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