Calciphylaxis associated with the fibroblast growth factor receptor inhibitor erdafitinib

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INTRODUCTION

Erdafitinib is a fibroblast growth factor receptor (FGFR) inhibitor approved to treat advanced and metastatic urothelial carcinoma with *FGFR2* or *FGFR3* mutations. While hyperparathyroidism is a known on-target effect of this class of medications, we report calciphylaxis as a novel adverse event associated with erdafitinib in the treatment of *FGFR*-mutant uterine adenosarcoma.

CASE REPORT

We report the case of a woman in her 50s with a past medical history of obesity (body mass index 45-49.9), type 2 diabetes mellitus, and stage IV adenosarcoma of the uterus who underwent total hysterectomy with bilateral salpinogoopherectomy and adjuvant radiation as well as multiple chemotherapy regimens. She was initially treated with a combination of ifosfamide and doxorubicin for 2 months. Her treatment was then transitioned to gemcitabine and docetaxel for 2 months and ultimately to erdafitinib for 3 months. Erdafitinib was discontinued due to the development of ulcerations on her thighs, shins, and calves. Laboratory values obtained shortly after cessation of erdafitinib showed serum phosphorus level of 3.8 mg/dL (normal, 2.4-4.7 mg/dL) and serum calcium level of 8.4 mg/dL (normal, 8.9-10.3 mg/dL) compared with a serum calcium level of 9.0 mg/dL prior to erdafitinib administration. Deep thigh induration with overlying erythema, bilateral lower extremity purpura (Fig 1), and ulcerations (Fig 2) also developed. A punch biopsy taken from the lower extremities demonstrated subdermal calcium deposits associated with small-caliber blood vessels and fat necrosis, findings consistent with calciphylaxis (Fig 3). She had normal renal function at the time of diagnosis, as demonstrated by a creatinine of 0.55 mg/dL. She was offered sodium thiosulfate but opted for topical nitroglycerin due to possible side effects of the medication. Given the inability to restart erdafitinib therapy, she chose palliative treatment and died approximately 1 month after her diagnosis of calciphylaxis.

Abbreviation used:

FGFR: fibroblast growth factor receptor

DISCUSSION

Erdafitinib is a selective targeted inhibitor of FGFR1-4[1] and has been shown to produce an objective tumor response in 40% of patients with locally advanced or metastatic urothelial carcinoma.[2] However, gain of function mutations in the FGFR protein have been identified in a wide variety of other malignancies, such as uterine, breast, gastric, lung, ovarian, neural, bone, bile duct, muscular, and hematologic malignancies, making adverse events of FGFR inhibitors increasingly relevant for dermatologists.[3]

Previously established risk factors for calciphylaxis include stage-V kidney disease, hyperparathyroidism, elevations in calcium-phosphate product, diabetes mellitus, female sex, obesity, warfarin use, and protein C or S deficiency.[4] Fibroblast growth factor 23 is a circulating factor that activates FGFR 1, 3, and 4.[5] When activated, it decreases serum levels of both inorganic phosphate and 1,25-dihydroxyvitamin D(3) and also regulates parathyroid hormone.[6] As such,

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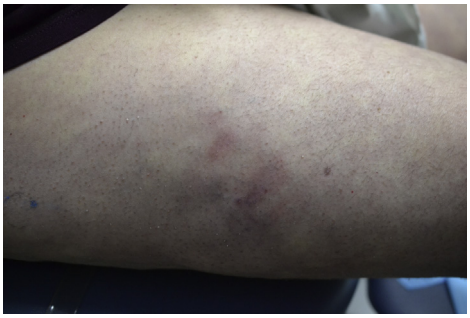

Fig 1. Calciphylaxis—purpura on the lateral thigh.

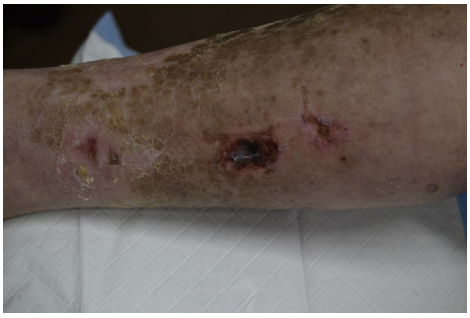

Fig 2. Calciphylaxis—cutaneous ulcers on the anterior leg.

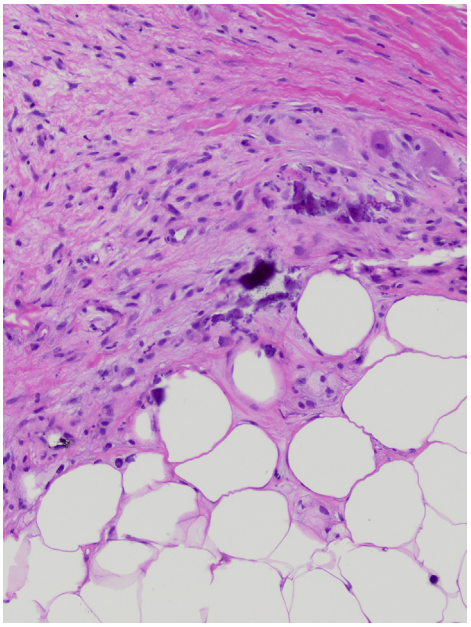

Fig 3. Calciphylaxis—punch biopsy histopathology, hematoxylin-eosin–stained section (original magnification: ×200) revealing subdermal calcium deposits in the blood vessels with fat necrosis.

FGFR inhibitors are known disruptors of parathyroid gland function. A phase 1, open-label, multicenter, single-arm, dose-escalation study of erdafitinib revealed hyperphosphatemia as a side effect in 73.7% of patients who received erdafitinib.[7] Elevations in phosphate promote secretion of parathyroid hormone, inducing an increase in serum calcium which, if unable to restore phosphate homeostasis, contributes to calcium deposition in extraskeletal spaces and subsequent calciphylaxis.[4]

While FGFR inhibitors have previously been associated with the development of metastatic calcinosis,[8] this case report illustrates an instance of calciphylaxis associated with erdafitinib use. Although our patient did not show significant abnormalities in her calcium and phosphate levels, these values were measured after she had stopped erdafitinib due to her ulcerations. It is important to recognize that some of the risk factors for the development of calciphylaxis, including hyperparathyroidism and elevations in calcium-phosphate product, are potential direct adverse effects of FGFR inhibitor therapy. Although calcinosis cutis has also been reported with the use of FGFR inhibitor therapy and could be considered, a key differentiating factor in this case was evidence of subcutaneous fat necrosis within her histopathology sample, a feature expected in calciphylaxis but not in calcinosis cutis.[9] This necrosis, along with the presence of ulcerations and rapid deterioration seen in this patient, made calciphylaxis a more likely diagnosis.

Although this complication appears to be rare, clinicians should take a patient's underlying risk factors for calciphylaxis into account and counsel patients accordingly. Given that this patient had several risk factors before initiating therapy with erdafitinib, specifically obesity and diabetes mellitus, it is possible that erdafitinib induces calciphylaxis only in patients with significant underlying risk. Oncologists should closely monitor calcium-phosphate product and consider the use of phosphate binders prior to the development of calciphylaxis. Given the severity of the disease and the associated 50% mortality at 1.6 years,[10] drug discontinuation is recommended if calciphylaxis is diagnosed.

Conflicts of interest

None disclosed.

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