Dermatology Practical & Conceptual

Narrative Review of Drug-Associated Nail Toxicities in Oncologic Patients

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Key words: nail toxicity, nail changes, chemotherapy, targeted treatment, immune checkpoint inhibitors

Citation: Emvalomati A, Oflidou V, Papageorgiou C, et al. Narrative Review of Drug-Associated Nail Toxicities in Oncologic Patients. *Dermatol Pract Concept.* 2023;13(1):e2023064. DOI: https://doi.org/10.5826/dpc.1301a64

Accepted: August 23, 2022; **Published:** January 2023

Funding: None.

Competing Interests: None.

Authorship: Z. Apalla and M. Trakatelli equally contributed as senior authors.

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ABSTRACT

Introduction: Nail toxicity represents one of the most common cutaneous adverse effects of both classic chemotherapeutic agents and new oncologic drugs, including targeted treatments and immunotherapy.

Objectives: We aimed to provide a comprehensive literature review of nail toxicities derived from conventional chemotherapeutic agents, targeted therapies (EGFR inhibitors, multikinase inhibitors, BRAF and MEK inhibitors) and immune checkpoint inhibitors (ICIs), including clinical presentation, implicated drugs and approaches for prevention and management.

Methods: Retrieved literature from PubMed registry database was reviewed to include all articles published up to May 2021 relevant to the clinical presentation, diagnosis, incidence, prevention, and treatment of oncologic treatment-induced nail toxicity. The internet was searched for relevant studies.

Results: A wide spectrum of nail toxicities is associated with both, conventional and newer anticancer agents. The frequency of nail involvement, especially with immunotherapy and new targeted agents remains unknown and patients with different cancer types receiving different regimens may develop the same nail disorder, whereas patients with the same type of cancer under the same chemotherapeutic treatment may develop different types of nail alterations. The underlying mechanisms of the varying individual susceptibility and the diverse nail responses to various anticancer treatments need further investigation.

Conclusion: Early recognition and treatment of nail toxicities can minimize their impact, allowing better adherence to conventional and newer oncologic treatments. Dermatologists, oncologists and other implicated physicians should be aware of these burdensome adverse effects in order to guide management and prevent impairment of patients' quality of life.

Introduction

Nail toxicity represents one of the most common cutaneous adverse effects of both classic chemotherapeutic agents and new oncologic drugs, including targeted treatments and immunotherapy [1]. While drug-associated nail toxicity is almost never life-threatening, it significantly impairs patients' quality of life, often restricting their daily life and self-care activities.

Dermatologists, oncologists and other implicated physicians should be aware of these burdensome adverse effects in order to guide management and prevent impairment of patients' quality of life. Early recognition and treatment can minimize the impact of these toxicities, allowing better adherence to conventional and newer oncologic treatments. The aim of this article is to provide a comprehensive literature review of nail toxicities derived from conventional chemotherapeutic agents, targeted therapies (EGFR inhibitors, multikinase inhibitors, BRAF and MEK inhibitors) and immune checkpoint inhibitors (ICIs), including clinical presentation, implicated drugs and approaches for prevention and management.

Materials and Methods

Search Strategy and Study Selection

The retrieved literature was reviewed to include all articles relevant to the clinical presentation, diagnosis, incidence, prevention, and treatment of oncologic treatment-induced nail toxicity. The PubMed registry database was searched for relevant studies published up to May 2021. The literature evidence predominantly comprises case reports, case series and systematic reviews. The following Medical Subject Headings search terms were used: nails, nail changes, nail toxicity; chemotherapy, chemotherapeutic drugs/agents, antineoplastic agents. The "related articles" function in PubMed was used to broaden the search, and all retrieved abstracts, studies and citations were reviewed. In addition, we identified other relevant studies by searching the reference lists of the relevant articles and by contacting known experts in the field. No language restrictions were applied.

Data Extraction

Two reviewers independently assessed all relevant studies and specifically extracted data regarding study design, study population characteristics, inclusion and exclusion criteria, nail toxicity parameters, class of chemotherapeutic drugs and their mechanism of action. The individually recorded decisions of both reviewers were compared and any disagreements were resolved by the other reviewers. Study authors were contacted for additional information when necessary.

Discussion

Conventional Chemotherapeutic Drugs (Figure 1)

Cancer therapy has always been a challenging area in clinical medicine and research. Traditionally, chemotherapeutic drugs work by disrupting specific phases of the cell cycle in actively dividing cancer cells (Table 2). Conventional chemotherapeutic drugs continue to be an important part of cancer management but may cause various cutaneous and appendageal reactions including nail toxicity. Nail involvement in cancer therapy is reported in fragmented literature from all over the world. Although it is mostly of cosmetic concern, at times it may require alteration or modification of the therapy, especially if very painful or functionally debilitating nail toxic effects are present. Pain and associated discomfort impair patients' quality of life, commonly resulting in the inability to perform daily activities [2].

The nail apparatus is characterized by the presence of continuously dividing nail matrix cells, thus making it an easy target of the antimitotic activity of chemotherapeutics [3]. Nail changes in the context of chemotherapy involve multiple or even all 20 nails and usually appear in a temporal relation with the drug intake, due to an acute insult of the nail matrix epithelium. Effects mostly subside upon withdrawal of the responsible chemotherapeutic agent, but occasionally may persist. Because of the specific kinetics of nail formation and growth, it is important to note that the occurrence of these nail toxic effects is often delayed relative to treatment initiation.

Clinical presentation varies, depending on the nail structure affected and the severity of the insult [4]. In terms of topography, when the nail bed is affected, onycholysis, apparent leukonychia and splinter haemorrhages may be observed. Toxicity targeting the nail matrix may result in the appearance of Beau's lines, onychomadesis, true leukonychia, slower nail growth, nail thinning, brittle nails and melanonychia. Finally, adverse effects involving the perionychium may result in paronychia and pyogenic granuloma [5, 6]. A combination of the aforementioned nail changes is frequent. The most common nail changes reported in the literature include leukonychia, Beau's lines, brittle thin nails, and nail hyperpigmentation, which may be diffuse or horizontal [7- 10]. Taxanes and anthracyclines are the antineoplastic regimens mostly associated with nail changes. However, considering that a majority of the reported patients were on multiple chemotherapeutic agents, pinpointing the offensive drug was not always feasible. Therefore, a combination of agents was implicated in most cases.

Alkylating Agents

Classical Alkylating: Cyclophosphamide

Classical alkylating agents attach an alkyl group to the guanine base of DNA and are used to treat leukaemia, lymphoma, Hodgkin disease, multiple myeloma, sarcoma, and

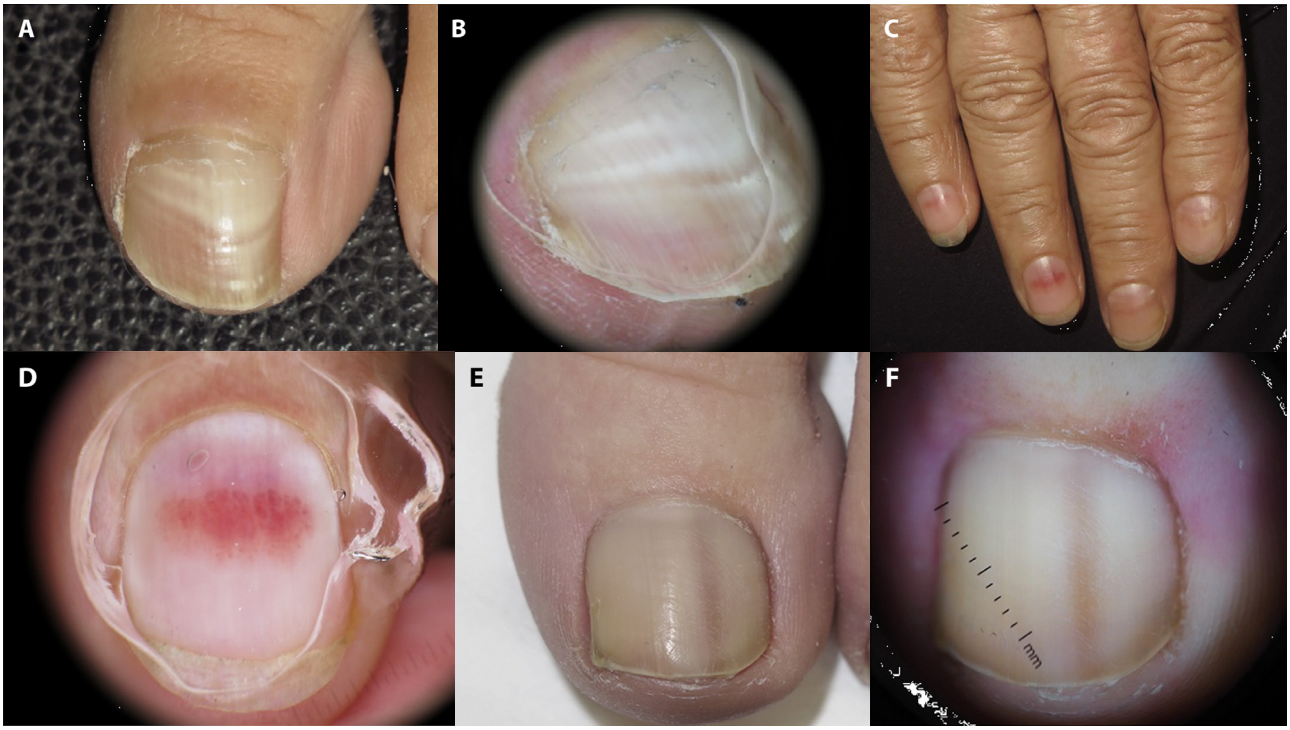

Figure 1. Nail toxicities due to conventional chemotherapeutic drugs. **A.** Muehrcke's lines due to treatment with cisplatin: Transversal white lines with healthy nail bed between them. **B.** Dermosopic examination of the same patient with clear visualization of the leukonychia in the form of Muehrcke's lines. **C.** Red-brown discoloration of the nails associated with painful subungual hematomas and onycholysis following treatment with taxol. **D.** Dermoscopic image of the chemotherapy-induced central subungual hematoma that differs from traumatic subungal hematoma: note the bright red color with an orange/brown halo (in trauma: dark violet with globular pattern accompanied by transversal whitish line). **E.** Longitudinal melanonychia following cyclophosphamide treatment. **F.** Dermoscopy image of the cyclophosphamide-induced melanonychia with a homogenous brown band with absence of Hutchinson or micro-Hutcinson's sign. Borders appear blurry but this may happen in the great toenail due to thickness of the nail plate. This is a false positive sign that should be interpreted together with the clinical history of the patient.

Table 1. Proposed management algorithm for taxane-related onycholysis [38].

Grade 0*	• Preventive nail care instructions given • Frozen gloves should be considered
Grade 1* Asymptomatic separation of the nail bed from the nail plate or nail loss	• Continue drug at current dose and monitor for change in severity • Obtain bacterial/fungal cultures if infection is suspected; apply topical antibiotics or fungal agent • Reassess after 2/3 weeks. If reaction worsens proceed to next step
Grade 2* Symptomatic separation of the nail bed from the nail plate or nail loss; Limiting instrumental activities of daily living	• Continue drug at current dose and monitor for change in severity • Obtain bacterial/fungal cultures if infection is suspected • If infection, begin oral antibiotics with anti –Staphylococcus aureus and gram-positive coverage • If painful hematoma or subungual abscess is suspected, partial or total nail avulsion is required • Pain control • Reassess after 2 weeks; if reactions worsen or do not improve interrupt treatment until severity decreases to Grade 0-1
Grade 3* **Severe pain and/or superinfection; Limiting self-care activities of daily living**	Interrupt treatment until severity decreases to Grade 0-1, obtain bacterial/fungal cultures if infection is suspected and continue treatment of nail reaction with the following: • If infection, begin oral antibiotics with anti –Staphylococcus aureus and gram-positive coverage • If painful hematoma or subungual abscess is suspected, partial or total nail avulsion is required • Pain control • Reassess after 2 weeks; if reactions worsen or do not improve, consider dose interruption or discontinuation per protocol and switch to another antineoplastic agent

*From nail loss clinical grading, Common Terminology Criteria for Adverse Events (CTCAE), V4.02

Table 2. Conventional chemotherapeutic drugs, mechanism of action and associated nail toxicity.

Drug Class	Chemotherapeutic Drugs	Mechanism Of Action	Nail Disorders
Alkylating agents Classical alkylating Platinum agents	Cyclophosphamide Cisplatin Carboplatin Oxaliplatin	Crosslink with DNA molecules and damage cells in all phases of the cell cycle	Diffuse hyperpigmentation Longitudinal melanonychia Beau's lines Onychomadesis Mees' lines Muehrcke's lines Onycholysis Beau's lines Hyperpigmentation Muehrcke's lines Diffuse hyperpigmentation Muehrcke's lines
Antimetabolites Analogs Fluorouracil	Pemetrexed 5-Fluorouracil Capecitabine Tegafur	Substitute building blocks of DNA and RNA and damage cells in the S phase	Melanonychia Onycholysis Beau's lines Muehrcke's lines Paronychia Subungual hyperkeratosis Hyperpigmentation Half and half nails Onycholysis Onychomadesis Onycholysis Hyperpigmentation Longitudinal melanonychia
Antitumor antibiotics Anthracyclines Bleomycin	Doxorubicin Daunorubicin Epirubicin	Intercalate with DNA base pairs and interfere with topoisomerase II in all cell cycle phases Induce DNA strand breaks at G2 phase	Diffuse hyperpigmentation Beau's lines Mees' lines Muehrcke's lines Diffuse hyperpigmentation Mees' lines Beau's lines Diffuse hyperpigmentation Longitudinal melanonychia Beau's lines
Mitotic inhibitors Taxanes Vinca alkaloids	Docetaxel Paclitaxel Vincristine	Prevent the formation of spindles or microtubules during the M phase	Diffuse hyperpigmentation Beau's lines Onychomadesis Mees' lines Paronychia Subungual hyperkeratosis Pyogenic granuloma Subungual & splinter hemorrhage Onycholysis/Exudative Onycholysis Brittle nails Onychorrhexis Koilonychia Diffusehyperpigmentation Longitudinal melanonychia Beau's lines Onychomadesis Mees' lines Muehrcke's lines
Topoisomerase inhibitors Topoisomerase II	Etoposide	Interfere with topoisomerase I or II during DNA replication in all cells in the S or G2 phase	Paronychia

cancers of the lung, breast and ovary [11]. All can be administered intravenously, though cyclophosphamide can be also taken orally [12]. Cyclophosphamide may cause diffuse hyperpigmentation, longitudinal melanonychia, Beau's lines, onychomadesis, Mees' lines, Muehrcke's lines and onycholysis (Table 2).

Platinum Agents: Cisplatin, Carboplatin, and Oxaliplatin

Platinum agents form reactive platinum complexes that crosslink with DNA molecules, inhibiting DNA synthesis and repair, and are given intravenously. Cisplatin is an older drug that causes many side effects (eg, ototoxicity, neurotoxicity, nephrotoxicity, and emetogenicity) and is used to treat a wide variety of solid tumors. Cisplatin may cause Beau's lines, hyperpigmentation or Muehrcke's lines. Carboplatin and oxaliplatin are newer-generation platinum agents with less toxicity [13]. These chemotherapeutic agents may cause diffuse hyperpigmentation or Muehrcke's lines (Table 2).

Antimetabolites

Analogs: Pemetrexed

Pemetrexed is an intravenously administered folate analogue that interferes with enzymes required for pyrimidine and purine synthesis, and is used for the treatment of mesothelioma, non-small cell lung carcinoma (NSCLC), and breast, head, and neck carcinoma. Uncommon reported nail reactions to pemetrexed include melanonychia and onycholysis [14] (Table 2).

Fluorouracil: 5-Fluorouracil, Capecitabine and Tegafur

5-Fluorouracil (**5-FU**) is a pyrimidine analog that inhibits the enzyme thymidylate synthase, thereby interrupting thymidine synthesis required for DNA replication, and can cause myelosuppression, diarrhea, mucositis, and dermatitis [12].

Capecitabine and Tegafur are orally administered prodrugs especially used for colon and gastrointestinal neoplasms. They are designed to be well absorbed from the gastrointestinal tract and converted to 5-FU in the liver or within the tumor at lower concentrations than 5-FU intravenous dosages, thereby minimizing toxicity [15].

In the nails, 5-FU may cause diffuse melanonychia, transverse bands, or half and half-like nails (Lindsay nails), while there have also been reports of onycholysis, paronychia, and thickening of the nail with its use [16]. Capecitabine and tegafur also cause longitudinal melanonychia [16]; however, onycholysis and onychomadesis have only been seen with capecitabine [12] (Table 2).

Antitumor antibiotics

Anthracyclines: Doxorubicin and Daunorubicin

The anthracyclines doxorubicin and daunorubicin are derived from the bacterium Streptomyces peucetius var. caesius and are used to treat various hematologic malignancies and solid tumors. Their main adverse effect is cardiotoxicity, which is limited in the liposomal pegylated or encapsulated form of anthracyclines used for non-Hodgkin lymphoma, multiple myeloma, NSCLC, AIDS-related Kaposi sarcoma, and refractory ovarian cancer. Both drugs are administered intravenously [12]. Doxorubicin may cause diffuse hyperpigmentation, Beau's lines, Mees' lines or Muehrcke's lines. Daunorubicin may also cause diffuse hyperpigmentation or Mees' lines (Table 2).

Bleomycin

Bleomycin is a glycopeptide produced by the bacterium Streptomyces verticillus and is used for the treatment of squamous cell carcinoma, lymphoma, testicular carcinoma, and malignant pleural effusion. It can be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or given as an intralesional injection in recalcitrant warts, keloids, and scars [17]. Toxicity to bleomycin occurs in the lungs and skin because these organs lack bleomycin hydrolase, an inactivating enzyme [18]. Pulmonary fibrosis is a serious complication of high doses (>400 units), while cutaneous reactions usually occur between 200 to 300 units [17].

Bleomycin may cause nail dystrophy, and horizontal or vertical nail pigmentation [17] (Table 2).

Mitotic/Spindle Inhibitors

Taxanes: Paclitaxel and Docetaxel

Taxanes are among the most commonly prescribed anticancer drugs and were initially derived from yew trees. Paclitaxel is a natural extract derived from the bark of the pacific yew tree (Taxus brevifolia) that became commercially available in 1992. On the other hand, docetaxel is a semisynthetic analogue of paclitaxel synthesized from the needles of the European yew tree (Taxus baccata). Both drugs act as antimicrotubule agents by promoting the polymerisation of tubulin into highly stable intracellular microtubules, thus disrupting mitosis and normal cell division, and eventually leading to cell death [19- 21]. Because of their highly hydrophobic properties, they require the use of solvents (non-ionic polyoxyethylated castor oil -Cremophor EL®- for paclitaxel; non-ionic surfactant polysorbate 80 for docetaxel) to facilitate parenteral administration. The drugs are approved for a number of indications in the US and Europe. Paclitaxel was the first taxane discovered, is generally administered by weekly infusion (80 mg/m2) and is currently approved by the US Food and Drug Administration for the treatment of breast cancer, NSCLC, AIDS-related Kaposi sarcoma, and ovarian cancer.

Docetaxel, developed later, is infused (100 mg/m2) every three weeks and is used for the management of advanced breast, gastric, NSCLCs, hormone-refractory prostate

cancer, and advanced head and neck squamous cancer [22]. Docetaxel appears to have recently become most specifically associated with nail toxicity, occurring in up to 30 – 40% of patients [6, 23].

Nail changes with taxanes are very common with some series reporting rates as high as 89% after three treatment cycles [24- 29]. These chemotherapeutic agents may cause diffuse hyperpigmentation, Beau's lines, onychomadesis, Mees' lines, paronychia, subungual hyperkeratosis, pyogenic granuloma, subungual & splinter hemorrhage, onycholysis/ exudative onycholysis, brittle nails, onychorrhexis or koilonychia (Table 2).

Nab-paclitaxel is a novel, solvent-free, albumin-bound, colloidal suspension (with a size of 130 nm) of paclitaxel that has led to a significant improvement in progression-free survival, median overall survival, and overall response rates in patients with metastatic breast and pancreatic cancers [21, 30]. It has received FDA and EMA approvals for the treatment of certain forms of both cancers [30]. It is also approved in the US for metastatic non-small cell lung cancer and is still under evaluation for several other indications, such as metastatic urothelial tumors [31, 32]. Nab-paclitaxel was developed to circumvent the highly hydrophobic properties of taxanes and to improve intratumoral paclitaxel penetration [30, 33]. Since it is devoid of Cremophor EL® (the solvent for paclitaxel), several significant adverse events such as hypersensitivity reactions are less likely to develop [30]. Nail toxicity has only been sporadically reported with nab-paclitaxel, especially onycholysis, and is easily manageable [34]. The overall incidence of all-grade nail toxic effects with nab-paclitaxel is significantly lower in comparison with paclitaxel or docetaxel (19.4%) (95% CI: 11.8-30.3%) [35].

Vinca Alkaloids: Vincristine

Vinca alkaloids were historically extracted from the leaves of the Madagascar periwinkle (Catharanthus roseus). Vincristine has been approved for intravenous use in the United States and is often used in combination chemotherapy regimens because of its lack of myelosuppression. Vincristine is commonly used to treat acute lymphocytic leukemia, multiple myeloma, chronic lymphocytic leukemia, lymphoblastic crisis of chronic myelogenous anemia, sarcomas, and small cell lung cancer with distant metastases [12]. Vincristine may cause diffuse hyperpigmentation, longitudinal melanonychia, Beau's lines, onychomadesis, Mees' lines or Muehrcke's lines (Table 2).

Topoisomerase Inhibitors

Topoisomerase II: Etoposide

Etoposide is an inhibitor of the enzyme topoisomerase II, which relieves the helical strain during DNA replication by cutting both strands of DNA simultaneously. Topoisomerase II inhibitors frequently induce rearrangements of the mixed lineage leukemia gene and can cause a secondary leukemia side effect [36]. Etoposide has been approved by the US Food and Drug Administration to be used in combination with other medications to treat small cell lung cancer and testicular cancer. It is a derivative of podophyllotoxin. It is typically taken orally, but can also be administered intravenously, though care must be used to prevent extravasation because it is an irritant and can cause tissue damage. Nail toxic side effect caused by etoposide is paronychia [12] (Table 2).

Targeted Biologic Drugs (Figure 2)

Targeted cancer therapies are drugs that selectively block specific parts of cancer cells, such as proteins or genes, that help cancers grow and spread. Targeted biologic therapies are well-known causing factors of cutaneous adverse effects, including changes in the nail apparatus [37, 38].

Cutaneous and nail reactions may be attributed to the mode of action of these regimens that target specific molecules that are also expressed in the skin and appendageal epithelium.

EGFR-Inhibitors

Epidermal growth factor receptor inhibitors (gefitinib, erlotinib, cetuximab, panitumumab) block the signal transduction pathway, needed for cell proliferation, migration and angiogenesis of tumor cells [37- 40].

Gefitinib and erlotinib are orally administered EGFR tyrosine kinase inhibitors, whilst cetuximab and panitumumab are humanized monoclonal antibodies that are given intravenously. These regimens are used for colorectal cancer, breast cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, and head and neck squamous cell carcinoma (SCC) [38- 40]. A common nail reaction in the context of EGFR inhibition is paronychia, representing the second most frequent skin toxicity induced by EGFR after papulopustular eruption [41]. It involves the nails and the digits, with the first digit being the site most commonly affected. Other ungual adverse reactions include discoloration, pitting, nail thinning/fragility (inhibition of nail matrix keratinocytes), periungual pyogenic granuloma (an overgrowth of granulation tissue and a formation of painful, bleeding nodule), cracked and swollen nail folds and cuticles, partial or complete loss of nails and ingrowth of nails [37, 38] (Table 3). The aforementioned alterations may appear 1 to 2 months after treatment initiation and affect about 15% of patients [38]. Secondary infection is not unusual and in this scenario, a culture swab is recommended. In patients treated with Cetuximab that developed paronychia, Staphylococcus aureus was found in 23%, while 31% had coagulase-negative, Gram (+) bacteria (nosocomial colonization) [37, 38]. Prevention of superinfection was achieved

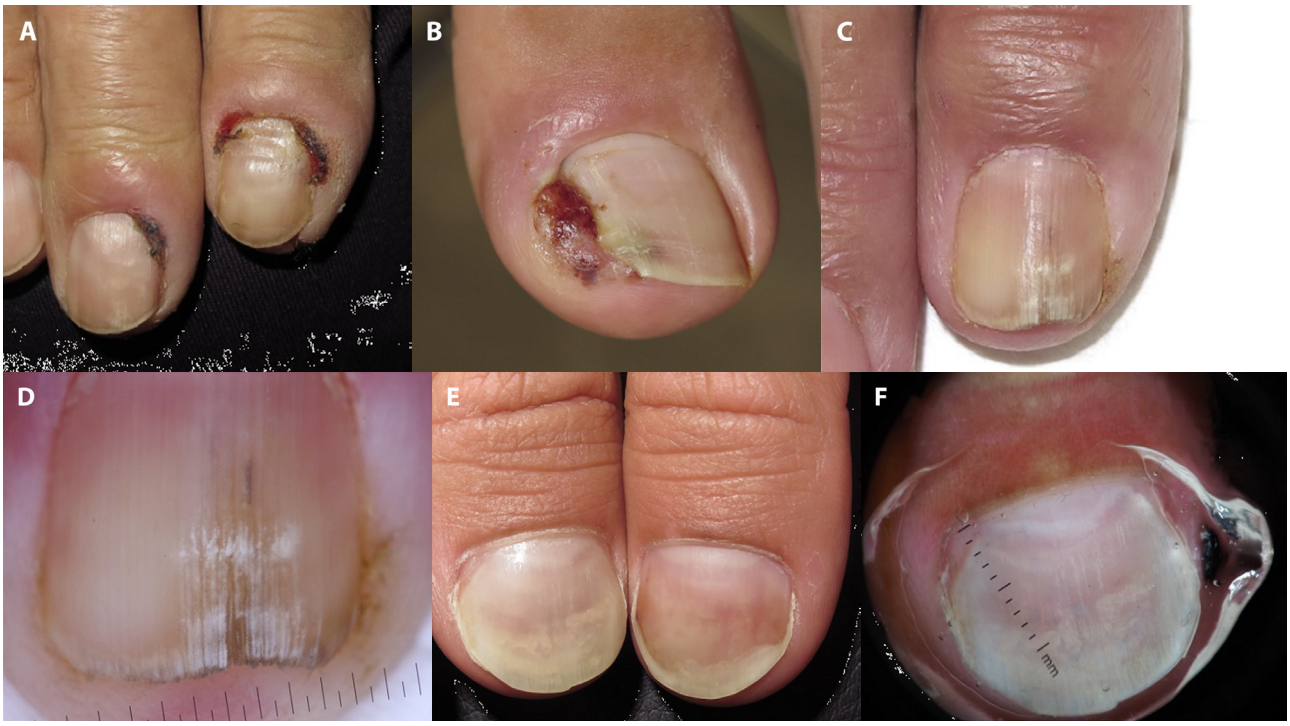

Figure 2. Nail toxicities due to targeted biologic drugs. **A.** Paronychia due to treatment with EGFR tyrosine kinase inhibitor (panitumumab) for colorectal cancer: proximal nail fold is painful, erythematous and swollen with presence of oozing and crusting, **B.** Same patient as a.: close-up to a pyogenic granuloma that frequently accompanies paronychia due to EGFR inhibitors. **C** and **D.** Clinical and dermoscopy image of brittle nails during EGFR inhibitor therapy for lung cancer. The nail plate is fragile and the surface of the nail presents longitudinal fine fissures while the distal edge of the plate appears to crumble and is not sharply delineated. In dermoscopy presence of splinter hemorrhages can also be detected. **E** and **F.** Acute photo-onycholysis in a melanoma patient treated with BRAF inhibitors: clinical and dermoscopic image. The nails were extremely painful with almost total detachment of the nail plate and presence of oozing and subungual hematoma.

with antibacterial soaks (chlorhexidine or vinegar in water) [38]. Warm compresses, silver nitrate, topical corticosteroids and systemic tetracyclines are recommended in order to reduce periungual inflammation, depending on the grade of the toxicity.

Angiogenesis-Inducing Inhibitors

Sorafenib and **sunitinib** are multikinase inhibitors that specifically target tumor cell angiogenesis and proliferation via VEGFR (vascular endothelial growth factor), PDGRF (platelet-derived growth factor receptor) and other kinases [38]. Sorafenib is indicated in renal cell carcinoma, non-small cell lung cancer, hepatocellular carcinoma, melanoma, pancreatic and colon cancers, whilst sunitinib is prescribed for renal cell carcinoma, breast cancer, colon cancer and gastrointestinal stromal tumor. Both are orally administered. Studies report that during the first 2 months of therapy, 70% and 25% of patients taking sorafenib and sunitinib, respectively, developed fingernail subungual splinter hemorrhages [41] (Table 3). The latter resolved spontaneously without treatment. This may be linked to the role VEGFR play in the renewal of capillaries and their sustain despite frequent injuries at the distal fingers, which is now inhibited due to sorafenib and sunitinib intake [38, 41].

Bruton's Tyrosine Kinase (BTK) Inhibitors

Bruton's tyrosine kinase inhibitor, **ibrutinib**, is a small molecule that binds to a protein, important in B-cells. It is used for the treatment of chronic lymphocytic leukemia, Waldenström's macroglobulinemia, refractory and relapsed mantle-cell lymphoma. Brittle nails are the most common nail change, seen in about 2/3 of treated patients, followed by onychoschizia, onychorrhexis and mild onycholysis [38] (Table 3).

Anti-HER2/Anti-HER

Anti-human epidermal growth factor receptor 2 (Anti-HER2) is a class of medicines used to treat all stages of HER2-positive breast cancer, from early-stage to metastatic disease. **Trastuzumab** was shown to cause thin nails [37, 38]. **lapatinib** (breast cancer and solid tumors), **afatinib** (NSCLC) and **dacomitinib** (NSCLC), besides thin nails, may induce nail reactions such as paronychia, pyogenic granuloma, slower growth rate and mild onycholysis [37, 38] (Table 3).

Anti-MEK

Mitogen-activated protein kinase enzymes MEK1 and/or MEK2, **trametinib** (metastatic melanoma), **cobimetinib** (melanoma) and **selumetinib** (Neurofibromatosis type I

Table 3. Main nail toxicities induced by targeted anticancer therapies [38].

Drug Class	Target	Chemotherapeutic Drugs	Nail Disorders
Anti-EGFR	EGFR (HER1 or ErbB1)	Cetuximab Panitumumab, Erlotinib Gefitinib Necitumumab	Paronychia Pyogenic granuloma Slower growth rate Mild onycholysis Thin nails Brittle nails
Anti-HER2	HER2	Trastuzumab	Thin nails
Anti-HER	HER1-4 (ErbB1-4)	Lapatinib Afatinib Dacomitinib	Paronychia Pyogenic granuloma Slower growth rate Mild onycholysis Thin nails Brittle nails
Anti-MEK	MEK 1/2	Trametinib Cobimetinib Selumetinib	Paronychia Pyogenic granuloma Slower growth rate Mild onycholysis Brittle nails
mTOR inhibitors	mTOR	Everolimus Temsirolimus	Paronychia Pyogenic granuloma Yellow nail discoloration Slower growth rate-thin nails Mild onycholysis Brittle nails
Angiogenesis multikinase inhibitors	VEGRF 1-3 PDGFR α/β and other molecular targets	Sunitinib Sorafenib Cabozantinib Axitinib Pazotinib Regorafenib	Splinter subungual hemorrhage Brittle nails
RET inhibitor	EGFR VEGFR 2/3 RET	Vandetanib	Paronychia Pyogenic granuloma Photoonycholysis Splinter subungual hemorrhage
BCR-ABL inhibitor	BCR-ABL c-KIT PDGFR	Imatinib	Melanonychia Lichenoid reactions
Bruton inhibitors	Bruton tyrosine kinase	Ibrutinib	Brittle nails Onychoschizia Onychorrhexis Mild onycholysis

treatment) have been associated with paronychia, pyogenic granuloma, slower growth rate, mild onycholysis and brittle nails [38, 41].

M-TOR Inhibitors

The mammalian target of rapamycin regulates cellular metabolism, growth and proliferation by forming and signalling through two protein complexes, mTORC1 and mTORC2 [38]. **Everolimus** (indicated in advanced renal cell carcinoma, advanced breast cancer, pancreas, stomach, intestines, lungs, subependymal giant cell astrocytoma, tuberous sclerosis complex, certain types of seizures in adults and children and prevention of transplant rejection), as well as **temsirolimus** (indicated in renal cell carcinoma), may cause yellow nail discoloration, paronychia, pyogenic granuloma, slower growth rate-thin nails, mild onycholysis and brittle nails [38] (Table 3).

RET Inhibitor

RET inhibitors are targeted therapies used on tumors characterized by activated alterations in the RET proto-oncogene. These include non-small cell lung cancer (NSCLC), medullary thyroid cancer and papillary thyroid cancer.

Vandetanib is an oral multikinase inhibitor which targets the RET, proto-oncogene, EGF and VEGF receptors. The most prevalent nail adverse event associated with Vandetanib therapy is subungual hemorrhage (due to VEGFR inhibition), paronychia/pyogenic granuloma (EGFR inhibition) and a painful type 1 photo-onycholysis [38] (Table 3). Patients should be informed about UVA/UVB photo-protection.

BCR-ABL Inhibitors

BCR-ABL is a gene produced by the BCR gene and the C-ABL proto-oncogene and is considered to be the main cause of chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL) that are Philadelphia chromosome-positive, certain types of gastrointestinal stromal tumors, hypereosinophilic syndrome, chronic eosinophilic leukemia, systemic mastocytosis and myelodysplastic syndrome [38]. **Imatinib** is an oral medication of this group that may induce melanonychia and lichenoid reactions (Table 3). Melanonychia appears 1-2 months after treatment initiation. It results from the direct toxic action of the regimen on the melanocytes of the nail matrix, with secondary melanin production. Melanonychia striate, as well as total melanonychia do not require any treatment. They regress spontaneously several months after treatment discontinuation [38]. Lichenoid reactions are very rare but may provoke a destruction of the matrix and a subsequent scar formation.

Immunotherapy (Figure 3)

The immune system, as part of its normal function, detects and destroys abnormal cells and prevents or suppresses cancer growth. Despite that, cancer cells have ways to evade the immune system. They may present genetic changes that make them less visible to the immune system, have proteins on their surface that turn off immune cells or affect the normal cells surrounding a tumor in a way that they interfere with the immune response to cancer cells.

The most prevalent immune-related dermatologic adverse events (irAE) are triggered by immune checkpoint inhibitors (CPIs).

Immune Checkpoint Inhibitors (CPIs) are targeted molecules that modulate the immune system, assist with self-tolerance, and minimize collateral tissue damage when immune responses are activated. These checkpoints are a normal part of the immune system and keep immune responses from being too strong. By blocking them, these drugs allow immune cells to respond more efficiently to cancer. This blockade has been associated with autoimmune-like toxicities, named immune-related adverse events (irAE) [24, 43].

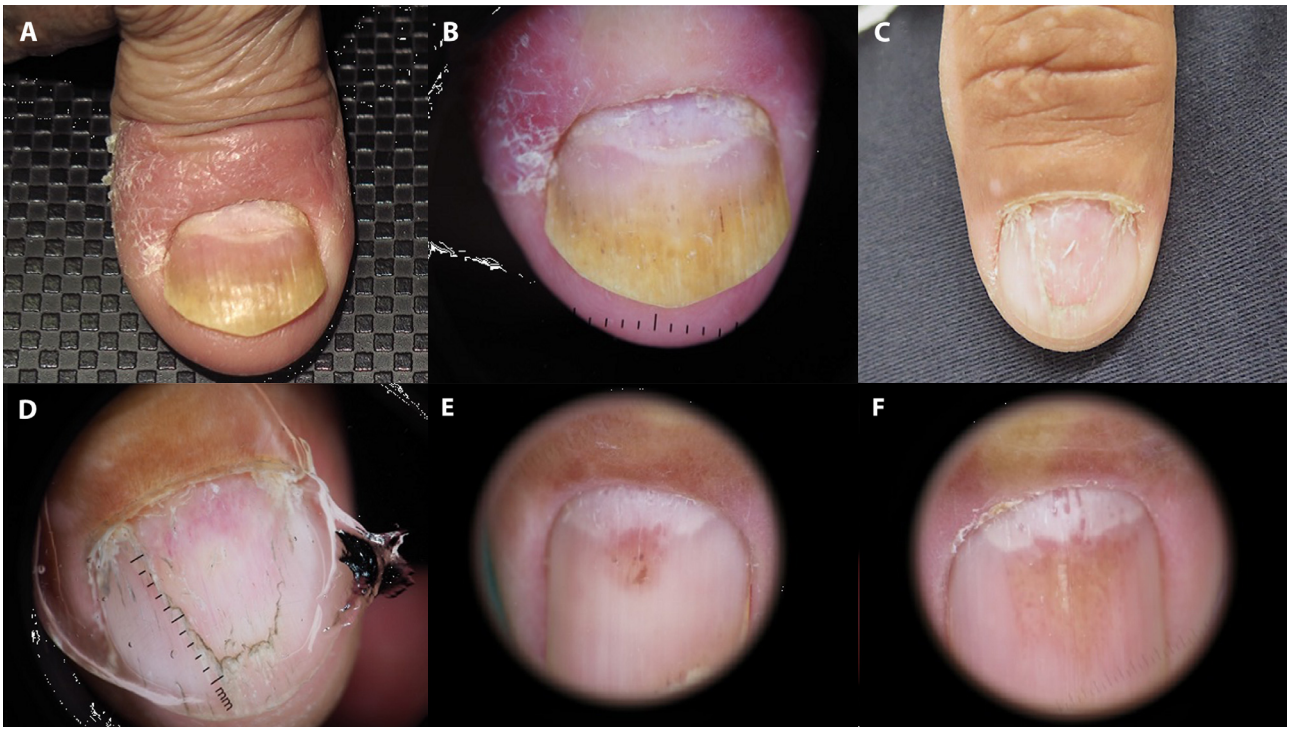

Figure 3. Nail toxicities due to immunotherapy. **A**. Psoriatic changes in nails following treatment with immune checkpoint inhibitor (pembrolizumab): presence of subtle pitting, onycholysis and paronychia with scaling of the skin. **B**. Same patient as a, dermoscopic image: Remark the presence of splinter hemorrhages as well as the yellow discoloration of the onycholysis suggestive of psoriatic disease. **C, D.** Lichenoid-like reactions in a melanoma patient treated with nivolumab: Onychorhexis visualized both clinically and with dermoscopy. In the dermoscopic image the presence of dust in the nail fissures gives the characteristic image of "dirty nail" that is a common finding in lichen-like reactions of the nail plate. **E, F:** Same patient as c, d different nails, dermoscopic images. Characteristic presence of erythema in the lunula seen in patients treated with nivolumab.

Immune checkpoints include cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1). The CTLA-4, PD-1, and PD-L1 pathways mediate immune responses at different levels. CTLA-4 controls the amplitude of immunologic response at early stages of T-cell activation, whereas PD-1 and PD-L1 pathways act at later stages, limiting T- cell activity in the peripheral tissues. By activating cytotoxic CD4+/CD8+ T cells, immune checkpoint blockade therapy shifts the immune system towards anti-tumor activity [42- 44].

The etiopathogenetic mechanism seems to be connected to the T-cell activation, mediated by the blockade of PD-1/PD-L1 and CTLA-4 receptors.

CPIs include anti-PD-1 (nivolumab and pembrolizumab) and anti-CTLA-4 (ipilimumab, tremelimumab) agents, as well as the newly developed anti-PD-L1 agents (atezolizumab, durvalumab, avelumab) [42- 44].

ICIs nail alterations have not been systemically investigated and are considered uncommon. Nail toxicity presents late in time, with an onset extended up to several months from ICI initiation [42, 43].

Persistence of the nail change after ICI discontinuation has been also reported.

Diverse nail changes have been reported in relationship to ICIs, including onycholysis, onychomadesis, longitudinal fissures, onychorrhexis, layered splitting of the nail plate, lunular erythema, thinning of the nail plate and fragility. Commonly, more than one finger- or toenails are involved. Nail psoriasis is the most common immunotherapy-related toxicity [42, 45].

Since the majority of nail alterations appear in conjunction with psoriasiform or lichenoid rashes, they are most probably of the same nature. In line with this theory are the histopathologic alterations found in two patients exhibiting onycholysis that were consistent with lichenoid reaction. This develops either as a deterioration of pre-existing nail psoriasis, or as a de-novo appearance. Histopathologically confirmed psoriasis of the nail has been described in association with nivolumab, clinically characterized by nail thickening combined with periungual erythema [43, 45].

First-line treatment for these nail changes is topical therapy. If topicals fail and there is also skin involvement, systemic therapy should be considered [43, 45].

Pathogenesis of certain nail changes and potentially responsible anticancer drugs. Table 4 highlights the diagnostic challenges related to drug-induced nail toxicities.

Melanonychia

Melanonychia represents one of the most common adverse effects of chemotherapeutic agents. Saraswat et al. [4] and Pavey *et al*. [1] found nail hyperpigmentation as the most common nail toxicity of chemotherapeutic drugs. This pigmentation develops after 1–2 months of treatment and is proposed to be the outcome of matrix melanocyte activation, which usually affects several nail plates. Nail melanocytes are quiescent and generally do not produce melanin. Melanonychia results from the direct toxic action of chemotherapy on the melanocytes of the nail matrix, with secondary melanin production analogous to that of post-inflammatory hyperpigmentation seen in the skin [46- 49].

The activation of a subgroup of melanocytes produces a single or several longitudinal pigmented bands (melanonychia striata) whereas diffuse activation of melanocytes gives rise to diffuse nail pigmentation (total melanonychia). Transverse melanonychia may also be observed [2]. Skin or mucosal pigmentary changes are frequently associated.

Nail hyperpigmentation is more often reported with chemotherapeutic agents like cyclophosphamide, cisplatin, fluorouracil and its prodrug capecitabine, taxanes, doxorubicin, bleomycin and Imatinib [16, 38, 50- 54] (Table 5).

Chemo-induced hyperpigmentation does not require any treatment and progressively regresses several months after treatment discontinuation. For patients who would like to conceal this melanonychia, dark-colored nail polish may be proposed.

Beau's Lines

Beau's lines correspond to the formation of transverse linear depressions in the dorsum of the nail plate and result from a transitory decrease in mitotic activity of the proximal nail matrix keratinocytes. The depth of the groove is strictly

Table 4. Challenges in the diagnosis of drug-induced nail toxicity.

Several factors may pose diagnostic difficulties in the scenario of drug-induced nail toxicity [2, 3, 7, 81]
1. Nail changes may appear several weeks after drug intake, due to the kinetics of nail formation and the slow growth rate of the nail plate
2. Patients are often on multiple potentially causative medications
3. Symptoms often improve or resolve without drug withdrawal
4. Rechallenge is commonly uneventful
5. Non-drug causes may be involved
6. Abnormalities do not necessarily involve all nails
7. Poor understanding of the pathogenesis of nail damage.

Table 5. Nail changes presented in association with the potentially responsible anticancer regimen.

Nail Changes	Conventional Chemotherapeutic Drugs	Targeted Chemotherapeutic Drugs
Diffuse hyper-pigmentation	Cyclophosphamide, vincristine, cisplatin, carboplatin, oxaliplatin, 5-fluorouracil, capecitabine, doxorubicin, daunorubicin, bleomycin, hydroxyurea, busulfan, docetaxel, paclitaxel, pemetrexed, etoposide combination of cyclophosphamide/adriamycin/ vincristine/cyclophosphamide/adriamycin/ docetaxel	Imatinib
Longitudinal melanonychia	Cyclophosphamide, vincristine, bleomycin, tegafur, combination of cyclophosphamide/ adriamycin/vincristine	Imatinib
Beau's lines	Docetaxel, paclitaxel, cisplatin, doxorubicin, bleomycin, combination of epirubicin/ vincristine/cyclophosphamide cyclophosphamide/doxorubicin/fluorouracil	
Onychomadesis	Paclitaxel, docetaxel, capecitabine, combination of cyclophosphamide/vincristine/procarbazine/ prednisolone	
Mees' lines	Cyclophosphamide, doxorubicin, vincristine, docetaxel, paclitaxel, combination of cytarabine/ daunorubicin cyclophosphamide/doxorubicin/vincristine/ prednisolone (CHOP)	
Muehrcke's lines	Combination of cyclophosphamide/ doxorubicin/5-fluorouracil vincristine/doxorubicin/dexamethasone cisplatin, oxaliplatin	
Half and half nails (Lindsay's nails)	5-Fluorouracil	
Onycholysis	Docetaxel, paclitaxel, cyclophosphamide, pemetrexed, 5-fluorouracil, capecitabine	Cetuximab, panitumumab,erlotinib, gefitinib, necituumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, ibrutinib, vandetanib
Paronychia	Fluorouracil, docetaxel, paclitaxel, etoposide	Cetuximab, panitumumab,erlotinib, gefitinib, necituumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, vandetanib
Subungual hyperkeratosis	Docetaxel, paclitaxel, fluorouracil	
Pyogenic granuloma	Docetaxel, paclitaxel	Cetuximab, panitumumab,erlotinib gefitinib, necituumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, vandetanib
Subungual & splinter hemorrhage	Docetaxel, paclitaxel	Vandetanib, sunitinib, sorafenib, cabozantinib, axitinib, pazotinib, regorafenib
Brittle nails	Docetaxel, paclitaxel	Cetuximab, panitumumab,erlotinib, gefitinib, necituumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus temsirolimus, ibrutinib, sunitinib, sorafenib, cabozantinib, axitinib, pazotinib, regorafenib
Onychorrhexis	Docetaxel, paclitaxel	Ibrutinib
Koilonychia	Docetaxel, paclitaxel	

correlated to the extent of nail matrix damage. The width is proportional to the duration of the insult. Beau's lines have been described with nearly all chemotherapeutic agents, especially when used in combination or with a high-dose regimen. They are probably the most frequent nail changes noted in patients exposed to chemotherapy [46- 48]. Beau's lines often affect all nails but are more frequent in fingernails and appear after a few weeks of chemotherapy [4, 55]. After repeated courses of chemotherapy, several depressions can be noted in the same nail. They move distally with nail growth. The presence of regular transverse Beau's lines in the nail plate reflects the temporary cessation of matrix proliferation during each chemotherapy cycle. Chemotherapeutic agents such as docetaxel, paclitaxel, a combination of epirubicin/vincristine/cyclophosphamide, and cyclophosphamide/doxorubicin/fluorouracil are associated with Beau's lines [4, 56, 57] (Table 5).

Onychomadesis

Onychomadesis is a spontaneous separation of the nail plate from the nail bed in its proximal portion. It implies a limited lesion affecting the proximal part of the matrix. It results from temporary cessation of nail growth lasting for more than 2 weeks. Initially, a small cleavage appears under the proximal portion of the nail. This forms a shallow ulcer that does not involve the deeper layers. When the injury is healed, the nail regrows over again distally. In latent onychomadesis, the nail plate demonstrates transverse split because of complete inhibition of nail growth for 1–2 weeks. Beau's lines may evolve into the formation of onychomadesis, which essentially corresponds to the extreme form of Beau's lines. The nail plate is then divided into two parts by a transverse thick groove, which remains latent for a long period before the nail plate ultimately sheds [58]. Onychomadesis induced by chemotherapeutic agents is thought to be the result of arrested mitotic activity in the nail matrix resulting in nail separation and shedding [59, 60].

Onychomadesis induced by chemotherapeutic agents was originally described by Kochupillai *et al* [61]. Since then only five cases have been reported in the literature. In Saraswat et al. the drugs associated with the development of onychomadesis were imatinib, paclitaxel, capecitabine, and a combination of cyclophosphamide/vincristine/procarbazine/prednisolone (Table 5).

Leukonychia

Leukonychia is characterized by white discoloration of a part of the nail plate or the complete nail plate, and can be divided into true leukonychia and apparent leukonychia. Leukonychia induced by chemotherapeutic agents usually occurs in the form of apparent leukonychia [10, 46- 48, 62].

True Leukonychia (white opaque coloration - total or transverse: Mees' lines) results from altered keratinization of the distal nail matrix. Parakeratotic nuclei are retained in the nail plate and thus the nail appears opaque and white in color owing to the diffraction of light by parakeratotic cells. True leukonychia does not disappear with pressure and moves distally as the nail grows. Mees' lines are transverse white, non-blanching parallel lines to the lunula across the entire nail bed and have no palpable ridges [63, 64]. In chemotherapy-induced true transverse leukonychia, the sessions of transverse white bands and the distance between them seemed to coincide with the number and duration of chemotherapy cycles, respectively.

Apparent Leukonychia (white transparent coloration) is observed because of changes in the nail bed vasculature on pressure, visible through the translucent nail plate. True and apparent leukonychia may be differentiated clinically by diascopy. The whitish discoloration disappears (or fades) with digital compression and is not modified by nail growth. Apparent leukonychia can present as three different clinical types: Muehrcke's lines (the most frequent form in association with chemotherapy), Half and half nails (Lindsay's nails), or Terry's nails.

a. **Muehrcke's Lines** (the most frequent form in association with chemotherapy) are present as multiple, paired, transverse, whitish bands, parallel to the lunula. Chen *et al*. [6] found Muehrcke's lines as the most common nail toxicity of chemotherapeutic drugs in children. This change is commonly seen after chemotherapy and in chronic hypoalbuminemia of less than 2 mg/dl (seen in nephrotic syndrome, glomerulonephritis, liver disease, and malnutrition), and is commonly found on the second, third, and fourth fingernails. Thumbnail involvement is rare. The lines tend to resolve with correction of hypoalbuminemia. The exact pathogenesis is unknown, but the suggested reasons are edema of the nail bed, which occurs due to hypoalbuminemia, and an alteration of nail plate attachment to the nail bed, which occurs due to vascular compromise following chemotherapy [6].
b. **Half and Half Nails** (Lindsay's nails) where there is a definite border between the proximal area (opaque white) and the distal area (pink or reddish brown) occupying 20%–60% of the nail bed. Distal red-brown pigmentation does not fade with pressure.
c. **Terry's Nails**, where the whole nail appears white, except a 1–2 mm pink-to-brown distal band, and the lunula may or may not be visible.

In most cases, leukonychia involves all fingernails and may coexist with melanonychia. It has been described in association with numerous chemotherapeutic agents but

generally develops when chemotherapy is used in combination. Systematic screening for associated hypoalbuminemia should be performed in this context.

Mees' lines are usually observed with the use of docetaxel and a combination of cytarabine/daunorubicin and cyclophosphamide/doxorubicin/vincristine/prednisolone [65- 67] (Table 5).

Muehrcke's lines have been reported with cisplatin, oxaliplatin and a combination of cyclophosphamide/doxorubicin/5-fluorouracil and vincristine/doxorubicin/dexamethasone [68] (Table 5).

Nail growth is faster in children and adolescents, and is estimated to be at a rate of 0.12 mm/day [23]. However, chemotherapy-induced nail changes in children, in comparison to adult cases, are less well characterized in the literature. Reviewing the limited case reports, transverse leukonychia seems to be the most frequently described nail change in children receiving chemotherapy, with doxorubicin/daunorubicin, vincristine and cyclophosphamide being the main causative agents [23, 66].

Onycholysis

Onycholysis is defined by the separation of the nail plate from the underlying nail bed [48]. It usually starts from the distal portion of the nail bed, progresses proximally, and can involve the entire nail with the formation of a space. This may result in the formation of painful subungual abscesses and hemorrhages and finally loss of the nail plate. It is noteworthy that the chemotherapeutic agents that most frequently induce nail changes are taxanes: docetaxel and paclitaxel, resulting from a direct toxic effect [22, 25, 26, 46, 59].

However, mild to moderate onycholysis may also be noted with other chemotherapeutic agents as well (capecitabine, etoposide, cytarabine, cyclophosphamide, doxorubicin, or combination therapy) [24, 46, 48]. The targeted chemotherapeutic agents, which may cause onycholysis are cetuximab, panitumumab, erlotinib, gefitinib, necitumumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, ibrutinib and vandetanib [38] (Table 5).

Onycholysis is one of the most prevalent adverse events induced by docetaxel or paclitaxel [22]. Recently, the overall incidence of taxane-induced nail toxicity has been systematically investigated [35]; all-grade incidence was 43.7% with paclitaxel (95% CI: 18.0-73.3%) and 34.9% (95% CI: 29.9-40.2%) with docetaxel. For the latter, the relative risk was 77.74 (95% CI: 41.88-144.32; $p<0.001$) as compared to controls [22].

Nail changes are evident after several weeks of treatment because of the slow growth rate of the nail plate [29]. The development of nail changes is strongly associated with weekly administration, the number of chemotherapy cycles given and the cumulative dose of taxanes [29, 46, 47, 59]. Although it is more common in patients receiving the once-weekly regimen, it can also be observed with the every 3-week regimen [29, 46].

The onycholytic portion of the nail plate becomes opaque, loses its translucency, and can take on a white, black, or brown-red color, depending on the type of lesion [57, 59, 60]. The fingernails are more often involved than toenails and the number of digits affected varies, although involvement may also be diffuse [29, 59, 69- 72]. Onycholysis is initially asymptomatic; however, pain may occur due to acute trauma, progression of the detachment, or development of subungual hemorrhagic blisters or abscesses with purulent malodorous discharge (exudative onycholysis) [22, 26, 48, 60, 71]. Secondary bacterial or fungal infections may also develop because of the debris collected in the ventral part of the detached plate. Cosmetic and functional impacts depend on the number of nails involved, the severity of the detachment, and the extent of pain [29].

Taxane-related onycholysis is sometimes associated with inflammatory erythema of dorsal hands or the perimalleolar and Achille's areas (PATEO syndrome: periarticular thenar erythema with onycholysis) [22, 24].

The changes may affect both the nail matrix (melanonychia, true leukonychia, Beau's lines and onychomadesis, brittle nails with ridging and thinning, onychorrhexis, koilonychias), the nail bed (onycholysis and apparent leukonychia) or the periungual tissue (paronychia or pyogenic granuloma), may also be affected at the same time with taxane chemotherapy [22, 24, 26, 47].

The pathophysiological origin of taxane-induced onycholysis is not clearly established. It may be the result of direct cytotoxic damage to the nail matrix and epithelial cells of the nail bed with epidermolysis and the secondary loss of adhesion of the nail plate to the nail bed [24, 47]. An intrinsic antiangiogenic activity of taxanes has also been postulated [22]. Similarly, a phototoxic mechanism for photo-onycholysis has been advanced by some authors but remains to be confirmed [59]. Lastly, unilateral onycholysis has been reported in patients suffering from contralateral peripheral palsy, suggesting a taxane-induced neurotropic effect (neurogenic or prostaglandin-mediated inflammation) [73].

More recently, Schepisi et al. [34] hypothesized that paclitaxel-related onycholysis may be directly correlated to the duration of the infusion. Indeed, onycholysis may develop more frequently with a shorter infusion (1 hour) than with a prolonged infusion, because of increased systemic exposure to the Cremophor vehicle (paclitaxel solvent). That may explain, at least in part, the higher incidence seen in patients receiving the weekly paclitaxel regimen (1-hour infusion) in comparison with the every 3-week regimen (3-hour infusion).

The impact of taxane-related onycholysis on the quality of life and daily activities varies; effects depend on the number of digits involved, the degree of detachment, and the extent of pain and if significant it can result in treatment interruption [28, 29]. Therefore, management of onycholysis depends on the clinical grading (i.e., National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) v4.02) and impact on activities of daily living [38] (Table 1). Onycholysis is slowly reversible after treatment, however chronic onycholysis can lead to nail bed keratinization and persistent subungual hyperkeratosis [22, 74]. Therefore, it is crucial to promote nail reattachment as early as possible by preventing further toxicity and treating underlying infections, otherwise onycholysis may become permanent.

Paronychia

Paronychia is the result of inflammation of proximal/lateral nail folds with erythema, edema, tenderness or pain of the nail folds and impaired activity. It usually develops soon after intake of the drug, involves one or several nails and is thought to be the result of the toxic effect of the drug on nail epithelium [2, 8]. Paronychia is a frequent but uncommonly reported adverse effect of epidermal growth factor inhibitors which is the result of aberrant vascular response affecting nail folds [75, 76]. Except for anti-EGFR targeted therapy, RET inhibitor, mTOR inhibitors, anti-MEK, anti-HER, 5-fluorouracil and docetaxel have been reported to develop paronychia as well [4] (Table 5).

Brittle Nails and Decreased Nail Growth

A decrease in nail plate growth is commonly noted with chemotherapy, although it will usually go unnoticed by patients or physicians. The nails are often fragile and thinner, which can lead to koilonychia, onychorrhexis, or onychoschizia after several cycles of chemotherapy [74]. Chemotherapeutic agents such as cetuximab, panitumumab, erlotinib, gefitinib, necitumumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, ibrutinib, sunitinib, sorafenib, cabozantinib, axitinib, pazotinib, regorafenib, docetaxel and paclitaxelare associated with brittle nails (Table 5).

Koilonychia is a common nail dystrophy in which the dorsal surface of the nail plate becomes flat or truly concave. It is derived from the Greek word koilos, meaning hollow.

Pathogenesis of koilonychia is not known but it is suggested that anoxia and atrophy of the distal matrix are contributory. Koilonychia is the converse of clubbing and it is more appreciated when viewed from the side. When a drop of water is put on the surface, it will not fall off. It should be noted that nails in koilonychia are brittle. It is commonly seen in fingernails rather than toenails. Docetaxel and Paclitaxel may cause koilonychia more often (Table 5).

Onychorrhexis is a type of longitudinal groove wherein a series of shallow and narrow furrows are present running parallel on the nail surface. Docetaxel, paclitaxel and ibrutinib may cause onychorrhexis (Table 5).

Onychoschizia is clinically characterized by the splitting of the nail plate at the free edges in the fingers and toes. It may be localized or the full length of the free edge may be involved. Electron microscopy reveals horizontal separation of the nail plate, which may, sometimes, extend up to the proximal nail fold. It also demonstrates individual cells lying in the empty spaces. These observations indicate lamellar splitting in onychoschizia occurs between the cell layers.

Management and Prevention

Counselling for the prevention of nail toxic effects is mandatory. Healthcare professionals should provide patients with clear and detailed information. The patients should avoid repeated trauma or pressure on nails and nail beds or irritant regimen, including manipulation of the cuticles and nail biting, use of fingernails as "tools," prolonged soaking in water, exposure to solvents or hard chemicals, and application of artificial nails. They are encouraged to trim their nails regularly and smooth the edges. The nails should be straight/squared and not too short. Prophylactic measures include the use of cotton gloves, comfortable wide-fitting footwear and cotton socks. Housework should be performed only with glove protection. When UV-associated toxicity is related to the drug regimen patients should be informed and wear gloves when outside. Nail lacquers are recommended to limit water loss from the nail plate (especially for brittle nails). Furthermore, daily use of topical emollients on the total nail apparatus (cuticles, plate, and periungual folds) is a prophylactic management for chemotherapy-induced nail toxicity [48]. In addition, Scotté et al. [25] have demonstrated that the preventive use of frozen gloves/socks in patients treated with docetaxel allowed a significant reduction in changes from 51% to 11% (p=0.0001) in fingernails, and from 21% to 0% in toenails, with a trend towards a prolongation (albeit non-significant) of the median time to development of these lesions. Importantly, the Grade 2 or greater nail AEs were reduced from 22% to 0% (p=0.0001) [25, 69]. Therefore, the preventive use of frozen gloves/socks should be advised in patients treated with taxanes [25]. Alternatively, the use of ice packs may be a less expensive and effective strategy with similar efficacy [27]. In addition to preventing nail toxicities, frozen gloves or ice packs have been shown to decrease the incidence of peripheral neuropathy, another potentially dose-limiting adverse event. It is intriguing that despite the simplicity and effectiveness of this intervention, it is not universally employed.

In case onycholysis develops, excising the nail plate (partially or totally) may be necessary (Figure 4), especially in severe and painful lesions, or when associated with a pressure

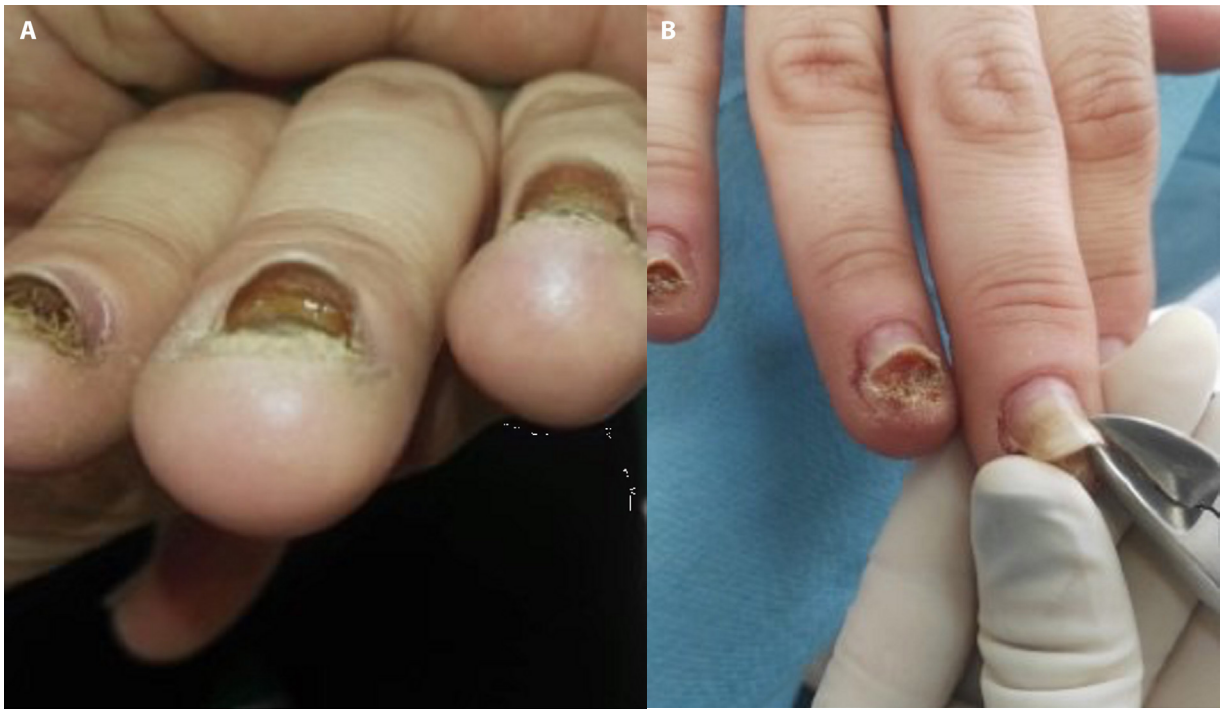

Figure 4. A. Onycholysis due to taxane treatment. Observe important detachment of plate from bed and presence of purulent discharge, **B.** Clipping of the onycholytic part of the nails relieves pain and allows for better hygiene.

hematoma or subungual abscess [7]. The nail bed should be cleaned and a sample for culture collected at the same time, and in case of suspected infection should be also promptly treated with topical/oral antibiotics antiviral or antifungal therapy [48]. The detached nails should be cut regularly until the nail plate grows and covers the nail bed. In the setting of paronychia without infection, potent topical steroids are recommended.

Except for the aforementioned traditional management modalities, some other clinical methods, such as cryotherapy and nail solution (nail balm), have been reported and promoted. Huang et al. [77] in their meta-analysis revealed that both nail solution-based and cryotherapy-based prophylactic management (frozen gloves, frozen socks and ice packs) were effective for treating taxane-induced nail toxicity. Nail solution use is known to reduce the levels of substance P, a neurotransmitter that induces inflammation, which adversely affects nails [78]. Moreover, plant-based waxes and essential oils are naturally rich in phytochemicals, particularly phenolic polyphenols, which have been reported to exhibit antioxidant, anti-inflammatory, DNA repair-enhancing and antimicrobial properties [79, 80]. In addition to their abilities to moisturize the skin and prevent the drying and splitting of nails, the waxes and essential oils were hypothesized to be sufficiently absorbed into the nail beds to act as local antidotes to the chemotherapeutic agent, thus preventing damage to the proliferating stem cells, avoiding secondary damage from inflammation or secondary infection as well as delaying the time to nail toxicity [79, 80]. Cryotherapy's effect is related to cold-induced vasoconstriction, which reduces the quantity of drugs reaching the proliferating stem cells. For patients who can afford them, tolerate discomfort and exhibit compliance, these prophylactic managements of taxane-induced nail toxicity can be suggested as an option to improve patients' quality of life and functional statuses. However, future investigations and studies are needed to establish the routine usage protocols, standard outcome measures, long-term efficacy and safety for these interventions [77].

Conclusions

A wide spectrum of nail toxicities has so far been described in association with both, conventional and newer anticancer agents; however, less importance has been given to nail changes as compared to other skin toxicities. Considering that nail toxicity is indeed almost never life-threatening, discontinuation of oncologic therapy is only rarely necessary. However, drug interruptions or dose modifications may be warranted, mostly due to serious impairment of patients' quality of life. Management is primarily directed at symptom control and relief of the patient. Nail changes that result from matrix interruption of blood flow often induce cosmetic changes (not requiring intervention), with the nail eventually growing out normally after treatment discontinuation. On the other hand, nail changes due to disruption of the nail folds frequently require therapeutic intervention, and depending on the severity, also dose modifications.

At present, there is a paucity of data regarding nail involvement and its impact on the functional and emotional status of the patient, during the course of the diverse oncologic treatments. The frequency of nail involvement, especially with immunotherapy and new targeted agents remains unknown.

Based on the literature, it has been observed that patients with different cancer types receiving different regimens may develop the same nail disorder, whereas patients with the same type of cancer under the same chemotherapeutic treatment may develop different types of nail alterations. The underlying mechanisms of the varying individual susceptibility and the diverse nail responses to various anticancer treatments need further investigation. It is critical to improve our understanding of the underlying pathogenesis of nail toxicity and potential risk factors in order to develop effective evidence-based management strategies, maintain patients' health-related quality of life and ensure optimal dosing of potentially life-prolonging anticancer therapy.

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