International Journal of Women's Dermatology 7 (2021) 363–364

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Case Letter

Atypical presentation of nonuremic calciphylaxis in a female patient with metastatic breast cancer

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Dear Editor,

Nonuremic calciphylaxis (NUC) is a painful, life-threatening condition that occurs in patients with normal renal function and serum calcium and phosphate levels (Nigwekar et al., 2008). Classically it presents as livedo racemosa that progresses to retiform purpura with stellate ulcerations and black eschar. Skin biopsies demonstrate medial calcification and proliferation of the intima of small- to medium-sized arteries (Bosler et al., 2007; Nigwekar et al., 2008). Herein, we present an atypical presentation of NUC.

An 84-year-old Caucasian woman with triple-negative, stage IV breast cancer metastatic to bone who was on treatment with paclitaxel, atezolizumab, and denosumab, with a history of deep vein thrombosis treated with rivaroxaban, presented with a 2-month history of several painful, pink, firm, subcutaneous nodules on the bilateral lower extremities (Fig. 1). There was no overlying livedo, retiform purpura, or ulceration. Telescoping punch biopsies of a nodule showed focal calcification of small vessel walls in the lower dermis and subcutaneous fat with associated intimal fibroplasia (Fig. 2). Extensive calcium deposition in the interstitium of subcutaneous septae was noted. Serum calcium, phosphorus, parathyroid hormone, and creatinine levels were normal.

A diagnosis of early NUC was made. Owing to the focal nature, intralesional sodium thiosulfate (STS) injections (250 mg/mL) were attempted. However, after four weekly injections, the patient's NUC continued to progress. Intravenous STS three times weekly was initiated and titrated to 18.75 g per dose because the patient did not tolerate 25 g per dose and experienced nausea and vomiting. Significant improvement was noted after 2 weeks and sustained for 9 months, at which point an enlargement of plaques was noted. The dose was then increased to 25 g three times a week, leading to significant improvement in her skin.

Unlike classic calciphylaxis, our patient was atypical in having only painful subcutaneous nodules without overlying livedo changes. This early presentation of calciphylaxis is rare, but it is crucial for clinicians to be keenly aware of it given that prompt intervention is essential (Ghosh et al., 2017). The 1-year mortality of calciphylaxis is approximately 45.8%, but this increases to 80% with the development of ulceration (Altman and Shinohara, 2019; Ghosh et al., 2017). However, the prognosis of NUC improves with STS treatment, and Altman and Shinohara (2019) reported a 75% survival rate.

Associated risk factors for NUC are important to recognize and screen for. Our patient's female sex is a noteworthy risk factor; approximately 75% of cases occur in women (Nigwekar et al., 2008). In addition, her metastatic breast cancer with bone involvement is likely a significant risk factor, albeit rare (Bosler et al., 2007). Her specific chemotherapy agents may also turn out to be novel risk factors given reports of other chemotherapies being associated, including cyclophosphamide, doxorubicin, and fluorouracil (Nigwekar et al., 2008). Warfarin is a common risk factor for both uremic and nonuremic calciphylaxis (Altman and Shinohara, 2019; Bosler et al., 2007; Nigwekar et al., 2008). Instead, our patient was anticoagulated with rivaroxaban. Research is needed to investigate whether direct factor Xa inhibitors have a protective effect and minimize disease progression, but there have been rare cases of its successful use in patients with calciphylaxis (Ghosh et al., 2017). Additional risk factors for NUC include hyperparathyroidism, obesity, other malignancies, glucocorticoid use, diabetes, hypercoagulable states, autoimmune connective tissue diseases, alcoholic liver disease, and weight loss (Bosler et al., 2007; Ghosh et al., 2017; Nigwekar et al., 2008). Histopathology is required for a definitive diagnosis. The histopathologic differential diagnosis includes Monckeberg medial calcific sclerosis and cutaneous oxalosis (Ghosh et al., 2017).

Treatment of NUC includes discontinuation of offending agents, treatment of associated systemic diseases or secondary infection, pain control, and diligent wound care (Nigwekar et al., 2008). The most commonly used treatment for calciphylaxis is intravenous STS. In patients with NUC, STS is often administered as 25 g three to five times weekly. There are limited reports of successful intralesional STS injections to calciphylaxis ulcers

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https://doi.org/10.1016/j.ijwd.2020.12.009

Fig. 1. Left lower extremity with a subtle, broad, ill-defined, indurated erythematous plaque. Centrally, a tender subcutaneous nodule could be palpated.

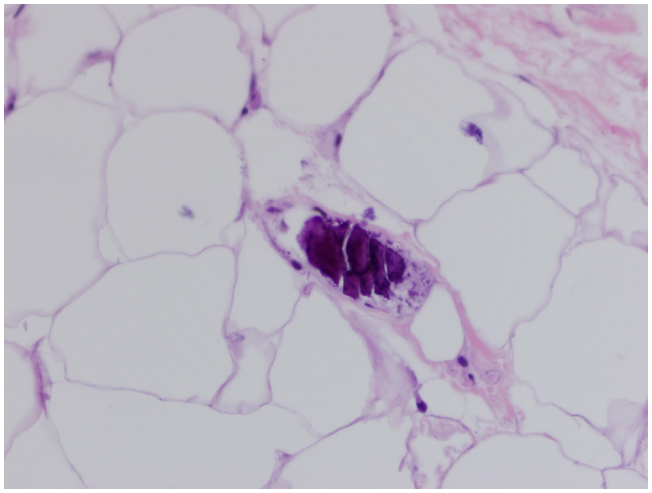

Fig. 2. Punch biopsy of the subcutaneous nodule showed focal calcification of small vessel walls in the lower dermis and subcutaneous fat with associated intimal fibroplasia (hematoxylin and eosin stain, 20× magnification).

(Strazzula et al., 2013). However, our patient's disease continued to progress until intravenous treatment was initiated.

Our patient's presentation illustrates the need for a high index of suspicion for NUC to prevent delays in lifesaving treatment.

Conflicts of interest

None.

Funding

None.

Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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