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ABSTRACT

Calciphylaxis is a rare and life-threatening disease characterized by cutaneous arteriolar stenosis and vascular thrombosis leading to skin ischemia and necrosis. While calciphylaxis occurs mostly in patients with end-stage renal disease, the disorder has been described in patients with normal renal function, namely non-uremic calciphylaxis (NUC). A 48-year-old Caucasian woman presented with a painful ulcerative rash on both legs 1 month after undergoing an orthotopic liver transplantation (OLT). She underwent edge/wedge biopsy of one of the lesions, which revealed calciphylaxis. She was treated with sodium thiosulfate, wound care, and hyperbaric oxygen with complete resolution of the lesions 3 months after presentation. While she was treated with a course of high-dose glucocorticoids after the transplant, she did not have other risk factors for calciphylaxis. NUC should be considered in the differential diagnosis of necrotic skin lesions in postliver transplant patients.

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INTRODUCTION

- Calciphylaxis is a syndrome where calcium accumulates in the fat and skin vessels, leading to necrosis, infections, and potentially death.
- The one-year mortality is more than 50%.
- There are two types: uremic, and NUC. The latter is rare and has poorly understood associations.
- In the literature thus far, there are only three reported cases of NUC post OLT with varied prognoses.
- Etiology is largely unclear, but high doses of steroids have been associated with this in post-transplant patients.
- Further studying of possible correlation is vital to improve outcomes in OLT population. Herein we report a rare case of NUC after liver transplantation due to alcoholic cirrhosis who had an excellent prognosis afterward.

CASE PRESENTATION

A 48-year-old woman with decompensated alcoholic cirrhosis was transferred for liver transplant evaluation after presenting with jaundice, ascites, and a MELD score of 41. She underwent OLT, and postoperative course was complicated by rapid liver enzymes elevation (AST 2503 units/L, ALT 2015 units/L) following initial down-trending values (AST 100 units/L, ALT 153 units/L) in the week following transplantation due to moderate acute cellular rejection (BANF stage V) leading to aggressive immunosuppressive management with a repeat five days course of pulse methylprednisolone 250 mg IV tapered to 20 mg of oral prednisone on discharge, in addition to increasing tacrolimus therapeutic goal to (8-10 ng/mL) that was achieved by taking 3 mg of tacrolimus twice daily, and taking mycophenolic acid 360 mg twice daily. A month later, she developed non-healing ulcers on her legs of unclear cause. So, she was evaluated by dermatology, where she underwent an initial punch biopsy, and subsequent histopathology could not distinguish between autoimmune vasculitis versus calciphylaxis. As a result, prednisone dose was increased to 60 mg to tackle any potential autoimmune pathology. However, her skin lesions were getting worse by the day despite that, prompting a second evaluation via wedge/edge biopsy, which demonstrated distinctly multiple calcified small vessels in the subcutis and local fat necrosis consistent with calciphylaxis. Her kidney functions, calcium, phosphorus, vitamin D, and parathyroid hormone levels were within normal range (Table 1). Similarly, auto-immune workup, protein C and protein S screen were unremarkable. Her prednisone was tapered off, sodium thiosulfate infusions were started, wound care, and hyperbaric oxygen follow-ups were arranged; resulting in marked improvement, and healing of the lesions within 3 months.

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Table 1: Calcium Phosphate Metabolism “Calciphylaxis” Lab Values

Test	Lab value	Reference range
Creatinine	1.05 mg/dL	0.57 - 1.2 mg/dL
eGFR	63 mL/min	>59 mL/min/1.73
Blood Urea Nitrogen	20 mg/dL	8.0 - 25.0 mg/dL
Calcium	9.6 mg/dL	8.4 - 10.1 mg/dL
Phosphorus	4.2 mg/dL	3.0 - 4.3 mg/dL
Vitamin D	25 ng/mL	20 - 80 ng/mL
Parathyroid hormone level	21 pg/mL	15 - 65 pg/mL

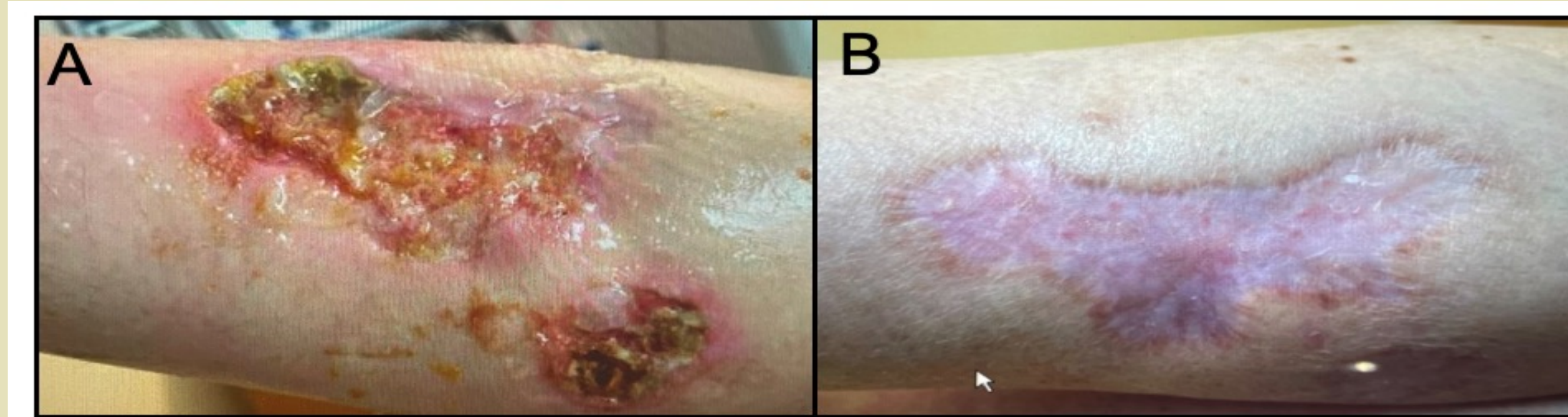


Figure 1

A: Subcutaneous nodules with ulceration and sloughing of overlying skin involving the posterior calf.
B: Healed lesions with residual scarring after 3 months of treatment with sodium thiosulfate, wound care, and hyperbaric oxygen.

Table 2 : Clinical characteristics of NUC in four liver transplant patients

Trait	Present case	Case 1	Case 2	Case 3
Gender	Female	Female	Female	Male
Race	Caucasian	Caucasian	African American	Not reported
Age (years)	48	65	41	53
Cause of liver failure	Alcoholic	Hepatocellular Carcinoma	Alcoholic	Alcoholic
Calcium (mg/dL)	9.6	8.4	8.8	9.3
Phosphorus (mg/dL)	4.2	4.7	5.2	4.5
Parathyroid hormone level (pg/mL)	21	11	56	96
Creatinine (mg/dL)	1.05	0.96	0.72	2.2
Vitamin D2 level	25	84.2	10	20
Parathyroid ultrasound	Normal	Not available	Normal	Normal
Treatment	STS-Hyperbaric oxygen-wound care.	STS-Hyperbaric oxygen.	STS-Cinacalcet-Hyperbaric oxygen.	STS-Cinacalcet-Hyperbaric oxygen-subtotal parathyroidectomy.

DISCUSSION

- Calciphylaxis is a serious condition characterized by calcium deposition in the small vessels supplying the cutaneous and subcutaneous tissues.
- More than half of the patients don't make it beyond one year after diagnosis, and die from sepsis. Therefore, early recognition and management are crucial.
- Underlying pathophysiology is thought to be related to abnormal calcium phosphate metabolism.
- Clinically it presents with painful skin lesions that progress to necrotic eschars and non-healing ulcers. Lesions can be mistaken for vasculitis. As with our patient, and they got worse in response to the steroid dose increase.
- Diagnosis can be challenging even with a skin biopsy, which is the gold standard method. Our patient required two types of biopsies to confirm the diagnosis.
- Histopathology reveals calcified vessels in the cutis and subcutis layers, along with signs of infarction, intimal proliferation and endovascular fibrosis.
- NUC is a rare subtype with poorly understood associations such as: female sex, white race, hyperparathyroidism, connective tissue diseases, alcoholic liver disease, protein C and S deficiency, vitamin D deficiency, and preceding use of some medications like (warfarin, corticosteroids, and certain chemotherapy).
- Risk factors identified in our case were mainly female sex, Caucasian race, liver disease, and the steroid received with transplantation.
- Though alcoholic liver disease, has been identified as a risk factor, the development of NUC post liver transplant is unusual. To date, an association between NUC after liver transplant has been described in only three other case reports (Table 2). Similar to these cases, our patient developed NUC post liver transplant and high dose glucocorticoid therapy.
- This suggests that high dose glucocorticoid therapy post transplant is a risk factor for developing NUC. However, further studying of correlation with liver transplantation as an isolated potential risk factor for NUC without the steroids use is vital to establishing possible association, and improving outcomes in the OLT population.
- Given the rarity and low incidence of calciphylaxis, there are no randomized control trials to establish the best practice. However, multidisciplinary approach is essential for successful treatment with elimination of modifiable risk factors, pain control, sodium thiosulfate infusions (STS), hyperbaric oxygen, and wound care.
- Our case showed that successful treatment of NUC is possible with early intervention and an aggressive approach despite its well-known poor prognosis using a combination of the above. In refractory cases, parathyroidectomy is a proposed last resort solution.

CONCLUSIONS

- NUC is a rare life-threatening condition and should be considered in orthotopic liver transplantation patients with ulcerative skin lesions.
- Despite its well-known poor prognosis, successful treatment is possible through early recognition, and aggressive treatment using a combination of elimination of modifiable risk factors like steroids use, STS, hyperbaric oxygen, and wound care.
- Further research of possible correlation between NUC and liver transplantation as an isolated risk factor without the steroids use is required to establish any possible association, and can help improve the outcomes in the OLT population.