DOI: 10.7860/JCDR/2019/41701.13007

Case Report

Internal Medicine Section

Hyperpigmentation Induced by Hydroxychloroquine: A Case Report

BHANUKUMAR MUTHAIAH[1], GEORGE MATHEW PANACHIYIL[2], TIRIN BABU[3]

ABSTRACT

Hydroxychloroquine is an antimalarial drug which is widely used in the treatment of rheumatoid arthritis, owing to its immunosuppressive and anti-inflammatory properties. Mucocutaneous hyperpigmentation induced by hydroxychloroquine is rarely reported. The time temporal relationship between the starting of hydroxychloroquine therapy and the onset of hyperpigmentation of the skin ranges from three months to 22 years. This report presents a case of 48-year-old female with rheumatoid arthritis who developed hyperpigmentation on the face and skin during the treatment with hydroxychloroquine. She was treated with hydroxychloroquine for one year. Hyperpigmentation on the face and skin started after nine months of initiation of hydroxychloroquine therapy and skin biopsy showed skin with epidermis displaying increased basal melanin. The superficial dermis showed increased collagenisation. Perls stain was done, which did not stain the pigment. This presentation of melanin deposition alone is rare as previous reports of hyperpigmentation indicate the presence of both melanin and haemosiderin in patients being treated with antimalarial medication. The patient was advised to stop hydroxychloroquine and as an alternate drug, methotrexate 7.5 mg (two times per week) was started for her. Stoppage of hydroxychloroquine resulted in the decline of the pigmentation over the course of several months.

Keywords: Antimalarial drug, Dyschromia, Rheumatoid arthritis

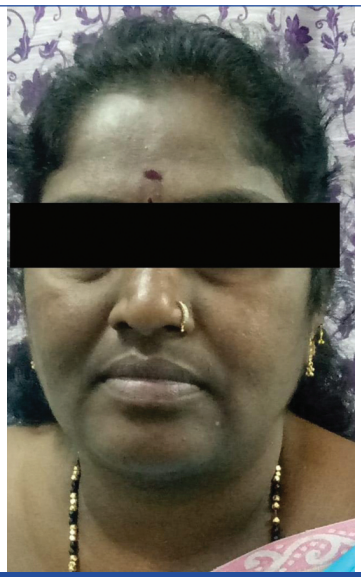
CASE REPORT

A 48-year-old female, diagnosed with rheumatoid arthritis one year back, presented to the outpatient department of the hospital with the complaint of discolouration of face and skin since three months. She was treated with hydroxychloroquine for one year. She reported improvement with respect to joint pains and early morning joint stiffness. General examination revealed: temperature of 37°C, heart rate of 95 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 140/90 mmHg and SpO_2 was 98% at room air.

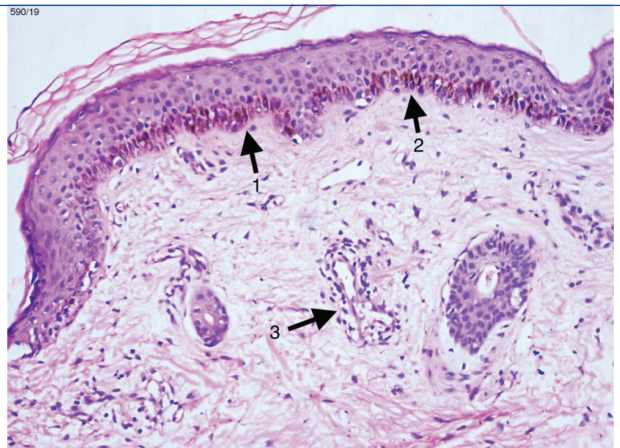
Hyperpigmentation on face [Table/Fig-1] and upper limb skin particularly over the exposed area was noted on examination, but there was no involvement of oral mucosa. The skin lesions were macular or patchy, with hyperpigmentation due to black discolouration. They were flat without any induration or scaling. Skin biopsy sample from neck region revealed multiple sections showing epidermis displaying increased basal melanin induced by drug but iron staining was negative. The superficial dermis showed increased collagenisation and perivascular lymphocytic infiltrates [Table/Fig-2]. The fundoscopy results showed normal mucosa.

Hydroxychloroquine was suspected to be the cause of hyperpigmentation on the face and skin, based on the drug history. First, the patient was not on any drug except hydroxychloroquine for one year. Second, hydroxychloroquine is known to cause dyschromia but the frequency is not defined [1]. Third, the onset of hydroxychloroquine related hyperpigmentation ranges from three months to 22 years following the initiation of therapy, with a median of 6.1 years [2].

Based on the clinical findings, laboratory findings and drug history, the final diagnosis made was hydroxychloroquine induced hyperpigmentation on the face and skin. The patient was advised to stop hydroxychloroquine and as an alternate drug, methotrexate 7.5 mg (two times per week) was started for her. Discontinuation of hydroxychloroquine resulted in the decline of the pigmentation over the course of several months [Table/Fig-3]. With methotrexate, the patient symptoms of rheumatoid arthritis have improved significantly, however there are intermittent exacerbations. In this

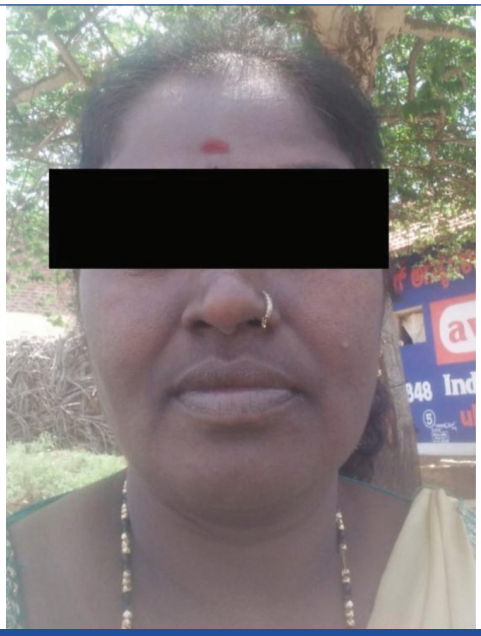


[Table/Fig-1]: Pre-treatment image (Hyperpigmentation on face).



[Table/Fig-2]: Skin biopsy histomicrograph (H&E, 200X).
Arrow 1 and 2 Indicates increase in basal melanin;
Arrow 3 Indicates perivascular lymphocytic infiltrates

case, the causality assessment total score according to Naranjo's algorithm was 7 (probable), and as per the WHO assessment scale also it was probable.



[Table/Fig-3]: Follow-up image.

DISCUSSION

Mucocutaneous hyperpigmentation, as a result of antimalarial therapy, has been stated from the time of World War 2, but, hydroxychloroquine related hyperpigmentation appears to be less common than with other antimalarial drug such as chloroquine [2,3]. However, the precise biochemical basis for the hyperpigmentation is unknown. It has been suggested that hydroxychloroquine binds to melatonin and concentrates in the skin that may cause the hyperpigmentation of the skin [4].

The treatment of skin hyperpigmentation related to hydroxychloroquine consisted of withdrawal of the culprit drug which tends to cause the gradual decrease in hyperpigmentation of lesions within several months [5,6]. The melanin and haemosiderin can be present within the epidermis in hyperpigmented lesions induced by hydroxychloroquine [7-9]. The presentation of melanin deposition alone in the index case is rare as previous reports of hyperpigmentation indicated the presence of both melanin and haemosiderin in patients being treated with antimalarial medication. Puri PK et al., reported two cases of hydroxychloroquine induced hyperpigmentation in a 50-year-old Caucasian female (case 1) and in a 78-year-old female (case 2). The biopsies from both patients showed superficial dermal, yellow-brown, non-refractile and coarsely granular pigment deposition. A Fontana-Masson stain highlighted some of these granules, supporting the presence of melanin. The Perl's iron stain for haemosiderin was negative in both cases [10].

CONCLUSION

The hyperpigmentation on the face and the exposed parts of the body may matter in women particularly those with fair skin. The patient should be well informed about this potential adverse effect while beginning the therapy and recommended to consult health care professionals in case of development of any adverse reaction related to drug therapy for the further management of the same.

ACKNOWLEDGEMENTS

The authors would like to thank JSS Academy of Higher Education and Research and Department of General Medicine, JSS Hospital for their constant support and encouragement.

REFERENCES

[1] Lexicomp Online | Clinical Drug Information [Internet]. Wolterskluwercdi.com. 2019 [cited 1 May 2019]. Available from: http://www.wolterskluwercdi.com/lexicomp-online/.
[2] Sawalha AH. Hydroxychloroquine-induced hyperpigmentation of the skin. The Journal of Rheumatology. 2015;42(1):135-36.
[3] Millard TP, Kirk A, Ratnavel R. Cutaneous hyperpigmentation during therapy with hydroxychloroquine. Clinical and Experimental Dermatology: Viewpoints in Dermatology. 2004;29(1):92-93.
[4] Melikoglu MA, Melikoglu M, Gurbuz U, Budak BS, Kacar C. Hydroxychloroquine-induced hyperpigmentation: A case report. J Clin Pharm Ther. 2008;33(6):699-701.
[5] Rood MJ, Vermeer MH, Huizinga TW. Hyperpigmentation of the skin due to hydroxychloroquine. Scand J Rheumatol. 2008;37(2):158.
[6] Amichai B, Gat A, Grunwald MH. Cutaneous hyperpigmentation during therapy with hydroxychloroquine. J Clin Rheumatol. 2007;13(2):113.
[7] Tracy CL, Blakey B, Parker G, Roebuck J. Hydroxychloroquine-induced hyperpigmentation. JCR: Journal of Clinical Rheumatology. 2013;19(5):292.
[8] Jallouli M, Francès C, Piette JC, Moguelet P, Factor C, Zahr N, et al. Hydroxychloroquine-induced pigmentation in patients with systemic lupus erythematosus: A case-control study. JAMA Dermatology. 2013;149(8):935-40.
[9] Coulombe J, Boccara O. Hydroxychloroquine-related skin discoloration. Canadian Medical Association. Journal. 2017;189(5):E212.
[10] Puri PK, Lountzis NI, Tyler W, Ferringer T. Hydroxychloroquine-induced hyperpigmentation: The staining pattern. Journal of Cutaneous Pathology. 2008;35(12):1134-37.

PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of General Medicine, JSS Medical College and Hospital, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India.
2. PharmD, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India.
3. PharmD, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Tirin Babu,
PharmD, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research,
Mysuru-570015, Karnataka, India.
E-mail: erumalat@yahoo.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Apr 05, 2019**
Date of Peer Review: **Apr 25, 2019**
Date of Acceptance: **Jun 12, 2019**
Date of Publishing: **Jul 01, 2019**