

# Capecitabine-Induced Hand-Foot Syndrome Complicated by Pseudomonal Superinfection Resulting in Bacterial Sepsis and Death

## Case Report and Review of the Literature

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**Background:** Hand-foot syndrome (HFS) is a relatively common dermatologic toxic reaction to certain anticancer therapies. Although not life-threatening, this complication can reduce patient quality of life. Dose modification of the inciting agent serves as the most effective management of HFS, although a variety of anecdotal reports suggest that other agents may also be efficacious. We present the first reported case of fatal HFS (to our knowledge) and provide a comprehensive review of this condition.

**Observations:** A 61-year-old woman with metastatic breast cancer who was undergoing treatment with capecitabine developed erythema, fissuring, and erosions

over both hands and feet, consistent with HFS. Pseudomonal superinfection leading to bacterial sepsis and death rapidly ensued.

**Conclusions:** Although HFS is widely regarded as a non-life-threatening toxic reaction to cancer treatment, our case demonstrates that infectious complications of this condition can prove fatal. Prevention, early recognition, and implementation of various management strategies for HFS and its infectious complications are important in optimizing patient quality of life and minimizing unfavorable outcomes.

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**H**AND-FOOT SYNDROME (HFS), also known as palmo-plantar erythrodysesthesia or acral erythema, is a localized skin eruption associated with the initiation of therapy with certain chemotherapeutic agents.<sup>1,2</sup> It is considered a subtype of toxic erythema of chemotherapy, a term that encompasses a broad spectrum of anticancer medication-induced cutaneous reactions.<sup>3</sup> The clinical presentation of HFS is characterized by a prodrome of dysesthesia followed by the development of painful, symmetrical edema and erythema of the palms, digits, and soles that may evolve into blisters and erosions.<sup>4,5</sup> Although HFS has the potential to substantially affect quality of life, it is not recognized as a life-threatening condition<sup>6</sup> and rarely leads to hospitalization.<sup>7</sup> We report a case of HFS that was complicated by pseudomonal superinfection resulting in bacterial sepsis and death and provide a review of the HFS literature focusing on the management of this condition. To our knowledge, this is the first reported case of fatal HFS.

## REPORT OF A CASE

A 61-year-old woman with metastatic breast cancer who had been treated with oral lapatinib (1250 mg/d) and capecitabine (1250 mg/m<sup>2</sup> twice daily) over the previous 4 years presented with a 3-week history of painful erosions and ulcerations of her hands and feet along with bilateral lower extremity swelling. She denied any other symptoms, and her medical history was otherwise unremarkable. Her other medications included fulvestrant and pamidronate. During the previous 3 years, she had experienced intermittent flares of grades 1 and 2 HFS due to capecitabine use. Her symptoms were successfully treated with fluocinonide cream, 0.05%, and ammonium lactate cream, 12%, although she had not been treating her skin with topical agents before her appointment. Physical examination revealed erythema and fissuring over both palms and circumferential erosions involving her right thumb and left middle finger (**Figure 1A**). She had bilateral lower extremity edema as well as erythema and erosions over both soles and the web spaces of

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**Figure 1.** Diffuse erythema and fissuring of the palms with focal erosions on the fingers (A) and the right foot (B).

her feet (Figure 1B). A diagnosis of grade 3 HFS was made according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0, and capecitabine therapy was discontinued. Treatment with mupirocin ointment, econazole cream, and oral ciprofloxacin was initiated because of a clinical suspicion of cutaneous superinfection and the patient's history of *Pseudomonas aeruginosa* paronychia of her left great toe 7 months earlier. Wound cultures obtained from both the hands and the feet during the initial evaluation yielded pansensitive *P aeruginosa*. The patient was contacted to discuss the culture results, and at that time she reported the onset of malaise and scleral icterus. She was instructed to go to the emergency department, and on arrival she was found to be in septic shock, with acute kidney injury and hepatic dysfunction, resulting in coagulopathy. Pseudomonal superinfection of the patient's HFS was considered the most likely source of sepsis, although the results of blood cultures remained negative. Despite broad-spectrum intravenous antibiotic therapy and aggressive resuscitative measures, she died less than 24 hours later.

#### COMMENT

It is well known that HFS can have a dramatic impact on quality of life and can necessitate dose modification or discontinuation of cancer therapy; however, it is not considered a dangerous condition in and of itself. There have been a few reports of HFS leading to tissue necrosis and requiring amputation,<sup>8,9</sup> but we report the first death (to our knowledge) due to complications of HFS. In a study evaluating weekly docetaxel plus capecitabine therapy for advanced non-small cell lung cancer, there was 1 reported death due to sepsis as a result

of a subungual abscess that formed after onycholysis; however, HFS was not identified as a contributing factor.<sup>10</sup> Our case demonstrates the life-threatening potential of HFS and highlights the importance of its prevention, prompt recognition, and appropriate management.

The NCI grading scale is commonly used to rate HFS (categorized as palmar-plantar erythrodysesthesia syndrome and described as redness, marked discomfort, swelling, and tingling of the palms and/or soles) severity on a scale of 1 to 3 (**Table 1**).<sup>11</sup> Almost 80% of patients with HFS present with NCI grade 1 toxicity.<sup>4</sup>

The most common causes of HFS include capecitabine, cytosine arabinoside (cytarabine), doxorubicin, 5-fluorouracil, and the taxanes.<sup>3,4</sup> Our patient developed HFS as a result of capecitabine therapy, which causes this condition in 28% to 74% of treated patients.<sup>12</sup> Capecitabine is a prodrug that is enzymatically converted to 5-fluorouracil within tumor cells. The onset of HFS can range from within 24 hours to 10 months of the initiation of chemotherapy, with shorter time to onset and greater severity being associated with higher peak plasma levels and total cumulative dose.<sup>2,4,12</sup> Capecitabine-related HFS usually appears within the first 3 cycles of treatment<sup>13</sup> and commonly worsens in subsequent cycles,<sup>1</sup> as occurred in this case. Our patient was also taking lapatinib, a dual inhibitor of epidermal growth factor receptor and human epidermal growth factor receptor 2; however, this drug is most commonly associated with the development of skin eruptions that are localized to the trunk.<sup>14</sup> In one review, fewer than 1% of the 926 patients who were receiving lapatinib monotherapy developed HFS.<sup>14</sup> Of interest, multikinase inhibitors such as sorafenib and sunitinib also cause a similar cutaneous toxic reaction

**Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 Grading of Hand-Foot Syndrome<sup>a</sup>**

| Adverse Event Term  | Grade  |  |   |
|---|--|--|---|
|   | 1  | 2  | 3   |
| Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) | Minimal skin changes (erythema, edema, or hyperkeratosis) without pain | Skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting instrumental ADL <sup>a</sup> | Severe skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting self-care ADL |

Abbreviation: ADL, activities of daily living.

<sup>a</sup>Data from the National Cancer Institute.<sup>11</sup>

**Table 2. Comparison of Hand-Foot Syndrome and Hand-Foot-Skin Reaction**

| Variable                    | Hand-Foot Syndrome  | Hand-Foot-Skin Reaction   |
|-----------------------------|---|---|
| Frequently implicated drugs | Capecitabine, cytarabine, doxorubicin, 5-fluorouracil, taxanes <sup>4</sup>   | Sorafenib, sunitinib (multikinase inhibitors) <sup>6</sup>  |
| Histopathologic findings    | Hyperkeratosis, parakeratosis<br>Spongiosis<br>Focal vacuolization and pyknosis in basal cell layer<br>Dermis with ectatic blood vessels, mild perivascular lymphohistiocytic infiltrate <sup>4,15,16</sup> | Hyperkeratosis, parakeratosis<br>Well-defined horizontal zone of keratinocyte necrosis and discohesion (distinct from basal vacuolization or scattered pyknotic cells often seen in hand-foot syndrome)<br>Dermis with ectatic blood vessels, mild perivascular lymphohistiocytic infiltrate with or without eosinophils in dermis <sup>15,17</sup> |
| Clinical appearance         | Edema, erythema, and scale with or without blisters and erosions <sup>4,5</sup>   | Scale with surrounding erythema progressing to hyperkeratosis with or without blisters and erosions <sup>6,18</sup>   |
| Distribution                | Symmetrical and diffuse over the palms, soles, and digits <sup>4,5</sup>  | Localized to pressure-bearing or flexural areas on palms and soles <sup>6</sup>   |
| Onset                       | 24 h to 10 mo after initiation of therapy <sup>2,4</sup> (median, 79 d <sup>12</sup> )  | Within 45 d of initiation of therapy in >95% of cases <sup>6</sup>  |

termed *hand-foot-skin reaction*. This entity has several distinguishing features (**Table 2**), including localized hyperkeratosis with surrounding erythema over flexural and pressure-bearing areas (**Figure 2A**),<sup>6,19</sup> as opposed to the confluent erythema and desquamation on acral sites that are seen with HFS (Figure 2B). Specifically, the lesions of hand-foot-skin reaction tend to affect the fingertips, heels, and skin over the metatarsophalangeal, metacarpophalangeal, and interphalangeal joints (Figure 2C).<sup>6</sup> Some of the histologic findings of hand-foot-skin reaction also differ from those of HFS (Table 2). Both conditions tend to exhibit hyperkeratosis, parakeratosis, and ectatic dermal blood vessels with perivascular lymphohistiocytic infiltrates.<sup>4,15,16</sup> Hand-foot-skin reaction, however, frequently has a well-defined horizontal zone of keratinocyte necrosis and discohesion that is distinct from the basal vacuolization or scattered pyknotic cells that are often seen in HFS.<sup>15,17</sup>

The pathogenesis of HFS is unknown, although a direct toxic effect of chemotherapeutic agents on the skin is considered the most likely mechanism.<sup>4,17</sup> Some authors suggest that these medications cause local damage after accumulating within eccrine sweat ducts, helping to explain the typical anatomical distribution of the disease.<sup>5,20</sup> Others believe that there may be overexpression of cyclooxygenase 2 in the skin as a result of chemotherapy, with resultant inflammation.<sup>1,5</sup> Mechanical pressure on the hands and feet occurring during day-to-

day activities may also play a primary role through capillary damage, increasing toxic injury to the skin.<sup>2</sup> Thymidine phosphorylase plays a large role in the activation of capecitabine and is more prevalent on the palms of the hands than on the dorsal surfaces. Therefore, the anatomical location of this enzyme may contribute to higher concentrations of toxic capecitabine metabolites in these areas, resulting in local tissue damage.<sup>21</sup>

The only proven effective treatment for HFS is dose reduction or discontinuation of therapy with the causative medication, depending on HFS severity, with resolution usually occurring within 2 weeks of discontinuation.<sup>4</sup> In patients taking capecitabine, treatment should be interrupted for NCI grade 2 or 3 HFS until the grade has improved to 1 or 0. After the first appearance of grade 3 HFS or after the second appearance of grade 2 HFS, dose reduction should occur on reinitiation of treatment, as described in the capecitabine package insert ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2005/020896s016lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020896s016lbl.pdf)).

Several interventions, both nonpharmacologic and pharmacologic, have been implemented, with varying success, in the prophylaxis and treatment of HFS. Patients should be counseled on strategies to reduce mechanical trauma to the skin, such as avoidance of tight-fitting garments, using gel inserts and cotton socks for the feet, and avoiding excess heat exposure.<sup>6,12,22</sup> Minimizing edema through elevation of the



**Figure 2.** Hand-foot-skin reaction (A and C) and hand-foot syndrome (B). A, Hand-foot-skin reaction characterized by localized hyperkeratosis with surrounding erythema over pressure-bearing areas. B, Hand-foot syndrome distinguished from hand-foot-skin reaction by more diffuse and confluent erythema over the plantar surface of the foot. C, Localized hyperkeratosis with a surrounding halo of erythema overlying the metatarsophalangeal joints, typical of hand-foot-skin reaction.

hands and feet may be helpful.<sup>23</sup> Regional cooling with ice packs has been reported to be useful in HFS prevention, possibly by reducing toxic metabolite levels in cooled areas through vasoconstrictive effects.<sup>24</sup> For patients taking capecitabine, the practitioner should ensure that the dosage is adjusted appropriately if the creatinine clearance is less than 50 mL/min to avoid drug accumulation, which can result in increased risk of HFS.<sup>12,25</sup>

Reported management strategies for HFS due to capecitabine- and 5-fluorouracil-containing regimens are summarized in **Table 3**. Routine application of topical emollients such as petrolatum-lanolin-based ointments<sup>26</sup> and udder cream can be implemented in both the prevention and the treatment of HFS.<sup>7,23</sup> Some authors have found treatment with urea cream to be effective,<sup>27</sup> although the percentage of patients with moderate or severe HFS symptoms was not decreased by twice daily urea-lactic acid cream in a randomized, double-blind, placebo-controlled phase 3 trial evaluating 137 patients who were receiving capecitabine.<sup>37</sup> Topical anesthetics and cold compresses can be useful for symptomatic control.<sup>12,23</sup>

Treatment with systemic medications, including pyridoxine,<sup>28-33</sup> celecoxib,<sup>34</sup> vitamin E,<sup>7</sup> and nicotine patches,<sup>35</sup> may be tried alone or in conjunction with topical therapies (Table 3). Notably, a randomized, double-blind phase 3 study of 360 patients who were receiving capecitabine did not show any benefit from the use of pyridoxine (200 mg/d) in the prophylaxis or treatment of HFS.<sup>38</sup> Although there is a lack of data to strongly support its use, pyridoxine is appealing given its favorable safety profile and the lack of other proven options. Lin et al<sup>34</sup> found that the use of celecoxib in patients who were taking capecitabine for metastatic colorectal cancer was associated with a reduced incidence of HFS as well as an increase in

tumor response. Nicotine patches<sup>35</sup> may help prevent HFS, perhaps through their vasoconstrictive effects.

Adequate control of our patient's HFS was achieved over the course of more than 2 years with the use of high-potency topical steroids and keratolytic creams until she developed grade 3 HFS, requiring capecitabine dose interruption. It is unclear whether our patient would have been able to prevent the onset and severity of HFS had she been using the topical agents before her presentation at our clinic.

There is a paucity of data describing the incidence and best approach to the management of HFS superinfection. Infections complicating HFS are most commonly caused by *Staphylococcus* or gram-negative organisms.<sup>1</sup> In contrast to our case, however, these infections rarely result in significant clinical deterioration.<sup>1</sup> Nonetheless, every effort should be made to prevent infectious complications through proper wound care and minimizing loss of skin integrity using the management strategies described herein. Patients should be educated about the symptoms of HFS so that the syndrome can be recognized and treated in a timely manner. This recognition is especially important for patients who are taking oral medications such as capecitabine in an outpatient setting as opposed to medications administered at infusion centers, where nurses and physicians may be available to examine patients with early HFS. Our patient presented for management of her HFS 3 weeks after it developed. Minimizing time between the onset of HFS and evaluation will help prevent potentially serious complications and preserve quality of life.

Cutaneous superinfection is suggested clinically by the development of yellow crust, frank purulence, characteristic odor, or systemic signs such as fever and an elevated white blood cell count. In such cases, infected-

**Table 3. Reported Interventions for Hand-Foot Syndrome (HFS) Caused by Capecitabine and 5-Fluorouracil Therapy**

| Source                                    | Inciting Drug(s)  | No. of Patients                                | Treatment Regimen   | Outcome  | Level of Evidence <sup>a</sup> /<br>Recommendation Grade <sup>b</sup> |
|---|---|--|---|--|---|
| <b>Topical Agents</b>                     |   |  |   |  |   |
| Chin et al, <sup>26</sup> 2001            | Doxorubicin, capecitabine, troxacitabine, or 5-fluorouracil | 13 (Capecitabine in 4 and 5-fluorouracil in 1) | Petroleum-lanolin-based ointment w/hydroxyquinoline (udder cream) TID           | Improvement in 12 of 13 patients   | 4/D   |
| Pendharkar and Goyal, <sup>27</sup> 2004  | Capecitabine  | 13   | Urea cream, 12.5%   | Improvement in 13 of 13 patients   | 4/D   |
| <b>Systemic Agents</b>                    |   |  |   |  |   |
| Yoshimoto et al, <sup>28</sup> 2010       | Capecitabine  | 38   | Pyridoxine, 60 mg/d (prophylaxis)   | HFS developed in 52.6% (n = 20) taking pyridoxine compared with 82.5% (historical data) not taking pyridoxine  | 3/C   |
| Beveridge et al, <sup>29</sup> 1990       | 5-Fluorouracil  | 26   | Pyridoxine, 50 mg BID   | Improvement in 5 of 13 patients and deterioration in 6 of 13 patients receiving pyridoxine compared with 0 of 13 and 12 of 13 not receiving pyridoxine, respectively | 3/C   |
| Mortimer and Anderson, <sup>30</sup> 1990 | 5-Fluorouracil  | 11   | Pyridoxine, 150 mg/d  | Improvement in 11 of 11 patients   | 4/C   |
| Fabian et al, <sup>31</sup> 1990          | 5-Fluorouracil  | 5  | Pyridoxine, 50 or 150 mg/d  | Resolution in 4 of 5 patients  | 4/C   |
| Mortimer et al, <sup>32</sup> 2003        | Capecitabine  | 99   | Pyridoxine (mean dose, 235 mg/d; range, 50-800 mg/d)                            | Improvement in 65% of patients receiving pyridoxine compared with 12% not receiving pyridoxine   | 3/C   |
| Chalermchai et al, <sup>33</sup> 2010     | Capecitabine  | 56   | Pyridoxine, 200 or 400 mg/d (prophylaxis)                                       | 20 of 28 Patients receiving a low dose and 11 of 28 patients receiving a high dose developed HFS   | 2/C   |
| Lin et al, <sup>34</sup> 2002             | Capecitabine  | 67   | Celecoxib (prophylaxis, dosage not available)                                   | 13% of Patients taking celecoxib had >grade 1 HFS compared with 34% of patients not taking celecoxib   | 3/C   |
| Kingsley, <sup>35</sup> 1994              | 5-Fluorouracil  | 1  | Nicotine patch, 7.0 mg (administered 1 h before and removed 1 h after infusion) | Resolution without recurrence with subsequent cycles   | 5/D   |
| Kara et al, <sup>7</sup> 2006             | Docetaxel-capecitabine                                      | 5  | Vitamin E, 300 mg/d   | Improvement or resolution in 5 of 5 patients   | 4/D   |

Abbreviations: BID, twice daily; TID, 3 times daily.

<sup>a</sup>Level 1 includes meta-analyses of randomized controlled trials and randomized trials of high power; level 2, randomized trials of lower power; level 3, nonrandomized trials (cohort or case-controlled series); level 4, descriptive and case studies; and level 5, case reports and clinical examples.<sup>36</sup>

<sup>b</sup>Grade A indicates level 1 evidence or consistent findings from multiple studies of levels 2, 3, or 4; B, levels 2, 3, or 4 evidence with generally consistent findings; C, similar to grade B but with inconsistencies; and D, little or no evidence.<sup>36</sup>

appearing areas should be swabbed, and the swabs should be sent for culture and sensitivity analysis. Our patient decompensated rapidly because of bacterial sepsis, resulting in death, despite the initiation of appropriate antibiotic therapy promptly after infection was suspected. Oral antibiotic therapy should therefore not be delayed pending culture results when superinfection is suspected, and we suggest providing coverage against *Staphylococcus aureus* and gram-negative organisms, including *Pseudomonas* species, until culture results are available. If the patient has a history of superinfection, past culture data may indicate the most likely causative pathogens and their sensitivities. The patient should be assessed for methicillin-resistant *S aureus* risk factors and treated appropriately for this organism if necessary. If there

is a suspicion of concomitant dermatophyte infection, the use of topical antifungal agents may also be beneficial. There is no currently accepted, evidence-based role for prophylactic topical or systemic antibiotic therapy for HFS of any severity.

In conclusion, HFS should not be merely considered a threat to patient quality of life or as an obstacle that may interfere with cancer therapy. Infectious complications of this condition, although relatively uncommon, can cause significant patient morbidity, with the potential to be fatal in rare instances. Implementing a variety of HFS management strategies, providing good patient education, and appropriately treating HFS superinfection are all important components in ensuring favorable patient outcomes.

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