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HAND-FOOT SYNDROME
A COMMON SIDE-EFFECT OF CHEMOTHERAPY

Hand-foot syndrome is a relatively common side-effect of patients undergoing chemotherapy, particularly those taking cytarabine, doxorubicin and 5-fluorouracil (including its prodrug, capecitabine). The condition ranges from paraesthesia affecting the palms and soles to painful blistering and fissures. Patients with this condition may present in the podiatry clinic seeking advice or treatment. Here, Ivan Bristow presents a case of a 70-year-old woman with metastatic breast cancer undergoing chemotherapy with capecitabine and discusses the background to this unusual condition, rarely documented within podiatry texts

CASE

A 70-year-old woman presented to the podiatry clinic with a history of soreness, blistering and fissuring affecting both plantar surfaces of her feet (Figure 1). Medically, she had been diagnosed with breast carcinoma three years previously. Following a recent scan, she was discovered to have developed advanced metastatic disease and had been prescribed a course of capecitabine. Within a few days of taking the drug she developed erythema, paraesthesia and shortly afterwards fissuring of her hands and feet. Blisters appeared around both halluces (Figure 2). Based on history and assessment, a diagnosis of hand-foot syndrome (HFS) was made.

WHAT IS HFS?

HFS is a common condition that may develop in cancer patients undergoing chemotherapy. The condition may develop within a day or sometimes after a few weeks of treatment. Initially, patients typically complain of tingling or burning in their hands and feet. They may also describe sensations such as walking on hot sand or gravel.[1] Shortly afterwards, the palmo-plantar surfaces develop a symmetrical erythema accompanied by oedema, which may limit movements of the digits. In time, the skin may develop scale and fissures. In severe cases, it may progress to blistering and skin ulceration.

Extreme symptoms associated with HFS can have an adverse effect on the patient's activity levels and quality of life.[2] The condition is almost exclusively found on the palms and soles, occurring below the line of Wallace, although lesions arising on the dorsa of the hands, face and trunk have been reported.[3] In a small number of cases, some patients may only exhibit limited or no erythema and only a fine scale on the palms and soles.[4] The condition is said to be non-life threatening although reports of digital amputation have been published,[5] and there was one case where a patient with HFS and diabetes died following sepsis secondary to a pseudomonas infection occurring on her feet.[6]

AETIOLOGY

The condition is caused as a side-effect of chemotherapy treatment. HFS was first discussed in 1974 by Zuehlke[7] in patients taking mitotane for adrenal gland tumours, and latterly in 1991 by Baack & Burgdorf,[8] who also observed the condition being caused by other chemotherapy agents, describing the condition as a 'chemically induced acral erythema'.[3] Latterly, the condition has been formally titled 'palmar plantar erythrodysaesthesia (PPE)' as well as HFS.

A range of drugs have been known to cause the condition, including anthracycline antibiotics, cytarabine and docetaxel, but especially 5-fluorouacil and its prodrug, capecitabine.[9] Newer agents such as multikinase inhibitors (MKI), including sorafenib and sunitinib, are also known to provoke the condition[10, 11] although some authors differentiate the condition caused by MKIs as 'Hand-foot skin reaction' on the basis of histological differences, claiming these drugs are more likely to cause hyperkeratosis over pressure points with accompanying erythema rather than a confluent, symmetrical erythema and scale of classic HFS.[6] The appearance of HFS is dose dependent and arises most frequently at peak drug concentration, although the total cumulative dose can also predict its occurrence.[4] Most cases arise within the first or second cycle of treatment, with HFS occurring most severely in the second cycle of chemotherapy.[12]

The incidence of HFS is difficult to determine as no formal work has studied this aspect. However, Nagore *et al*[4] has suggested that 6-64% of patients may develop HFS while undergoing chemotherapy. Walko & Lindley,[13] in their review specifically of 5-fluorouacil and capecitabine patients, reported that 55% of patients developed HFS during chemotherapy, while Chu *et al*[14] reported a rate of nearly 34% in patients receiving sorafenib. The condition is reported to be more common in older patients receiving chemotherapy, particularly women, in those with diabetes and in more active patients.[15]

The exact cause of the condition remains unknown, although several theories have been suggested. Firstly, accumulation of metabolites of the drugs is particularly high in keratinocytes of the palms and soles due to the abundance of the enzyme thymidine phosphorylase in these areas.[16] This can rapidly degrade capecitabine to its metabolites, leading to toxic effects.[9]

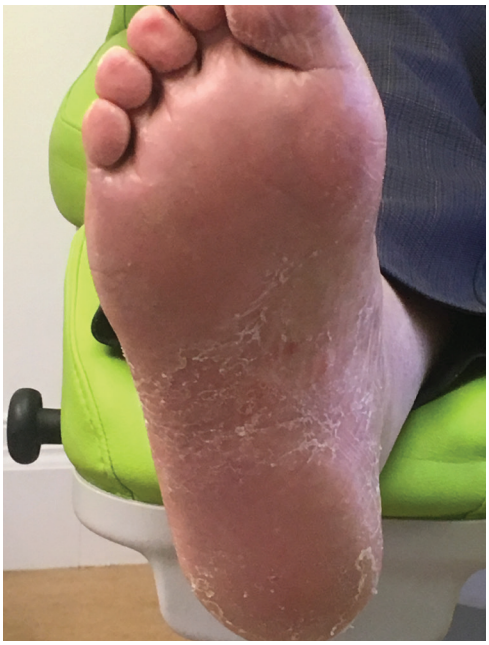
Other theories postulate that cytotoxic drugs are more readily secreted by the eccrine sweat glands, particularly numerous across the palmar and plantar surfaces, causing the skin reaction to occur.[17] Mechanical damage to the plantar surface through activity may lead to minor capillary damage and leakage of metabolites, leading to HFS,[18] potentially explaining why the condition is more prevalent in active patients.

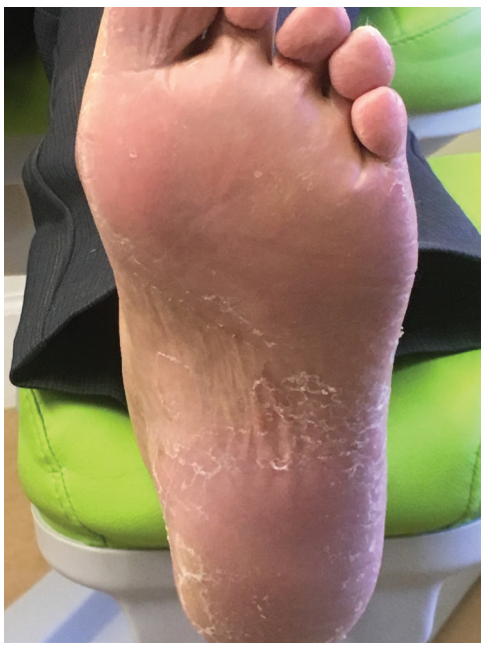
Histological examination of the skin has been undertaken and pathological changes in the tissues can be observed as vacuolation and degeneration of cells within the basal layer and infiltration around blood vessels, with lymphocytes, dermal oedema and degeneration of basal keratinocytes and apoptosis of epidermal keratinocytes.[19]

ASSESSMENT OF HFS

Two grading systems have been proposed for research and clinical purposes. The first is the National Cancer Institute (NCI) Grading of HFS. This is based on three grades (Table 1).

GRADE	FEATURES
1	Minimal skin changes or dermatitis (e.g. erythema, peeling) with altered sensations (e.g. numbness, tingling, burning) but do not interfere with activities of daily living
2	Skin changes present with accompanying pain interfering little with activities of daily living; skin surface remains intact
3	Ulcerative dermatitis or skin changes with severe pain interfering with activities of daily living; tissue breakdown is evident (e.g. peeling, blisters, bleeding, oedema)





ABOVE Table 1. NCI Grading of HFS

LEFT (L-R) Figure 1. Blistering and fissuring affecting both plantar surfaces of her feet
Figure 2. Blisters appeared around both halluces

The second is the World Health Organization's grading system (Table 2).

In addition, a Hand-Foot Skin Reaction and Quality of Life Questionnaire has been developed specifically to measure the impact of the disease.[20]

MANAGEMENT OF HFS

Specific measures to improve the symptoms of HFS have been explored, but ultimately cessation of chemotherapy or dose reduction is the key to resolving the condition. HFS will normally fully resolve 2-3 weeks after treatment has ended. However, during therapy, it has been recommended that if symptom levels reach 2 to 3 on the NCI grading system (Table 1) that treatment with capecitabine be suspended until the HFS resolves, whereupon it can be recommenced without affecting the clinical outcome of treatment.[21] However, this is not true of other chemotherapy agents where suspension of treatment may lead to a decrease in their performance.

Studies have been undertaken to investigate treatments that may reduce the effects of the disease. Firstly, supplemental vitamin B6 (pyridoxine) has been reported to improve symptoms. Subsequent meta-analyses have consistently reported there is no clinical evidence to support this claim.[22, 23] The use of a urea-based cream has also been investigated in one study but showed no benefit over a placebo cream.[24] The use of topical steroids has been proposed[25] but no trials have been undertaken to date.

SUPPORTIVE MEASURES

In addition, a range of supportive measures have been documented. Overall, the evidence for these interventions is variable and, for most, they have not been fully investigated, although small-scale studies and case reports suggest they maybe be a useful adjunct. Suzuki and colleagues[26] in a study of patient compliance for treating HFS, produced a list of suggested measures to reduce the effects of the condition (Table 3).

BELOW (Top to bottom) Table 2. The World Health Organization Grading system for HFS

Table 3. Suggested measures to help improve HFS (adapted from Suzuki *et al.*[26])

GRADE	DEFINITION	CLINICAL LESIONS	HISTOLOGICAL FINDINGS
1	Dysaesthesia/paraesthesia (tingling) of hands and feet	Erythema	Dilated blood vessels of the superficial dermal plexus
2	Discomfort in holding objects and upon walking; painless swelling or erythema	Grade 1 + oedema	-
3	Painful erythema and swelling of palms and soles; periungual erythema and swelling	Grade 2 + fissures	Isolated necrotic keratinocytes in higher layer of the epidermis
4	Desquamation, ulceration, blistering, severe pain	Grade 3 + blisters	Complete epidermal necrosis

INTERVENTION
Applying a moisturiser
Immersing feet in cold water
Keeping skin clean, e.g. washing hands and feet
Avoiding strenuous exercise, e.g. long walks, jogging or aerobics
Wearing soft, comfortable footwear
Not wearing tight-fitting footwear or socks
Refraining from taking hot baths or showers
Avoiding wearing high-heeled shoes since they concentrate pressure on the toes
Avoid direct sunlight (using an umbrella/hat/gloves/long sleeves)
Wearing thick cotton socks

CONCLUSION

Despite its absence within the podiatric literature, HFS is a well-documented side-effect of chemotherapy treatment, particularly with the agents 5-fluoruracil and its prodrug, capecitabine. Symptoms can range from erythema and swelling of the palmo-plantar surfaces to blistering and skin breakdown. Suspension or cessation of treatment is always curative within a week or two but, where this is not an option, supportive measures are suggested. ■

REFERENCES

1. Webster-Gandy JD, How C, Harrold K, Palmar–plantar erythrodysesthesia (PPE): a literature review with commentary on experience in a cancer centre. *Eur J Oncol Nurs* 2007; **11**(3): 238-246.
2. Scheithauer W, Blum J, Coming to grips with hand-foot syndrome. Insights from clinical trials evaluating capecitabine. *Oncology* (Williston Park) 2004; **18**(9): 161-1168, 1173; discussion 1173-1176, 1181-1184.
3. Demircay Z, Gurbuz O, Alpdogan TB, Yucelten D, Alpdogan O, *et al.* Chemotherapy-induced acral erythema in leukemic patients: a report of 15 cases. *Int J Dermatol* 1997; **36**(8): 593-598.
4. Nagore E, Insa A, Sanmartín O, Antineoplastic therapy—induced palmar plantar erythrodysesthesia ('hand-foot') syndrome. *Am J Clin Derm* 2000; **1**(4): 225-234.
5. Guenova E, Weber H, Voykov B, *et al.* Palmar-plantar erythrodysesthesia secondary to sunitinib treatment resulting in necrotic foot syndrome aggravated by background diabetic vascular disease. *Arch Dermatol* 2008; **144**(8): 1081-1082.
6. 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**(12): 1418-1423.
7. Zuehlke RL, Erythematous eruption of the palms and soles associated with mitotane therapy. *Dermatologica* 1974; **148**(2): 90-92.
8. Baack BR, Burgdorf WH, Chemotherapy-induced acral erythema. *J Am Acad Dermatol* 1991; **24**(3): 457-61.
9. Do JE, Kim YC, Capecitabine-induced diffuse palmoplantar keratoderma: is it a sequential event of hand–foot syndrome? *Clin Exp Dermatol* 2007; **32**(5): 519-521.
10. Lacouture ME, Reilly LM, Gerami P, Guitart J, Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. *Ann Oncol* 2008; **19**(11): 1955-1961.
11. Nakamura M, Miyachi Y. Sunitinib-induced subungual splinter haemorrhage and acral erythema. *Eur J Dermatol* 2008; **18**(3): 344-345.
12. Abushullaih S, Saad ED, Munsell M, Hoff PM, Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with

capecitabine: a single-institution experience. *Cancer Invest* 2002; **20**(1): 3-10.
13. Walko CM, Lindley C, Capecitabine: a review. *Clin Ther* 2005; **27**(1): 23-44.
14. Chu D, Lacouture ME, Fillos T, Wu S, Risk of hand-foot skin reaction with sorafenib: a systematic review and meta-analysis. *Acta Oncol* 2008; **47**(2): 176-186.
15. Yokokawa T, Kawakami K, Mae Y, Sugita K, Watanabe H, *et al*. Risk factors exacerbating hand-foot skin reaction induced by capecitabine plus oxaliplatin with or without bevacizumab therapy. *Ann Pharmacother* 2015; **49**(10): 1120-1124.
16. Asgari MM, Haggerty JG, McNiff JM, Milstone LM, Schwartz PM, Expression and localization of thymidine phosphorylase/platelet-derived endothelial cell growth factor in skin and cutaneous tumors. *J Cutan Pathol* 1999; **26**(6): 287-294.
17. Mrozek-Orlowski ME, Frye DK, Sanborn HM, Capecitabine: nursing implications of a new oral chemotherapeutic agent. *Oncol Nurs Forum* 1999; **26**(4): 753-762.
18. Lipworth AD, Robert C, Zhu AX, Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology* 2009; **77**(5): 257-271.
19. Lou Y, Wang Q, Zheng J, Hu H, Liu L, *et al*. Possible pathways of capecitabine-induced hand-foot syndrome. *Chem Res Toxicol* 2016; **29**(10): 1591-1601.
20. Anderson RT, Keating KN, Doll HA, Camacho F, The Hand-Foot Skin Reaction and Quality of Life Questionnaire: an assessment tool for oncology. *Oncologist* 2015; **20**(7): 831-838.
21. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, *et al*. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999; **17**(2): 485-493.
22. Chen M, Zhang L, Wang Q, Shen J, Pyridoxine for prevention of hand-foot syndrome caused by chemotherapy: a systematic review. *PLoS ONE* 2013; **8**(8): e72245.
23. Jo SJ, Shin H, Jo S, Kwon O, Myung S-K, Prophylactic and therapeutic efficacy of pyridoxine supplements in the management of hand–foot syndrome during chemotherapy: a meta-analysis. *Clin Exp Dermatol* 2015; **40**(3): 260-270.
24. Wolf SL, Qin R, Menon SP, Rowland KM, Jr, Thomas S, *et al*. Placebo-controlled trial to determine the effectiveness of a urea/lactic acid-based topical keratolytic agent for prevention of capecitabine-induced hand-foot syndrome: North Central Cancer Treatment Group Study N05C5. *J Clin Oncol* 2010; **28**(35): 5182-5187.
25. Brown J, Burck K, Black D, Collins C, Treatment of cytarabine acral erythema with corticosteroids. *J Am Acad Dermatol* 1991; **24**(6 Pt 1): 1023-1025.
26. Suzuki S, Nawata S, Inada Y, Sato D, Kusano J, *et al*. A cross-sectional survey of methods for controling hand-foot syndrome in patients receiving capecitabine treatment. *Mol Clin Oncol* 2018; **9**(4): 443-448.

WWW.FOOT.EXPERT

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The podiatric dermatology blog was created by accident rather than design. As I continued to deliver lectures and speak to podiatrists about foot dermatology it was evident there was a lot of interest but also many unanswered questions. My inbox would be full of questions about courses, requests for diagnoses and patient queries. Many of the queries were the same, for example: Is there a dermatology education group I can join? What dermatology meetings could I attend?

As a result, I set about putting some simple information together on a website in 2015, and in 2016 this was officially launched as the podiatric dermatology blog. Since then the site has grown, with over 1000 subscribers and visitors from across the world. The events calendar and a regular monthly blog feature on dermatological topics remain the most visited areas of the whole site. This is designed to deliver the most up-to-date information in this subject area, which can help podiatrists in everyday practice.

The site is free to subscribe. For a regular update of all things dermatological: **www.foot.expert/subscribe**