CASE REPORT

Calciphylaxis of the Breast: A Rare Disease in the Differential Diagnosis of Breast Cancer

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SUMMARY
Calciphylaxis is a rare, but potentially life-threatening condition usually observed in patients with end-stage chronic renal disease and characterized by small- and medium-sized blood vessel calcification leading to tissue ischemia. The clinical features are primarily cutaneous, consisting of skin necrosis and ulceration, mostly located in the lower extremities. We report a case of a 56-year-old woman with a previous history of renal disease and atypical lobular hyperplasia of the right breast, who developed painful skin necrosis on both breasts. Differential diagnosis comprises acute bacterial infection with ulceration, cutaneous vasculitis, cancer and calciphylaxis.

KEY WORDS: calciphylaxis, calcific uremic arteriolopathy, chronic renal failure, breast cancer, breast necrosis

Abbreviations: DDx: Differential diagnosis; CUA: calcific uremic arteriolopathy; PTH: parathyroid hormone.

INTRODUCTION
Calciphylaxis, recently renamed as “calcific uremic arteriolopathy” (CUA) (1), is a rare, but potentially life-threatening complication typically developing in patients with end-stage renal disease (2). Histologic examination shows involvement of small- and medium-sized blood vessels in the dermis and subcutaneous tissue with medial calcification and intimal hypertrophy. Microthrombosis with complete occlusion of vascular lumen and subcutaneous tissue calcification can also be observed (3).

The exact etiology of CUA still remains uncertain. High serum levels of the calcium-phosphate product and/or parathyroid hormone (PTH) have been implicated in the pathogenesis and possibly represent predisposing factors in patients with chronic renal failure; other factors might be the triggers of ischemic changes in CUA (4-7).

The main clinical involvement is cutaneous and consists of painful violaceous plaque and subcutaneous nodules which progress to tissue necrosis, sometimes associated with livedo reticularis. Generally, the lesions are symmetrical and affect distal limbs, buttocks or abdomen (4,8).

CUA of the breast has rarely been reported in the literature so far. Since most patients with
chronic renal failure present an altered immune function with chronic hypertension, chronic anemia and impaired coagulation, several differential diagnoses should be taken into account (9-12).

CASE REPORT

A 56-year-old Caucasian woman was admitted to our department for painful and necrotizing lesions on both breasts without history of local trauma. She was affected by chronic renal failure secondary to membranoproliferative glomerulonephritis treated with chronic hemodialysis. Her medical history included atypical lobular hyperplasia of the right breast, hypertensive cardiomyopathy, hypothyroidism, obesity and nicotine abuse.

Physical examination revealed ulcerated, violaceous, subcutaneous plaques located symmetrically on both breasts close to the areola mammae (Fig. 1); axillary lymph nodes were bilaterally enlarged.

On admission, laboratory investigations showed microcytic anemia, high serum values of creatinine (6.70 mg/dL; range: 0.7-1.4 mg/dL), blood urea nitrogen (173 mg/dL; range: 17-50 mg/dL), PTH (1800 pg/mL; range: 11-64 pg/mL), phosphate (6.65 mg/dL; range: 2.50-4.50 mg/dL), and hypoalbuminemia. All other laboratory tests including autoantibodies were within the normal range.

Sonography of the breast showed acute inflammation around the areola mammae. The patient refused to give her consent for mammography because of the severe local pain. Firstly she was treated with cefodizime and ciprofloxacin. Biopsy of the lesion revealed mural calcification and intimal hypertrophy of the small arterioles of the dermis (Fig. 2) of adipose tissue, and calcifications in the subcutaneous tissue. These findings were confirmed by von Kossa’s silver staining (Fig. 3), suggesting the diagnosis of CUA. During hospitalization the patient developed symmetric necrotic lesions on the upper abdomen with livedo reticularis, again confirmed as CUA on histologic examination.

Due to the enlargement of tissue damage, right mastectomy had to be performed. Postoperative histologic analysis showed severe ischemic necrosis caused by complete vascular occlusion together with extensive calcification of subcutaneous adipose tissue.

Partial parathyroidectomy was also performed for secondary hyperparathyroidism; after the surgery serum PTH levels decreased and serum phosphate values returned to normal.

The patient’s condition further improved and she could be dismissed. The 4-month follow up period was unnoticeable, but subsequently an

Figure 1. Calciphylaxis of the breast: violaceous and necrotizing skin lesions. Note involvement of areola mammae.

Figure 2. Arterioles of the dermis show medial calcification and intimal hypertrophy (hematoxylin-eosin stain).

Figure 3. Subcutaneous adipose tissue: calcium deposits in the vessel wall (von Kossa’s stain).
abrupt increase in PTH (up to 1600 pg/mL) was observed. Treatment with cinacalcet was started (30 mg/day/os). This dose was increased to 60 mg/day/per 2 weeks later; cinacalcet was always well tolerated. The patient was followed-up for another 6 months; her skin as well as serum calcium and phosphate levels were within the normal values.

**DISCUSSION AND CONCLUSIONS**

In this report we describe a case of CUA presented with painful necrotizing lesions of the breast, surrounding inflammation and palpable lymph nodes in both axillae. CUA of the breast has rarely been described in literature so far. The disease can clinically mimic several disorders, among them acute bacterial infection, cutaneous vasculitis or breast cancer. CUA is in most cases associated with chronic renal failure, but has also been described in patients with normal renal function (9-12).

Our patient was affected by chronic renal failure with secondary hyperparathyroidism. No laboratory signs of autoimmunity were detected. She also had a history of atypical lobular hyperplasia of the right mammary gland. Atypical lobular hyperplasia is a benign condition, but is associated with an increased risk of developing invasive cancer in both breasts, often located close to the areola mammae; it was the case in this patient (13). Histological examination of breast tissue was crucial to exclude a breast neoplasm and to achieve the final diagnosis of CUA.

CUA is a rare condition. It is associated with a high mortality, often due to secondary sepsis of cutaneous gangrenous ulcers (7).

Therapeutic options for CUA are aimed at preventing infections and including modifications of factors such as elevated calcium-phosphate product and/or PTH level, which can affect disease progression. Medical interventions include cinacalcet, a calcimimetic recently approved for the treatment of patients with secondary hyperparathyroidism and chronic kidney disease (7,15-17). Surgical treatment of CUA consists in parathyroidectomy, with better wound healing and longer-term survival according to several reports (18). Conventional ulcer therapies are usually ineffective for cutaneous lesions in calciphylaxis (7).

The patient was firstly treated with systemic antibiotics, and secondly with mastectomy of the right breast. Partial parathyroidectomy was also performed to correct hyperparathyroidism. After that, impressive improvement of cutaneous lesions and pain relief were observed. Partial parathyroidectomy was preferred to total parathyroidectomy because of the risk of permanent hypoparathyroidism (18). Nevertheless, 4-6 months after surgery, a significant increase of PTH levels was observed again. Recurrent hyperparathyroidism has been described as a possible complication of partial parathyroidectomy treatable by new gland resection (19). The use of cinacalcet as a second line therapy reduced hyperparathyroidism within a few days. During the next 6 months cinacalcet was continued, achieving good control of the calcium-phosphate product and PTH serum levels as well as of the skin condition.

CUA of the breast is a rare disease which can present with cutaneous necrosis and reactive lymphadenopathy, thus mimicking breast cancer. CUA of the breast should be considered as a differential diagnosis in all cases of breast necrosis, particularly when associated with chronic renal failure.

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**References**

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In the air and the Sun always with Nivea cream, year 1934. (from the collection of Mr. Zlatko Puntijar)