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Original Article

Dermatology Section

Recognising Nail Changes Induced by Chemotherapy with Taxane-based Regimens and their Dermoscopic Confirmation: A Prospective Observational Study from Northern India

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ABSTRACT

Introduction: Taxanes are chemotherapeutic agents used in a variety of solid tumours. They are known to cause cutaneous as well as nail changes which are temporally associated with intake of drug. Nail involvement is reported in literature from some parts of the world.

Aim: To study the pattern of nail changes occurring due to taxane-based chemotherapy regimens in patients suffering from malignancies.

Materials and Methods: This prospective observational study was carried out in a tertiary care hospital in GMC, Patiala, Punjab, India from October 2020 to September 2021. A total of 160 adult patients undergoing cancer chemotherapy with taxanes were included in the study. After taking detailed history, nail changes were examined and confirmed by dermoscopy. The data was analysed using Epi Info 7 by Centers for Disease Control and Prevention (CDC) and Chi-square test was used to calculate the p-value. A p-value<0.05 was considered significant.

Results: A total of 144 patients (87 females and 57 males), with the mean age of 53.8 years, were screened for six chemotherapeutic cycles. Drug-induced Nail Pigmentation (DINP) was the most common nail abnormality seen in 43/144 (29.9%) patients after third cycle and in 105/144 (72.9%) patients after the sixth cycle. The most common pattern was diffuse nail pigmentation 40/105 (38.1%) followed by longitudinal melanonychia 22/105 (21%) after six cycles. Maximum pigmentation 52/60 (86.7%) was observed in patients who received taxane+adriamycin+ cyclophosphamide combination. On onychoscopy, DINP appeared as thin grey regularly arranged parallel longitudinal lines on homogenous grey background.

Conclusion: Taxanes cause varied pattern of nail changes with DINP being the most common. It ranges from longitudinal bands after three cycles to diffuse pigmentation after six cycles. These nail changes show temporal relation with dose, duration, number of drugs, and colour of skin. Dermoscopy is a novel non invasive method with a good diagnostic accuracy.

Keywords: Longitudinal melanonychia, Nail pigmentation, Taxanes

INTRODUCTION

The taxanes (paclitaxel and docetaxel) have proven to be effective in the treatment of a variety of solid tumours including breast, ovarian, lung and bladder cancers [1]. These exert cytotoxic effect by disrupting the balance between polymerisation and depolymerisation of microtubule leading to arrest at G2/M phase of the cell cycle [2]. Paclitaxel and docetaxel are usually administered intravenously every three weeks either alone or in combination. The standard dose of paclitaxel according to this schedule is 175 mg/m^2 (3 hours infusion) while Docetaxel is administered as a one hour intravenous infusion at 75-100 mg/m^2 [3]. The most common side-effects observed are myelosuppression, neuropathy, fatigue, alopecia, stomatitis, hypersensitivity reaction and a fluid retention syndrome [4,5].

Cutaneous toxicity has been reported with taxanes and includes erythema and desquamation, involving primarily the hands [3]. The nail matrix cells which are continuously dividing, also become a target of antimitotic activity of chemotherapeutic agents. The nail changes may involve some or all nails and have a temporal onset with drug intake. In most cases the nail changes are only cosmetically disturbing, however at times associated pain and discomfort may require alteration in chemotherapy [6]. Nail changes are mostly transitory, with the nail eventually growing out normally after discontinuation of treatment but at times these changes may persist [7]. Common nail changes reported include a wide spectrum depending upon the nail constituent involved. Drug Induced Nail Pigmentation (DINP) is the most common followed by splinter haemorrhages, subungual haematoma, Beau's lines, acute paronychia and onycholysis [3].

The overall incidence of nail changes with taxanes has not been systematically investigated and tends to vary widely across the literature. The overall incidence varies from 44% [3] to some series reporting it as 89% with three treatment cycles of docetaxel [7]. Yet another study has reported that nail changes increased above 10% after 2.8 weeks upto 40% at six months [8]. A meta-analysis conducted for all grade of nail changes reported it as 34.9 % (95% CI 29.9-40.2) with docetaxel and 43.7% (95% CI 18.0-73.3 for paclitaxel) [9].

The clinical spectrum varies widely from DINP to painful onycholysis and subungual haematoma [10]. As DINP is the most frequent side-effect [3] it was relevant to see if it showed racial variation. There is paucity of studies undertaken for taxanes in Indian population, so this study was conducted to identify the clinical spectrum of nail changes, induced by taxane-based regimens, along with their dermoscopic evaluation in North Indian population over a period of one year.

MATERIALS AND METHODS

This prospective, observational study was carried out at GMC, Patiala, Punjab from October 2020 to September 2021.The study was conducted after taking clearance from the Institutional Ethical Review Committee {(Trg).EC/NEW/INST/2020/997/30364}.

Inclusion criteria: All adult patients undergoing cancer chemotherapy with taxane both as monotherapy as well as combination therapy during the above mentioned period were included in the study.

Exclusion criteria: Patients with history of nail problems, those having cutaneous or systemic diseases causing nail changes, or in occupations involving contact with chemicals were excluded from the study.

Study Procedure

A total of 160 patients undergoing cancer chemotherapy with taxane both as monotherapy as well as combination therapy were included. After taking informed consent, the demographic data along with the type of primary malignancy, chemotherapeutics used prior to taxane (if given), type and dose of taxane, adjuvant therapy and chemotherapeutic cycle with respect to occurrence of nail changes were recorded. Nail examination was done in broad daylight and the nail changes were photographed and recorded thrice during the course of therapy at baseline and subsequently after 3 cycles and 6 cycles. Dermoscopy was performed using Heine delta 20T (Heine optotechnik, Herrsching, Germany) handheld dermatoscope. Sixteen patients were lost to follow-up during the study period.

STATISTICAL ANALYSIS

The data was collected and analysed using Epi Info 7 by CDC. Chi-square test was performed on the data, and a p-value <0.05 was considered to be significant.

RESULTS

Out of total 144 patients, 57 were males and 87 were females. The mean age of the study population was 53.8 years (31-77 years). The most common malignancy was carcinoma breast 67 (46.5%), and the chemotherapy protocol followed in maximum patients 60/144 (41.6%) was taxane+adriamycin+cyclophosphamide [Table/Fig-1]. Postchemotherapy nail changes were seen in 126/144 (87.5%) patients, 87 amongst them reported changes after 3rd cycle. Most common first affected site was finger nails with atleast one or two nails affected. Toe nails were the first affected site in six patients only. With an increase in the number of cycles, nail involvement extended to other digits of the hands and feet [Table/Fig-2].

Variables	Number of patients
Gender	
Males	57
Females	87
Age	
Less than 50 years	49
50-70 years	85
More than 70 years	10
Site of cancer	
Breast	67
Oral cavity	41
Ovary	8
Testes/penis	5
Cervix/vulva	8
Lung	11
GIT/anal canal	3
Urinary bladder	1
Chemothearpy regimen	
Taxane+adriamycin+cyclophosphamide	60
Taxane+platinum analogoues	36
Taxane+platins+5 FU	39
Taxanes	9

[Table/Fig-1]: Demographic profile and other characteristics of the study participants.
GIT: Gastrointestinal tract

Drug-induced Nail Pigmentation (DINP) was the most common change observed. It was seen in 43 (29.9%) patients after the third cycle, and105 (72.9%) patients after the sixth cycle. Other nail changes recorded were longitudinal ridging, Beau's lines, Mees' lines, and nail plate thinning [Table/Fig-3].

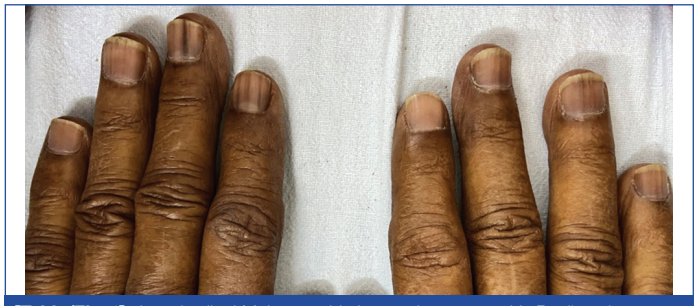
Site	3rd cycle	6th cycle
Fingers only	51	30
Toes only	6	-
Both fingers and toes	30	96

[Table/Fig-2]: Distribution of the participants according to the site involved.

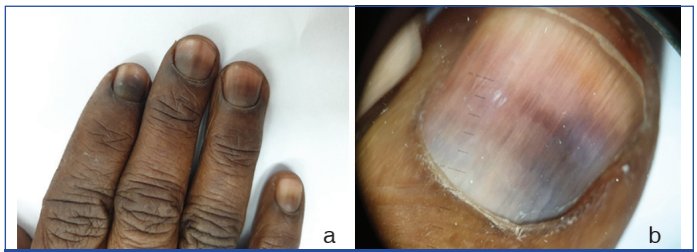
After 3rd cycle, one or more longitudinal lines (longitudinal melanonychia striata [Table/Fig-4] were seen in 14/43 (32.5%) followed by diffuse pigmentation in proximal nail in 10/43 (23.3%) [Table/Fig-5a,b] whereas after the 6th cycle diffuse pigmentation in whole nail was the most common DINP 40/105 (38.1%) [Table/Fig-6].

Nail changes	No. of patients	Percentage (%)
Nail plate		
DINP	105	72.9
Longitudinal ridging	42	29.17
Mees' lines	16	11.11
NP thinning	15	10.41
Beau's lines	9	6.25
Onychoschizia	9	6.25
Muehrcke's lines	5	3.47
Nail bed		
Subungual haematoma	9	6.25
Onycholysis	8	5.55
Subungual hyperkeratosis	4	2.8
Nail fold		
Pigmentation	24	16.66
Nail fold xerosis	12	8.3
Ragged cuticle	6	4.16

[Table/Fig-3]: Nail changes observed.
DINP: Drug-induced nail pigmentation; NP: Nail plate



[Table/Fig-4]: Longitudinal Melanonychia in a patient on weekly Paclitaxel.



[Table/Fig-5]: a) Diffuse pigmentation of proximal nails in a patient on combination of paclitaxel, adriamycin and cyclophosphamide; b) Dermoscopy showing gray background and longitudinal parallel grey lines in between which are fading distally as captured by Heine delta 20T dermatoscope (Heine Optotechnik, Hershing Germany) in a non polarised mode, 10x.

On analysis of the chemotherapy protocol of patients, maximum pigmentation (86.7%) was observed in patients who received taxane+adriamycin+cyclophosphamide. In the other three regimes the incidence of pigmentation was in the range of 61-66%. Melanonychia caused by taxanes and combination drug regimens have been found to be statistically significant (p=0.018) [Table/Fig-7].

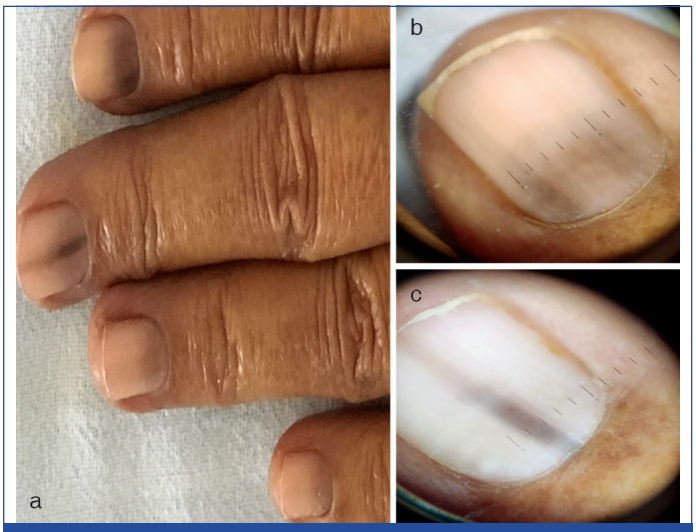
Pattern of pigmentation	No. of patients (3rd cycle) (n=43)	No. of patients (6th cycle) (n=105)
Longitudinal melanonychia	14 (32.6%)	22 (21%)
Transverse bands	08 (18.6%)	10 (9.5%)
Diffuse pigmentation in proximal nail	10 (23.3%)	3 (2.9%)
Diffuse pigmentation in whole nail	-	40 (38.1%)
More than one pattern	11 (25.6%)	30 (28.6%)

[Table/Fig-6]: Patterns of Drug Induced Nail Pigmentation (DINP).

Chemotherapy regimen	No. of patients	No. of patients developing DINP	Chi-square test	p-value
Taxanes+Platins	36	23 (63.9%)	9.964	0.018*
Taxanes+Adriamycin+ Cyclophosphamide	60	52 (86.7%)		
Taxanes+Platins+5 FU	39	24 (61.5%)		
Taxanes	9	6 (66.7%)		

[Table/Fig-7]: DINP with chemotherapy regimens used.
*represents statistically significant result

On dermoscopy, DINP appeared as homogenous grey coloration of background with longitudinal, regularly placed parallel grey lines [Table/Fig-8a,b,c].



[Table/Fig-8]: a) Clinical examination showing longitudinal and diffuse melanonychia, (b&c) Dermoscopic image of nail of the same patient captured by Heine delta 20T (Heine optotechnik, Herrsching, Germany) dermatoscope in non polarised mode, 10x, showing longitudinal, regularly placed parallel grey lines.

DISCUSSION

Taxane-based regimes, one of the most commonly used chemotherapeutic agents in the treatment of solid neoplasms, are burdened by the development of side-effects in different organs. Involvement of the skin, hair and nail cause cosmetic disfigurement affecting quality of life of the patient. Proper knowledge of these changes will help in counselling of patients for better compliance.

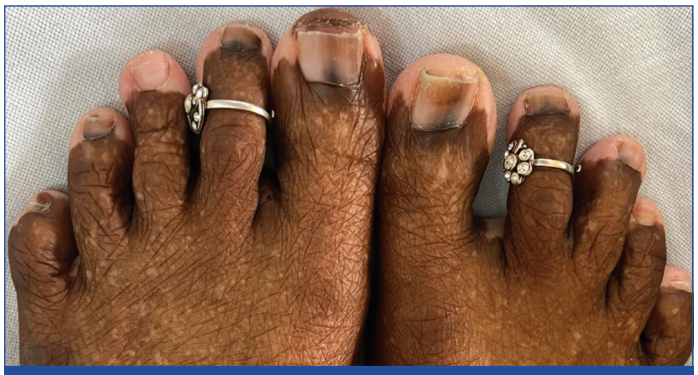
In this study, by adopting a proactive approach, even the slightest nail abnormalities which was otherwise of little concern to the patient was picked. Hence a significant percentage of nail abnormalities (87.5%) were noticed giving a more realistic picture of the incidence of nail changes. This is in contrast to those studies which included only referrals from Oncology Department who had more severe nail changes mostly with associated pain [3,11].

The average age of patients were 53.8 years (range 31-77 years), suggesting that nail toxicity affects mainly the adult population; however, this evidence is probably distorted by the fact that the malignancies authors reported mostly affect the adult population, saving the younger age. The male:female ratio was 1:1.5. Females were more as breast cancer was the most common malignancy in our study.

Alessandrini A et al., reported that most of the patients presented simultaneous involvement of hands and feet (46.8%) [11]. But in this study, 51/87 patients had only fingers involved after 3rd cycle while 96/144 showed involvement of both fingers and toes after six cycles [Table/Fig-2]. The earlier involvement of finger nails can be attributed to faster rate of growth of finger nails.

DINP, being the most frequent change, was seen in 43/144 (29.9%) patients during midtreatment and 105/144 (72.9%) at six months. Thus, the development of nail alterations is strongly associated with the number of chemotherapy cycles, and it increases with the taxane cumulative dose [12]. However the frequency of therapy cannot be commented on as only one patient was on weekly regime. Pavey RA et al., also found melanonychia to be the most common [13] and Trivedi M et al., reported it in 54.26% patients with use of chemotherapeutic combinations [14]. In the study conducted by Puri KJPS, melanonychia was seen in 58% (91/158) with various taxane based combination [15].

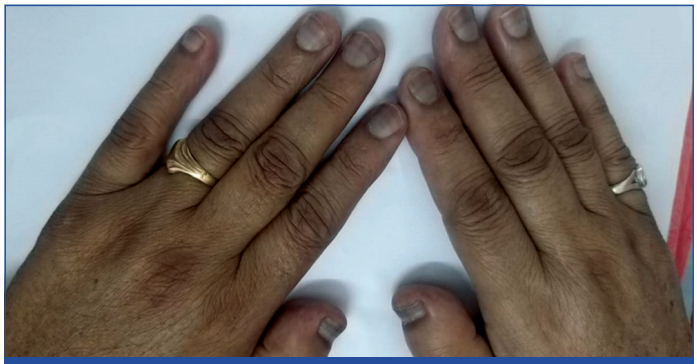
Clinical presentation of DINP depends on anatomic component of the nail unit that has been affected. Postulated mechanisms include accumulation of drug in nail plate or at dermal level causing toxic effect on melanocytes in nail matrix leading to activation of matrix melanocytes inducing increased melanin production [6]. The occurrence of DINP in one patient of vitiligo in our study support the toxic effect of the drug accumulated at nail plate or dermal level [Table/Fig-9]. The nail matrix contains melanocytes in the lowest two cell layers, unlike in normal skin, where they are confined to the basal layer [15]. Matrix melanocytes also differ from melanocytes elsewhere by their inability to produce melanin in normal circumstances, especially in white people, which explains the increased incidence of melanonychia observed in darker races.



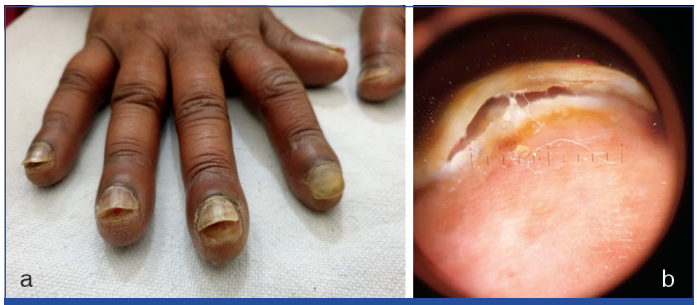
[Table/Fig-9]: DINP seen in a patient of vitiligo on chemotherapy.

Varied incidence of melanonychia due to taxanes has been reported in different races that is, 2.5% in Caucasians (may not represent the real picture as includes those patients only who reported nail signs associated with pain or discomfort), 35.7% in Turkish population, 58% in Indians, while in this study it was 73% [11,14,16]. Activation of a cluster of melanocytes give rise to longitudinal melanonychia while diffuse activation of melanocytes would result in diffuse nail pigmentation. In the present study, longitudinal melanonychia predominated during initial cycles, while diffuse pigmentation (38.1%) was most common after six cycles. Diffuse pigmentation of nails was also the most common nail plate change (16.1%) in study by Shanmugam PK et al., following chemotherapy with taxanes [17]. Nail fold pigmentation was seen in 24/144 (16.7%) patients, whereas, it was reported as 20% with taxanes in the study by Shanmugam PK et al., similar to the index study [17]. Periungual xerosis was observed in 12/144 (8.3%) and ragged cuticle in 6/144 (4.16%). Longitudinal ridging was observed in 42/144 (29.17%) and Mees'lines, which appear as transverse white bands parallel to lunula due to retention of matrix keratinocyte nuclei in nail plate (parakeratosis), were seen in 11.11% [Table/Fig-10]. Both the above observations were in accordance to previous studies [15,17]. Subungual haematoma was seen in 9/144 (6.25%) cases. Taxane-induced thrombocytopenia and impaired nail blood flow are implicated in subungual haematoma [Table/Fig-11a,b]. Zawar V et al., reported splinter/subungual haemorrhages in 11.9% patients on taxane- and doxorubicin-containing chemotherapy [18]. Beau's lines were observed in 6.25% patients in the present study. It is produced due to

acute toxicity to nail matrix with transient arrest in nail plate production [19]. Saraswat N et al., observed Beau's lines in 25% of their patients on all chemotherapeutics [6]. Zawar V et al., observed Beaus lines in 11.9% with taxanes, indicating that Beau's lines are mainly due to other chemotheraputic agents [18]. In this study, onychoscope was used to evaluate DINP. Characteristic dermoscopic finding consisted of a homogeneous gray colouration of the background with longitudinal, regularly placed, parallel gray lines. Yorulmaz A et al., have also reported similar onychoscopic findings in DINP [16]. Homogenous grey colouration indicates melanocyte activation while regularly placed parallel grey lines support benign character [20]. Pigmentation occurring due to benign melanocyte proliferation shows brownish hue [21] while exogenous pigmentation does not have longitudinal pattern.



[Table/Fig-10]: Mees' lines in a patient on docetaxel.



[Table/Fig-11]: a) Onycholysis with subungal haemorrhage after six cycles of docetaxel based combination regimen; b) Dermoscopy showing onycholysis and subungual haemorrhage captured by Heine delta 20T (Heine Optotechnik, Hershing Germany) in a non polarised mode, 10x.

Thus patient's history, correlating the beginning of symptoms with the timing of drug exposure, clinical pattern and dermoscopy can help the clinician in reaching the diagnosis of drug induced nail changes.

Limitation(s)

In this study, taxane as monotherapy was given only in nine patients, while majority were administered taxane-based combination regimens. Also, the correlation between the morphological patterns of nail changes and the underlying malignancy or its staging could not be established.

CONCLUSION(S)

Chemotherapeutic drugs can cause different types of nail changes invarying frequency causing significant morbidity, cosmetic disfigurement, and psychological distress. They may cause undue fear regarding the progression of underlying malignancy. Dermoscopic confirmation of these changes will help to increase diagnostic accuracy regarding the cause of nail changes. This will allow achievement of ideal duration of chemotherapy administration, as well as optimisation of response rates.

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