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Calciphylaxis Following Coronary Artery Bypass Surgery: An Underappreciated Cause of Wound Complications?

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ABSTRACT

Wound complications following cardiac surgery are typically infectious and associated with a high morbidity and mortality. Calciphylaxis, vascular calcification of small and medium sized vessels, often associated with end-stage renal disease, can result in extensive tissue necrosis. We hypothesize that calciphylaxis is an under-recognized and under-reported precipitating wound and breast complication following coronary artery bypass surgery and thereby necessitates further study.

INTRODUCTION

Calciphylaxis is a vascular calcification of small and medium sized vessels that can be debilitating and cause a devastating and painful ischemic necrosis of the dermis, subcutaneous issue, fascia, and muscle with progression to gangrene. Although the pathogenesis is not well understood, it is commonly found in patients with end-stage renal disease, particularly those with elevated serum calcium, calcium-phosphate product, parathyroid hormone, and alkaline phosphatase levels. It has been associated with non-uremic conditions including malignancies, alcoholic hepatic disease, protein C and S deficiency, antiphospholipid syndrome, and obesity [Weenig 2007]. The prevalence is 4% of patients requiring hemodialysis and increases with the duration of dialysis. The mortality ranges from 50% to 80% with infections being a main cause of death [Angelis 1997]. Here we report a case of calciphylaxis in a 47-year-old woman with end-stage renal disease that occurred after coronary artery bypass grafting.

CASE DESCRIPTION

Our patient was a 47-year-old African-American woman with a 14-year history of end-stage renal disease requiring hemodialysis, morbid obesity, insulin-dependent diabetes, hypertension, and coronary artery disease. At an outside hospital, she had undergone coronary artery bypass grafting (CABG) in which the left internal mammary artery was harvested and used as a conduit. Additionally, her past surgical history included a right arm arteriovenous fistula and an open cholecystectomy. Following her CABG, she developed an extensive lesion on her breast and sternotomy incision (Figure 1). She underwent operative debridement with a presumed diagnosis of sternal wound infection, but the operative cultures were negative. She was transferred to our institution for postoperative care and wound management. Upon arrival, laboratory studies were significant for a phosphate level of 3.6 mg/dL, serum calcium of 7.9 mg/dL, intact parathyroid hormone of 159.5 ng/L, alkaline phosphatase of 117 units/L, and a white blood cell count of 11.9×10^9 cells/L. A skin biopsy revealed epidermal necrosis with thrombotic vasculopathy and organizing fibrin thrombi in the vascular channels of superficial dermis consistent with a diagnosis of calciphylaxis (Figure 2). Blood and skin gram stains and cultures were negative for bacteria and fungus. Her postoperative course was further challenged by respiratory failure and gastrointestinal bleeding. Surgical management, including aggressive debridement with possible skin flaps, was refused by the family in the context of her poor prognosis, poor baseline functional status, and other comorbidities. Support was subsequently withdrawn, and she died with comfort care.

DISCUSSION

Sternal wound infections are well-described complications after cardiac surgery, particularly after coronary artery bypass surgery in which the left internal mammary has been dissected off of the chest wall. Well-known risk factors for sternal wound complications include many factors such as the use of bilateral internal mammary arteries, insulin-dependent diabetes, morbid obesity, and multiple transfusions [Loop 1990]. Additional sternotomy complications include sternal dehiscence, chronic pain syndromes, and foreign body reactions to the sternal wires and are often linked to an underlying infectious process. While advances in wound care have dramatically decreased the mortality of sternal wound infections, mortality rates are still between 5% and 20% for 1-year all cause mortality and occasionally

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as high as 40% for in-hospital mortality when associated with deep mediastinal infections [Baillot 2010]. While there have been isolated cases of breast necrosis with calciphylaxis reported, we hypothesize—as was assumed in our case initially—that many cases of sternal wound infections are actually extensive acute calciphylaxis that might undergo secondary opportunistic infection in an already severely compromised patient. Since the primary diagnosis might not be considered, it is probably under-reported and potentially rarely considered as a significant cause of post-sternotomy morbidity and/or mortality. Given the number of sternotomies performed annually and the increasing number performed on patients with end-stage renal disease, this hypothesis is not unreasonable.

First described by Selye in 1962, calciphylaxis was initially believed to be a process of extensive metastatic calcification typically associated with patients with end-stage renal disease [Selye 1962]. The pathophysiology is believed to be secondary to extensive calcification of small and medium sized vessels and is linked to localized ischemia with cutaneous necrosis. Risk factors for development include obesity, corticosteroid use, an elevated calcium-phosphate product (> 70 mg^2/dL^2), an elevated aluminum level (> 25 ng/mL), liver disease, and end-stage renal disease [Wilmer 2002]. In a retrospective study of 64 patients, the 1-year survival was 45.8% from the time of initial diagnosis. Disease development is believed to follow a 2-hit model in which patients with underlying risk factors ("first hit") subsequently sustained a "second hit" from any process leading to end-organ ischemia or worsening of disease that precipitates further tissue necrosis and plaque nodule formation in an ongoing cycle of tissue damage. Unless this cycle is broken, the prognosis is extremely poor [Wilmer 2002]. Using this hypothesis for disease progression, it is easy to appreciate how the balance of perfusion after routine harvesting of the internal mammary artery during CABG (a disease inherently associated with extensive vasculopathy, particularly in patients with end-stage renal failure) can precipitate a non-infectious progressive sternal and breast tissue necrosis [Rashid 2004]. The diagnosis often requires a high index of suspicion and a tissue biopsy specifically looking for cutaneous tissue necrosis with medial calcification and intimal fibroplasia of pannicular arterioles and often-extensive calcium deposits. Thrombosis of dermal arterioles is also common [Wilmer 2002].

Treatment options are limited. Aggressive local surgical debridement with skin graft and flap reconstructions can improve survival, but often patients are extremely debilitated and are critically ill at the time of diagnosis with sepsis being a common cause of death [Nigliazzo 2009]. Furthermore, since the diagnosis is rarely considered, there is on-going and rapid disease progression without appropriate treatment. Symptomatic improvements have been reported with total parathyroidectomy [Angelis 1997; Nigliazzo 2009]. Recent evidence suggests that long-term intravenous sodium thiosulfate can reverse disease progression. Unfortunately, there are no standardized guidelines and clinical improvements often require months of therapy—hardly effective for acutely ill patients [Hayden 2008; Subramaniam 2008].

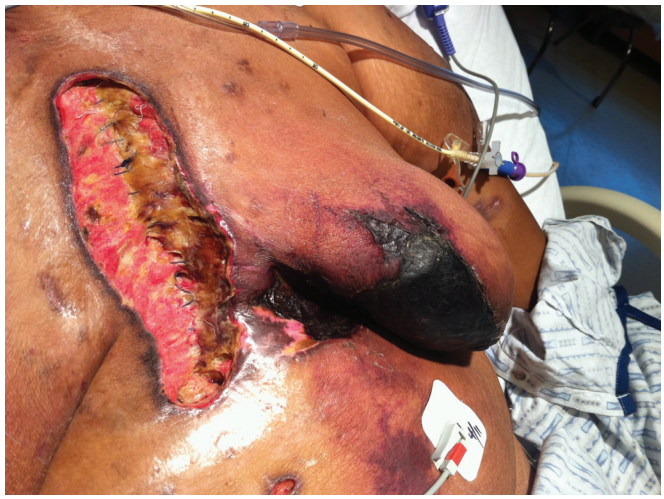

Figure 1. Post-sternal debridement with extensive necrosis of left breast tissue.

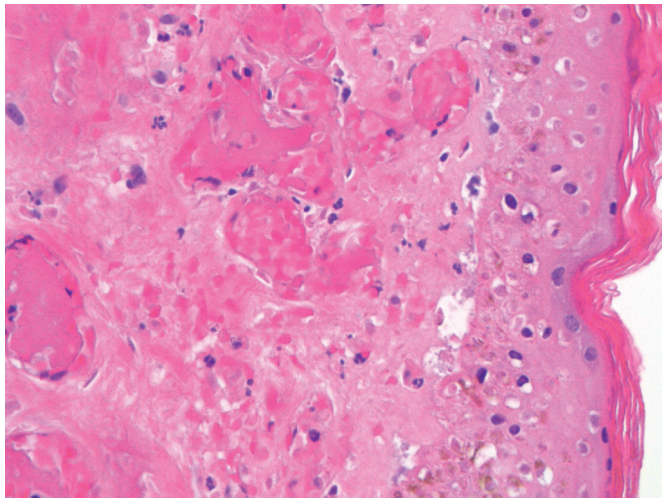

Figure 2. Breast biopsy showed thrombotic vasculopathy and associated epidermal necrosis. Organizing fibrin thrombi are present in vascular channels in the superficial dermis. Areas of necrosis of the overlying epidermis are present. Infiltrate of neutrophils, scattered lymphoid cells, and a few histiocytes are present in the reticular dermis. Though extravasated red blood cells are seen, there is no evidence of a leukocytoclastic vasculitis. Pathologic findings are characteristic of calciphylaxis.

CONCLUSIONS

Although the use of the internal mammary artery is considered standard of care in CABG, its use is not without potential complications. Prompt recognition and treatment of any infectious complications can improve outcomes, particularly with aggressive debridement and wound care [Fleck 2002]. In high-risk patients, however, calciphylaxis should be considered because it can provide useful information for clinical decision making, especially in a critically ill patient for whom there is consideration for withdrawing of support as treatment options are limited and the associated prognosis is extremely poor.

We hypothesize that calciphylaxis is often an unrecognized cause of mediastinal and breast necrosis, and since it may occur independently of an infectious process, the 2 must be considered, treated, managed, and studied as 2 different pathophysiologic processes if the morbidity and mortality from each is to improve. Clearly, a potentially greater recognition of this problem is needed to better understand the pathophysiology and management of post-cardiac surgery wound complications—an infrequent, but potentially devastating event.

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