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Case Report

A Case Report of Futibatinib-Induced Calciphylaxis

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INTRODUCTION

Calciphylaxis is a rare disorder characterized by the calcification of the intima and media of arterioles and small arteries.[1] This pathological calcification typically affects cutaneous vessels in patients with end-stage renal disease (ESRD), leading to reduced perfusion, tissue ischemia, and subsequent necrosis. The resulting skin lesions often are intensely painful and highly susceptible to infection, which can progress to sepsis. This combination of severe pain and infection risk makes calciphylaxis a significant cause of morbidity and mortality in ESRD patients, with a one-year mortality rate of approximately 50% and frequent hospitalizations.[1]

Calciphylaxis occurs in approximately 0.04-4.00% of ESRD patients and is thought to be associated with disturbances in parathyroid hormone (PTH), calcium, phosphorus, and vitamin D levels, common metabolic abnormalities in ESRD.[1] Elevated phosphorus levels in secondary or tertiary hyperparathyroidism can bind with calcium, leading to vascular deposits and cutaneous necrosis. However, the pathophysiology is not fully understood, as many ESRD patients with PTH axis disturbances do not develop calciphylaxis. Moreover, calciphylaxis has been documented in individuals with normal PTH, calcium, phosphorus, and vitamin D levels.[1]

While calciphylaxis is most seen in ESRD patients, it also can occur in those without renal disease, a condition referred to as *non-uremic* calciphylaxis (NUC).[2] NUC has been associated with autoimmune and connective tissue disorders, obesity, diabetes mellitus, and solid organ malignancies, including cholangiocarcinoma. Certain medications, such as warfarin, glucocorticoids, and calcium-based phosphate binders, also are recognized as risk factors for NUC.[2]

Futibatinib, a novel fibroblast growth factor receptor-2 (FGFR2) inhibitor, is used in the treatment of FGFR2-rearranged cholangiocarcinoma.[3] The phase II FOENIX-CCA2 study demonstrated a 42% response rate and a median duration response of 9.7 months for patients treated with futibatinib.[3] However, a meta-analysis of three clinical trials involving futibatinib revealed that 82% of participants developed hyperphosphatemia, often within six days of initiating therapy.[4] The following case describes a patient with FGFR2-positive metastatic intrahepatic cholangiocarcinoma who developed NUC associated with futibatinib use.

CASE REPORT

A 64-year-old female was diagnosed with unresectable cholangiocarcinoma in January 2024 after an abdominal and pelvic computed tomography (CT) scan revealed a large, ill-defined mass in the right hepatic lobe. Biopsy confirmed the diagnosis. The patient began treatment with gemcitabine, cisplatin, and pembrolizumab in February 2024. Subsequent Guardant 360® genetic testing in March 2024, a high-sensitivity panel evaluating mutations in 739 genes, identified an FGFR2-ciliary rootlet coiled-coil, rootletin (CROCC) gene fusion. However, a chest CT in early April 2024 revealed disease progression with extensive metastases. Due to poor tolerance of the initial chemotherapy regimen, the patient was transitioned to futibatinib in late April 2024 to target her FGFR2 mutation. She tolerated the therapy well until June 2024, when she presented with worsening bilateral lower extremity edema and painful, necrotic wounds on her medial calves, prompting hospital admission (Figure 1).

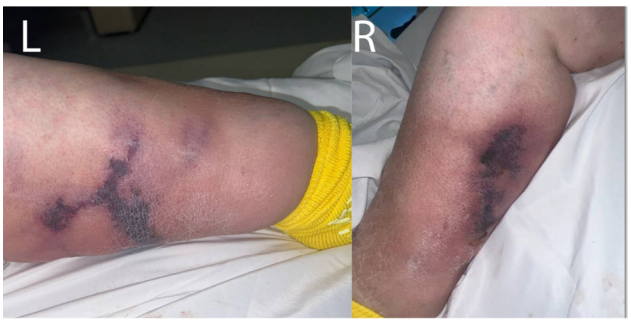

Figure 1. Images of patient's lower extremity wounds upon her initial admission in June 2024.

On admission, her phosphorus level was 6.4 mg/dL, calcium was 9.6 mg/dL, and creatinine was 0.76 mg/dL. The patient was started on sevelamer (1,600 mg three times daily) and underwent lesion biopsy. Futibatinib was discontinued due to suspected FGFR inhibitor-induced hyperphosphatemia and calciphylaxis. Additionally, her outpatient calcium acetate for hyperphosphatemia prophylaxis was discontinued. By the second day of admission, her phosphorus levels normalized, and sevelamer was discontinued. Biopsy results, returned four days post-admission, confirmed calciphylaxis. She was initiated on sodium thiosulfate (STS) at 25 grams three times weekly and received maintenance intravenous (IV) fluids. Over the next 10 days in the hospital, her phosphorus levels normalized; however, she developed symptomatic hypercalcemia, with levels peaking at 12 mg/dL and symptoms of nausea, vomiting, and constipation. These were managed with normal saline, calcitonin, and zoledronate.

After initial improvement and discharge, the patient was readmitted two weeks later for worsening pain in her bilateral lower extremity wounds, which were malodorous with occasional bleeding. She denied fever, purulent drainage, or other systemic symptoms. On admission, her calcium was 13.2 mg/dL, while phosphorus remained normal at 3.1 mg/dL. CT imaging showed marked bilateral subcutaneous stranding, edema, and superficial defects at the wound sites, while magnetic resonance imaging (MRI) revealed bilateral cellulitis without osteomyelitis. Treatment included resumed STS (25 grams three times weekly), calcitonin, and IV fluids, leading to normalized calcium levels.

Wound cultures identified a polymicrobial infection, and the patient was started on a seven-day IV course of ampicillin/sulbactam (3

grams every six hours). Despite treatment, STS was discontinued on the fourth day due to limited response. Surgical options were deemed inadvisable by plastic surgery. Endocrine evaluation revealed normal levels of thyroid-stimulating hormone, thyroxine, cortisol, osteocalcin, parathyroid hormone-related peptide, and procalcitonin, with low levels of vitamin D (29.5 ng/mL) and parathyroid hormone (5.6 pg/mL). She was discharged after one week on a three-day course of oral amoxicillin/clavulanate, with follow-up for wound care and oncology.

Five days post-discharge, she returned to her oncologist with worsening pain, nausea, and further deterioration of her wounds, which were more erythematous and malodorous (Figure 2). Her calcium was elevated at 12.7 mg/dL, necessitating readmission. Treatment included normal saline, calcitonin, and zoledronate. Repeat wound cultures showed heavy growth of *Escherichia coli*, prompting a resumed IV course of ampicillin/sulbactam. Her calcium levels normalized within two days, allowing her to transition to denosumab for long-term hypercalcemia management. After a six-day IV antibiotic course, she transitioned to oral amoxicillin/clavulanate for four days. Wound care focused on supportive measures, including normal saline rinses, *MediHoney*® application, and daily dressing changes. Following her third hospitalization, the patient elected hospice care and passed away shortly thereafter. A timeline of her three hospital admissions is summarized in Table 1.

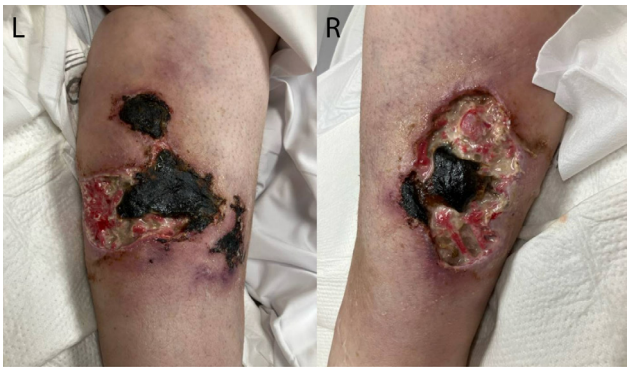

Figure 2. Images of patient's lower extremity wounds upon her third admission in August 2024.

DISCUSSION

To our knowledge, this is the first reported case of NUC in a patient taking futibatinib. However, similar cases have been documented with other FGFR inhibitors, such as erdafitinib and pemigatinib.[5,6] Additionally, data from the FOENIX-CCA2 trial have prompted the inclusion of a statement in futibatinib's safety profile acknowledging the association of soft tissue mineralization with its use. However, this profile does not explicitly warn providers about the potential for calciphylaxis.[7]

The exact mechanism of calciphylaxis remains unclear, but much of the current understanding stems from Hans Selye's 1962 theory of "sensitizers" and "challengers."[8] Sensitizers, including secondary hyperparathyroidism, hypercalcemia, and hyperphosphatemia, create a predisposed state, while challengers initiate the disease process.[8] Modern studies have built on this theory, highlighting that abnormalities in calcium-phosphate homeostasis play a central role.[9,10] In particular, low levels of calcium-phosphate binding proteins, such as matrix G1a protein, and imbalances between calcification promoters (e.g., bone morphogenetic proteins 2 and 4) and inhibitors (e.g., fetuin-A) appear to contribute to the ectopic deposition of hydroxyapatite crystals, a hallmark of calciphylaxis.[9]

Table 1. A detailed timeline of the patient's diagnosis with cholangiocarcinoma and subsequent development of *non-uremic* calciphylaxis.

Date	Event
January 2024	The patient was diagnosed with cholangiocarcinoma
April 2024	The patient began futibatinib after her disease progressed on her initial regimen and cytogenetics revealed an FGFR2 mutation
June 2024	The patient presented to her medical oncologist with bilateral lower extremity edema and painful, necrotic wounds on her medial thighs bilaterally, leading to hospital admission.
Hospital Admission 1 (June 2024)	Biopsy of the wounds demonstrated calciphylaxis. The patient undertook a two-week course of sodium thiosulfate (25 grams, three times per week) before being discharged.
Hospital Admission 2 (July 2024)	The patient was readmitted to the hospital for worsening wound pain. She undertook an additional four-day course of sodium thiosulfate before discontinuation due to lack of improvement.
Hospital Admission 2 (July 2024)	The patient developed sepsis, with wound cultures demonstrating polymicrobial infection and MRI demonstrating bilateral cellulitis. The patient was started on a seven-day course of IV ampicillin/sulbactam (3 grams every six hours) before being discharged on PO amoxicillin/clavulanate for a three-day course. Her infection improved with this therapy.
Hospital Admission 3 (August 2024)	Five days after discharge from her second admission, the patient was directly admitted from her medical oncologist's office due to worsening pain and malodorous discharge from her wounds. Evaluation revealed sepsis.
Hospital Admission 3 (August 2024)	Wound cultures demonstrated heavy growth of Escherichia coli. The patient undertook a six-day course of IV ampicillin/sulbactam (3 grams every six hours) before being transitioned to PO amoxicillin/clavulanate for an additional four days. Her infection improved with this therapy.
September 2024	Following discharge from her third hospitalization, the patient elected for hospice care. She passed away within her first week in hospice.

Note: FGFR2, fibroblast growth factor receptor-2; MRI, magnetic resonance imaging; IV, intravenous; PO: oral

In this case, cholangiocarcinoma, previously identified as a risk factor for calciphylaxis,[2] may have acted as a sensitizer, while futibatinib and the subsequent development of hyperphosphatemia and hypercalcemia likely served as challengers, catalyzing the onset of NUC. Interestingly, cholangiocarcinoma has been associated with elevated levels of fetuin-A, which might ostensibly reduce the risk of calciphylaxis.[10] Despite this, it is plausible that other, unidentified imbalances between calcification

promoters and inhibitors exist in patients with cholangiocarcinoma, which could underlie its link to calciphylaxis.

Finally, the patient's use of calcium acetate for hyperphosphatemia prophylaxis may also have contributed, as calcium-based supplements are recognized risk factors for NUC.[11] Further research is needed to better elucidate the interplay of these factors in the development of calciphylaxis in patients with cholangiocarcinoma and those receiving FGFR inhibitors.

Calciphylaxis is associated with significant morbidity and mortality, with one-year mortality rates exceeding 50%.[1] Although the combination of dialysis and STS has shown efficacy in non-randomized trials for patients with uremic calciphylaxis, demonstrating improvement in up to 70% of cases,[1] there is no established therapy for patients with NUC.[2] Moreover, a recent meta-analysis on STS use in uremic calciphylaxis found no significant benefit, raising questions about its therapeutic potential.[12] Given the lack of validated, effective treatments for NUC, health care providers administering futibatinib should remain vigilant about the potential for this adverse effect.

When patients taking futibatinib develop suspicious skin lesions, the medication should be immediately held, and the patient referred for biopsy to confirm the diagnosis. If calciphylaxis is diagnosed, futibatinib should be permanently discontinued. Given the role of elevated phosphate levels in calciphylaxis pathophysiology, hyperphosphatemia should be managed with phosphate binders like sevelamer or lanthanum. Calcium-based phosphate binders, such as calcium acetate, should be avoided, as calcium supplementation has been identified as a risk factor for calciphylaxis.[11] Patients using calcium-based binders for osteopenia or osteoporosis should discontinue these medications upon starting futibatinib.

Patients require close monitoring, particularly for systemic or local signs of wound infection, as sepsis secondary to wound infection is the leading cause of death in calciphylaxis.[1] Referrals to wound care teams and provision of adequate analgesia are essential.

Although no definitive treatment exists for NUC, STS commonly is used due to its efficacy in uremic calciphylaxis and reports of successful outcomes in NUC.[13] If STS proves ineffective, alternative approaches include combination therapy with iloprost and STS or surgical debridement with split-thickness skin grafting.[13,14] Both strategies have shown promise in case reports, but further research is needed to establish their role as first-line treatments.

Emerging therapies for NUC focus on targeting vascular calcification pathways. These include agents like fetuin-A or matrix G1a protein (MGP), with potential benefits from vitamin K supplementation in patients with vitamin K deficiency to activate MGP. SNF472, a selective inhibitor of vascular calcification that prevents hydroxyapatite deposition in vessel walls, has demonstrated improved wound healing and quality of life in calciphylaxis patients during phase 2 trials.[15] Currently in phase 3 trials, SNF472 represents a promising advancement in NUC management.

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