Skin and Nail hyperpigmentation (Melanonychia) due to Cyclophosphamide in case of steroid dependant nephrotic syndrome (SDNS): A rare association

Lakshminarayana GR[1*], Sahiba E Ummer[2], Raghunath KV[3], Muthukumar R[4]

[1,2]Consultant, [3,4]Resident Medical Officer, Dept. of Nephrology, EMS Memorial Cooperative Hospital and Research Centre, Perinthalmanna, Malappuram, Kerala, India

***Corresponding Author: Lakshminarayana GR**
Email: drlng23@gmail.com

Abstract
Cyclophosphamide (CYC) is one the most commonly used second line drug in treatment of nephrotic syndrome, especially in those who are steroid dependant or with frequent relapses. Use of CYC may rarely cause skin or nail hyperpigmentation (melanonychia) apart from other adverse effects related to immunosuppression or cytopenias or hemorrhagic cystitis. We present a patient of steroid dependent nephrotic syndrome (SDNS) who developed blackish brown discoloration of nails and periungual skin folds.

Keywords: Nephrotic syndrome, Cyclophosphamide, Melanonychia, Hyperpigmentation, Black chromonychia.

Introduction
Cyclophosphamide a chemotherapeutic agent belongs to the nitrogen mustard group of alkylating agents.[1] It acts after being metabolized in the liver to the active metabolite phosphoramide, which alkylates DNA and inhibits replication. The CYC induced nail pigmentation is probably under-reported adverse effect.

Case Report
An 47-year-old male, a case of type 2 diabetes mellitus, systemic hypertension, hypothyroidism since 2 years, steroid-dependent idiopathic nephrotic syndrome (June 2020 - renal biopsy showing near normal glomeruli with negative immunofluorescence (for IgA, IgM, C3, C1q, kappa and lambda) and no vascular changes) was put on oral cyclophosphamide (2 mg/kg/day) along with prednisolone (1 mg/kg/day) in August 2020. He received a cumulative dose of 9.0 gm of CYC in 3 months. His nephrotic syndrome responded to combination of Prednisolone and CYC.

He started noticing hyperpigmentation of nails and proximal skin folds of all the fingers towards the end of 3rd month of therapy. Pigmentation started proximally, first involving lunulae and then progressed distally in a longitudinal fashion. There was no associated onycholysis, pruritus, and fever or skin rash. The maximally affected were bilateral thumbs (melanonychia/ black chromonychia), periungual skin folds [Fig. 1]. The pigmentation started decreasing after stopping the therapy starting from lunulae progressing distally [Fig. 2].

His evaluation showed hemoglobin - 13.5 g/dl, WBC count - 10500 c/cmm, platelets - 250000 c/cmm. His WBC counts were followed every 2 weeks while receiving CYC and were normal. His urine albumin was trace, UPCR 0.1 g/g, no active urinary sediments during last follow-up. His Liver function test was normal. His cholesterol was 214 mg/dl, FBS & PPBS were 124 & 236 mg/dl respectively.

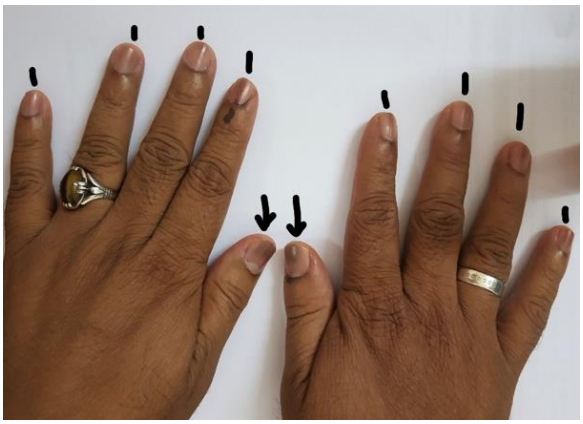

Fig. 1: Hyperpigmentation affecting nail (melanonychia/ black chromonychia) and nail folds (thumb nails more than others)

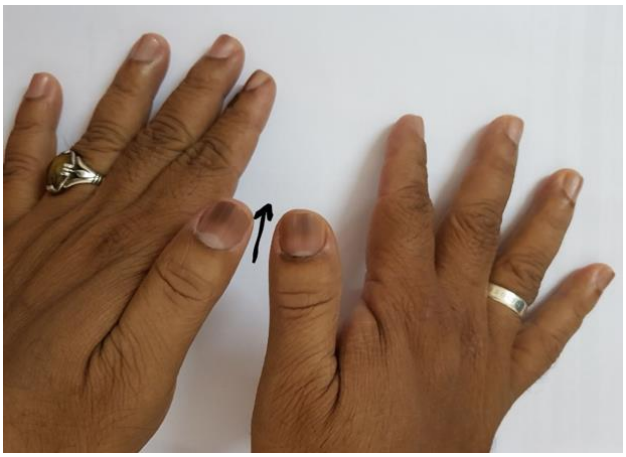

Fig. 2: Resolving melanonychia/ black chromonychia starting from lunulae of nail and progressing distally (arrow)

Discussion

Cyclophosphamide (CYC) is a one of the commonly prescribed drug in Nephrology and Oncology, an alkylating agent whose main target is the cell cycle; thus, tissues with high proliferation rates are more susceptible.[1-7] Alkylating agents form cross-links with DNA filaments and prevent DNA replication, therefore entailing cytotoxicity.[1-4] The patients receiving CYC needs close monitoring for adverse effects like myelosuppression, haemorrhagic cystitis, alopecia, and gastrointestinal upset.[7] The CYC can cause nail changes such as diffuse, black pigmentation, longitudinal striae ranging in colour from slate grey to black (black chromonychia), and diffuse, dark grey pigmentation located proximally, with overlying transverse, black bands and also skin hyperpigmentation.[1-8] Hyperpigmentation in nails (melanonychia) induced by CYC begins proximally in the lunulae and then spreads distally, probably with the growth of the nail plate, similar to our case.[5] The pattern of involvement may be varied, and may involve the proximal nail fold, knuckles and toe nail, oral mucosa and tongue as well.[2,5] The pigmentation may deeper and extensive in the hand nails (fingernails) compared to the toe nails, as in present case.[1]

Toxicity may be asymptomatic and limited to cosmetic concerns; however, more severe side effects involving pain and discomfort have been reported in adults.[1,4] On stopping the drug, the pigmentation reverts back in the fashion it appeared and may take up to 4-6 months and rate of disappearance may vary among different among digits as in present case.[5] CYC induced pigmentary changes occur after a range of cumulative doses (1.2-12.3 g) and treatment durations (10 days to 26 weeks).[7] Skin and nail discoloration have also been reported with other chemotherapeutic agents such as Ifosfamide, Doxorubicin, Bleomycin, Hydroxyurea, Dactinomycin, Mithramycin (Plicamycin) previously.[4-8]

There are many mechanisms proposed for cyclophosphamide-induced nail pigmentation such as genetic predisposition, toxicity to the nail bed and matrix, focal activation of melanocytic matrix, photosensitization drug-induced adrenal suppression and a direct stimulation of melanocytes.[1-4, 6, 7] There is no specific treatment for melanonychia; it is mostly self-limiting regressing slowly after discontinuation of the offending agent.[1-7] The discoloration subsides as the nail grows although it takes a long duration depending on the severity of toxicity, the dose and duration of drug use, and also, the time of cessation of the offending agent.[4] Patients who are worried about the appearance of the nails can mask it using cosmetics like nail polish.[4]

Conclusions

The CYC induced nail/skin hyperpigmentation is a rare adverse event that is underreported. In majority on patients it is asymptomatic with only cosmetic changes affecting the nails and skin. Clinicians using CYC needs to be aware of this uncommon side effect of the drug.

Conflict of Interest

None.

Sources of Funding

None.

References

1. Kumar S, Dixit R, Karmakar S, Paul S. Unusual nail pigmentation following cyclophosphamide containing chemotherapy regimen. *Indian J Pharmacol* 2010;42:243-44. DOI: 10.4103/0253-7613.68433: 10.4103/0253-7613.68433
2. Marien L, Clarice J, Rachel G, Celso S, Marcia Ramos S. Chromonychia Secondary to Chemotherapy. *Case Rep Dermatol* 2013; 5:163-7. DOI: 10.1159/000351874

3. Cristiana R, Beltrame G, Fenoglio R, Ferro Mi, Mesiano P, Quattrocchio G et al. Blue Fingernails during Treatment with Cyclophosphamide for Minimal Change Disease: A Very Rare Side Effect. *Clin Med Rev Case Rep* 2017;4:162. DOI: 10.23937/2378-3656/1410162
4. Mehta S, Makkar V, Soha PM, Sethi S, Kaur S. Cyclophosphamide-Induced Melanonychia in a Patient with Steroid Dependent Nephrotic Syndrome: A Rare Presentation. *Saudi J Kidney Dis Transpl* 2019;30(4):978-81.
5. Ranawaka RR. Patterns of chromonychia during chemotherapy in patients with skin type V and outcome after one year of follow-up. *Clin Exp Dermatol* 2009; 34:e920-6.
6. Prajapati VB, Madhyastha S, Acharya R, Gopalaswamy V, Doddamani A. Cyclophosphamide and Doxorubicin Induced Melanonychia: A Case Report. *J Clin Diagn Res*. 2017;11(1):OD04-OD05. DOI:10.7860/JCDR/2017/23041.9216
7. Mary ET, Daryl Murry, & Albert SC. Ifosfamide- Induced Hyperpigmentation. *Cancer* 1993; 71: 2873-5.
8. Mendiratta V, Jain A. Nail dyschromias. *Indian J Dermatol Venereol Leprol* 2011;77:652-8.

How to cite: Lakshminarayana GR, Ummer SE, Raghunath KV, Muthukumar R. Skin and Nail hyperpigmentation (Melanonychia) due to Cyclophosphamide in case of steroid dependant nephrotic syndrome (SDNS): A rare association. *IP J Urol Nephrol Hepatol Sci* 2020;3(4):85-7.