Chemotherapy-induced hand-foot syndrome and nail changes: A review of clinical presentation, etiology, pathogenesis, and management

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Chemotherapy-induced hand-foot syndrome and nail changes are common complications of many classic chemotherapeutic agents and the newer molecular targeted therapies. They significantly impact patient quality of life, and frequently necessitate chemotherapy dose intensity modification or reduction. We aim to describe the epidemiology, pathogenesis, clinical presentation, and current evidence-based treatment options for these entities. (J Am Acad Dermatol 2014;71:787-94.)

Key words: chemotherapy complications; chemotherapy nail complications; hand-foot skin reaction; hand-foot syndrome; molecular targeted therapy complications; palmoplantar erythrodysesthesia.

Hand-foot syndrome (HFS), also known as palmoplantar erythrodysesthesia or acral erythema, is a well-documented adverse effect of numerous chemotherapeutic agents. It was originally described in 1974 in association with mitotane.[1] The most common causes are pegylated liposomal doxorubicin (PLD), capecitabine and 5-fluorouracil (FU), cytarabine, and docetaxel. Newer targeted multikinase inhibitors (MKIs) such as sorafenib, sunitinib, axitinib, pazopanib, regorafenib, and vemurafenib also cause a reaction involving the hands and feet. Because the constellation of findings differs somewhat and is unique to these agents (Table I), this entity has been named "hand-foot skin reaction" (HFSR). Numerous additional drugs have also been implicated (Table II).[2,3]

HFS incidence ranges from 6% to 64%, but this is detailed mostly in case reports and case series and thus difficult to accurately assess.[4] Incidence also varies with causative agent (Table I). PLD and capecitabine have the highest reported HFS incidence at 40% to 50% and at 50% to 60%, respectively. The MKIs sorafenib and sunitinib cause HFSR in 10% to 28% and in 10% to 62% of patients, respectively.[5]

Abbreviations used:

FU:	fluorouracil
GVHD:	graft-versus-host disease
HFS:	hand-foot syndrome
HFSR:	hand-foot skin reaction
MKI:	multikinase inhibitor
NCI:	National Cancer Institute
PLD:	pegylated liposomal doxorubicin
WHO:	World Health Organization

In addition, certain chemotherapeutic combinations can increase the risk of HFS. Doxorubicin plus continuous 5-FU, for example, has a reported incidence of 89%.[3]

The risk of developing HFS appears to be dose-dependent. Drug formulations that prolong serum drug levels or that concentrate drug at affected sites have higher rates. This may be one reason why PLD, the liposome-encapsulated form of doxorubicin, is associated with a higher HFS incidence than the standard, nonencapsulated formulation. Capecitabine, an oral prodrug of 5-FU that produces sustained tissue drug levels, also increases HFS risk. Administration schedules that maintain high serum drug levels, such as 5-FU

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administered as a continuous infusion, carry a much higher risk of HFS development than bolus injections.[4] The risk factors associated with the development of HFS include dosage, female sex, and genetic variations impacting drug metabolism.[5] Tumor type may be important for MKI-induced HFSR, with sorafenib-treated patients with renal cell carcinoma displaying higher rates of HFSR compared with other malignancies.[5] A recently developed risk assessment index grading the severity of MKI-induced HFSR found that normal pretreatment white blood cell count, female gender, good performance status, liver metastases, and affected organ number were predictors for moderate to severe HFSR.[6]

CAPSULE SUMMARY

- Chemotherapy-induced hand-foot syndrome and nail changes are a common complication of many traditional and newer molecular targeted chemotherapeutic regimens. These complications can significantly impact quality of life and be dose-limiting.
- This review provides an update on clinical presentation, etiology, pathogenesis, and current evidence-based management.
- Practicing clinicians would benefit from updated understanding of this entity, as comprehensive clinical reviews are lacking in the dermatologic literature.

CLINICAL FINDINGS

HFS has a distinctive clinical presentation. Onset is typically within 2 to 21 days but may occur up to 10 months later in agents with sustained pharmacokinetics such as oral capecitabine or continuous infusion cytarabine.[3,7-9] Patients report a palmoplantar dysesthesia that begins as a tingling sensation and progresses to burning pain within several days. Pain and temperature sensation are decreased but strength, light touch, and proprioception is preserved, likely as a result of small nerve fiber neuropathy.[10] A well-demarcated plaque of palmoplantar erythema and edema accompanies the onset of neuropathic symptoms and is most prominent on the lateral aspect of the fingers and distal fat pads (Fig 1).[11] If the patient is thrombocytopenic, purpura may be present. The erythema can progress to blistering with subsequent desquamation, erosion, and ulceration (Fig 2). In African American patients, HFS can present with hyperpigmentation, especially when a result of capecitabine (Fig 3). Symptoms recur with repeated exposure to the inciting agent.

HFS affects the palms more frequently than the soles. It may also involve the dorsal hands and feet. If confluent upper epidermal necrosis is seen histologically, a shellac-like scale similar to that seen in nutritional deficiencies may be present.[8] The MKI-induced HFSR presents with focal hyperkeratosis overlying an erythematous base distributed over flexural and pressure-bearing areas, including the fingertips, heels, and over joints (Fig 4). In contrast to classic HFS, HFSR affects the soles more than palms and involves friction-prone areas such as interdigital web spaces and lateral aspect of feet.[5,12]

HISTOPATHOLOGY

Histopathologic findings in HFS are nonspecific but resemble patterns seen in cytotoxic reactions. Epidermal changes range from scattered necrotic keratinocytes with basal layer vacuolar degeneration to full-thickness epidermal necrosis, and reflect the degree of clinical severity. Papillary dermal edema, a perivascular lymphocytic infiltrate with eosinophils, and eccrine squamous syringometaplasia or ductal epithelial changes seen in neutrophilic eccrine hidradenitis may be present.[8,9,13] MKI-induced HFSR may show a well-defined horizontal band of discohesive dyskeratotic keratinocytes within the epidermis that is distinct from basal vacuolar degeneration seen in classic HFS.[5,12]

There is significant overlap between HFS and other diagnoses such as "eccrine squamous syringometaplasia," "chemotherapy-induced eccrine reaction," "epidermal dysmaturation," and "intertrigo eruption of chemotherapy," as all represent cutaneous toxicities of chemotherapy distinguished either by body location or nonspecific histologic findings.[3,8] Bolognia et al[8] suggest "toxic erythema of chemotherapy" as an umbrella term to describe the toxic damage to the epidermis and eccrine ducts seen to varying degrees in these entities.

DIAGNOSIS

HFS is largely a clinical diagnosis. The differential includes allergic drug eruptions, contact dermatitis, vasculitis, erythema multiforme, erythromelalgia, or acral bleomycin toxicity.[5] Acute graft-versus-host disease (GVHD) can masquerade as HFS after bone-marrow transplantation, as both entities may present identically and occur simultaneously.[5,8] Although acute GVHD typically presents with hepatitis, gastrointestinal involvement, and declining CD4 cells, rare cases limited to the skin have been reported. Palmoplantar acute GVHD manifests as diffuse erythematous macules and papules in

Table I. Major differences between hand-foot syndrome and hand-foot skin reaction

	HFS	HFSR
Causative agents	Pegylated liposomal doxorubicin, capecitabine, 5-fluorouracil, cytarabine, docetaxel and doxorubicin, other cytotoxic agents	Multikinase inhibitors (sorafenib, sunitinib, axitinib, pazopanib, regorafenib, bevacizumab, and vemurafenib)
Risk factors	Dosage, female gender	Tumor type (RCC); normal pretreatment white blood cell count; female gender; good performance status, liver metastases, and affected organ number
Areas involved	Can affect palms; soles; dorsal hands and feet; and areas of occlusion, friction, and pressure Affects palms more than soles	Affects flexural and pressure-bearing areas, including fingertips, interdigital web spaces, heels, lateral aspect of feet, and over joints Affects soles more than palms
Clinical findings	Symmetric erythema and edema in palms and soles, accompanied by onset of neuropathic pain Can progress to blistering with desquamation, erosion, and ulceration	Localized, tender lesions over areas subjected to friction or trauma May appear as blisters or focal hyperkeratosis overlying an erythematous base
Histopathology	Basal layer vacuolar degeneration or full-thickness necrosis; spongiosis, hyperkeratosis, parakeratosis	Well-defined band of discohesive dyskeratotic keratinocytes

HFS, Hand-foot syndrome; *HFSR*, hand-foot skin reaction; *RCC*, renal cell carcinoma.

Table II. Chemotherapeutic agents commonly causing hand-foot syndrome (list not exhaustive)

Agent	Incidence (all grades)	Incidence (high grade)
Doxorubicin + continuous 5-fluorouracil	89%[3]	24%[3]
Docetaxel + capecitabine	56%-63%[3]	24%-26%[3]
Pegylated liposomal doxorubicin	40%-50%[3]	1%-20%[3]
Capecitabine	50%-60%[3]	11%-24%[3]
Doxorubicin	22%-29%[3,4]	
Cytarabine	14%-33%[3,4]	
5-Fluorouracil		
Continuous infusion	34%[4]	7%[3]
Bolus	6%-13%[4]	0.5%[3]
Docetaxel	6%-58%[3,4]	0%-4%[3]
Targeted multikinase inhibitors	**Incidence**	
Sorafenib + bevacizumab	79%[3]	57%[3]
Sorafenib	10%-62%[5]	2%-36%[5]
Sunitinib	10%-50%[3,5,42]	4%-11%[5,42]
Pazopanib	4.5%-29%[42,43]	1.8%-6%[42,43]
Regorafenib	47%[44]	17%[44]
Axitinib	29%[24]	9.6%[24]
Vemurafenib	60%[45]	

contrast to the well-demarcated painful erythematous plaques seen in HFS. If the diagnosis is unclear, multiple biopsies may be required as early acute GVHD and HFS are histologically identical within the first 2 to 3 weeks of chemotherapy administration. It is also important to differentiate HFS from infectious

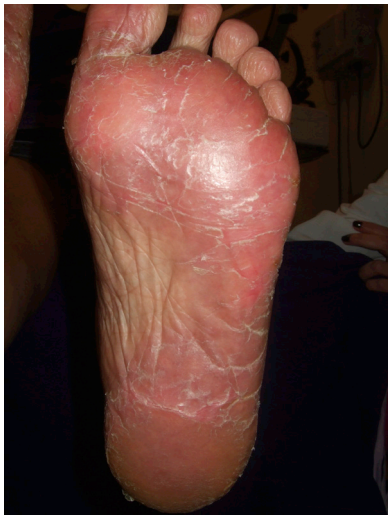

Fig 1. Hand-foot syndrome as a result of 5-fluorouracil in a patient with breast cancer. National Cancer Institute grade 1.

causes more common in immunosuppressed patients.

The clinical severity of HFS varies widely. Classification systems from the World Health Organization (WHO) and National Cancer Institute (NCI) are used to grade clinical involvement (Tables III and IV).[4,14] Using these grading indices can aid communication between dermatologists and oncologists when assessing a patient's clinical status. Grade-3 (NCI) reactions often indicate to an oncologist the need for dose reduction or change in

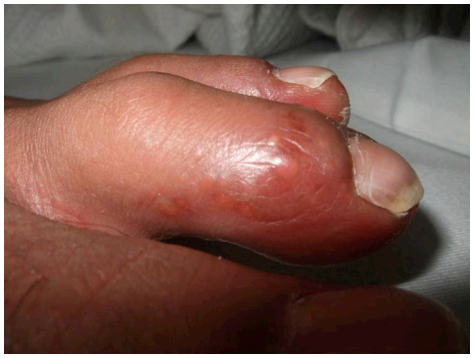

Fig 2. Vesicobullous hand-foot syndrome in a patient with leukemia treated with high-dose methotrexate. National Cancer Institute grade 2.

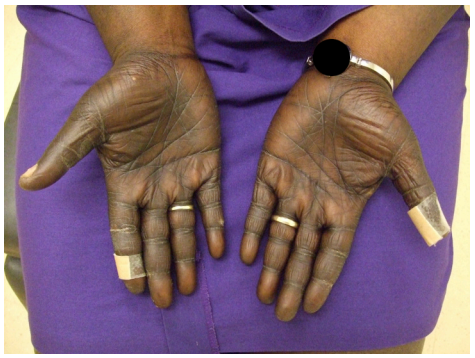

Fig 3. Hyperpigmented hand-foot syndrome. An African American patient with breast cancer presenting with hyperpigmentation of the palms while receiving capecitabine. National Cancer Institute grade 1.

drug. Although the majority of patients develop mild grade-1 or -2 (WHO) or grade-1 (NCI) HFS, many report significant functional impairment.[5] A quality-of-life scale titled "HFS-14" was recently developed to better address this issue, and attempts to quantify the impact on daily activities.[11] HFS severity may also indicate a response to treatment, as a recent study showed a significant correlation between capecitabine-induced HFS grade and efficacy biomarkers in patients with metastatic breast cancer.[15]

Although HFS can significantly impact patients' quality of life, it is not typically life-threatening. One report attributing a patient's death to sepsis from superinfection of the skin with *Pseudomonas aeruginosa* lacks enough clinical information to be sure of the cause of death.[12] Although HFS symptoms usually resolve within 1 to 2 weeks of stopping treatment, permanent sequelae may also occur.[3,9,16] Loss of fingerprints as a result of epidermal destruction has been reported with the use of capecitabine.[16] In addition, repeated episodes of HFS can result in a palmoplantar thickening of the cornified layer resembling a keratoderma.[3]

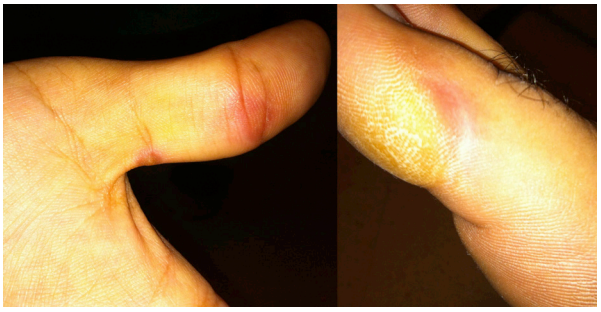

Fig 4. Hand-foot skin reaction in a patient who was unable to walk or dress himself secondary to severe pain in hands and feet. National Cancer Institute grade 3.

Table III. World Health Organization criteria for classification of hand-foot syndrome

Grade	
1	Dysesthesia/paresthesia, tingling in hands and feet
2	Discomfort in holding objects and upon walking, painless swelling and erythema
3	Painful erythema and swelling of palms and soles, periungual erythema and swelling
4	Desquamation, ulceration, blistering, severe pain

PATHOGENESIS

The pathogenesis of HFS is poorly understood. Although there is no consensus that different causative agents share a single underlying mechanism, current evidence suggests an underlying direct toxic effect as the most likely cause. A recent study demonstrated that, after infusion, PLD initially surrounds the deep and superficial eccrine ducts and subsequently permeates the stratum corneum of the palms and soles. Hydrophilic coating of liposomes in PLD favors excretion in the sweat, leading to an accumulation of drug in the eccrine ducts. The thick stratum corneum of the palms and soles acts as a reservoir, leading to oxidative damage and production of toxic free radicals.[17] The predilection of HFS for the palms and soles may be a result of the high concentration of eccrine ducts in these areas. Additional factors such as local vascular anatomy, temperature gradient, and high cell turnover may also contribute.[12] A recent animal model of HFS caused by PLD suggests that interactions between doxorubicin and copper ions generate reactive oxygen species, which induce apoptosis of keratinocytes. Chemokines mediating this reaction include interleukin (IL)-8, GRO, fractalkine, IL-1β, IL-1α, and IL-6, suggesting possible targets for future therapeutics.[18]

Local enzyme activity or trauma may also play a role. Capillary microtrauma at sites predisposed to

Table IV. National Cancer Institute criteria for classification of hand-foot syndrome[14]

Grade	
1	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain
2	Skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental activities of daily life (activities that allow an individual to live independently within the community, eg, housework, paying bills, grocery shopping)
3	Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care activities of daily life

mechanical and frictional stress, such as the hands, feet, axillae, and intertriginous areas results in drug extravasation into surrounding tissue. This may contribute to MKI-induced HFSR as these agents also block vascular endothelial growth factor receptor– and platelet-derived growth factor–mediated vessel repair, further exacerbating localized tissue damage. This is evidenced by a higher HFSR incidence when MKIs are combined with vascular endothelial growth factor blockers such as bevacizumab and cediranib.[3,5,12,19] Increased levels of active drug as a result of local keratinocyte enzyme activity may be important in capecitabine-induced HFS. As compared with the back, keratinocytes in the palms display increased activity of thymidine phosphorylase, which converts capecitabine to active 5-FU. Localized toxic levels of 5-FU may explain the distribution of HFS with respect to this agent.[12,20]

Individual genetic variability could also modify the risk of developing HFS. An activating gene polymorphism in cytidine deaminase, which encodes the purine salvage pathway enzyme cytidine deaminase, was recently associated with increased rates of grade-3 HFS. This enzyme is involved in capecitabine conversion to 5-FU, and coupled with high cell turnover in the palms and soles, may explain increased HFS susceptibility in certain patient populations.[21] Deficiencies in dihydropyrimidine dehydrogenase, an enzyme involved in capecitabine catabolism, may explain ethnic variations in HFS susceptibility, although this requires further research.[22,23] Similar genetic polymorphisms likely also explain the higher incidence of HFSR from MKIs in Asian patients compared with Western patients.[24]

TREATMENT

Large controlled trials evaluating the efficacy of treatment for HFS are lacking, and currently the most effective management of HFS is treatment interruption or dose intensity modification, with symptoms typically improving in 1 to 2 weeks.[9,12] Treatment is otherwise aimed at symptom control. Supportive measures include high-potency topical corticosteroids to decrease inflammation, wound care for erosions and ulcerations to prevent infection, topical keratolytics to decrease hyperkeratosis, frequent emollient use, and pain control.

Preventative measures are central to treatment strategy. Several studies have examined interventions aimed at prophylaxis. A recent large, prospective, randomized controlled trial found twice-daily application of urea-based creams to be effective in preventing the onset of mild to moderate MKI-associated HFSR.[25] Another prospective, randomized controlled trial showed a trend toward decreased HFS incidence with the application of antiperspirant to the palms and soles of patients receiving PLD compared with placebo.[26] Regional cooling may also be effective in preventing HFS, likely through temperature-induced vasoconstriction limiting delivery of chemotherapy to the extremities. Two retrospective reviews and a recent prospective study documented a decrease in HFS with the use of ice packs or ice water immersion during PLD infusion.[3,12,27] Two additional prospective case-control studies also found a reduction in docetaxel-induced HFS with the use of frozen gloves or socks.[28,29] Cooling is not feasible for drugs given via continuous infusion or orally. Other prophylactic measures have been recommended and include avoiding bathing with hot water, vigorous exercise, and wearing tight clothing and shoes around the time of drug administration, although little evidence exists to support these measures.[5,9]

Effective pharmacologic intervention is an active area of research. Although current data are insufficient, dexamethasone has shown promise in treating PLD-induced HFS.[5,13] A recent phase III prospective, randomized controlled trial examining the use of celecoxib in capecitabine-induced HFS found a significant reduction in incidence of grade-1 and -2 HFS in the treatment group. Cyclooxygenase (COX)-mediated inflammation in the setting of local drug-mediated vascular damage may explain this outcome.[30] The use of pyridoxine is less clear-cut. Retrospective case series, case reports, and animal models initially documented successful prevention of HFS associated with 5-FU, docetaxel, and PLD, and a recent randomized controlled trial found a decreased rate of grade-3/-4 HFS induced by capecitabine.[3,12,31] Two additional prospective, randomized controlled trials, however, found no benefit with pyridoxine in preventing capecitabine-associated HFS.[32,33]

Limited case reports and small case series propose that topical dimethyl sulfoxide, nicotine patch, oral vitamin E, and the cytoprotective agent amifostine may be of use in HFS.[5,13] A recent study examined the use of topical heparin in the treatment of HFSR and observed a reduction in skin inflammation, dosing interruption, and MKI discontinuation.[34] Further research and prospective randomized studies, however, are needed to further understand the pathogenesis and management options in both HFS and MKI-induced HFSR.

NAIL CHANGES CAUSED BY CHEMOTHERAPY

Chemotherapy-induced nail toxicity can cause considerable cosmetic concern, pain, infection, and impact on patient quality of life. The clinical severity of nail toxicities varies, and classification schemes from the NCI are used to grade clinical involvement (Table V).[14] Onycholysis occurs as a result of toxic insults to the nail bed and is common with taxanes such as docetaxel and paclitaxel (Fig 5). Taxane-induced onycholysis incidence ranges from 0% to 44%, with docetaxel the more frequent cause. A unique taxane-specific form of HFS, termed "periarticular thenar erythema with onycholysis" features violaceous erythema localized over thenar and hypothenar eminences and Achilles tendon with associated onycholysis (Fig 6).[33] Additional taxane-related nail changes include Beau lines, subungual hemorrhage, nail pigmentation, acute paronychia, and splinter hemorrhage, and can occur in up to 88% of patients. COX-mediated inflammatory pathways and integrity of peripheral nerve fibers may be necessary for the development of nail changes.[35-37]

In addition to cosmetic issues, nail changes can cause functional impairment and associated morbidity. A recent survey showed 42% of patients with docetaxel-induced nail changes reported functional disability.[35,37] Promising data exist for the use of regional cooling in the prevention of taxane-induced nail changes. Scotté et al[28,29] reported that the incidence of nail changes decreased from 51% to 11% in the hands and 21% to 0% in the feet with the use of frozen socks and gloves. A case report of improvement with a COX-2 inhibitor supports the participation of the COX inflammatory pathway in pathogenesis of taxane-induced onycholysis.[35-38]

Other chemotherapeutic agents can also cause nail findings. The anthracyclines such as doxorubicin, daunorubicin, and idarubicin cause both diffuse and banded (longitudinal and transverse) patterns of nail pigmentation (Fig 7) that resolve with discontinuation of therapy and subsequent nail growth. Pigmentation of the skin and mucous membrane may coexist.[39,40] Epidermal growth factor receptor inhibitors can cause paronychia and

Table V. National Cancer Institute criteria (Common Terminology Criteria for Adverse Events, Version 4.0) for classification of nail changes[14]

Grade	
1	Nail discoloration Nail loss (asymptomatic) Nail ridging Nail infection (localized, localized intervention indicated) Paronychia (nailfold edema or erythema, disruption of the cuticle)
2	Nail loss (symptomatic, limiting ADLs) Nail infection (oral intervention indicated) Paronychia (nailfold edema or erythema with pain, associated with discharge or nail plate separation, limiting ADLs; localized and oral intervention indicated)
3	Nail infection (intravenous, radiologic or operative intervention indicated) Paronychia (limiting self-care ADLs, intravenous intervention indicated)

Instrumental ADLs consist of activities that allow an individual to live independently within the community, eg, housework, paying bills and grocery shopping. Self-care ADLs consist of self-care activities, eg, bathing, dressing, eating, and personal hygiene.
ADL, Activities of daily living.

Fig 5. Taxane-induced onycholysis. National Cancer Institute grade 1.

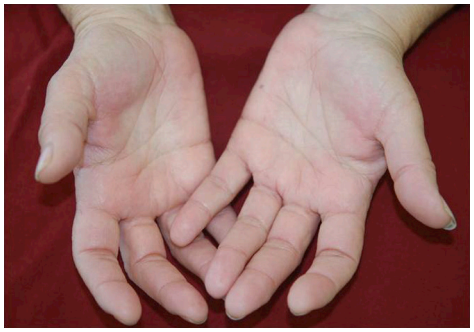

Fig 6. Periarticular thenar erythema with onycholysis (PATEO). National Cancer Institute grade 2.

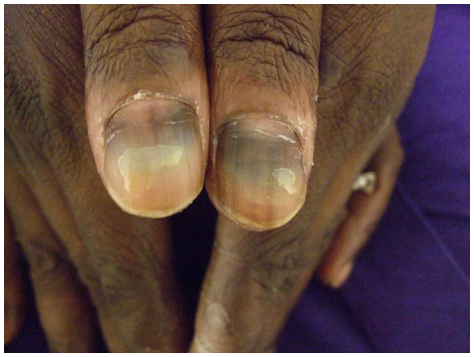

Fig 7. Pigmented nail bands in a patient with breast cancer treated with doxorubicin. National Cancer Institute grade 1.

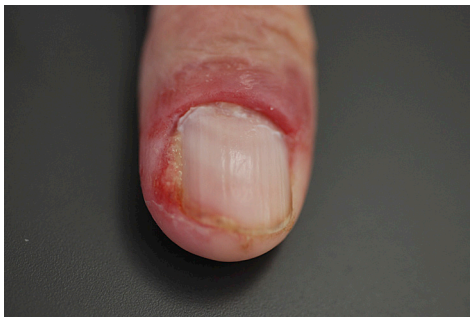

Fig 8. Paronychia with pyogenic granuloma formation in a patient receiving erlotinib for metastatic nonsmall-cell lung cancer. National Cancer Institute grade 3.

pyogenic granuloma formation in 10% to 30% of patients (Fig 8), commonly complicated by secondary infection and pain. Epidermal growth factor receptor inhibitors may also cause slowing or cessation of nail growth and the development of brittle nails and onycholysis.[41]

Conclusion

Chemotherapy-induced reactions of the hands, feet, and nails are long-standing and well-recognized side effects that cause significant morbidity and quality-of-life issues in affected patients. To date, there is a paucity of data regarding management of chemotherapy-induced toxicities affecting the hands, feet, and nails.

This review provides an overview of the current literature and highlights the need for further research to better delineate underlying mechanisms along with strategies for prevention and treatment.

REFERENCES

1. Zuehlke RL. Erythematous eruption of the palms and soles associated with mitotane therapy. Dermatologica 1974;148:90-2.
2. Alley E, Green R, Schuchter L. Cutaneous toxicities of cancer therapy. Curr Opin Oncol 2002;14:212-6.
3. Degen A, Alter M, Schenck F, Satzger I, Völker B, Kapp A, et al. The hand-foot-syndrome associated with medical tumor therapy—classification and management. J Dtsch Dermatol Ges 2010;8:652-61.
4. Nagore E, Insa A, Sanmartin O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome: incidence, recognition and management. Am J Clin Dermatol 2000;1:225-34.
5. Lipworth AD, Robert C, Zhu AX. Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. Oncology 2009;77:257-71.
6. Dranitsaris G, Vincent MD, Yu J, Huang L, Fang F, Lacouture ME. Development and validation of a prediction index for hand-foot skin reaction in cancer patients receiving sorafenib. Ann Oncol 2012;23:2103-8.
7. Baack BR, Burgdorf WH. Chemotherapy-induced acral erythema. J Am Acad Dermatol 1991;24:457-61.
8. Bolognia JL, Cooper DL, Glusac EJ. Toxic erythema of chemotherapy: a useful clinical term. J Am Acad Dermatol 2008;59:524-9.
9. Farr KP, Safwat A. Palmar-plantar erythrodysesthesia associated with chemotherapy and its treatment. Case Rep Oncol 2011;4:229-35.
10. Stubblefield MD, Custodio CM, Kaufmann P, Dickler MN. Small-fiber neuropathy associated with capecitabine (Xeloda)-induced hand-foot syndrome: a case report. J Clin Neuromuscul Dis 2006;7:128-32.
11. Sibaud V, Dalenc F, Chevreau C, Roché H, Delord JP, Mourey L, et al. HFS-14, a specific quality of life scale developed for patients suffering from hand-foot syndrome. Oncologist 2011;16:1469-78.
12. Hoesly FJ, Baker SG, Gunawardane ND, Cotliar JA. Capecitabine-induced hand-foot syndrome complicated by pseudomonal superinfection resulting in bacterial sepsis and death: case report and review of the literature. Arch Dermatol 2011;147:1418-23.
13. von Moos R, Thuerlimann BJ, Aapro M, Rayson D, Harrold K, Sehouli J, et al. Pegylated liposomal doxorubicin-associated hand-foot syndrome: recommendations of an international panel of experts. Eur J Cancer 2008;44:781-90.
14. National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009 NIH publication # 09-7473.
15. Azuma Y, Hata K, Sai K, Udagawa R, Hirakawa A, Tohkin M, et al. Significant association between hand-foot syndrome and efficacy of capecitabine in patients with metastatic breast cancer. Biol Pharm Bull 2012;35:717-24.
16. Wong M, Choo SP, Tan EH. Travel warning with capecitabine. Ann Oncol 2009;20:1281.

17. Martschick A, Sehouli J, Patzelt A, Richter H, Jacobi U, Oskay-Ozcelik G, et al. The pathogenetic mechanism of anthracycline-induced palmar-plantar erythrodysesthesia. Anticancer Res 2009;29:2307-13.
18. Yokomichi N, Nagasawa T, Coler-Reilly A, Suzuki H, Kubota Y, Yoshioka R, et al. Pathogenesis of hand-foot syndrome induced by PEG-modified liposomal doxorubicin. Hum Cell 2013;26:8-18.
19. Azad NS, Aragon-Ching JB, Dahut WL, Gutierrez M, Figg WD, Jain L, et al. Hand-foot skin reaction increases with cumulative sorafenib dose and with combination anti-vascular endothelial growth factor therapy. Clin Cancer Res 2009;15:1411-6.
20. Milano G, Etienne-Grimaldi MC, Mari M, Lassalle S, Formento JL, Francoual M, et al. Candidate mechanisms for capecitabine-related hand-foot syndrome. Br J Clin Pharmacol 2008;66:88-95.
21. Caronia D, Martin M, Sastre J, de la Torre J, García-Sáenz JA, Alonso MR, et al. A polymorphism in the cytidine deaminase promoter predicts severe capecitabine-induced hand-foot syndrome. Clin Cancer Res 2011;17:2006-13.
22. Mattison LK, Fourie J, Desmond RA, Modak A, Saif MW, Diasio RB. Increased prevalence of dihydropyrimidine dehydrogenase deficiency in African-Americans compared with Caucasians. Clin Cancer Res 2006;12:5491-5.
23. Saif MW. Capecitabine and hand-foot syndrome. Expert Opin Drug Saf 2011;10:159-69.
24. Fischer A, Wu S, Ho AL, Lacouture ME. The risk of hand-foot skin reaction to axitinib, a novel VEGF inhibitor: a systematic review of literature and meta-analysis. Invest New Drugs 2013;31:787-97.
25. Ren Z, Zhu K, Kang H, Lu M, Qu Z, Lu L, et al. A randomized controlled phase II study of the prophylactic effect of urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced hepatocellular carcinoma [abstract]. J Clin Oncol 2012 (suppl).
26. Ruhstaller T, Ribi K, Sun H, Schmitz S, Borner M, Winkler A, et al. Prevention of palmoplantar erythrodysesthesia (PPE) with an antiperspirant in breast cancer patients treated with pegylated liposomal doxorubicin (PLD), a placebo-controlled, double blinded, phase III trial (SAKK 92/08) [abstract]. J Clin Oncol 2012 (suppl).
27. Mangili G, Petrone M, Gentile C, De Marzi P, Vigano R, Rabaiotti E. Prevention strategies in palmar-plantar erythrodysesthesia onset: the role of regional cooling. Gynecol Oncol 2008;108:332-5.
28. Scotté F, Banu E, Medioni J, Levy E, Ebenezer C, Marsan S, et al. Matched case-control phase 2 study to evaluate the use of a frozen sock to prevent docetaxel-induced onycholysis and cutaneous toxicity of the foot. Cancer 2008;112:1625-31.
29. Scotte F, Tourani JM, Banu E, Peyromaure M, Levy E, Marsan S, et al. Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. J Clin Oncol 2005;23:4424-9.
30. Zhang RX, Wu XJ, Wan DS, Lu ZH, Kong LH, Pan ZZ, et al. Celecoxib can prevent capecitabine-related hand-foot syndrome in stage II and III colorectal cancer patients: result of a single-center, prospective randomized phase III trial. Ann Oncol 2012;23:1348-53.
31. Corrie PG, Bulusu R, Wilson CB, Armstrong G, Bond S, Hardy R, et al. A randomized study evaluating the use of pyridoxine to avoid capecitabine dose modifications. Br J Cancer 2012;107:585-7.
32. Kang YK, Lee SS, Yoon DH, Lee SY, Chun YJ, Kim MS, et al. Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: results of a randomized, double-blind, placebo-controlled study. J Clin Oncol 2010;28:3824-9.
33. von Gruenigen V, Frasure H, Fusco N, DeBernardo R, Eldermire E, Eaton S, et al. A double-blind, randomized trial of pyridoxine versus placebo for the prevention of pegylated liposomal doxorubicin-related hand-foot syndrome in gynecologic oncology patients. Cancer 2010;116:4735-43.
34. Li JR, Yang CR, Cheng CL, Ho HC, Chiu KY, Su CK, et al. Efficacy of a protocol including heparin ointment for treatment of multikinase inhibitor-induced hand-foot skin reactions. Support Care Cancer 2013;21:907-11.
35. Childress J, Lokich J. Cutaneous hand and foot toxicity associated with cancer chemotherapy. Am J Clin Oncol 2003;26:435-6.
36. Minisini AM, Tosti A, Sobrero AF, Mansutti M, Piraccini BM, Sacco C, et al. Taxane-induced nail changes: incidence, clinical presentation and outcome. Ann Oncol 2003;14:333-7.
37. Winther D, Saunte DM, Knap M, Haahr V, Jensen AB. Nail changes due to docetaxel—a neglected side effect and nuisance for the patient. Support Care Cancer 2007;15:1191-7.
38. Wasner G, Hilpert F, Baron R, Pfisterer J. Clinical picture: nail changes secondary to docetaxel. Lancet 2001;357:910.
39. Borecky DJ, Stephenson JJ, Keeling JH, Vukelja SJ. Idarubicin-induced pigmentary changes of the nails. Cutis 1997;59:203-4.
40. Giacobetti R, Esterly NB, Morgan ER. Nail hyperpigmentation secondary to therapy with doxorubicin. Am J Dis Child 1981;135:317-8.
41. Peuvrel L, Bachmeyer C, Reguiai Z, Bachet JB, André T, Bensadoun RJ, et al. Semiology of skin toxicity associated with epidermal growth factor receptor (EGFR) inhibitors. Support Care Cancer 2012;20:909-21.
42. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722-31.
43. Balagula Y, Wu S, Su X, Feldman DR, Lacouture ME. The risk of hand foot skin reaction to pazopanib, a novel multikinase inhibitor: a systematic review of literature and meta-analysis. Invest New Drugs 2012;30:1773-81.
44. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicenter, randomized, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.
45. Boussemart L, Routier E, Mateus C, Opletalova K, Sebille G, Kamsu-Kom N, et al. Prospective study of cutaneous side-effects associated with the BRAF inhibitor vemurafenib: a study of 42 patients. Ann Oncol 2013;24:1691-7.