Photo Vignette

Adverse dermatologic effects of erdafitinib in a patient with metastatic urothelial carcinoma

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Abstract

Erdafitinib is a fibroblast growth factor receptor 1–4 inhibitor used for locally advanced or metastatic urothelial carcinoma in patients who have experienced disease progression after at least 1 prior systemic therapy. Various cutaneous side effects of erdafitinib have been reported, most commonly stomatitis and nail changes such as onycholysis, nail dystrophy, and paronychia. However, onychomadesis is a rarer nail toxicity that can cause significant discomfort and may necessitate treatment interruption. We present the case of a 61-year-old White man with metastatic urothelial carcinoma treated with 8 mg of erdafitinib daily who developed diffuse onychomadesis within a few months of initiating therapy. Awareness of the potential cutaneous side effects of erdafitinib and timely referral for specialty dermatologic care are important to allow treatment continuation.

Introduction

Erdafitinib is a fibroblast growth factor receptor (FGFR) 1–4 inhibitor that was recently FDA-approved for the treatment of adults with locally advanced or metastatic urothelial carcinoma.[1] It is used in patients with susceptible genetic alterations in FGFR2 or FGFR3 who have disease progression on or after at least 1 prior systemic therapy.[1] Among all cancer types, 7.1% harbor FGFR pathway mutations.[2] Alterations in FGFR genes result in constitutive activation of downstream pathways, with urothelial carcinoma being the most common cancer to exhibit this process.[3,4] Erdafitinib inhibits FGFR to halt unregulated cell proliferation, cell survival, and angiogenesis.[2] Many adverse effects of erdafitinib have been identified, with dermatologic toxicities comprising 11% and contributing significantly to therapy interruption.[2] To the authors' knowledge, only 1 case of onychomadesis secondary to erdafitinib therapy has been reported to date outside of trial data.[4] Herein, we present this case to raise awareness of this new class of antineoplastic agents and their associated rare cutaneous side effects.

Case Synopsis

The patient is a 61-year-old White man with metastatic urothelial carcinoma treated with erdafitinib. He was diagnosed with renal pelvis urothelial carcinoma 2 years prior and underwent nephroureterectomy. He experienced disease recurrence approximately 4 months later and underwent cystectomy and prostatectomy. Subsequent imaging revealed lung metastases, and he was treated with chest radiation before starting erdafitinib 8 mg daily.

The patient initially presented to an outside emergency department and was transferred for hospital admission owing to 1 week of increasing lethargy, concerns for a urinary tract infection, and worsening dermatologic changes attributed to erdafitinib therapy. He reported that 2–3 months after starting erdafitinib, he developed painful desquamation of the hands and scrotum, in addition to progressive diffuse fingernail loss. Approximately 5–6 months after starting therapy and leading up to hospital admission, he developed 1 week of painful oral mucosal sores, periorbital rash, and ocular pain with white-colored drainage, which limited his activities of daily living.

On physical examination, the patient had scaly acral erythema of the bilateral palms and erythema of the fingertips and periungual skin (**Figure 1**). Acral erythema is a painful cutaneous entity that may develop predominantly on the palms and soles in a dose-dependent response to chemotherapeutic agents, hypothesized to have a direct toxic effect on epidermal cells.[5,6] This reaction is thought to be multifactorial, related to high rates

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of epidermal cell turnover, large numbers of eccrine glands, temperature gradients, and vascular structures of the palms and soles.[6] He had diffuse onychomadesis of the fingernails with periungual hemorrhagic crusting (Figure 2) and several thin erythematous plaques on the bilateral periorbital skin and scrotum. There was no visible stomatitis, although he reported pain with swallowing.

The oncology team held erdafitinib and recommended dermatology and ophthalmology consultations. The dermatology team attributed all cutaneous lesions to erdafitinib therapy and initiated supportive treatment. Clobetasol 0.05% ointment was prescribed for the hands and nails and applied twice daily, and desonide 0.05% cream was applied twice daily to the scrotal skin. Barrier ointments, including zinc oxide and a petrolatum-based ointment, were applied to the affected groin areas. A compounded mouthwash (diphenhydramine, hydrocortisone, and nystatin solution), dexamethasone oral solution, and lidocaine 2% solution were administered twice daily as needed for stomatitis and pharyngitis. Erythromycin 0.5% ophthalmic ointment and artificial tears were prescribed for ocular symptoms. His symptoms improved within 24 hours, and he was discharged 3 days later with follow-up appointments with dermatology, ophthalmology, and oncology. Owing to concern for medication-related adverse effects, he was instructed to continue holding erdafitinib for 3 weeks until follow-up with his oncologist.

Follow-up occurred a few days before restarting erdafitinib. The patient reported loss of 2 toenails within 2 weeks of discharge. He noted that clobetasol 0.05% ointment did not improve hand changes, but his oncologist prescribed diclofenac cream, which substantially improved discomfort in both hands and feet, suggesting a potential benefit of topical nonsteroidal anti-inflammatory drugs (NSAIDs) for chemotherapy-induced acral erythema, though limited by patient report and short-term use. Desonide 0.05% cream resolved the scrotal dermatitis, and erythromycin ophthalmic ointment and artificial tears relieved ocular symptoms. Oral solutions for stomatitis and pharyngitis provided minimal benefit.

He was restarted on the same 8 mg daily dose of erdafitinib and followed closely by outpatient dermatology. With a comprehensive dermatologic regimen, progressive nail growth and symptomatic improvement of the hands, feet, scrotum, and groin were noted over the following weeks. However, his course was complicated by ulceration and osteomyelitis of the right first toe and a wound of the left first toe, attributed to diabetic neuropathy and erdafitinib therapy. This required amputation of the right hallux and debridement of the left hallux. Given these complications, erdafitinib was discontinued owing to cutaneous side effects, osteomyelitis, and minimal disease observed on positron emission tomography imaging. Radiation therapy was recommended for a progressed right lung nodule, with plans to consider systemic therapy if further disease progression occurred.

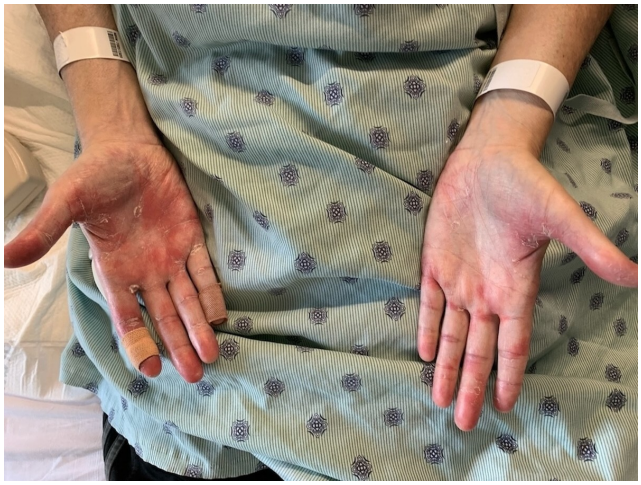

Figure 1. *Adverse cutaneous reaction from erdafitinib therapy causing poorly defined scaly erythematous plaques on the bilateral palms and erythema of the fingertips.*

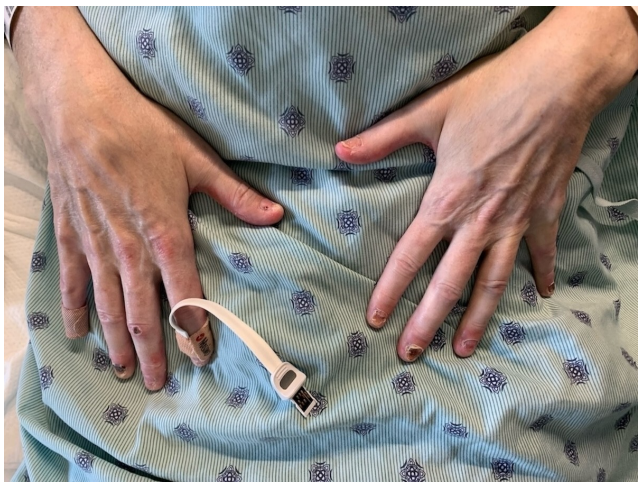

Figure 2. *Diffuse onychomadesis of the fingernails with periungual hemorrhagic crusting and erythema attributed to erdafitinib therapy.*

Case Discussion

Erdafitinib is a novel FGFR inhibitor that has shown promising results for patients with locally advanced or metastatic urothelial carcinoma harboring FGFR mutations.[1] However, numerous adverse effects have been reported, including hyperphosphatemia, alopecia, xerosis, stomatitis, nail changes and loss, ocular events, and diarrhea.[1] Of the cutaneous side effects, stomatitis often presents first.[3] In phase I studies, 45% of patients reported dry mouth and 35% reported nail toxicity.[1] Dermatologic adverse effects can be significant, contributing to dose reductions in 16% of patients in phase II trials.[3]

Nail changes owing to erdafitinib can substantially impact quality of life. Previously reported nail changes include nail dystrophy, onycholysis, paronychia, onychomadesis, and Beau's lines.[1,4] Both onychomadesis and Beau's lines result from cessation of nail matrix pro-

liferation, but onychomadesis is more severe as it involves shedding of the entire nail. Additionally, periungual hemorrhage (believed to be mediated by direct blood vessel damage and thrombocytopenia in the context of other chemotherapeutic agents such as taxanes) may also be induced by erdafitinib.[7] Among phase II studies, approximately 18% of patients experienced onycholysis, 17% had paronychia, and 16% had nail dystrophy.[1]

A previously reported 71-year-old man with metastatic urothelial carcinoma and an FGFR3 Y373C mutation treated with erdafitinib developed diffuse onycholysis and paronychia of several fingernails within 8 weeks of initiating therapy.[2] He also developed macular erythema of the hands and feet, eyelash hypertrichosis, and coarsened scalp hair.[2] Another report described a 42-year-old Hispanic man with metastatic urothelial carcinoma and an FGFR3 S249C missense mutation treated with 8 mg daily erdafitinib who developed skin purpura and erosions, onycholysis, onychomadesis, and Beau's lines.[4] Unlike our case, this individual developed nail superinfection that required 14 days of treatment cessation, after which he was restarted on a lower 6 mg daily dose that was better tolerated. Additionally, our patient had involvement of the periorbital and scrotal skin, whereas the previous case reported only extremity skin changes.

A noteworthy finding in our case was the potential benefit of topical NSAIDs in managing acral erythema. We propose that the anti-inflammatory effects of topical NSAIDs may provide relief from chemotherapy-induced skin pain and inflammation. However, the patient discontinued erdafitinib, had limited use of topical NSAIDs, and has not received further dermatology follow-up, making it difficult to assess a sustained response to topical diclofenac for chemotherapy-induced acral erythema in this instance. Nonetheless, this observation warrants further investigation.

Conclusion

Given the impact of erdafitinib's cutaneous adverse effects, patients should be referred for specialty dermatologic care, preferably oncodermatology. Early initiation of supportive interventions can provide significant improvement and allow continuation of cancer therapy. It is therefore important for both dermatologists and oncologists to be aware of this new class of FGFR inhibitors, which may cause a range of adverse cutaneous reactions.

Potential conflicts of interest

The authors declare no conflicts of interest.

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