Fibroblast growth factor receptor inhibitor therapy induced calcinosis cutis treated with sodium thiosulfate

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INTRODUCTION

Fibroblast growth factor receptor (FGFR) inhibitors have emerged as a promising therapeutic option for a variety of solid and hematologic malignancies with aberrant activation of FGFR signaling. While calcinosis cutis has been documented as a side effect of FGFR inhibitor therapy, reported cases have been self-limited and associated with marked hyperphosphatemia. We report a case of severe, diffuse calcinosis cutis of the legs in a 62-year-old male with pancreatic adenocarcinoma treated with the FGFR inhibitor pemigatinib, despite the presence of only mild hyperphosphatemia. Treatment with phosphate binding agents and sodium thiosulfate (STS) infusions resulted in significant improvement. This report highlights calcinosis cutis as a potential toxicity from treatment with FGFR inhibitors, and its management with phosphate binders and STS infusions.

Abbreviations used:

CT:	computed tomography
FGFR:	fibroblast growth factor receptor
STS:	sodium thiosulfate

CASE REPORT

A 62-year old male presented to the oncology clinic with complaints of new tender swelling and erythema beginning at the ankles and progressing superiorly to the thighs along with triangular areas of erythema on the bilateral axillae (Fig 1). He had been on pemigatinib therapy for 25 days. His medical history was significant for locally invasive adenocarcinoma of the head of the pancreas initially treated with 24 cycles of modified FOLFIRINOX and radiation therapy. After discovery of metastatic disease to the liver, genetic testing revealed a FGFR1-TACC1 fusion mutation. The patient was subsequently enrolled in a clinical trial evaluating the efficacy and safety of the FGFR tyrosine kinase inhibitor in previously treated metastatic or surgically unresectable solid tumor malignancies harboring FGFR mutations, pemigatinib (Fig 2). Phosphate levels were normal prior to starting therapy (3.4 mg/dL) but had risen to 6.2 mg/dL within 6 days of starting therapy, eventually reaching a peak of 6.4 mg/dL. The patient was subsequently treated with a low-phosphate diet and Tums as a phosphate binder (500-600 mg per meal). In the oncology clinic, deep vein thromboses were excluded through doppler ultrasonography, and pemigatinib therapy was halted.

The patient then presented to emergency department 4 days after stopping pemigatinib use with 3+ tender pitting lower extremity edema to the upper

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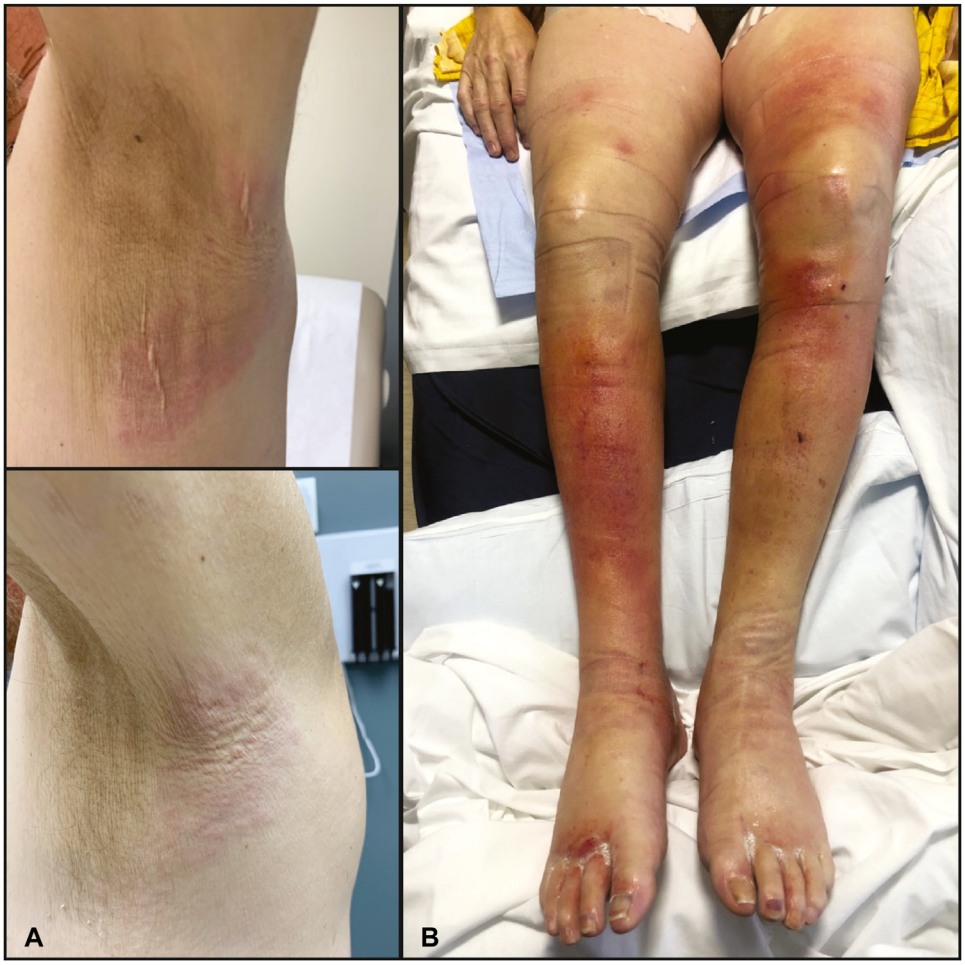

Fig 1. Clinical appearance of FGFR inhibitor-induced calcinosis cutis. **A,** Two images showing axillary metastatic calcinosis cutis. *Pink*, indurated plaque in the right axillae. **B,** Poorly circumscribed, circumferential sclerotic plaques of the legs with pitting edema of the lower extremities.

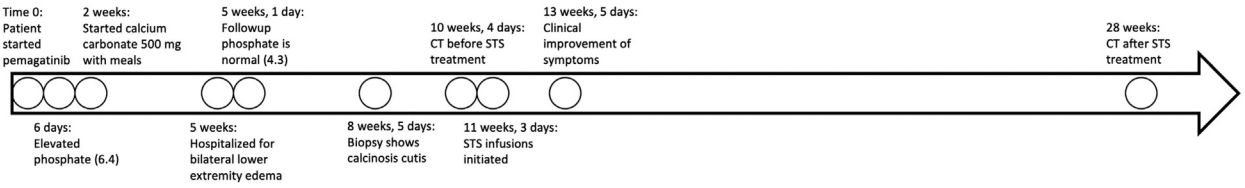

Fig 2. Timeline of clinical course. The timeline begins with the first pemigatinib dose and ends with follow-up computed tomography demonstrating resolution of calcinosis cutis with sodium thiosulfate therapy. *CT*, Computed tomography; *STS*, sodium thiosulfate.

thighs causing restriction of ambulation, extreme pain, and scrotal edema. Furosemide and clindamycin were administered due to concern for cellulitis. Phosphate levels during admission were normal (4.3 mg/dL). The patient was evaluated by dermatology as an inpatient who recommended treatment of acute inflammatory edema with elevation, compression, and topical clobetasol 0.05%. At an outpatient follow-up visit 2 weeks later, despite improvement of the erythema and acute edema, the legs remained notably sclerotic. A telescoping punch biopsy of the left thigh was taken. Histopathology revealed deposition of basophilic calcium salts with surrounding granulomatous inflammation in the dermis (Fig 3). Computed tomography (CT) scans were ordered to exclude

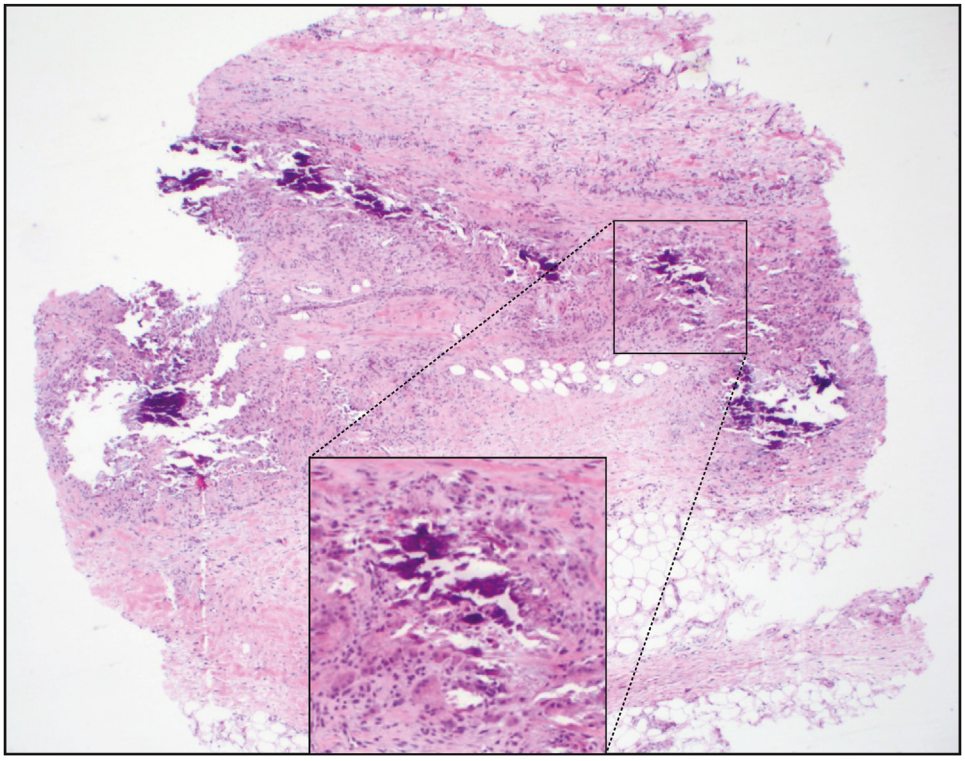

Fig 3. Histopathological appearance of calcinosis cutis. Telescoping punch biopsy from left thigh demonstrating basophilic aggregates in the dermis and superior subcutaneous tissue septum (original magnification 40×). Higher magnification (inset, original magnification 100×) reveals uniformly basophilic deposits characteristic of calcium salts.

involvement of vessels or deeper fascia or tissue. CT of the bilateral lower extremities demonstrated subcutaneous and superficial fascial calcifications in a linear pattern in the bilateral gluteal areas and thighs, right greater than left, with prominent calcifications seen in the lower legs (Fig 4). Because published reports have demonstrated that STS infusions can improve calciphylaxis and connective tissue disease associated calcinosis cutis, the patient was initiated on 12.5 mg IV STS twice weekly. The dose was increased to 25g twice weekly after the patient tolerated the treatments well.[1] The patient was also referred to a mineral metabolism specialist in endocrinology.

Two weeks after starting STS, the patient reported subjective improvements in induration, edema, and pain in most of the lower extremities. There was some residual pain and edema in the bilateral lower legs with prolonged standing. Seven weeks after starting STS, the patient was restarted on pemigatinib at a reduced dosage, from 13.5 mg orally daily, to 9 mg daily. Calcium and phosphate levels were monitored closely, and the phosphate levels were further reduced with sevelamer. With continued STS (25g twice weekly), the patient experienced continuous improvement of calcinosis cutis. Four months after the patient began STS, a CT of the bilateral lower extremities demonstrated a reduction of over 90% in the subcutaneous and superficial fascial calcifications in the bilateral lower legs (Fig 4).

Disease control was maintained with lower dose pemigatinib (4.5 mg daily) for approximately 8 months. Unfortunately, follow-up imaging revealed tumor progression, and pemigatinib was discontinued in favor of gemcitabine and paclitaxel protein-bound particles. The patient ultimately passed away due to complications of pancreatic cancer.

DISCUSSION

FGFRs are a family of receptor tyrosine kinases expressed on the cell membrane whose dysregulation has been implicated in a variety of cancers. FGFR inhibitors are emerging as a promising targeted oncologic therapy for solid and hematologic malignancies containing molecular aberrations involving this pathway.[2,3] Pemigatinib is one such selective FGFR inhibitor being approved for patients with tumors containing FGFR mutations. As this is a recently approved agent, potential adverse effects, including calcinosis cutis, and their treatment are still being elucidated.

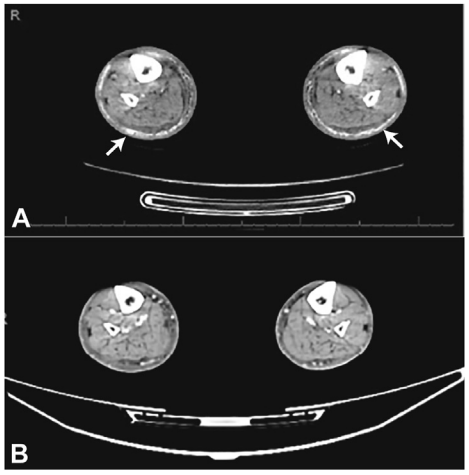

Fig 4. Imaging of calcinosis cutis. **A,** Computed tomography (CT) imaging of the bilateral lower legs exhibiting prominent calcifications in the subcutaneous tissues, skin, and superficial fascial layers, before sodium thiosulfate therapy. *Arrows* highlight subcutaneous calcifications. **B,** CT of the lower legs demonstrating marked reduction in calcification of 90% in the subcutaneous tissues, skin, and superficial fascial layers, taken 4 months after starting sodium thiosulfate therapy.

FGFR inhibitors are generally categorized into specific and nonspecific, the latter of which has a combination of FGFR and non-FGFR targets. In relation to the specific FGFR inhibitors infigratinib and pemagatinib, case reports have identified metastatic calcinosis cutis secondary to hyperphosphatemia as a potential adverse effect.[4,5] These reports identified mild cutaneous involvement of intertriginous regions, specifically bilateral axillary, popliteal, and inguinal folds. The primary patient complaints were skin thickening, with one patient developing pain of the affected areas. Unlike this case, previous cases involved persistent hyperphosphatemia peaking in the 7.9-8.4 mg/dL range.[4,5] Treatment was not discussed in previous case reports, aside from drug cessation. Metastatic calcinosis cutis has not been observed in nonspecific FGFR inhibitors and other specific inhibitors. Hyperphosphatemia has been identified as one of the most common adverse reactions with other FGFR tyrosine kinase inhibitors (over 70% in some), with usually no resulting serious complications.[6,7] Other dermatologic toxicities have included pruritus, maculopapular rash, paronychia, alopecia, dermatitis, dry skin, nail discoloration, and herpes zoster.[6,7]

The mechanism of calcinosis cutis has been theorized to be due to alteration of the fibroblast growth gactor-23 (FGF23) feedback loop. FGF23 is 1 of 22 known ligands for FGFR. Produced by the bone, it maintains phosphate levels in the kidney. Under inhibition from FGFR inhibitors, FGF23 levels increase, resulting in increased phosphate levels.[8] Metastatic calcinosis is the result of deposition of calcium phosphate in the skin and soft tissue, usually due to altered calcium or phosphate metabolism. Patients classically present with firm, white-yellow papules or nodules focused in the intertriginous regions. This patient did initially present with mild involvement of the axilla but progressed to have notable and severe involvement of the lower extremities. Normally, hyperphosphatemia is controllable with phosphate chelators and requires no dose-reduction, as seen in other clinical trials.[9,10] Despite the fact that this patient had only a mild and brief period of hyperphosphatemia, one that was rapidly corrected with low-phosphate diet and oral calcium carbonate, he still developed a severe dermatologic toxicity involving the deep reticular dermis and dense connective tissue.

This case highlights a severe presentation of metastatic calcinosis cutis in a patient undergoing FGFR inhibitor therapy with only mild hyperphosphatemia. Awareness of this potential adverse reaction, as well as sodium thiosulfate infusions as a treatment option is important as FGFR inhibitors increase in use.

Conflicts of interest

None disclosed.

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