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LETTER TO THE EDITOR

Differentiating hand-foot syndrome from tinea in patients receiving chemotherapy

To the Editor,

Hand-foot syndrome (HFS), also known as acral erythema and palmar-plantar erythrodysesthesia, is a common potentially dose-limiting cutaneous toxicity secondary to many chemotherapeutic agents [1]. HFS can begin from 24 hours to 10 months after starting a chemotherapeutic agent [2]. Although HFS is usually a non-life-threatening reaction to antineoplastic agents, it has an impact on a patient's quality of life and often prompts dose modification or discontinuation of a patient's chemotherapy [3–8].

As they also involve the hands and feet, tinea manuum and pedis can be easily mistaken for HFS. Appropriate diagnosis and differentiation between HFS and tinea is important not only for proper treatment, but also to minimize interruption of a patient's chemotherapy. We report three cases of women who developed skin eruptions on the hands and feet while receiving chemotherapy. All were diagnosed with tinea, responded to antifungal therapy, and were able to continue their cancer therapy with minimal or no interruption.

Cases

Case 1

A 53-year-old Caucasian female was diagnosed with metastatic breast cancer. She was treated with a right total

mastectomy, right axillary sentinel lymphadenectomy, and complete right axillary lymph node dissection in October 2011. Postoperatively, she received four cycles of liposomal doxorubicin and cyclophosphamide (AC) chemotherapy and had just completed her first of four cycles of paclitaxel when she was referred to a dermatologist for scaling, pain and pruritus of the hands and feet.

On examination, there were hyperkeratotic, scaly, pruritic plaques on the palmar aspects of her hands. She had cracking and bleeding from areas on the fingers and described pain after applying any topical moisturizer. There were similar plaques on the plantar, medial, and lateral aspects of her feet in a moccasin distribution (Figure 1). A skin scraping stained with potassium hydroxide (KOH) from the foot revealed branching hyphae and a fungal culture was positive for *Trichophyton rubrum*. The patient was treated with terbinafine



Figure 1. Pink scaly plaques in a moccasin distribution on dorsal surface of feet due to tinea pedis before antifungal treatment.

200 mg daily for two weeks, econazole 1% cream twice daily, and moisturizer as needed. She received her remaining cycles of paclitaxel as planned.

After completing the two-week oral dose of systemic antifungal therapy, there was clinical improvement of the patient's tinea pedis and manuum but she continued to have some scaling and erythema of the hands and feet. KOH preparation at this time was once again positive for hyphae. As she had mild elevation in her liver function tests, terbinafine was not restarted. She was treated with econazole 1% cream and urea 40% cream twice daily. Two months after her initial presentation, the patient had significant improvement with just mild scaling on her hands and feet bilaterally.

Case 2

A 47-year-old female with a history of stage III colon cancer with metastases to the pancreas underwent transverse colon resection and distal pancreatectomy in April 2015. After completing five cycles of adjuvant capecitabine chemotherapy, she was referred to a dermatologist in September 2015 for a two-week history of a diffuse itchy rash on her left thigh that spread to the left abdomen. On examination, there were erythematous papules on her abdomen, and bilateral upper extremities. She was started on a two-week trial of topical triamcinolone 0.1% ointment twice daily for contact dermatitis of the left thigh and abdomen.

Follow-up two weeks later showed resolution of the rash on the extremities, but new onset development of scaly plaques with interdigital maceration on both feet diagnosed as HFS by her oncologist (Figure 2). The patient reported that she mistakenly was using the steroid ointment exclusively on her feet. KOH preparation of the feet revealed branching

hyphae. She was treated with topical econazole 1% cream twice daily for tinea pedis, likely worsened by her previous exposure to topical corticosteroids on the feet. Capecitabine was continued without interruption. Triamcinolone was continued as needed for residual dermatitis on the left thigh and abdomen.

Case 3

An 85-year-old female with a history of stage I uterine papillary serous carcinoma underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and tumor debulking in 2007. She received subsequent "sandwich" chemotherapy – adjuvant pelvic radiation administered between combination paclitaxel and carboplatin [9]. In March 2014, she presented with metastatic disease and was started on liposomal doxorubicin in July 2014.

Her first dose was well tolerated, but she developed scale, pruritis, and pain in her hands and feet following her second dose in August 2014. At the time she was referred to a dermatologist, she had elected to skip an infusion of doxorubicin due to these perceived skin side effects. On examination, there were erythematous scaly plaques with fissures on the hands and fingertips. There were similar erythematous scaly annular plaques on the dorsal feet and ankles, along with erythematous papules on the lower legs. The nails appeared thickened and yellow in color (Figure 3). KOH preparation of skin scrapings from the right ankle was positive for branched hyphae. Fungal culture grew *Trichophyton rubrum*. The patient was treated with fluconazole 150 mg weekly for three weeks, and econazole 1% cream twice daily. Doxorubicin treatment was resumed. The patient reported improvement but did not return for follow-up care.



Figure 2. (A) Scaly plaques on the plantar surfaces of both feet. (B) Interdigital maceration due to tinea pedis.



Figure 3. Erythematous scaly plaques due to tinea pedis.

Discussion

These cases demonstrate the importance of dermatologic care in patients with skin problems during cancer treatment. Although both HFS and tinea are self-limited and generally non-life-threatening, they are treated very differently and prompt diagnosis and treatment of cutaneous fungal infections can prevent unnecessary reductions and cessations of cancer therapy.

HFS was first described by Zuehlke [10] in 1974 as a cutaneous reaction observed in a group of patients receiving mitotane for hypernephroma. Since then, HFS has been associated with various chemotherapeutic agents, the most common including capecitabine [2,3], fluorouracil (5-FU) [4], cytarabine [5], liposomal doxorubicin [6], and docetaxel [7,8]. Although the pathogenesis of this cutaneous side effect is still poorly understood, proposed mechanisms include capillary damage leading to drug extravasation and, especially in the case of liposomal doxorubicin, drug accrual in the eccrine sweat ducts of the hands and feet [11]. The typical clinical presentation of HFS includes a prodromal paresthesia followed by painful, symmetrical erythema, scale, and edema of the palms and soles that may evolve into blisters and fissures [11,12].

Tinea is a common superficial fungal infection most often caused by one of three pathogens – *Trichophyton*, *Microsporum*, and *Epidermophyton*. Moccasin-type tinea pedis, which is typical of a *T. rubrum* infection, is characterized by scale, inflammation, and hyperkeratosis that covers the soles and heels of the feet in a pattern that resembles a slipper (as suggested by its name). Tinea manuum, a fungal infection of the hands, presents with erythema, mild scaling, and hyperkeratosis of the palms [13]. Of note, tinea manuum virtually always occurs in a patient who has coexisting tinea pedis,

sometimes only involving the dominant hand in a “2 foot 1 hand” infection.

Dermatophyte infections often affect otherwise healthy individuals – up to 20–25% of the world’s general population has skin mycoses [14]. The incidence of dermatophyte infections in patients undergoing chemotherapy has not been quantified, but as can be expected, people with compromised immune systems are especially susceptible. Diagnosis is based on history and clinical presentation, and confirmed by KOH microscopy of lesion scrapings or nail clippings (depending on the affected anatomical system) and/or fungal cultures. Most tinea infections can be managed with topical antifungal cream, such as azoles (econazole, ketoconazole) and allylamines (terbinafine) [15]. Oral treatment, such as terbinafine, itraconazole, or fluconazole, may be required in patients with persistent or widespread infections.

Physical examination findings that suggest tinea infection rather than HFS include spread outside of the palms and soles, a more erythematous, scaly, advancing border, nail thickening and discoloration suggestive of onychomycosis, and finer, powder-like scale rather than thick peeling of the skin. Maceration of the skin between the toes is another common finding in tinea pedis. When fungal infections are suspected, KOH examinations and/or fungal cultures should be performed.

Conclusion

Chemotherapy can lead to multiple cutaneous side effects, ranging from pigmentary changes to exanthematous eruptions. When patients undergoing chemotherapy present with new onset painful, itchy, erythematous scaling of the hands and/or feet, it is important to consider the diagnosis of dermatophyte infection as well as HFS. Accurate diagnosis is important to guide treatment and also to avoid the unnecessary interruptions in chemotherapy.

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LETTER TO THE EDITOR

Combination chemotherapy with 5-fluorouracil and dacarbazine in advanced medullary thyroid cancer, a possible alternative?

To the Editor,

Medullary thyroid cancer (MTC) is a rare neuroendocrine cancer arising from the parafollicular C cells of the thyroid [1]. For patients with metastatic disease, standard treatment modalities include local treatments (radiofrequency ablation, radiation therapy, embolization) and systemic treatments [chemotherapy and more recently tyrosine kinase inhibitors (TKIs) targeting the RET protein [2,3].

Conventional chemotherapies may still be indicated for TKI non-responders, patients with rapidly progressive tumors or those presenting contraindications for these new drugs. A consensus has not yet been reached for a chemotherapeutic regimen in advanced MTC, as experience has been limited to case reports or case series, with response rates (RR) ranged from 0% to 25% and for periods of up to a few months [4].

Here, we report a series of four cases with rapidly progressive metastatic MTC treated by a combination of an anti-metabolite agent (5-FU) and an alkylating agent (dacarbazine). Unexpected prolonged responses with significant symptomatic improvements occurred in two patients.

Material and methods

Patients and chemotherapy

Four patients with rapidly progressive advanced MTC were treated with 5-FU and dacarbazine between 2011 and 2014.

Chemotherapy was administered every two weeks, except for one patient (every three weeks). The 5-FU dose was 400 mg/m² + 2400 (bolus injection then 2400 mg/m² infused over two days) and the dacarbazine dose was 400 mg/m² (perfused in two hours). Calcium levofolinate (200 mg/m²) was administered before 5-FU. The study was conducted according to Helsinki guidelines and was approved by the ethical committee of our institution.

Efficacy assessment

Serum calcitonin (Ct) was measured by an immunoradiometric method (IRMA; Cisbio International) and serum carcinoembryonic antigen (CEA) was measured by a method of immunochemiluminescence (LOCI, Dimension Vista, Siemens).

We analyzed the tumor responses obtained in accordance with Response Evaluation Criteria In Solid Tumors (RECIST) v1.1.

RET mutation analysis

Tumor DNA was isolated using the EPICENTER Tissue DNA extraction kit (Tebu Bio). RET gene mutations were analyzed by PCR and sequencing.

O⁶-methylguanine-DNA methyltransferase Status

As previously described [5], O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was studied using methyl-specific PCR and pyrosequencing, performed using a PyroMark Q96 MGMT kit (Qiagen, Courtaboeuf, France) on a PSQTM96 MA system (Biotage, Uppsala, Sweden).

Results

Before treatment, all patients had a rapidly progressive metastatic disease (time of tumor evolution inferior or equal to