

Case Report

End stage renal disease patient presenting with breast pain: Case report

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INTRODUCTION

Calciphylaxis is an infrequently observed disease observed in end stage renal disease (ESRD) patients with an incidence of about 5% and carries a high mortality of up to 80% despite treatment (Rogers and Coates, 2008). Its basic pathophysiology is the deposition of calcium in small- and medium-sized vessel walls. The diagnosis may be challenging in the presence of other confounding factors such as prior radiation therapy to the specified part involved and patients on warfarin who can develop skin necrosis. A comprehensive history and physical examination provides clue to the diagnosis, while biopsy is the confirmatory test. We describe a case of an end-stage renal disease young female with prior history of breast radiation treatment that was on warfarin therapy, presented with a painful necrotic breast.

Case presentation

This is a case of a 55 year old African- American female with past medical history significant for end stage renal disease (ESRD) on hemodialysis since 1997; had hypertension, diet controlled diabetes, coronary artery disease status-post coronary artery bypass, metallic AV valve replacement, right adrenalectomy in 1987; and also functioning adrenocortical tumor, breast cancer status-post right lumpectomy and radiation therapy were diagnosed in 2002. Three months prior to presentation

she was found to have a 3 X 3 cm mass over central portion of the breast which was firm, non tender, and not fixed to the chest wall; which was resected surgically. The pathology report was negative for any malignancy. She was also recently found to have a large left parotid pleomorphic adenoma which was awaiting left superficial parotidectomy.

She presented to our hospital complaining of progressively increasing right breast pain since the recent breast surgery. She also noticed dark discoloration of the breast after the surgery, which started as isolated macula-popular lesions and later progressed and coalesced to involve almost entire breast. This was followed by central ulceration and thick purulent discharge. Review of system was positive for several episodes of diarrhea over the past couple of days. However, she denied any fevers, chills, nausea, vomiting or abdominal pain.

On examination, she was a febrile and vital signs were within normal range. Positive pertinent findings include a necrotic tender right breast with eschar formation, central necrosis and serosanguinous discharge. Lower extremities showed several non-tender maculopapular round to oval black lesions in her bilateral thighs; some of which were nodular, and some had central ulcerations.

Trunk, abdomen and rest of the body did not reveal any other similar lesions.

The pictures of her breast and thigh lesions are attached (Figures 1 and 2). Her home medications included losartan, verapamil, warfarin, cinacalcet 60 mg PO once a day, sevelamer 800 mg PO thrice daily, folic acid, and PRN hydromorphone for pain control. On laboratory

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Figure 1: Mastectomy Breast tissue showing thick necrotic skin with ulcerations.



Figure 2: Bilateral thighs depicting several maculopopular lesions.

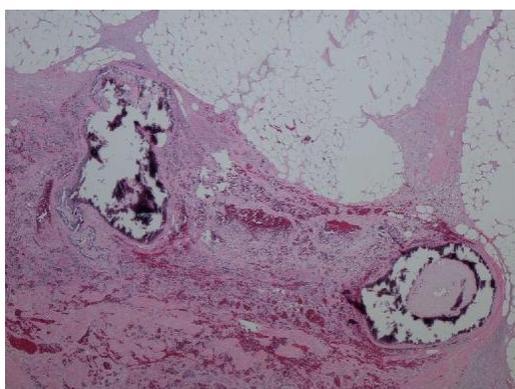


Figure 3: Histo-pathological breast tissue slide showing diffuse calciphylaxis.

examination, she was noted to have a calcium of 8.1 mg/dL (8.8-10.5 mg/dl); albumin, 3 g/dl (3.9-5.2 g/dl); corrected calcium, 8.9 mg/dl; phosphorous, 2 mg/dl (2.5-4.5 mg/dl); intact PTH, 393.7 pg/mL (15-65 pg/mL), while rest

of the basic metabolic panel and CBC were within normal limits except for chronically elevated BUN and serum creatinine. Prior chemistry records over the past 5 months revealed serum calcium ranging from 9.1 to 10.4 mg/dL (8.8-10.5 mg/dl) with albumin of 3.6- 3.9 g/dl (3.9-5.2 g/dl). Phosphorous ranged from 4.9 – 8.5 mg/dl (2.5-4.5 mg/dl), with average calcium, 9.52 mg/dL; average phosphorous, 6.25 mg/dL, and average calcium X phosphorous product, 59.5, even though her calcium X phosphorous product on admission was 17.8 (low phosphorous due to diarrhea likely confounded the results).

Based on the history, physical findings and uncontrolled secondary hyperparathyroidism secondary to ESRD, she was diagnosed presumptively with calciphylaxis. On ultrasound of the neck, three of the four parathyroid glands were identified. The upper right parathyroid measured 18 x 10 x 9 mm. The lower right parathyroid gland was not visualized. In the left, the superior parathyroid gland measured 11 x 9 x 6 mm and the inferior parathyroid gland measured 12 x 7 x 9 mm. She underwent parathyroidectomy of upper two lobes, as lower lobes could not be located on exploration. After surgery her calcium levels remained stable and PTH levels dropped to 97.2 pg/mL. Subsequently, she also had a right total mastectomy and left breast quadrantectomy. The histopathology of mastectomy tissue revealed extensive areas of fat necrosis with granulation tissue, acute inflammation as well as severe diffuse calciphylaxis (Figure 3).

DISCUSSION

Calciphylaxis or calcific uremic arteriopathy is a rare condition characterized by medial calcification and intimal hypertrophy in the small arteries. The resultant effect is ischemia and often necrosis of the skin and subcutaneous tissue. Calciphylaxis is described most often in patients with chronic kidney disease (stages 4 and 5).

Clinically, calciphylaxis presents on the skin as painful, violaceous discoloration that progresses to non healing ulcers and then to necrosis and gangrene. The lesions are often distal involving the extremities and genitalia, and rarely proximal, involving the shoulders, trunk, buttocks and thighs. The incidence has been reported to be 1-5% per year in dialysis-dependent patients (Levin et al., 1993; Rogers and Coates, 2008). There is a female preponderance, and it is increasingly seen in whites and obese individuals.

The term *calciphylaxis* was originally coined by Selye in 1962 (Selye, 1962), who produced soft tissue calcification or calcinosis in rats. He sensitized the animals with high doses of vitamin D, parathyroid hormone, calcium or phosphorus and subsequently challenged them with proteins, metallic salts, local trauma or corticosteroids, and calciphylaxis was induced after a certain “critical time frame”. The reaction is not IgE mediated and hence the

term is a misnomer.

In patients with stage 4 or 5 chronic kidney disease and resulting secondary hyperparathyroidism, PTH, increased calcium-phosphate product, hyperphosphatemia (Ahmed et al., 2001) and treatment with vitamin D analogues (Fine, 2002) may act as "sensitizers." Parathyroid hormone can increase the expression of receptor activator of nuclear factor- κ B ligand (RANKL) (Huang et al., 2001; Ma et al., 2001), involved in regulation of extracellular mineralization. The "challengers" that increase the risk of calciphylaxis include warfarin therapy (Coates et al., 1998), local trauma, calcium carbonate therapy, (Campistol et al., 1989) corticosteroids (Gipstein et al., 1976) and intravenous dextran (Braden et al., 1997). Warfarin can enhance vascular calcification through inhibition of vitamin K-dependent gamma carboxylation of the Matrix Gla Protein (MGP), (Luo et al., 1997) a calcium-binding protein that participates in the organization of bone tissue. In addition, protein C deficiency associated with warfarin can lead to hypercoagulability and thrombosis, which may contribute to skin necrosis seen in calciphylaxis.

It is important to differentiate calciphylaxis from vascular calcification *per se* since the vascular obliteration is from intimal changes rather than solely due to medial calcification. Monckeberg calcification, a form of dystrophic calcification, can be seen in patients with renal failure who do not have calciphylaxis. It is medial calcification of larger arteries without endovascular hyperplasia, giant cell reaction and ischemia; it is distinguished from calciphylaxis by biopsy. Warfarin induced necrosis usually is seen in the first week of starting therapy, with biopsy revealing thrombi at the site, which is not a prerequisite for calciphylaxis.

Our patient had stage 5 chronic kidney disease with secondary hyperparathyroidism and elevated calcium-phosphate product. She had been on warfarin for 7 years which, as described, could contribute to calciphylaxis. Although the "critical time frame" from sensitizer to the challenger is unclear, the patient had a right breast lumpectomy and radiation therapy 4 years prior, with recent debridement of breast skin wound, which may have instigated the process of calcification due to local trauma.

The treatment of calciphylaxis is directed at lowering calcium -phosphate product and removal of precipitating factors. Avoiding the use of calcium-containing phosphate binders and vitamin D analogs are the initial steps. Substituting warfarin therapy with low molecular heparin may help to restore the protein C and protein S activity and thus help in ulcer healing.

The role of parathyroidectomy, which our patient underwent in the treatment of calciphylaxis is controversial. Lowering parathyroid hormone levels and the calcium-phosphate product may downgrade their role as sensitizers. There have been reports of the surgery reducing large vessel calcifications (Nichols et al., 1990) However, small vessel calcifications seen in calciphylaxis may not

benefit from the surgery, (Defrancisco et al., 1985) and therefore this may not obviate progression to ulceration and necrosis.

Hyperbaric oxygen therapy has been reported to heal the cutaneous ulcers by mitigating small vessel ischemia (Benedetto and Emhoff, 2000; Dean and Werman, 1998; Vassa et al., 1994). Recently, there have been reports on the use of intravenous sodium thiosulfate in the treatment of calciphylaxis with the hypothesis that thiosulfate would increase calcium solubility and promote the dissolution of intravascular calcium deposits (Kyriakopoulos and Kontogianni, 1990; Yatzidis and Agroyannis, 1987; Papadakis et al., 1996).

Conclusion

Although it is a fascinating disease which still carries high morbidity and mortality, improved care and control of the underlying etiologies and contributing factors may entail better outcome. Newer epidemiological studies with focus on mortality can provide better answers to this query. Nonetheless, physicians should be fully aware of this potentially life threatening illness and an astute clinician should intervene untimely to reduce the affliction of this disorder.

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