136(9):1133–1138.
7. Pepine M, Flowers FP, Ramos-Caro FA. Extensive cutaneous hyperpigmentation caused by minocycline. *J Am Acad Dermatol*. 1993;28:292–295.
8. Enochs WS, Nilges MJ, Swartz HM. The minocycline-induced thyroid pigment and several synthetic models: identification and characterization by electron paramagnetic resonance spectroscopy. *J Pharmacol Exp Therapeut*. 1993;266(3): 1164–1176.
9. Bowles WH, Bokmeyer TJ. Staining of adult teeth by minocycline: binding of minocycline by specific proteins. *J Esthetic Dent*. 1997;9(1):33.
10. Al Awamlh SAH, Taubenslag KJ, Gangaputra S. Minocycline-induced scleral pigmentation. *Am J Ophthalmol Case Rep*. 2022;26, 101386.
11. Lapierre-Landry M, Carroll J, Skala MC. Imaging retinal melanin: a review of current technologies. *J Biol Eng*. 2018;4(12):29.
12. Boulton ME. Studying melanin and lipofuscin in RPE cell culture models. *Exp Eye Res*. 2014;126:61–67.
13. Keilhauer CN, Delori FC. Near-infrared autofluorescence imaging of the fundus: visualization of ocular melanin. *Invest Ophthalmol Vis Sci*. 2006;47(8):3556–3564.
14. He X, Hahn P, Iacovelli, et al. Iron homeostasis and toxicity in retinal degeneration. *Prog Retin Eye Res*. 2008;26(6):649–673.
15. Barza M, Brown RB, Shanks C, et al. Relation between lipophilicity and pharmacological behavior of minocycline, doxycycline, tetracycline, and oxytetracycline in dogs. *Antimicrob Agents Chemother*. 1975;8(6):713–720.
16. Cukras CA, Wong WT, Caruso R, Cunningham D, Zein W, Sieving P. Centifugal expansion of fundus autofluorescence patterns in Stargardt disease over time. *Arch Ophthalmol*. 2012;130(2):171–179.