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Case Report

Calciphylaxis of the breast with associated diffuse dermal angiomatosis

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ABSTRACT

In 2013, approximately 660,000 Americans had end stage renal disease (ESRD), requiring either dialysis or transplantation. Up to 5% of dialysis dependent patients may develop calcific uremic arteriolopathy or calciphylaxis (CPX) with vascular medial calcification of arterioles and subcutaneous capillaries with superimposed thrombotic occlusion. Risk factors other than chronic kidney disease include: female gender, diabetes mellitus, liver disease, warfarin, obesity, and hypercoagulability. CPX usually affects adipose rich areas on the trunk and proximal extremities, however an increasing number of reports document breast involvement. We report a case of unilateral breast CPX with a protracted clinical course and superimposed diffuse dermal angiomatosis (DDA). These two unusual cutaneous vaso-occlusive conditions have rarely been reported simultaneously. We review the literature and discuss the relationship and predisposing factors between these two conditions. We believe our case suggests that DDA could be precipitated by CPX secondary to calcific vaso-occlusion.

1. Introduction

Over 660,000 people in the US have end stage renal failure (ESRD) requiring either dialysis or transplantation. 63.7% of these patients receive clinic based hemodialysis [1], approximately 5% of whom will experience one or more episodes of calciphylaxis (CPX) [2]. CPX is a progressive cutaneous necrosis affecting the dermis and subcutaneous tissue usually affecting the proximal limbs and trunk. The characteristic finding is deposition of calcium hydroxyapatite within the media of arterioles and subcutaneous capillaries less than 0.6 mm in diameter. While the etiology of CPX is still somewhat uncertain, most investigators have found that hyperphosphatemia, combined with osteoblast-like changes in vascular smooth muscle cells and hypercoagulability are predisposing or causative factors in this vaso-occlusive phenomenon [3]. Diffuse dermal angiomatosis (DDA) is a rare skin condition, considered to be a reactive phenomenon related to hypoperfusion and presents as erythematous or violaceous, indurated plaques on the skin that may ulcerate [4]. We report a case of unilateral CPX of the breast in a 48-year-old woman with long-standing ESRD. This case is exceptional because of the protracted clinical course which may have been responsible for an associated superficial diffuse dermal angiomatosis (DDA).

2. Case report

A 48-year-old woman with longstanding ESRD was admitted to hospital on December 2014 with respiratory depression, drowsiness and hypotension following an opioid overdose from prescription medications given for chronic pain. She was treated with naloxone successfully for the overdose. During this admission, a 2 cm painful necrotic mass was found on the surface of her left breast. She refused all investigations and discharged herself against medical advice with a presumptive diagnosis of breast cancer.

Her past medical history includes ESRD related to reflux nephropathy, diagnosed at the age of 10 years. She had subsequent bilateral nephrectomies and two failed renal transplants in 1980 and 1988. She had multiple previous hospital admissions due to dialysis access failure and other complications of ESRD. These include parathyroidectomy for secondary hyperparathyroidism, renal osteodystrophy, dialysis-related amyloidosis and chronic hypotension (80/40 mm Hg). She had a history of recurring vaso-occlusive episodes including clotting of numerous previous access grafts notably one in the left axilla. She also had extensive calcifications involving blood vessels and the pericardium, and recurring CPX beginning in the right thigh in 2001. She was currently being treated with midodrine for hypotension, fentanyl for pain, warfarin with a target INR of 2.5–3.5, and hemodialysis with access via a left femoral AV graft.

She presented 6 months later in June 2015 with bleeding from an 8 cm ulcerated and extremely painful mass in her left breast. Large venous collaterals were noted throughout the breast along with palpable masses in the left axilla. The differential diagnosis included advanced breast cancer and a left total mastectomy with axillary lymph node dissection was performed. Her blood tests revealed a PTH of 145.2 (reference range 1.4–6.8 pmol/L) and calcium 2.08 (1.60–2.10 mmol/L).

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The patient was discharged home. A few weeks later she presented with sepsis and a suspected bowel perforation. She was deemed high risk for surgical intervention and a joint decision with her family was made for palliative measures. She passed away soon thereafter. No autopsy was obtained.

3. Pathology results

On gross examination the resected breast measured 20 (medial-lateral) × 10 (superior-inferior) × 5 (anterior-posterior) cm. There was a black, encrusted, necrotic focus just lateral to the areola involving much of the surface of the lower outer quadrant from the 2 to 6 o'clock position measuring 8.0 (medial-lateral) × 4.0 (superior-inferior) cm (Fig. 1A). On cut surface, the necrotic area was seen to be depressed and superficial which overlaid an irregular firm, hyperemic area measuring approximately 1 cm. Radiating out from this area was an ill-defined thickening of the dermis and superficial breast parenchyma. No discrete malignant mass was seen. The underlying yellow fatty breast parenchyma had variable consistency with areas of hard marble like texture alternating with more regular fatty tissue (Fig. 1B).

Microscopic examination showed ulceration of the skin and replacement of the dermis and superficial parenchyma of the breast by confluent masses of benign appearing small capillary channels. The differential diagnosis included lobular capillary hemangioma, Kaposi's sarcoma, and diffuse dermal angiomatosis. Lobular capillary hemangioma has distinct clinical and histological features. It presents as a discrete, bright red, and friable polypoid papule or nodule. This lesion lacked the distinctive architecture of cellular capillary lobules separated by fibrous stroma that characterize lobular capillary hemangioma thereby ruling out this pathological entity. Immunostains confirmed the presence of vascular channels lined by benign appearing endothelial cells (CD31 and CD34 positive, see Fig. 2C) surrounded by pericytes staining for actin (Fig. 2D) and interstitial dendritic type macrophages (Fig. 2E).

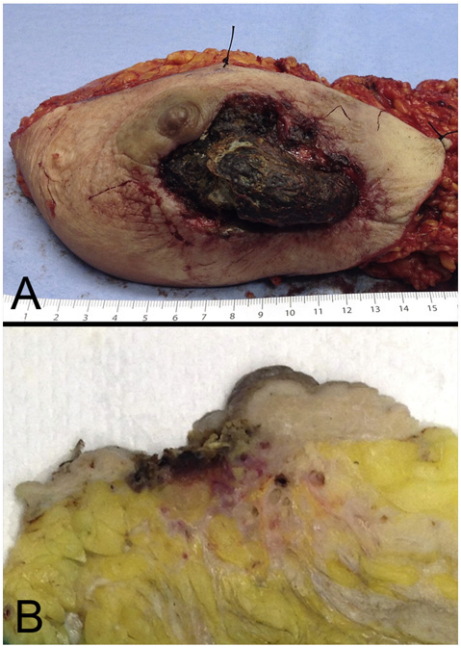

Fig. 1. Gross Appearance of the breast. A. Left mastectomy specimen showing the large area of black eschar replacing much of the lower outer quadrant of the breast. This tissue peripheral to this area shows collateral circulation and vascular injection. B. Cut slice through the nipple of the mastectomy specimen. The blackened area is shown to be a depressed ulcer with underlying expansion of the dermis and focal hyperemia. The breast parenchyma shows homogenization of the usual fatty lobules consistent with ischemic necrosis.

The proliferation was negative for Herpes Virus Type 8 (Fig. 2F) and any keratin positive cells. No cytologic atypia nor mitotic figures were seen and additional immunohistochemistry confirmed a low Ki67 proliferative fraction. These results generally excluded a diagnosis of Kaposi's sarcoma and was consistent with a diagnosis of DDA.

Within the deeper breast parenchyma, at the interface between the normal and firm breast, there was a distinct color difference between viable and ischemic necrotic breast tissue with ghost outlines of all tissue types (Fig. 3A). Elsewhere there were fibrous trabeculae with fat necrosis containing totally occluded vessels with intimal fibrosis and ring-like calcific medial sclerosis consistent with CPX. There was no evidence of malignancy. Eight lymph nodes showed reactive changes only with extra-nodal vessels showing prominent medial calcification and intimal fibroplasia.

Based on histopathological examination a diagnosis of CPX with associated DDA was made.

4. Discussion

CPX is caused by calcification in the dermal and subcutaneous vessels with superimposed thrombotic microangiopathy resulting in livedo reticularis-like skin lesions that progress to subcutaneous plaques and nodules, eventually forming into a necrotic ulcer with eschars. The skin around the lesion presents with hyperalgesia and allodynia [5]. It usually occurs in patients with end-stage renal disease (ESRD) with secondary hyperparathyroidism. It commonly affects the extremities, particularly the lower limbs [6], although there are an increasing number of reports of CPX affecting the inferior aspect of large pendulous breasts (see Table 1), likely due to vascular stasis or compromise in this area.

The exact pathogenesis is unclear, but it is thought that an imbalance in calcium and phosphate homeostasis leads to vascular calcification. Some investigators have suggested that the vascular calcification, similar to bone mineralization may be related to activation of the nuclear factor-κB pathway [6] and/or osteoblastic transformation of the vascular smooth muscle cells [7]. This is part of the "calcification paradox" where patients with chronic kidney disease develop demineralizing bone disease and vascular calcification [7]. The characteristic histopathological findings include medial calcification, small vessel endovascular fibrin thrombi, intimal fibroplasia and endovascular fibrosis with associated tissue ischemia and cutaneous necrosis involving the epidermis, dermis and subcutaneous fat [3,6].

Risk factors for CPX include chronic kidney disease, female gender, diabetes mellitus, liver disease, warfarin, obesity, proteins C and S deficiency, hyperparathyroidism, malignancies, alcoholic liver disease and connective tissue diseases. Several of these risk factors are thought to be responsible for the increasing number of non-uremic CPX [8]. Although vascular calcification may be systemically distributed, involvement has only rarely been reported in the gastrointestinal, cardiac, pulmonary and ocular systems [3]. Vascular stasis may be responsible for the superimposed thrombotic microangiopathy that is required to produce the lesions of calciphylaxis [9]. It may be significant in the present case that the CPX was unilateral on the same side as a previously clotted venous access graft. This may have contributed to vascular stasis and CPX in the ipsilateral breast.

CPX has a very poor prognosis with reported mortality rates after diagnosis over 50%, often due to uncontrolled sepsis from an infected, open cutaneous lesion [9]. Treatment usually involves a combination of reducing calcium-phosphate product, pain control, meticulous wound care to prevent superimposed infection and a trial of intravenous sodium thiosulfate [10]. The latter is thought to function as an antioxidant and promote local vasodilation in addition to chelation of intravascular and intraparenchymal calcium salts. It has been associated with rapid pain relief although prospective randomized controlled trial evidence is lacking. Although some advocate surgical debridement [6], others suggest that atraumatic debridement to prevent skin trauma and additional calciphylaxis lesions should be attempted [10].