International Journal of Urology and Nephrology ISSN 2756-3855 Vol. 8 (4), pp. 001-004, April, 2020. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Case Report

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

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Accepted 07 April, 2020

Key words: Calciphylaxis, end stage renal disease, breast necrosis, breast pain, secondary hyperparathyroidism.

INTRODUCTION

Calciphylaxis is an infrequently observed disease ob-served 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 exami-nation 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 hyper-tension, diet controlled diabetes, coronary artery disease status-post coronary artery bypass, metallic AV valve replacement, right adrenalectomy in 1987; and also func-tioning 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 progres-sively 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 extre-mities 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 includ-ed 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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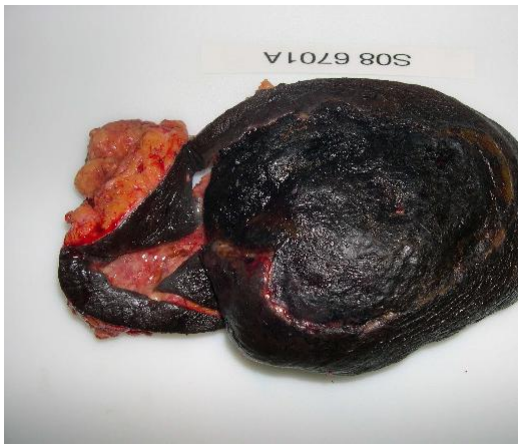

Figure 1: Mastectomy Breast tissue showing thick necrotic skin with ulcerations.

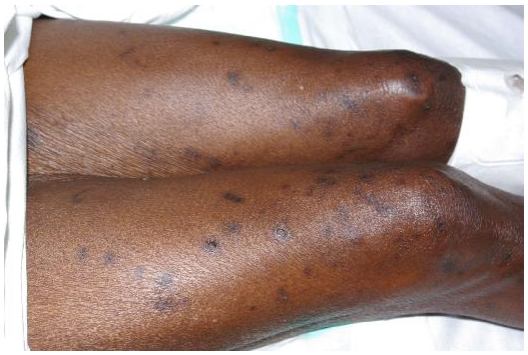

Figure 2: Bilateral thighs depicting several maculopopular lesions.

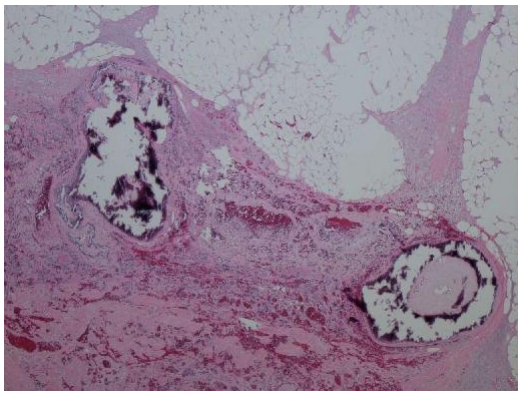

Figure 3: Histo-pathological breast tissue slide showing diffuse calciphylaxis.

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 upper 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 arteriolopathy 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 indivi-duals.

The term *calciphylaxis* was originally coined by Seyle in 1962 (Selye, 1962), who produced soft tissue calcification or calcinosis in rats. He senstitized 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-B ligand (RANKL) (Huang et al., 2001; Ma et al., 2001), involved in regulation of extraskeletal 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 in- crease 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.

ACKNOWLEDGMENTS

Informed consent and permission was obtained from the patient mentioned in the report.

REFERENCES

Ahmed S, O'Neill KD, Hood AF (2001). Calciphylaxis is associated with hyperphosphatemia and increased osteopontin expression by vascular smooth muscle cells. Am. J. Kidney Dis. 37: 1267-1276.

Benedetto BJ, Emhoff TA (2000). The use of hyperbaric oxygen for the management of calciphylaxis. Curr. Surg. 57: 507.

Braden G, Goerdt P, Pekow P (1997). Calciphylaxis in haemodialysis patients: patient profiles and temporal association with IV iron dextran. J. Am. Soc. Nephrol. 8: 549.

Campistol JM, Almirall J, Martin E (1989). Calcium carbonate induced calciphylaxis. Nephron. 51: 549-550.

Coates T, Kirkland GS, Dymock RB (1998). Cutaneous necrosis from calcific uremic arteriolopathy. Am. J. kidney Dis. 32: 384-391.

Dean SM, Werman H (1998). Calciphylaxis. A favorable outcome with hyperbaric oxygen. Vasc Med. 3:115-120.

Defrancisco AM, Cassidy MJ, Owen JP, Ellis HA, Farndon JR, Ward MK, Kerr DN (1985). Ectopic calcification. The role of parathyroid hormone. Proc Eur Dial Transplant Assoc Eur. Ren Assoc. 21: 888-894.

Fine AZ (2002). Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. Kidney Intern. 61:2210-2217.

Gipstein RM, Coburn JW, Adams DA (1976). Calciphylaxis in man: a syndrome of tissue necrosis and vascular calcification in 11 patients with chronic renal failure. Arch. Intern. Med. 136: 1273-1280.

Huang L, Xu J, Kumta SM, Zheng MH (2001). Gene expression of glucocorticoid receptor alpha and beta in giant cell tumor of bone: evidence of glucocorticoid-stimulated osteoclastogenesis by stromal-like tumor cells. Mol. Cell Endocrinol. 181: 199-206.

Kyriakopoulos G, Kontogianni K (1990). Sodium thiosulfate treatment of tumoral calcinosis in patients with end stage renal disease. Renal failure. 12: 213-219.

Levin A, Mehta R, Goldstein MB (1993). Mathematical formulation to help identify the patient at risk of ischemic tissue necrosis – a potentially lethal complication of chronic renal failure. Am. J. Nephrol. 13: 448-453.

Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR (1997). Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature. 386: 78-81.

Ma YL, Cain RL, Halladay DL, Yang X, Zeng Q, Miles RR (2001). Catabolic effects of continuous human PTH (1-38) *in vivo* is associated with sustained stimulation of RANKL and inhibition of osteoprotegerin and gene-associated bone formation. Endocrinol. 142: 4047-4054.

Nichols P, Owen JP, Ellis HA, Farndon JR, Ward MK (1990). Parathyroidectomy in chronic renal failure: a nine-year follow-up study. J. Med. 77: 1175-1193.

Papadakis JT, Patrikarea A, Digenis GE (1996). Sodium thiosulfate in the treatment of tumoral calcifications in a hemodialysis patient without hyperparathyroidism. Nephron. 72: 308-312.

Rogers NM, Coates PT (2008). Calcific uraemic arteriolopathy: an update. Curr. Opin. Nephrol. Hypertens. 17: 629-634

Selye H (1962). Calciphylaxis. Chicago, IL: University of Chicago Press.

Vassa N, Twardowski ZJ, Campbell J (1994). Hyperbaric oxygen therapy in calciphylaxis-induced skin necrosis in a peritoneal dialysis patient. Am. J. Kidney Dis. 23: 878-881.

Yatzidis H, Agroyannis B (1987). Sodium thiosulfate treatment of soft tissue calcifications in patients with end stage renal disease. Peritoneal Dial Bull. 7:250-252.