Calciphylaxis After Aortic Valve Replacement in a Patient with End-Stage Renal Disease

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In this study, we report a case of a patient on dialysis who presented necrotic lesions on the legs and penile ulceration 7 years after a mechanical aortic valve replacement. The diagnosis of calciphylaxis was not confirmed even after skin biopsy, and multidisciplinary management was not initiated until the patient was admitted with septic shock. Cardiovascular surgeons should be aware of warfarin-induced calciphylaxis, whose pathophysiology differs from that of atherosclerosis. Considering poor long-term survival of dialysis patients, mechanical valves should be reserved only for those patients whose estimated survival is longer than the time taken for a biological valve to deteriorate.

Keywords: calciphylaxis, end-stage renal disease, aortic valve replacement

Introduction

Calciphylaxis has been characterized by progressive skin necrosis associated with severe painful skin lesions. Necrotic skin lesions demonstrate poor healing and are frequently complicated by blistering and ulceration with superimposed infections. This disease has been recognized as a disorder of microvascular calcification and thrombosis; it predominantly affects patients with end-stage renal disease (ESRD) who undergo hemodialysis.1) The risk factors that predispose patients to calciphylaxis are ESRD, more than 50 years of age, hypoalbuminemia, hypercalcemia, diabetes, connective tissue disease, hypercoagulable disorders, medications including calcium-based phosphate binders, vitamin K antagonists (warfarin), corticosteroids, and subcutaneous injections of insulin or heparin.1–3) Warfarin administration is considered to be an important risk factor for the onset of this disease. Although the pathogenesis of warfarin-associated calciphylaxis is yet to be completely understood, evidence suggests that warfarin promotes vascular calcification by inhibiting the vitamin K-dependent matrix Gla protein that prevents calcium deposition in the arteries.4)

There is still some controversy among cardiac surgeons as to the optimal type of prosthetic valve for patients aged 50–65 years with ESRD who are undergoing hemodialysis. Most surgeons expect its long-term durability from mechanical valves, despite the potential risk of bleeding due to warfarin therapy. In contrast, biological valves have been presumed to undergo accelerated degeneration that causes the structural valve failure. In this study, we describe a patient with calciphylaxis who underwent hemodialysis with warfarin anticoagulation therapy for 7 years after valve replacement surgery.

Case Report

A 64-year-old man with ESRD undergoing peritoneal dialysis was admitted to our center in June 2012 for severe aortic stenosis due to a bicuspid aortic valve. Valve replacement surgery was then performed with a mechanical valve (St. Jude Medical Regent 19-mm valve; St. Jude Medical, Minneapolis, MN, USA) due to the patient’s preference for its durability. The postoperative course was uneventful, and the oral anticoagulation therapy with warfarin was maintained at the outpatient clinic.
In March 2015, the peritoneal dialysis was changed to hemodialysis due to a marked increase in right pleural effusion with persistent hypoalbuminemia. In December 2018, the patient complained of bilateral calf pain after 50-m ambulation. The arterial blood pressure of both legs was almost normal at this time.

In June 2019, the patient was unable to walk due to severe calf pain. A pulsatile blood flow was clearly detected using Doppler ultrasound on both dorsalis pedis and posterior tibial arteries. Computed tomography-angiography showed multiple calcifications from the abdominal aorta to the distal arteries including small vessels on the body surface such as the penile artery. Blood flow below the knees was difficult to evaluate. During the physical examination, the patient was noted to have extensive gangrenous necrotic lesions on both calves and ulceration on the glans of the penis. Considering that the percutaneous oxygen pressure of the toes was maintained in both feet, calciphylaxis was suspected rather than arteriosclerosis obliterans. The dermatology department then performed a skin biopsy wherein non-specific histological changes compatible with skin necrosis were found.

In August 2019, the patient was admitted with tachypnea and altered mental status. The physical examination revealed an arterial blood pressure of 91/40 mmHg, pulse rate of 81 bpm, respiratory rate of 34 bpm, and oxygen saturation of approximately 90%. The necrotic leg lesions extended and penetrated into the muscular fascia of both calves (Fig. 1).

The laboratory results were as follows: C-reactive protein, 34 mg/dL; creatinine, 5.71 mg/dL; blood urea nitrogen, 50 mg/dL; calcium, 9.4 mg/dL; hemoglobin, 10.3 g/dL; white blood cells, 19000/µL; platelets, 1.2 × 10^4/µL; and albumin, 2.2 g/dL. Warfarin was then discontinued on presentation because of the excessive anticoagulant state (prothrombin time-international normalized ratio > 9.9).

Computed tomography revealed massive bilateral pleural effusion and multiple air bubbles in the subcutaneous tissue and muscles of the right lower leg (Fig. 2).

Given the patient’s diagnosis of septic shock due to gas gangrene in the right leg, we performed an emergent amputation above the knee and debridement of the necrotic lesions of the left calf. His postoperative hemodynamic status remained unstable and required vasopressors. Although the antibiotic administration of vancomycin and tazobactam was started, the wound infection in the stump...
has rapidly exacerbated, and the patient expired after 7
days of intensive care. The diagnosis of calciphylaxis was
confirmed via histological findings, showing the medial
calcification and the intimal proliferation, with micro-
thrombi in the small vessels, which were obtained from
the specimen of the amputated leg (Fig. 3).

Discussion

The true incidence of calciphylaxis remains unclear and
has been difficult to ascertain using administrative data
due to lacking unique International Classification of Dis-
ases (ICD) 10th Revision code. Data from a nationwide
registry in Germany in 2017 estimated an annual inci-
dence rate of 0.04% in German dialysis patients. Among
them, the 1-year mortality for patients with calciphylaxis
is reported at 45%–80%, with ulcerated lesions associated
with higher mortality compared to non-ulcerated lesions
and sepsis being the leading cause of death.

Calciphylaxis is primarily a clinical diagnosis, obtained
by the presence of livedoid skin changes or ulcers, often
with a thick eschar overlying painful indurated subcutane-
ous plaques located predominantly in adipose-rich areas.

A skin biopsy is necessary to confirm the diagnosis.
Typical histologic features in calciphylaxis include dermal
and extravascular or pannicular small-vessel calcification
and thrombosis, along with intimal fibrosis. However,
such findings had low sensitivity and low specificity, and
the utility of a biopsy was questionable. Moreover, skin
biopsy might result in the exacerbation of the ulcer, infec-
tion, and even propagation of new lesions. Thus, there is
a need for further research in this area and for a proper
biopsy technique.

This present case could have been diagnosed earlier as
the patient had been exhibiting two risk factors, that is,EoRd on hemodialysis and warfarin therapy for the me-
chanical aortic valve.

In addition, we noted upon a review of the medical
history that the patient had experienced a penile ulcer 6
months prior to admission. Authors have reported that
ischemic necrosis or ulceration of the penis has been
recognized as proximal calciphylaxis, caused by calcified
changes in small arteries originating from the internal
pudendal artery, a branch of the internal iliac artery. Most
patients with proximal calciphylaxis have dismal progno-

There are no consensus guidelines on the management
of calciphylaxis. The reported treatment generally involves
a multi-interventional and multidisciplinary approach,
including wound care, pain management, administration
of sodium thiosulfate in dialysis solutions, cinacalcet for
bone mineral disease, hyperbaric oxygen therapy, and
discontinuation of offending medication, particularly
warfarin. In this present case, alternate anticoagulation
options were limited because the mechanical aortic valve
was implanted. Switching the drug to enoxaparin after
bridging to low-molecular-weight heparin is deemed a
controversial decision.

Mortality rates among dialysis patients remain to be
high. According to the data extracted from the US Renal
Data System in 2017, the 5-year survival rate for patients
with ESRD on dialysis was approximately 40%. Cardio-
vascular diseases have been identified as the leading cause
of death in this patient population.

It is believed that biological valves rapidly calcify in
patients undergoing dialysis. Kaplon et al. analyzed 42
patients undergoing dialysis, of which 25 received bio-
logical valve replacement and 17 received mechanical valve
replacement surgery. The estimated 5-year survival rate
was 27% for patients with biological valves, whereas it
was 33% for those with mechanical valves, and there
was no significant difference in terms of survival between
them. In their series, reoperation was required for one
patient (5%) due to calcific degeneration of the biological
valve. Brinkman et al. reported structural dysfunction of
a biological valve in 2 (7%) of the 30 patients who were
undergoing chronic renal dialysis within 15 months and
54 months of implantation, respectively. Despite anecdot-
al reports, accelerated calcification of biological valves in
patients on dialysis remains uncommon. Manghelli et al.
reviewed 423 dialysis-dependent patients, of which 341
had biological and 82 had mechanical valves. The 5-year
survival rates were 23% and 33% for the biological and
mechanical groups, respectively. After adjusting for age,
NYHA (New York Heart Association) class, and diabetes,
survival was similar between the groups. Cox regression
analysis was also performed to estimate survival based
on five different ages (30, 40, 50, 60, or 70 years old) and
the presence of diabetes and/or heart failure. They showed
that only patients aged 30 or 40 years with NYHA class I–
II failure without diabetes had a > 50% estimated 5-year
survival rate. Because anticoagulation carries an increased
risk of morbidity, they suggested that mechanical valves
should be reserved only for those patients with an estimated
long-time survival, i.e., longer than the time a biological
valve may deteriorate; this includes very young people
(e.g., 30 or 40 years old) without diabetes or NYHA class
III or IV symptoms.

In summary, further research is needed to understand
the pathogenesis and identify the risk factors for calci-
phylaxis. Clinicians, including cardiovascular surgeons,
should be aware of the clinical characteristics of calciphyl-
axis and the therapeutic dilemma of using warfarin and
maintain a high index of clinical suspicion for an early and
accurate diagnosis.
Conclusion

Warfarin use is relatively safe in the treatment for various diseases. However, considering its rare but serious complication of calciphylaxis, more caution should be observed when using warfarin. Also, greater sensitivity in identifying ischemic skin lesions, particularly in patients with ESRD on hemodialysis, is required. An early diagnosis of calciphylaxis is crucial for starting accurate multidisciplinary treatment, including the discontinuation of warfarin. Since hemodialysis-dependent patients who undergo valve replacement surgery have poor long-term survival, biological valves should be strongly considered to avoid further morbidities due to mechanical valves.

Disclosure Statement
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