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CASE REPORT
Other

New-onset acute rapidly deteriorating case of calciphylaxis after open heart surgery: a case report

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Background Calciphylaxis is a rare life-threatening condition that is characterized by calcification of small blood vessels and soft tissues. This condition is classically described in uraemic patients with end-stage renal failure who are on dialysis or had previous renal transplant. It has also been reported in non-uraemic patients and those who are on warfarin therapy. It is typically associated with high calcium/phosphorus product. Patients classically present with painful skin lesion that evolve into painful ulcers. There are multiple risk factors that were reported to trigger or worsen calciphylaxis. Treatment is a multidisciplinary approach that involves elimination of risk factors, wound management, pain control, and optimization of calcium/phosphorus metabolism. Reported mortality rates are very high especially in the uraemic group.

Case summary Here we present a case of a patient, who is on chronic renal dialysis for stage renal failure, who underwent mechanical mitral valve replacement and tricuspid valve repair. In the perioperative period, she was exposed to multiple risk factors that are known to potentially trigger prophylaxis. In the early postoperative period, she developed new-onset rapidly deteriorating skin lesions and the histopathological diagnosis confirmed calciphylaxis. Her treatment plan included pain control, frequent wound care, and optimization of nutritional and metabolic status.

Discussion Calciphylaxis is a very serious condition that is usually associated with poor outcome. In this case, we discuss the unusual presentation of this condition with particular emphasis on the multiple perioperative risk factors that can potentially trigger the onset of calciphylaxis in postoperative cardiac patients. We also discuss the epidemiology, pathogenesis, diagnosis, histopathological findings, and different lines of treatment of this serious condition and the potential preventative strategies.

Keywords Calciphylaxis • Postoperative complications • Cardiac surgery • Kidney disease • Case report

Learning points

- Calciphylaxis is a life-threatening condition that mainly affects patients with chronic end-stage renal disease, and it has poor prognosis.
- Multiple risk factors can trigger or worsen prophylaxis in this group of patients.
- During the perioperative period of cardiac surgery, these patients may be exposed to many of these risk factors which can potentially trigger calciphylaxis.
- Perioperative elimination of these risk factors and optimization of patients' metabolic and nutritional status can potentially prevent the occurrence of this dire condition.

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Introduction

Calciphylaxis, also known as calcific uraemic arteriopathy,[1] is a rare condition that is characterized by calcification and subsequent thrombosis of the micro-vessels of the subcutaneous fatty tissue and dermis.[1] This results in the development of a wide spectrum of ischaemic skin lesions (ranging from erythema and tenderness to necrotic ulcers) which are characteristically very painful.[2]

Serum levels of calcium and phosphate are typically elevated in calciphylaxis that can affect up to 35 per 10 000 patient-years among the patients with end-stage renal dysfunction (ESRD) on chronic haemodialysis in the USA.[1] It can also affect, to lesser extent, non-uraemic patients.[2] This condition can be triggered by multiple factors such as systemic corticosteroids, blood transfusions, low serum albumin, warfarin use, malnutrition, and weight loss.[2]

Treatment of calciphylaxis is largely supportive and includes wound care, control of risk factors, and the use of pharmacological agents that interfere with the process of calcium deposition in tissues.[3] Prognosis of calciphylaxis is usually very poor especially in the uraemic group of patients.[1]

Uraemic patients who undergo cardiac surgery under cardiopulmonary bypass (CPB) are frequently exposed to some of the risk factors that can trigger or worsen calciphylaxis during the immediate perioperative period. Perioperative optimization of this vulnerable group of patients and control of these risk factors is important to minimize the risk of occurrence of this dire condition.

Timeline

Ten years	Cadaveric renal transplant.
Eight years	Renal transplant failed.
Day -1	Patient was admitted for elective cardiac surgery
Day 0	Patient underwent cardiac surgery under cardiopulmonary bypass.
	She received multiple blood transfusions.
Day 0	Patient was admitted to intensive care unit.
	More blood units were given.
	Renal replacement therapy was started.
Day 2	Patient was extubated.
Day 3	Warfarin therapy was started.
Day 4	Patient was transferred to the floor.
Day 7	Patient started to develop skin lesions.
Days 7–18	Diagnosis of calciphylaxis was established and patient was treated conservatively.
Day 19	Patient was transferred to local district hospital for ongoing management of skin lesions.
Day 45	Patient deceased

Case presentation

We present the case of a 39-year-old female patient with past medical history of long-term ESRD and on chronic renal dialysis. She suffered from chronic vesicoureteral reflux and she had received a cadaveric renal transplant 10 years before the date of admission. Unfortunately, her renal transplant failed after 2 years from implantation due to graft rejection. She has remained dependent on renal dialysis for the last 8 years. She also had secondary hyperparathyroidism, secondary arterial hypertension, and chronic anaemia. Her regular medications included iron supplements, atorvastatin, aspirin, amlodipine, erythropoietin, and vitamin D supplements. She presented with worsening dyspnoea over a period of 6–12 months. On admission, physical examination showed a malnourished and cachectic patient. She had a very faint diastolic murmur and bibasal lung crepitations. Echocardiogram showed severe mitral stenosis with severely calcified mitral annulus and sub-valvular apparatus with mean gradient of 10 mmHg and mitral valve area of 0.8 cm^2. She also had severe tricuspid regurgitation with preserved biventricular ejection fraction. Coronary angiography did not show any flow-limiting coronary lesions. Her preoperative blood works showed levels of urea 111 (7–30 mg/dL), creatinine 4.7 (0.7–1.2 mg/dL), phosphorus 10 (2.8–4.5 mg/dL), calcium 8.6 (8.4–10.2 mg/dL), and parathormone hormone (PTH) 725 (50–330 pg/dL).

The patient underwent mitral valve replacement with mechanical prosthesis and tricuspid valve repair with annuloplasty ring. Intraoperatively, the mitral valve was found to be very severely calcified and required extensive tissue debridement and decalcification. She required the transfusion of multiple blood products (including red blood cells, plasma concentrates, platelets, and fibrinogen) for significant coagulopathy and bleeding both during surgery and in the intensive care unit (ICU). Postoperatively, she was immediately started on continuous renal replacement therapy for optimization of her metabolic parameters and for fluid off-loading. She was extubated on postoperative Day 2 and warfarin was started on postoperative Day 3 after her chest drains were removed. She was transferred from the ICU to the floor on Day 4 and she remained haemodynamically stable. After 3 days, she started to develop multiple rapidly worsening ulcerative lesions in the inner aspects of her thighs and calves (*Figure 1*). Ulcers were painful with necrotic base and erythematous borders and the widest lesion measured about 10 × 7 cm. She also developed rapidly deteriorating necrotic ulcers of her fingertips (*Figure 1*). Tissue biopsies from these lesions showed abundant deposition of calcium in walls of small vessels and surrounding tissues associated with necrotic changes. Histopathological diagnosis was confirmed to be compatible with calciphylaxis.

Patient wounds were treated conservatively with regular enzymatic debridement with collagenase-based ointment and frequent dressings. She was also started on empirical prophylactic antibiotics to minimize the risk of spreading any potential skin infection to her new mechanical mitral valve prosthesis. Repeated swab cultures from her ulcerative lesions remained negative for bacterial growth and her inflammatory markers remained within normal range. Based on risk and benefit, it was decided not to discontinue warfarin at any time due to the very high risk of prosthetic thrombosis. After a period of clinical stability, on Day 19, the patient was transferred to her local hospital for continued wound care and convalescence. Unfortunately, the patient's condition started to deteriorate with worsening wound infection and sepsis. She eventually passed away 45 days after her surgery.

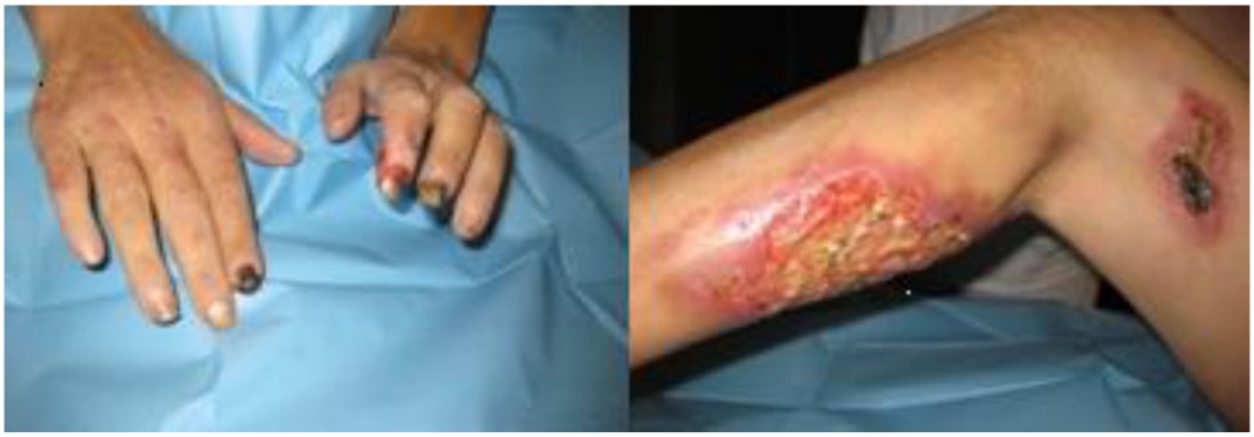


Figure 1 Necrotic lesions of fingertips (left) and thigh (right).

Discussion

Calciphylaxis is a rare condition characterized by progressive microvascular calcification and occlusion of cutaneous blood vessels.[4] It was first reported by Bryant and White[5] in 1898, who described the combination of skin gangrene and vascular calcification, but it was not until 1962 when the term 'calciphylaxis' was used by Selye[6] to describe the metastatic calcifications in various organs. It usually appears during the 5th decade of life, but it has also been described in younger patients and children as well.[7] It is classically described in uraemic patients with end-stage renal failure and also in those who had previous renal transplants.[3] Reported incidence varies in literature and in a recent major study from the Fresenius Medical Care North America (FMCNA), dialysis units reported calciphylaxis annual incidence rate of 35 per 10 000 ESRD patients who are on chronic haemodialysis.[1] Calciphylaxis was also reported in non-uraemic patients with lesser degrees of renal dysfunction especially those who have other risk factors such as obesity and diabetes mellitus.[2,7] In the German Calciphylaxis Registry, 10% of patients with calciphylaxis had either normal kidney function or had chronic kidney disease not requiring renal dialysis.[1,8]

The pathogenesis of this process is complex and the exact mechanism and sequence of events that lead to calcium deposition in vascular wall and thrombosis are not entirely clear.[1,2,9] One common feature in these patients is the imbalance in calcium/phosphate metabolism which lead to elevated calcium/phosphorus product usually in the context of chronic renal failure and secondary hyperparathyroidism.[2,9]

Also, matrix Gla protein (MGP), a potent inhibitor of vascular calcification that requires the activity of a vitamin K-dependent carboxylase, has been described to play a role in this complex vascular calcification process.[9]

In addition to ESRD, many other risk factors have been reported to trigger or aggravate calciphylaxis such as diabetes mellitus, obesity, autoimmune diseases, hypoalbuminaemia, hypercalcaemia, hyperphosphataemia, hyperparathyrodism, and corticosteroids.[1,2,7] Warfarin was also described as an important trigger for calciphylaxis including in non-uraemic patients. In some reports, it was found to increase the incidence of calciphylaxis by up to 10 folds.[10] This may be attributed to promoting vascular calcification by inhibiting the vitamin K-dependent MGP with subsequent calcium deposition in arteries.[11] Warfarin can also trigger thrombosis by reducing proteins C and S, both are essential for endothelial cells response to calcification and stress.[10,12] Also, the initiation of renal dialysis was reported as a triggering factor due to the abrupt influx of calcium from the dialysate into the patient's blood and the correction of acidosis that can lead to abundant substrate that can promote the formation of Ca-P complex.[13]

Patients classically present with a wide variety of painful skin lesions that usually start as erythema, induration, or nodule that eventually progress to necrotic painful skin ulcers.[2,7,9] Patients may also present with widespread calcifications of skeletal muscles, cerebral, and pulmonary vessels.[3,7] Cardiac lesions are variable and may include calcification of the aorta, heart valves, and the conduction system (bony heart).[14]

Typical laboratory findings in these patients include hyperparathyroidism, hypercalcaemia, hyperphosphataemia, and high calcium-phosphorus product. Also, elevated serum levels of alkaline phosphatase, urea, and creatinine are common findings.[2]

Once there is a clinical high suspicion for calciphylaxis, skin biopsy is usually indicated to establish the diagnosis. Histopathological findings may include medial and intimal calcium deposition, intimal hyperplasia, and thrombosis of the micro-vessels in the dermal and subcutaneous layers with subsequent epidermal ulceration and necrosis.[1,4] The most typical diagnostic histopathologic finding is calcification of small- to medium-size vessels with fat necrosis combined with proximal vascular thrombosis.[10]

Treatment of calciphylaxis should take a multidisciplinary approach and should involve different specialties including renal physicians, nutritionists, pain specialists, and wound care teams.[9] Initial efforts should be directed towards controlling and/or eliminating the triggering risk factors to prevent or slow down the progress of the disease.[3] Wound care is an essential part of the management plan and it is largely conservative and may include proper debridement of necrotic

tissues and frequent dressings. Surgical reconstruction may be considered to reduce pain and improve healing.[15] Multiple pharmacological agents have been used to optimize calcium and phosphate levels such as sodium thiosulphate and bisphosphonates with variable reported degrees of success.[3] Also, optimizing PTH levels have also been suggested to slow the disease progress.[3]

Finally, prognosis of calciphylaxis is generally poor especially in the uraemic patients and mortality rates are high and can reach up to 60–80%. Death usually results from severe sepsis and malnutrition.[1,2]

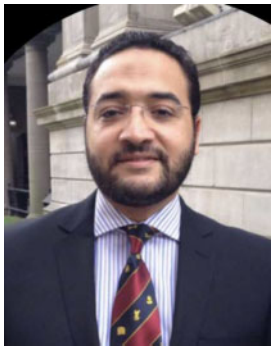
In this case report, a patient with ESRD on long-term dialysis presented with new-onset acutely worsening necrotic skin lesions very early after her mitral and tricuspid valve surgery. Currently, there is not enough evidence to support the link between heart surgery under CPB per se and the occurrence of calciphylaxis. To the best of our knowledge, there are no similar reported cases in literature. However, during the perioperative period of cardiac surgery, patients with ESRD are potentially exposed to a multitude of the risk factors that were previously reported to trigger calciphylaxis. Regarding the CPB itself, it is well known that CPB can trigger a cascade of systemic inflammatory reactions that can result in transient compromise in the immune system especially by interfering with cell-mediated immunity.[16] Previous studies reported the administration of immunosuppressant drugs as a potential trigger for calciphylaxis.[2] Whether the immune-suppressive effect of is comparable to the effect of these drugs remains unknown. Also, transfusion of blood products, which is very common after cardiac surgery, has also been reported to potentially trigger calciphylaxis.[2] Also, many of the cardiac surgical patients who present with worsening symptoms of heart failure may have varying degrees of malnutrition and hypoalbuminaemia.[17] Both of which have been described as risk factors for calciphylaxis.[2,3] Also, renal dialysis patients who undergo cardiac surgery will have some degree of worsening kidney parameters and electrolyte imbalance which again, may be a risk factor for calciphylaxis.[18] One more major factor that has been strongly associated with calciphylaxis is warfarin therapy.[10] Our patient was started on warfarin for her mechanical mitral valve shortly before the appearance of skin lesions, however, in literature, the reported timeframe between the commencement of warfarin therapy and the appearance of calciphylaxis is usually longer and ranges from 1 to 168 months (mean, 32 months).[10]

Finally, special care should be taken when managing patients with ESRD or patients on chronic renal dialysis who will undergo cardiac surgery. This group of high-risk patients may be exposed to multiple risk factors during their perioperative journey. Rigorous control of renal function, optimization of serum electrolytes, and avoidance of unnecessary blood transfusions should be considered. Patient nutritional status should also be optimized to avoid malnutrition and hypoalbuminaemia. The decision to use warfarin in this group of patients should be based on the benefit/cost balance and should be tailored on individual basis.

Conclusions

Calciphylaxis is a rare but major condition associated with poor outcome especially in uraemic patients. These patients are likely to be exposed to multiple risk factors during the perioperative period of cardiac surgery which may result in triggering this dire complication. All care should be taken to eliminate or control these factors to avoid the occurrence or worsening of this condition.

Lead author biography



Dr Mohammad El Diasty is currently working as a Clinical Fellow in Cardiac Surgery Department in Queen's University, Kingston, ON, Canada. He has received intensive training in adult cardiac and thoracic surgery in Spain, the UK, the USA, and Canada. He is particularly interested in analysing postoperative outcomes and he has been involved in multiple quality improvement projects that focused mainly on improving the standards of patient care.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The patient reported in this case is deceased. Despite the best efforts of the authors, they have been unable to contact the patient's next-of-kin to obtain consent for publication. Every effort has been made to anonymize the case. This situation has been discussed with the editors.

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