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Is Warfarin Usage A Risk Factor for Cutaneous Calciphylaxis? A Retrospective Analysis

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Abstract

Currently the pathogenesis of cutaneous calciphylaxis, also known as calcemic uremic arteriolopathy, is poorly understood. We sought to evaluate potential risk factors for cutaneous calciphylaxis (CC), specifically warfarin usage prior to CC diagnosis, other anticoagulant usage prior to CC diagnosis, an elevated serum calcium level, an elevated serum phosphate level, a serum calcium and phosphate product greater than 50, hyperparathyroidism, and a history of chronic (stage III-V) kidney disease. We performed a retrospective analysis of all histopathologically confirmed cases of cutaneous calciphylaxis diagnosed at Thomas Jefferson University Hospital between January 1st 1990 and March 1st 2010. Of the thirteen study patients, five (38%) patients had a history of warfarin use, 12 (93%) of patients had elevated intact parathyroid hormone levels, and 12 (93%) of patients suffered from chronic (stage III-V) kidney disease. Of those that are deceased, median and average survival since original cutaneous calciphylaxis diagnosis was 2 months (range 0-165 months). The constructed Kaplan – Meier survival rate suggests a rapid decline in survival rate during the first sixth months following CC diagnosis. Limitations of our study include the small patient population size, largely due to the rarity of cutaneous calciphylaxis, and the study's retrospective nature.

Keywords: Cutaneous calciphylaxis; Calcemic uremic arteriolopathy; Hyperparathyroidism; Chronic kidney disease; Matrix gla protein; Warfarin; Coumadin; Anticoagulant

Introduction

The goal of our research is to evaluate potential risk factors for cutaneous calciphylaxis (CC), specifically warfarin usage prior to CC diagnosis, other anticoagulant usage prior to CC diagnosis, an elevated serum calcium level, an elevated serum phosphate level, serum calcium and phosphate product greater than 50, hyperparathyroidism, and a history of chronic stage III-V kidney disease. In particular, the study will focus on the relationship between cutaneous calciphylaxis and exposure to warfarin. Current research suggests that warfarin usage may be a risk factor for the development of cutaneous calciphylaxis via the inhibition of matrix gla protein, a vitamin K-dependent protein [1,2,4,7,8,13]. The relationship has been well studied in rats; however, there are limited studies in human populations addressing this potential relationship. Matrix gla protein is thought to be involved with calcium trafficking in blood vessels, specifically via the inhibition of BMP-2 induced mineralization. Therefore, theoretically, if this protein was inactivated by warfarin, excess calcium would accumulate in endothelial cells [7]. This analysis will supplement the current available information by presenting a retrospective analysis on the relationship between warfarin usage and cutaneous calciphylaxis in patients treated at a tertiary university hospital.

Methods

Study design

IRB approval to conduct a retrospective chart review for patients diagnosed with cutaneous calciphylaxis was obtained from Thomas Jefferson University Hospital. A diagnosis keyword search of the Thomas Jefferson University pathology database from January 1, 1990 to the present was done for the term "cutaneous calciphylaxis." The description of each specimen was reviewed. Specimens consistent with cutaneous calciphylaxis were required to demonstrate vascular calcification with associated endothelial injury and overlying necrosis. Patients with specimens meeting these criteria were then located using Jefferson's electronic clinical record system, JeffChart. The patients' diagnoses were then confirmed by discharge summaries describing symptomatology consistent with cutaneous calciphylaxis and containing the ICD-9-CM diagnosis code 275.49. (This diagnosis code is used to bill for cutaneous calciphylaxis under the broad category of "other disorders of calcium metabolism.").

Additional information was then collected on patients who meet enrollment criteria using JeffChart and the Social Security Death Index. Variables obtained include patient's sex, age at diagnosis of cutaneous calciphylaxis, date of death, kidney transplant status (none or post), hemodialysis status (none or post), serum parathyroid hormone level, serum creatinine level, serum phosphate level, and serum ionized calcium level. All laboratory values were obtained within seven days of the specimen diagnostic of cutaneous calciphylaxis. Patients currently undergoing hemodialysis were designated as having stage 5 kidney disease. The four variable (serum creatinine, age, race, and gender) MDRD formula was used to determine the presence and/ or stage of chronic kidney disease in post renal transplant and transplant naive patients. Survival since diagnosis was calculated in months using the date of death cited in the social security death index.

Statistical analysis

Median survival since diagnosis was calculated for each patient.

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A Kaplan- Meier survival analysis was performed. The percentage of cutaneous calciphylaxis patients with warfarin usage prior to CC diagnosis, other anticoagulant usage prior to CC diagnosis, abnormal serum calcium level, abnormal serum phosphate level, serum calcium and phosphate product greater than 50 mg^2/dL^2, abnormal intact parathyroid hormone level, and a history of chronic (stage III-V) kidney disease was calculated.

Patients and enrollment

The keyword search for cutaneous calciphylaxis identified 17 specimens. A total of 4 specimens were excluded from the study. One specimen did not meet the study's histopathologic diagnostic criteria for cutaneous calciphylaxis. Two other specimens were taken from patients whose diagnoses could not be confirmed using Jefferson's electronic clinical records. Two specimens were obtained from the same patient. After the aforementioned exclusions, thirteen patients with cutaneous calciphylaxis were included in the study.

	Number of Patients:			
Risk Factor	**Present**	**Not Present**	**Total**	**% Cases**
Warfarin use	5	8	13	0.384615
Other Anticoagulant usage	5	8	13	0.384615
Elevated Total Serum Calcium	1	12	13	0.076923
Elevated Serum Phosphate	7	6	13	0.538462
Calcium X Phosphate > 50 mg^2/dL^2	5	8	13	0.384615
Elevated Intact Parathyroid Hormone (normal: PTH: 10- 55 pg/mL)	12	1	13	0.923077
History of Chronic Kidney Disease Stages III-V	12	1	13	0.923077

Table 1: Analysis of potential risk factors for cutaneous calciphylaxis.

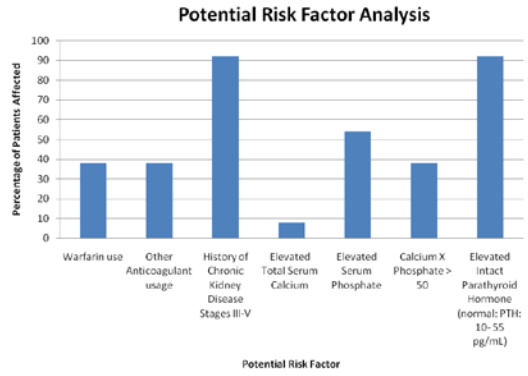

Figure 1: Graphical analysis of potential risk factors for cutaneous calciphylaxis.

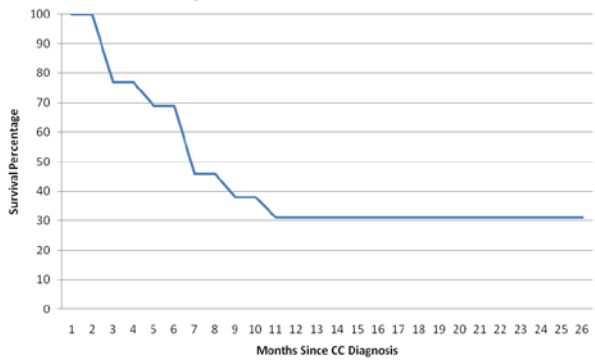

Figure 2: Kaplan – Meier survival rates of patients diagnosed with cutaneous calciphylaxis.

Results

A total of 13 patients with confirmed diagnoses of cutaneous calciphylaxis (CC) were included in this study. Of the thirteen patients, 8 were female (62%) and 5 were male (38%). The median age at cutaneous calciphylaxis diagnosis was 56 (range 27-75) years of age. One and six month survival rate was 31 %. Two and five year survival was 23 %. One patient is alive at the present time, diagnosed on 7/22/1999. Of those that are deceased, median and average survival since original cutaneous calciphylaxis diagnosis was 2 and 83.5 months, respectively (range 0- 165 months). A Kaplan – Meier survival rate was constructed and suggests a rapid decline in survival rate during the first sixth months following CC diagnosis (Figure 2).

Specific risk factors suspected to be associated with CC were evaluated and are presented in Table 1 and Figure 1. The risk factors of interest to this study include the use of warfarin prior to CC diagnosis, the use of other anticoagulant use prior to CC diagnosis, history of chronic stage III-V kidney disease, elevated serum calcium level, elevated serum phosphate level, a serum calcium and phosphate product greater than 50 mg^2/dL^2, and elevated intact parathyroid hormone level.

Five (38%) patients had a history of warfarin use. The documented duration of warfarin use prior to CC diagnosis varied considerably from 2 days to 17 years. The average warfarin dosage was 5mg daily. Anticoagulant use other than warfarin was found in 5 patients (38%) and included both high and low molecular weight heparin. Two of the thirteen patients were exposed to both warfarin and another anticoagulant.

Serum calcium levels varied from 7.7-11.4 mg/dL (reference range 8.5- 10.5 mg/dL) among the patient population. 6 patients (46%) had a low serum calcium level, 6 patients (46%) had a normal serum calcium level, and 1 patient (8%) had a high serum calcium level. The number of patients with low, normal, and high ionized serum calcium levels followed the same trend. Serum phosphate levels ranged from 2.5- 8.3 mg/dL (reference values 2.5- 4.5mg/ dL) among the patient population. 0 patients (0%) had a low serum phosphate level, 6 patients (46%) had a normal serum phosphate level, and 7 patients (54%) had a high serum phosphate level. Five (38%) of patients had a calcium-phosphate product greater than 50 mg^2/dL^2, range 19.04- 76.36 mg^2/dL^2 (mean = 42.02 mg^2/dL^2, median = 45.18 mg^2/dL^2). Intact parathyroid hormone was elevated in 12 (93%) patients, with levels ranging from 66- 944 mg/dL.

12 patients (92%) suffered from chronic kidney disease stages III-V, and eight (62%) of the patients were dialysis dependent at the time of CC diagnosis. One (8%) of the patients had no chronic kidney disease (MDRD stage 2). Since the patient did not suffer from chronic kidney disease and experienced cutaneous calciphylaxis, her history is of particular interest.

This patient was a 60 year old female diagnosed with cutaneous calciphylaxis 9/17/2008. She presented to the ER 9/14/2008 with a chief complaint of leg pain and skin ulcers. She had been started on warfarin 5mg due to atrial fibrillation two years prior. Her past medical history was significant for type II diabetes mellitus, congestive heart failure, and ulcerative colitis. At the time of CC diagnosis, total serum calcium was decreased at 7.7 (reference 8.5- 10.5 mg/dL), ionized serum calcium was decreased at 4.4 (reference 4.5-5.3 mg/dL), serum phosphate was within normal limits at 2.8 (reference 2.5- 4.5mg/ dL), calcium-phosphate product was within normal limits at 21.56 (reference <50), serum creatinine was within normal limits at 0.9 (reference 0.7-1.4 mg/dL), and GFR was 64 mL/min/1.73m^2. The patient's coumadin was stopped,

per hematology recommendation, and she was started on fondaparinux for anticoagulation (necessitated by her atrial fibrillation). The patient was given a trial of hyperbaric oxygen treatment, but was unable to tolerate it secondary to becoming anxious and short of breath when in the chamber. She refused further treatments with the hyperbaric chamber and opted for medical management including local wound care of her necrotic skin ulcers. There was also a question of starting the patient on sodium thiosulfate but it was deemed best to wait until outpatient follow up to consider this medication. The patient was discharged to her home 9/30/2008 and instructed to apply bacitracin ointment to her ulcers daily. The patient was asked to follow up with dermatology six weeks following discharge but died only four weeks later, 10/28/2008. (Records from her date of death are unavailable.)

Discussion

Cutaneous calciphylaxis is a relatively poorly understood syndrome which predominantly affects small and medium sized blood vessels and may manifest as ischemic cutaneous necrosis. It is usually associated with chronic renal disease and secondary hyperparathyroidism, but is known to occur in the absence of renal or parathyroid disease. Mortality ranges from 60-80%, with death most commonly related to sepsis and organ failure [7]. The condition typically presents clinically with violaceous reticulate or mottled areas of cutaneous discoloration which are painful. Eschar formation may or may not be present. Histopathologically, circumferential mural calcification of affected arterioles is often accompanied by perineural calcification with haematoxylin and eosin stain.

It has been postulated in previous studies that the use of warfarin may be a risk factor in the development of calciphylaxis [1-2,4,7-8,13]. In 1998, Price et al. established warfarin as a potential risk factor for calciphylaxis through the inhibition of matrix gla protein (MGP), a vitamin K dependent protein [6]. To review, warfarin inhibits vitamin K dependent proteins. Vitamin K is comprised of both vitamin K1 and Vitamin K2. It is postulated that vitamin K1 is most important in hepatic clotting factor activation. Vitamin K2 is involved in the inhibition of vascular calcium deposition through the activation of MGP [7]. Since the 1998 study, several papers have suggested warfarin as a potential risk factor, however to date; none have definitively confirmed this suspicion [2,7,8,19].

In our study, 5 (including one patient without CKD) of 13 patients had a documented history of warfarin use prior to the development of cutaneous calciphylaxis. It is important to note that one study patient did not suffer from chronic kidney disease and had a documented history of diabetes and warfarin use. This patient's history is similar to that of two cutaneous calciphylaxis' patients with a history of diabetes, warfarin usage, and no chronic kidney disease described by Asobie et al and Banerjee et al, respectively. [2,3] Mrs. M, the patient described in the case report by Banerjee et al, was successfully treated by discontinuation of warfarin therapy, enoxaparin 1mg/kg subcutaneously twice daily, and hyperbaric oxygen service. Similarly, in a case series by Coates et al, the only 2 surviving cutaneous calciphylaxis patients were on warfarin therapy with ESRD at the time of CC diagnosis and subsequently switched to therapeutic dose enoxaparin.[5] While no standard treatment exists for CC, these observations have lead some authors to assert that warfarin should be discontinued immediately and an alternative anticoagulant should be started among CC patients on warfarin therapy.[3]

While a causative relationship between diabetes or warfarin usage and the development of cutaneous calciphylaxis has not been proven, a plausible biological mechanism exists and thus further investigation should be pursued. Unfortunately, neither this study nor the existing published case reports can confirm or refute this suspicion due to their retrospective nature and small size. Clinicians must be aware that cutaneous calciphylaxis can occur in the absence of chronic kidney disease. A high degree of suspicion for cutaneous calciphylaxis should be maintained when evaluating any patient (i.e. those with or without chronic kidney disease) presenting with violaceous mottling or stellate-like livedo reticularis. If the presenting patient is taking warfarin, the existing literature suggests discontinuation and initiation of enoxaparin.

Other risk factors that have been implicated in calciphylaxis development include a history of chronic (stage III-V) kidney disease, renal transplant/dialysis, elevated parathyroid hormone level, and elevated serum creatinine level. Our study confirms these assertions, with 92% of patients having chronic kidney disease and an elevated serum parathyroid hormone level. Compared to a previous study by Weenig et al. [19] in which 51% of patients had a serum calcium-phosphate product greater than 50 mg^2/dL^2, 38% of our patients had a serum calcium phosphate product greater than 50 mg^2/dL^2 [19]. Our study supports Weenig et al. [19] conclusion that the calcium-phosphate product can not reliably confirm or exclude a diagnosis of calciphylaxis. In addition, our data also indicates that only one patient had an elevated serum ionized calcium level. The lack of correlation between high ionized serum calcium level and the development of cutaneous calciphylaxis has been noted in several other studies, thus serum ionized calcium's role in the development of calciphylaxis has yet to be determined. [2,18,19] As such, further analysis investigating the mechanism by which serum ionized calcium level contributes to the pathogenesis of cutaneous calciphylaxis is needed.

The treatment of cutaneous calciphylaxis remains difficult since there are currently no universally accepted treatment regimens proven to decrease disease morbidity or mortality. Anecdotal medical therapies for cutaneous calciphylaxis include parathyroidectomy, heparinization, hyperbaric oxygenation, long term intravenous sodium thiosulfate, and surgical debridement [17]. While appropriate prevention and treatment of cutaneous calciphylaxis remains undetermined, it is prudent to limit patient exposure to modifiable risk factors outlined in this and similar studies. In addition, the mortality rate among patients diagnosed with cutaneous calciphylaxis is very high, with survival rates reported as low as 20%.[19] We also found a very low survival rate (Figure 2) and that the average length of survival among currently deceased patients post-calciphylaxis diagnosis was 2 months. Of the 13 patients included in this study, only two are presently living. The Kaplan—Meier survival rate in Figure 2 demonstrates a rapid decline in the probability of patient survival post cutaneous calciphylaxis diagnosis, suggesting a 10% one year survival rate. Considering that studies have reported the incidence of cutaneous calciphylaxis among patients with chronic renal failure to be 1% and as high as 4.1% in patients on hemodialysis, the improvement of CC treatment and prevention is paramount [17]. These data necessitate the need for further research addressing the causes and, perhaps more importantly, the prevention and treatment of cutaneous calciphylaxis.

In conclusion, our study asserts that cutaneous calciphylaxis is a multi-factorial disease with a low survival rate and generally poor outcome. In addition, this study supports several of the key risk factors that have been suspected in the calciphylaxis disease process, including female gender, a history of chronic kidney disease, renal transplant/dialysis, and an elevated intact parathyroid hormone level. Until recently, calciphylaxis was considered a form of metastatic

calcification with passive precipitation of mineral deposits secondary to an elevated calcium- phosphate product [6]. Current insight into the pathophysiology of cutaneous calciphylaxis, including the role of matrix gla protein in vascular calcium trafficking, suggests that warfarin could potentiate cutaneous calciphylaxis. Although the exact role of warfarin in cutaneous calciphylaxis remains unknown, our study and previous case reports, featuring CC occurrences in patients with a normal calcium-phosphate product, normal intact parathyroid hormone level, and lack of chronic kidney disease suggest the process is more dynamic and complex than previously thought.

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