

## Original Research Article

# Nail changes in patients undergoing cancer chemotherapy

Praveen Kumar Shanmugam Reddy\*, Arakali Lakshminarayana Shyam Prasad,  
Tharayil Kunneth Sumathy, Rakesh Vibhakar Reddy

Department of Dermatology, M.S Ramaiah Medical College, Bangalore, Karnataka, India

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### \*Correspondence:

Dr. Praveen Kumar Shanmugam Reddy,  
E-mail: [drpraveen.1982@gmail.com](mailto:drpraveen.1982@gmail.com)

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## ABSTRACT

**Background:** Anti-cancer chemotherapy is associated with a myriad nail changes ranging from cosmetic disfigurement to severe changes which may require an alteration in the cancer chemotherapeutic regimens. The objective of the study was to analyse the nail changes in patients undergoing cancer chemotherapy.

**Methods:** Screening was done for all in-patients undergoing cancer chemotherapy and out-patients referred to Dermatology from Oncology. All nail changes were documented according to a proforma and an attempt was made to establish a relation, if any, with a chemotherapeutic agent group.

**Results:** A total of consecutive 150 patients undergoing cancer chemotherapy were screened, out of which nail changes were observed in 50 patients. The age group of patients ranged from 12yrs to 73yrs. The Male: Female ratio was 2.7:1. Following platinum based agents, the nail changes were seen in 54% of patients. There was a significant association of nail changes following chemotherapy with a p value of 0.00001%. Pigmentary changes were the most common nail plate changes. Longitudinal pigmentary bands were the most common pigmentary nail plate changes seen in 67.7% of patients following chemotherapy with platinum based agents, and 16.1% of patients following CHOP regimen. Diffuse pigmentation of nail plate was most common nail plate change (16.1%) following chemotherapy with taxanes. Muehrcke's lines were the most common nail bed changes seen in 57.1% of patients following treatment with platins. Half and half nails and onycholysis were seen in 42.85% of patients following CHOP chemotherapy. Pigmentation of the nail folds were the most common changes seen in 40% of patients following platinum based agents and CHOP chemotherapy.

**Conclusions:** A variety of nail changes can be associated with cancer chemotherapy. A knowledge about the various changes ranging from those of cosmetic concern to serious changes in patients who are undergoing chemotherapy is vital for the successful management of the patient.

**Keywords:** Chemotherapy, Pigmentary, Nail changes, Platinum based agents

## INTRODUCTION

There are different chemotherapeutic agents used in the management of various malignancies. Nail changes are often under-recognized or attributed to other causes and may be a cause of concern for the patient. The anti-cancer chemotherapeutic agents may cause a damage to the nail matrix<sup>1</sup> or the nail bed<sup>2</sup> and a variety of changes involving the nail plate, nail bed, hyponychium or the

nail folds may be seen. Pigmentary changes involving the nail plate are seen secondary to the damage to the nail matrix melanocytes by the offending chemotherapeutic agents. The damage to the nail bed may be as a consequence of direct damage by the offending drugs or an indirect damage to the underlying blood vessels<sup>2</sup>. In severe cases, the offending drug needs to be withdrawn or its dosage reduced. This study aims to report the various nail changes following cancer chemotherapy.

## METHODS

This is a prospective, cross-sectional study conducted at M. S. Ramaiah hospitals, after an ethical clearance from the Institutional ethical review board. Study duration was from January 2012 to December 2012. Screening was done for all in-patients undergoing cancer chemotherapy, out-patients referred to Dermatology from Oncology, for any cutaneous problem. All nail changes were documented according to a proforma and an attempt was made to establish a relation, if any, with a chemotherapeutic agent group. The inclusion criteria were male and female patients of all age groups undergoing cancer chemotherapy and all those patients who developed nail changes after starting chemotherapy. The exclusion criteria included all patients with a definite past history of nail problems and those patients who had cutaneous diseases causing nail changes and those patients with occupations involving contact with chemicals which could cause nail changes.

This study also excluded patients who have an associated endocrine, cardiac, renal or hepatic disorders which could be implicated in causing the various nail changes. The parameters studied were nail changes secondary to chemotherapy, with the identification of the causative agent. The ancillary data studied were the age, sex of the patients, with the average time duration for the onset of nail changes after the start of chemotherapy and the other concomitant therapies for the cancer. The data was analysed using descriptive statistics and a Chi-square test.

## RESULTS

A total of consecutive 150 patients undergoing cancer chemotherapy were screened, out of which nail changes were observed in 50 patients. The age group of patients ranged from 12 years to 73 years (median: 50 years). The Male: Female ratio was 2.7:1. The incubation period from the start of the chemotherapeutic agent and the onset of nail changes ranged from 3 to 6 weeks, with a median of 4 weeks.

The nail changes were classified into changes involving the nail plate, changes involving the nail bed and the

changes involving the nail folds. The most common chemotherapeutic agents which were given to patients prior to nail changes were platinum based agents, taxanes and CHOP regimens. Following platinum based agents the nail changes were seen in 54% of patients as shown in Table 1. There was a significant association of nail changes following chemotherapy with a p value of 0.00001% as given in Table 1. Nail plate changes were the commonest changes following chemotherapy as shown in Table 2. Pigmentary changes were the most common nail plate changes. Longitudinal pigmentary bands were the most common pigmentary nail plate changes seen in 67.7% of patients following chemotherapy with platinum based agents as given in Table 3, and 16.1% of patients following CHOP regimen. Diffuse pigmentation of nail plate was most common nail plate change (16.1%) following chemotherapy with taxanes as in Table 3. Beau's lines and leuconychia was seen in 1 patient each following chemotherapy with platinum based agents.

**Table 1: Association of nail changes with chemotherapeutic agents.**

Chemotherapeutic agents	Nail changes present	Nail changes absent	Total
<b>Platins</b>	27 (54%)	23 (46%)	50
<b>Taxanes</b>	6 (12%)	44 (88%)	50
<b>CHOP</b>	10 (20%)	40 (80%)	50
<b>Total</b>	43	107	150

N=50, Chi-square = 24.32, p value 0.00001.

**Table 2: Distribution of various nail changes related to chemotherapeutic agents.**

Chemotherapeutic agents	Nail plate	Nail bed	Nail fold	Total
<b>Platins</b>	21	4	2	27
<b>Taxanes</b>	5	0	1	6
<b>CHOP</b>	5	3	2	10
<b>Total</b>	31	7	5	43

**Table 3: Nail plate pigmentary changes associated with chemotherapeutic agents.**

Chemotherapeutic agents	Longitudinal pigmentary bands	Diffuse pigmentation	Longitudinal striations	Transverse pigmentary bands
<b>Platinum based agents</b>	21/31(67.7%)	13/31(41.9%)	14/31(45.15)	3/31(9.6%)
<b>Taxanes</b>	4/31(12.9%)	5/31(16.1%)	4/31(12.9%)	2/31(6.4%)
<b>CHOP</b>	5/31(16.1%)	4/31(12.9%)	-	1/31(3.2%)

Muehrcke's lines were the most common nail bed changes seen in 57.1% of patients following treatment with platinum based agents as in Table 4. Half and half nails and onycholysis were seen in 42.85% of patients following CHOP chemotherapy as in Table 4.

Pigmentation of the nail folds were the most common changes seen in 40% of patients following Platinum based agents and CHOP chemotherapy as tabulated in Table 5. The nail changes compared among nail plate, nail bed and nail folds following chemotherapy was not statistically significant as given in Table 6.

**Table 4: Nail bed changes associated with chemotherapeutic agents.**

Chemotherapeutic agents	Muehrcke's lines	Half and Half nails	Onycholysis
<b>Platinum based agents</b>	4/7 (57.1%)	3/7 (42.85%)	2/7 (28.57%)
<b>CHOP</b>	-	3/7 (42.85%)	3/7 (42.855%)

**Table 5: Nail fold changes associated with chemotherapeutic agents.**

Chemotherapeutic agents	Pigmentation
<b>Platinum based agents</b>	2/5(40%)
<b>Taxanes</b>	1/5(20%)
<b>CHOP</b>	2/5(40%)

**Table 6: Comparison of nail plate changes with other nail changes in relation to chemotherapeutic agents.**

Chemotherapeutic agents	Nail plate	Other nail changes
<b>Platinum based agents</b>	21 (77%)	6 (23%)
<b>Taxanes</b>	5 (83.3%)	1 (16.7%)
<b>CHOP</b>	5 (50%)	5 (50%)

Chi-square=3.237, p value=0.198

**Table 7: Nail plate changes in relation to the most common malignancy and the chemotherapeutic agent group.**

Most common malignancy	Most common chemotherapeutic agent group	Nail plate changes (n=31)
<b>Ca Cervix 15/21 (71.4%)</b>	Platinum based agents	Longitudinal pigmentary bands 21/31(67.7%)
<b>Lymphoma/ NHL 10/13 (76.9)</b>	Platinum based agents	Diffuse pigmentation 13/31(41.9%)
<b>Ca Breast 4/4 (100%)</b>	Taxanes	Longitudinal striations 14/31(45.1%)
<b>Ca breast 1/1 (100%)</b>	Platinum based agents	Beau's lines 1/31(3.%)
<b>Ca rectum with metastases 1/1 (100%)</b>	Platinum based agents	Leuconychia 1/31(3.2%)

The most common malignancy associated with longitudinal pigmentary bands as shown in Figure 1 and Table 7 was carcinoma cervix (71.4%). The diffuse hyperpigmentation of nail plates as in Figure 2 were associated with lymphomas (76.9%). Transverse

pigmentary bands as in Figure 3 were seen with 9.6% of patients who were treated with platinum based agents. Longitudinal striations as shown in Figure 4 were seen in all patients of carcinoma breast treated with Taxanes. Beau's lines as in Figure 5 were most common nail plate changes associated with carcinoma breast as given in Table 7. Leuconychia was seen in one patient of carcinoma rectum with metastases and patient was treated with platinum based agents.

**Table 8: Nail bed changes in relation to the most common malignancy and the chemotherapeutic agent group.**

Malignancy	Most common chemotherapeutic agent group	Nail bed changes (n=7)
<b>Ca breast 4/4 (100%)</b>	Platinum based agents	Muehrcke's lines 4/7 (57.1%)
<b>CA breast (T3N1M1 staging) 3/3 (100%)</b>	Platinum based agents	Half and Half nails 3/7 (42.85%)
<b>Ca GIT with metastases 2/2 (100%)</b>	Platinum based agents	Onycholysis 2/7 (28.57%)

**Figure 1: Longitudinal hyper pigmented band of the nail plate.****Figure 2: Diffuse hyperpigmentation of nail plate.**



**Figure 3: Transverse pigmented bands on nail plate.**



**Figure 4: Longitudinal striations over nail plate.**



**Figure 5: Muehrcke's lines.**

Muehrcke's lines were seen in 4 patients of carcinoma breast treated with platinum based agents. Half and Half nails were reported in 3 patients of carcinoma breast of T3N1M1 staging treated with platinum based agents. Onycholysis was reported in 2 patients of carcinoma of the GIT who had metastases and they were also treated with platinum based agents.

## DISCUSSION

Nail involvement is an uncommon side effect of cancer chemotherapeutic agents. There are myriad nail changes which can be caused by the cancer chemotherapeutic

agents. Depending on the part of the nail structure involved, the nail changes can be divided into those that involve the nail plate, the nailbed or the nailfolds. Nail matrix cells are continuously dividing cells and are the commonest to be affected during chemotherapy.<sup>1</sup> The involvement of the nail plate is usually secondary to the involvement of the nail matrix by the cancer chemotherapeutic agents. The nail bed can be directly involved by the chemotherapeutic agents or the changes in the nail bed may be secondary to the involvement of the blood vessels.<sup>2</sup>

### Changes involving the nail plate

As presented in Table 9 the nail plate changes which are seen include pigmentary changes which may be of cosmetic concern to serious side effects which may call for a change in the offending drug.<sup>3</sup> The pigmentary changes in the nail plate include longitudinal, transverse or diffuse pigmentation of the nail plate. There can be other changes involving the nail plate like Beau's lines, transverse grooves, pitting, onychorrhexis or leuconychia.

**Table 9: Nail plate changes and proposed etiopathogenesis.**

S. no.	Nail plate changes	Etiopathogenesis
1.	Pigmentary changes	
	a) Longitudinal pigmentary bands	-Direct toxic effect on melanocytes by drugs
	b) Transverse pigmentary bands	cause increased melanin production
	c) Diffuse pigmentation	-Increased ACTH/MSH
2.	a) Transverse grooves (Beau's lines)	-Acute toxic insult to nail matrix with transient arrest in nail plate production (Proximal germinative nail matrix is involved)
	b) longitudinal grooves	Damage to proximal germinative matrix
3.	Pitting	-Damage to proximal germinative matrix
4.	Leuconychia	-Damage to distal & proximal germinative matrix
5.	Onychorrhexis	-Damage to proximal matrix

### Pigmentary changes of nail plate

The exact mechanism of hyperpigmentation induced by cancer chemotherapeutic agents is not clearly understood. But it is postulated that the accumulation of the drug in the skin and nails can have a direct toxic effect on the melanocyte causing increased melanin production, or



there may be an associated increase in the adrenocorticotrophic hormone or the melanocyte stimulating hormone.<sup>4-8</sup>

In our study, the statistically significant changes observed were nail matrix melanocyte changes including longitudinal pigmentary bands as the most common change in 67.7% of cases, following administration of platinum based agents with an average onset of 6 weeks from the start of chemotherapy. Previous studies indicate that taxanes and anthracyclins were the most commonly implicated drugs in causing nail changes however in our study platinum based agents were the commonest drugs. In another cross sectional study performed on 30 pediatric patients, no pigmentary changes were documented.<sup>1,6-8</sup> In a study by Pavey et al, diffuse and transverse pigmentation of the nail plates were the commonest changes observed following treatment with platinum based agents.<sup>9</sup>

In our study, in the pediatric age group, 2 cases were documented. First was a 13 year old male who presented with a relapse of Hodgkin's lymphoma, who was treated with *Vinca* alkaloids and doxorubicin. The patient presented with diffuse hyperpigmentation of the nail plate. The second case was a 12 year old girl who presented with ALL (B cell Type) and was treated with BFM 90 protocol with cyclophosphamide and cytarabine and this child developed longitudinal striations on the nail plate. The changes developed 3 to 4 weeks after chemotherapy.

Longitudinal striations were seen in 58% of patients in our study treated with platinum based agents and Taxanes. The most common malignancy associated with this change was carcinoma of the breast.

Beau's lines are transverse depressions in the nail plate that moves distally as the nail grows.<sup>17</sup> They indicate acute toxicity to the nail matrix with transient arrest in the nail plate production.<sup>10</sup> The depth indicates the degree of damage and the width indicates the duration of insult.<sup>11</sup> Beau's lines were seen in 3.2% of our patients with breast carcinoma, on treatment with Platinum based agents.

Leuconychia is whitish discoloration of the nail plate as a consequence of damage to the distal and proximal germinative nail matrix. In our study, leuconychia was seen in 3.2% of cases and was seen in a patient treated with oxaliplatin for carcinoma of the rectum with bone metastasis.

#### **Changes involving the nail bed**

As shown in Table 10, the various changes involving the nail bed include subungual hyperkeratosis, half and half nails, Muehrcke's lines, Terry's nails, erythronychia and splinter haemorrhages. Muehrcke's lines are white lines with a pink in between the two white lines, seen parallel to the lunula, due to the involvement of the nailbed.

Muehrcke's lines are reported in patients with hypoalbuminemia, congestive heart failure, renal failure and following cancer chemotherapy. These lines are reversed in patients with hypoalbuminemia following albumin infusion. The exact mechanism is not known but the causes attributed are the edema of the nail bed due to hypoalbuminemia and the vascular compromise during chemotherapy may be the postulated hypothesis.<sup>13</sup> In our study Muehrcke's lines were seen in 57.1% of patients with nail bed involvement. However, a study in children<sup>1</sup> on the effects of cancer chemotherapeutic agents showed Muehrcke's lines to be the commonest nail change.

Platins were the most common group of drugs implicated. The most common malignancy associated was carcinoma breast (45.4%). Half and half nails (lindsay's nails, brown arcs) are usually seen in patients with renal diseases.<sup>14</sup> the proximal part is a white zone and the distal (20-60%) is brownish with a sharp demarcation. Histopathological examination reveals increased vessel wall thickness and melanin deposition in the distal portion of the nail.<sup>15</sup> Leyden and wood have proposed that the brownish discoloration of the distal portion of the nail, is due to melanin deposition which is seen as a result of insult to the nailbed melanocytes.<sup>16</sup> these changes disappear in a patient with renal failure after renal transplantation. They are associated with 9-50% of patients undergoing cancer chemotherapy.<sup>15</sup> In our study 42.85% of patients with nail bed involvement presented with half and half nails. Platinum based agents were the most common drugs implicated and the most common malignancy associated was carcinoma breast. In our study, there were no associated renal, cardiac or hepatic abnormalities.

**Table 10: Nail bed changes with proposed etiopathogenesis.**

S. no	Nail bed changes	Causes
1.	Subungual Hyperkeratosis	Damage to nail bed with abnormal cornification leading to accumulation of excess of squamous debris
2.	Terry's nails	Increased vascularity at distal edge and decreased vascularity of proximal portion
3.	Half and half nails	Pathogenesis unknown stimulation of nail bed melanocytes by increased level of plasma melanotropic hormones and increased vascularity of the distal half of nail is proposed
4.	Muehrcke's lines	Hypoalbuminemia Edema of nail bed due to hypoalbuminemia and vascular compromise.

Onycholysis was reported in 42.85% of patients with nail bed involvement and they were treated with CHOP regimen. In our study, there were 5 cases reported with hyperpigmentation of the proximal nail folds 3 to 4 weeks following administration of platins (40%) and CHOP regimen in 40% of cases with nail fold involvement.

Multiple types of cancers and multiple chemotherapeutic agents/regimens used were the confounding factors in statistical analysis. Similar studies are reported with similar difficulties in statistical analysis.<sup>10-12</sup> However, Platinum based agents were implicated in causing the nail plate and the nail bed changes in our study. Owing to a small sample size, logistic regression could not be carried out to assess the independent risk factors.

## CONCLUSION

Newer anti-cancer chemotherapeutics have improved the survival rates in patients suffering from malignancies. A variety of nail changes can be associated with cancer chemotherapy. The patients should be educated about the side effects of these drugs. Undue anxiety about the nail changes may affect the continuation of chemotherapy and cure of the patients. A knowledge about the various changes ranging from those of cosmetic concern to serious changes in patients who are undergoing chemotherapy is vital for the successful management of the patient. This study is presented to highlight the pigmentary changes produced by platins which were not reported in earlier studies. There is also paucity of data on studies with nail changes induced by cancer chemotherapeutic agents.

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