

Onychomycosis among cancer patients undergoing chemotherapy in Tehran, Iran: a cross-sectional study

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ABSTRACT

Background and Objectives: Due to the persistence of residual fungal elements, onychomycosis tends to have a high recurrence rate. It is essential to determine the etiology and frequency of onychomycosis across various factors. This study aimed to assess the prevalence of onychomycosis and identify its fungal agents in cancer patients undergoing chemotherapy. **Materials and Methods:** This cross-sectional study was conducted on cancer patients attending the Oncology Clinic and Cancer Institute of Tehran University of Medical Sciences. Among the 165 patients meeting the inclusion criteria, 75 individuals with nail alterations were referred to a dermatologist. Each patient's information, including demographics, disease-related data, and details about nail involvement, was recorded. When onychomycosis was suspected, nail samples were collected from the deepest part and examined using a light microscope after clarifying with 15% potassium hydroxide (KOH) to detect fungal elements.

Results: The prevalence of onychomycosis was 37.6% (n=62). Among the 75 patients with nail alterations and suspected onychomycosis, 17.3% (n=13) tested negative for pathogenic agents. The most common pathogen was *Candida albicans*, present in 21% (13/62) of patients with positive onychomycosis. The prevailing nail alteration was onycholysis, affecting 45.3% (34/75) of patients.

Conclusion: Onychomycosis exhibits associations with variables such as gender, age, cancer and chemotherapy.

Keywords: Cancer; Chemotherapy; Onychomycosis

INTRODUCTION

Various cancer treatments, including surgery, radiation, chemotherapy, biological therapy, and targeted therapy, are employed to manage different cancer

types. Chemotherapy, while effective, brings along significant side effects for patients. The prevalence of opportunistic infections has risen in cancer patients undergoing intense chemotherapy (1, 2).

Such infections impact various nail components nail

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plate, matrix, and substrate, and manifest as changes in nail appearance and structure, encompassing discoloration, onycholysis, and nail plate thickening (3). Common signs include increased nail thickness, discoloration, brittleness, roughness, nail chipping, and finger/toe discomfort during daily activities (4). Notably, other conditions such as contact dermatitis, psoriasis, nail bed tumors, lichen planus, yellow-nail syndrome, and unexplained onycholysis share similar symptoms with onychomycosis. As such, distinguishing onychomycosis relies on disease history, physical examination, and laboratory verification (5).

Onychomycosis can be caused by dermatophytes, non-dermatophyte molds, and yeasts. Approximately 90% of toenail onychomycosis and 75% of fingernail onychomycosis are caused by dermatophytes, especially *Trichophyton mentagrophytes* and *Trichophyton rubrum* (6-8). On the other hand, non-dermatophyte molds are the underlying cause of approximately 10% of onychomycosis cases worldwide (9). Also, some factors such as gender, age, and past medical history can be effective in onychomycosis occurrence (10).

Onychomycosis occurrence notably impacts a patient's personal and social life. Given the varying treatments required for onychomycosis caused by non-dermatophyte molds and yeasts versus that caused by dermatophytes, identifying the precise cause is imperative. Treating chronic onychomycosis poses a formidable challenge, demanding up to 18 months for complete recovery (11). Unfortunately, 20-25% of patients undergoing onychomycosis treatment do not experience a full recovery (12). Additionally, due to lingering fungal conidia or hyphae, the ailment is associated with a notably high recurrence rate (13). Hence, it's essential to ascertain the etiology and prevalence of onychomycosis across various factors.

Consequently, this study aims to uncover the prevalence of onychomycosis and its causal agents in cancer patients receiving chemotherapy at the skin and cancer clinics of Imam Khomeini Hospital in Tehran.

MATERIALS AND METHODS

Study sample. The present investigation adopts a cross-sectional approach and involves cancer patients referred to Tehran University of Medical Sciences' Oncology Clinic and Cancer Institute during

the timeframe from January 2021 to September 2022. The study enrolled a total of 165 cancer patients currently undergoing chemotherapy. All included patients underwent assessment by a hematologist and were directed to the dermatology clinic at Imam Khomeini Hospital in Tehran upon detecting any nail discoloration or deformities. During their dermatology clinic visit, a comprehensive examination of both skin and nails took place, and pertinent patient data were recorded in a specially designed questionnaire. The research received approval from the Ethics Committee of Tehran University of Medical Sciences, and written informed consent was secured from all participating patients.

Data collection. A custom questionnaire was created to retrospectively gather demographic, clinical, and therapeutic details from patients' medical records. Demographic information (age and gender), presence of any underlying medical conditions, cancer type, chemotherapy drug regimen, duration of chemotherapy, and data related to nail changes, including onycholysis, were among the parameters included.

Laboratory tests. All nail samples underwent direct microscopic evaluation utilizing KOH 15%. Another portion of nail chips obtained from each participant underwent cultivation on Sabouraud glucose agar (SGA Merck, Germany), SGA supplemented with chloramphenicol (50 mg/l) and SGA with chloramphenicol, cycloheximide and modified Dixon agar. Plates were incubated at 28°C for a duration of four weeks, with assessments of fungal growth conducted every two to three days. Plates without any fungal growth were categorized as negative after the four-week incubation period. Additionally, species-level identification tests were conducted for isolated fungi as part of this study. Dermatophytes and moulds were identified to species levels based on micro and macroscopic features (Fig. 1 and Fig. 2). *Candida* species were identified by germ tube test, chlamydospore formation and RapID YEAST Plus System. Lipid dependent yeasts and catalase reaction and assimilation test were used to identify *Malassezia* species.

Statistical analysis. All analyses were carried out at a 0.05 level of statistical significance using IBM SPSS version 16 (Build 1.0.0.1347; IBM, New York, USA), to report the frequencies of variables in participants with and without onychomycosis.

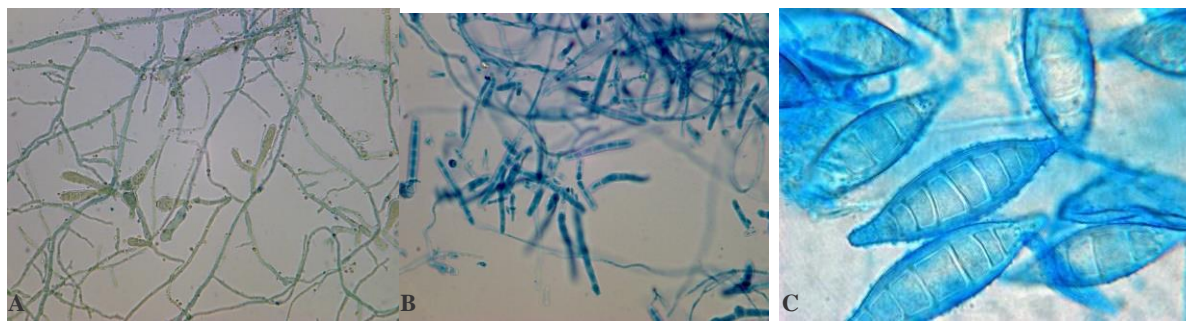


Fig. 1. Presents microscopy of some dermatophytes species have been identified from the samples related to this study.
 A. *Epidermophyton flucozum* with macro and micro conidia ×40.
 B. *Trichophyton rubrum* with macro and micro conidia ×40.
 C. *Microsporum canis* with macro conidia ×40.

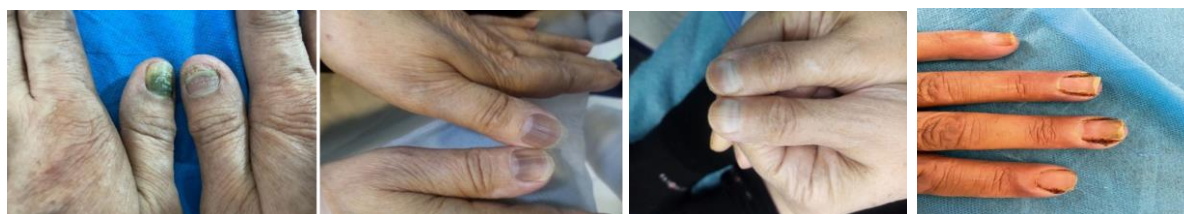


Fig. 2. A). Presents macroscopy features of nail changes due to onychomycosis (such as subungual hyperkeratosis, onycholysis and nail plate pigmentation).
 B, C and D) Nail changes caused by chemotherapy drugs (melanonychia, leukonychia and onycholysis).

RESULTS

Demographic, cancer type, chemotherapy, medical history and chemotherapy duration data. Table 1 presents a comprehensive overview of demographic attributes, cancer types, chemotherapy drugs, medical history, and chemotherapy duration for patients displaying indicators of suspected onychomycosis. A total of 165 participants were enrolled in this study, each undergoing a meticulous nail examination. Among them, 75 patients exhibited nail alterations such as melanonychia, pitting, ridging, pigmentation, etc., prompting referral to the dermatology clinic and finally were referred for mycological evaluation. Within this group of 75 patients with suspected onychomycosis, 13 cases (17.3%) yielded negative nail cultures for pathogenic agents. The overall prevalence of onychomycosis stood at 37.6%, encompassing 62 cases with positive nail culture results. Notably, participants with onychomycosis (n=62) exhibited a mean ± standard

deviation (SD) age of 55.8 ± 9.8 years, while those without onychomycosis (n=13) had a mean age of 47.8 ± 9.0 years.

Mycological agents in patients with positive onychomycosis. The frequency of mycological agents in patients with positive onychomycosis was *Candida albicans* in 13 patients (21%), *Candida glabrata* in 7 patients (11.3%), *Trichophyton mentagrophytes*, *Fusarium solani*, *Malassezia pachydermatis*, and *Candida guilliermondii* in 4 cases each (6.4%), *Candida tropicalis*, *Trichophyton rubrum* and *Trichophyton violaceum* in 3 cases each (4.8%), *Candida krusei*, *Candida famata*, and *Aspergillus flavus* in 2 cases each (3.2%), *Malassezia globosa*, *Candida parapsilosis*, *Trichophyton equinum*, *Microsporum canis*, *Malassezia furfur*, *Tricophyton mentagrophytes*, *Scopolariopsis berevicaulis*, *Aspergillus fumigatus*, *Trichophyton tonsuran*, *Epidermophyton floccosum*, and *Candida lusitaniae* in 1 case each (1.6%).

Table 1. Characteristics of participants with and without onychomycosis.

Variables	Onychomycosis (%)	
	No (n=13)	Yes (n=62)
Gender		
Female	7 (53.85)	39 (62.9)
Male	6 (46.15)	23 (37.1)
Age group (years.)		
<30	0 (0.0)	12 (19.3)
30-40	2 (15.4)	13 (21)
40-50	3 (23.1)	11 (17.7)
50-60	4 (30.8)	14 (22.6)
>60	4 (30.8)	12 (19.3)
Cancer type		
Breast	3 (23.1)	22 (35.5)
Colon	4 (30.8)	8 (12.9)
Leukaemia	4 (30.8)	6 (9.7)
Hepatoma carcinoma	0 (0.0)	8 (12.9)
Lung	0 (0.0)	5 (8.1)
Lymphoma	0 (0.0)	4 (6.4)
Melanoma	0 (0.0)	3 (4.8)
Pancreas	0 (0.0)	4 (6.4)
Prostate	1 (7.7)	1 (1.6)
Other	1 (7.7)	1 (1.6)
Chemotherapy drug		
Cetuximab	0 (0.0)	9 (14.5)
Cetuximab/Fluorouracil	0 (0.0)	5 (8.1)
Folfox regimen	0 (0.0)	10 (16.1)
Folfiri regimen	4 (30.8)	4 (6.4)
Taxel	0 (0.0)	25 (40.3)
Other	9 (69.2)	9 (14.5)
Past medical history		
Lupus	0 (0.0)	2 (3.2)
Eczema	0 (0.0)	5 (8.1)
HTN	1 (7.7)	6 (9.7)
IHD	1 (7.7)	3 (4.8)
Allergic Rhinitis	0 (0.0)	2 (3.2)
Contact dermatitis	0 (0.0)	3 (4.8)
Diabetes	0 (0.0)	33 (53.2)
Psoriasis	1 (7.7)	3 (4.8)
Diabetes and HTN	4 (30.8)	7 (11.3)
Other	4 (30.8)	0 (0.0)
Chemotherapy duration (sessions)		
1-6	3 (23.1)	6 (9.7)
7-12	4 (30.8)	24 (38.7)
13-18	6 (46.1)	32 (51.6)

HTN: hypertension, IHD: ischemic heart disease

Nail changes, malignancy types, and chemotherapeutic agents among patients with suspected onychomycosis. Table 2 provides insights into the prevalence of the nail changes, malignancy types, and chemotherapeutic agents observed among the cohort of 75 patients exhibiting signs of suspicious onychomycosis. Of the patients with nail changes (45.4%), a female-to-male ratio of 1.6:1 was noted. The most prevalent nail changes were onycholysis (34 patients, 45.3%), followed by subungual hyperkeratosis (11 patients, 14.6%) and ridging (8 patients, 10.7%).

The distribution of chemotherapeutic regimens revealed taxel as the primary choice (25 patients, 33.3%), trailed by the folfox regimen (including folinic acid, 5FU, and oxaliplatin, 10 patients, 13.3%) and cetuximab (9 patients, 12%).

Additionally, breast cancer (25 patients, 33.3%), colon cancer (12 patients, 16%), and leukemia (10 patients, 13.3%), were the most prevalent respectively.

Further details regarding less frequent nail changes, chemotherapeutic agents, and malignancy types can be found in Table 2.

Past medical history and chemotherapy duration in patients with nail changes. As depicted in our findings, the incidence of past medical history among the 75 patients displaying nail changes is outlined in the text. Diabetes was the most common medical history, noted in 33 patients (44%). Other medical conditions such as diabetes mellitus and hypertension in 11 patients (14.7%), hypertension in 7 patients (9.3%), eczema in 5 patients (6.7%), psoriasis and ischemic heart disease in 4 patients each (5.3%), contact dermatitis in 3 patients (4%) and lichen planus, systemic lupus erythematosus (SLE), allergic rhinitis and sweet syndrome in 2 patients each (2.7%) were also observed among the patient population.

The majority of patients underwent 13 to 18 chemotherapy sessions (38 patients, 50.7%), followed by 7 to 12 sessions (28 patients, 37.3%), and 1 to 6 sessions (9 patients, 12%).

DISCUSSION

Systemic chemotherapy often gives rise to various mucocutaneous and nail alterations. Nail matrix impairment following chemotherapy results in phenomena such as Beau's lines, onychomadesis, nail fragility (including onychoschizia and onychor-

Table 2. Prevalence of nail alterations, types of malignancies, and chemotherapeutic agents in 75 patients exhibiting signs of potential onychomycosis.

Malignancy types (Number, percentage)	Chemotherapy agents (Number, percentage)	Nail changes (Number, percentage)
Breast cancer (25, 33.3%)	Taxel (25, 33.3%)	Onycholysis (34, 45.3%)
Colon cancer (12, 16%)	Folfox regimen (10, 13.3%)	subungual hyperkeratosis (11, 14.7%)
Leukemia (10, 13.3%)	Cetuximab (9, 12%)	Ridging (8, 10.7%)
Hepatoma carcinoma (8, 10.7%)	Folfiri regimen (8, 10.7%)	Melanonychia (7, 9.3%)
Lung cancer (5, 6.7%)	Herceptin regimen (6, 8%)	Erythronychia (6, 8%)
Pancreas cancer (4, 5.3%)	Cetuximab/fluorouracil (5, 6.7%)	Leukonychia (5, 6.7%)
Lymphoma (4, 5.3%)	Paclitaxel (4, 5.3%)	Half and half nail (4, 5.3%)
Melanoma (3, 4%)	Interferon (3, 4%)	
Prostate cancer (2, 2.7%)	ABVD regimen (3, 4%)	
Glioma (1, 1.3%)	Docetaxel (2, 2.7%)	
ovary cancer (1, 1.3%)		

FOLFOX regimen includes the drugs leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin.

FOLFIRI regimen includes the drugs leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride.

ABVD regimen includes the drugs doxorubicin hydrochloride (Adriamycin), bleomycin sulfate, vinblastine sulfate, and dacarbazine.

rhexis), and true transverse leukonychia (known as Mees' lines), all of which disrupt normal nail plate growth. Similarly, harm to the proximal nail fold can lead to conditions like paronychia and periungual pyogenic granuloma, while nail bed damage can cause onycholysis and apparent leukonychia (referred to as Muehrcke's lines). Further consequences of compromised nail blood flow encompass subungual and splinter hemorrhages (14).

The involvement of the nail matrix by chemotherapeutic agents often precedes that of the nail plate. Chemotherapy can directly impact the nail bed or incite nail bed changes through vascular damage (15). Changes affecting the nail bed after chemotherapy include subungual hyperkeratosis, Muehrcke's lines, half-and-half nails, erythronychia, Terry's nails, and splinter hemorrhages (16). Chemotherapeutic agents

could induce hyperpigmentation, though the precise mechanism remains unclear. It is postulated that drug accumulation in the skin and nails could exert a direct toxic influence on melanocytes, triggering heightened melanin production (17, 18). According to our study, we have detected nail changes due to chemotherapy drugs like onycholysis (the most prevalent nail change), melanonychia, leukonychia, ridging, subungual hyperkeratosis, half and half nail and erythronychia (Fig. 2B, C and D).

In our study, nail alterations were observed in 75 patients (45.4%). Pavey et al. reported nail changes in 33 out of 53 patients undergoing chemotherapy (62.2%) (19), while Praveen Kumar et al. noted nail changes in 50 out of 150 cases receiving chemotherapeutic drugs (33.3%) (20).

Onychomycosis, a common fungal infection, con-

stitutes approximately 30% of all nail mycotic cutaneous infections. Despite its non-lethal nature, onychomycosis has become a public health concern due to its rising prevalence globally. This condition can significantly impact patients' personal and social lives (21).

In our study, the prevalence of onychomycosis among cancer patients undergoing chemotherapy was 37.6%. Factors such as chemotherapy, radiation therapy, broad-spectrum antibiotics, corticosteroid usage, and underlying diseases (diabetes, hypothyroidism, Addison's disease, etc.) can contribute to fungal invasion and elevate onychomycosis prevalence (22, 23). This is the first study in Iran examining onychomycosis prevalence among chemotherapy patients. Other studies in Iran have reported varying general population prevalence rates. For example, Isfahan exhibited a prevalence of 39.8% (24) and Aghamirian et al. in Qazvin reported 40.2% (25).

Identifying species like pathogenic yeasts is pivotal for epidemiology and selecting appropriate treatment. The etiology of onychomycosis varies across Iranian provinces. In our study, the most common agents causing onychomycosis were *Candida albicans* (21%), followed by *Candida glabrata* (11.3%) and *F. solani*, *M. pachydermatis*, and *C. guilliermondii* agents were the third most common strains with a prevalence of 6.4% each. Our results align with previous studies that demonstrated *Candida albicans* as the predominant yeast (26).

Gender-based analysis revealed higher onychomycosis prevalence among women, consistent with most studies (24, 25). Advanced age is also correlated with increased onychomycosis prevalence, aligning with prior findings.

Our study uniquely explored onychomycosis in cancer patients undergoing chemotherapy, examining factors like cancer type, chemotherapy drugs, and treatment duration. Breast cancer patients demonstrated the highest prevalence (33.3%), followed by colon cancer (16%). Taxel was the most prevalent chemotherapeutic drug (33.3%), while docetaxel/cyclophosphamide had the lowest prevalence (0.0). Further research is required to validate these findings. Cancer-induced immunodeficiencies, particularly the cell-mediated immune response, and the impact on the skin microbiome likely contribute to higher dermatophytosis and onychomycosis prevalence in these patients.

We also assessed the past medical history of patients

with onychomycosis in the current study. We found that the highest prevalence of onychomycosis in cancer patients undergoing chemotherapy was observed in patients with diabetes mellitus (44%) followed by patients with both diabetes mellitus and hypertension (14.7%), hypertension only (9.3%), eczema (6.7%), psoriasis and IHD (5.3% each), contact dermatitis (4%), lichen planus, SLE, allergic rhinitis and sweet syndrome (2.7% each). These results showed that the prevalence of onychomycosis in patients with diabetes mellitus was higher than in patients with other past medical histories, which is similar to the results of other studies (27, 28). In the present study, we found that only the simultaneous presence of diabetes mellitus and hypertension increases the prevalence of onychomycosis. In the study conducted by Ghasemi et al., it was shown that 52 of 700 patients with onychomycosis had past medical histories, the most prevalent of which were diabetes mellitus (48.1%), pemphigus disease (15.4%), psoriasis (7.7%), cardiovascular diseases (7.7%), chronic eczema (8.5%), hypothyroidism (8.3%), end-stage renal disease (ESRD) (3.8%), SLE (9.1%), and hepatitis C (1.9%), respectively (27). In another study, Onalan et al., found an increased prevalence of onychomycosis in patients with diabetes mellitus who also had subclinical atherosclerosis (28). In the present study, diabetes mellitus only and diabetes mellitus with hypertension had a higher prevalence, which is almost similar to the results of the mentioned study. However, further investigations are required to confirm the relationship between underlying diseases and onychomycosis.

Our study strengths include assessing onychomycosis prevalence in chemotherapy patients and evaluating its connections to chemotherapy drugs, cancer types, and sessions. However, sample size limitations must be acknowledged.

CONCLUSION

Onychomycosis prevalence among cancer patients undergoing chemotherapy was 37.6%, with *Candida albicans*, *Candida glabrata*, *F. solani*, *M. pachydermatis*, and *C. guilliermondii* as the most prevalent agents. Gender, age, cancer type, chemotherapy drugs, and sessions possibly influence onychomycosis occurrence. Further studies are necessary to confirm these relationships.

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