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Bilateral breast calciphylaxis in a patient who survived earlier extensive tissue necrosis 5 years previously: A case report

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ABSTRACT

INTRODUCTION: Calciphylaxis is a rare condition including patchy dermal necrosis that mostly affects chronic hemodialysis patients. The syndrome usually heralds impending death although patients may survive following a set of measures including an adapted dialysis regimen. The present case is a unique patient who recovered from an earlier episode of upper leg calciphylaxis 5 years previously but developed fatal bilateral breast necrosis.

PRESENTATION OF CASE: A 69 year old Caucasian woman with a history of atrial fibrillation, hypertension, CVA, hyperparathyroidectomy for secondary hyperparathyroidism and end stage renal disease with hemodialysis recovered in 2012 from extensive symptomatic left upper leg necrosis due to calciphylaxis. In 2017, she developed painful, necrotic ulcers on both breasts, again due to calciphylaxis. She had no history of anticoagulants use but she did use prednisolone 5mg/day. She received adequate wound care, pain medication, antibiotics and dialysis frequency was increased with an addition of sodium thiosulfate. A bilateral ablation was discussed but she decided to stop all treatment following pulmonary aspiration and passed away one week later.

DISCUSSION: Calciphylaxis is a rare diagnosis that should be considered in patients with renal insufficiency developing painful patches of skin necrosis.

CONCLUSION: A multidisciplinary treatment approach including hyperparathyroidectomy, modified hemodialysis and wound treatment is recommended. There is limited evidence for surgical intervention.

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1. Introduction

Calciphylaxis is a rare condition that mostly affects, but is not limited to, people with end stage renal disease (ESRD). It affects around 1% of the dialysis patients, but an upward trend is probable [1]. The prognosis is dismal with a 1-year-mortality up to 80% due to systemic complications [1,2]. Abundant deposition of calcium in cutaneous arterioles causes skin ischemia leading to very painful necrotic ulcers [1,3,4]. Calciphylaxis is a clinical diagnosis although imaging or pathologic examination may be used for confirmation. A handful of cases of breast calciphylaxis were described previously [5–8]. However, patients recovering from a first episode of extremity calciphylaxis but developing a second one 5 years later is unique. Unfortunately, this severe episode of bilateral breast tissue necrosis and subsequent sepsis proved fatal. This case report is written in line with the SCARE criteria [9].

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2. Presentation of a case

A 69 year old Caucasian woman with a history of atrial fibrillation, hypertension and CVA developed progressive renal disease requiring peritoneal dialysis which was started in 2008 and was followed by haemodialysis in 2010. In that year, she also received a parathyroidectomy for secondary hyperparathyroidism. She had no history of anticoagulants use but did use prednisolone 5mg/day. In October 2012 she developed painful, necrotic wounds on both upper legs strongly resembling patches of calciphylaxis (Fig. 1). A skin biopsy showed necrotic fatty tissue and calcium deposits in small and medial arterioles confirming the diagnosis (Fig. 2). A treatment regimen consisting of antibiotics (piperacillin/tazobactam 4000/500mg twice a day), surgical debridement, intensive wound care and daily hemodialysis sessions with the addition of 25g of sodium thiosulfate resulted in wound healing and total recovery in 2013 (Fig. 3).

In July 2017, she again presented with painful ulcers, but now covering both breasts (Figs. 4 and 5). In addition, numerous (>10) subcutaneous masses in upper and lower legs as well as chest were palpable. An ultrasound of the breasts demonstrated extensive calcium deposits supporting the diagnosis of calciphylaxis. Skin biopsies were not performed as this trauma was thought



Fig. 1. Calciphylaxis of the left upper leg (2012).



Fig. 3. Healed calciphylaxis of the left upper leg (2013).

to enhance the pain associated with the calciphylaxis. Lab testing demonstrated a hypercalcemia (2.82 mmol/l, ref. 2.15–2.55 mmol/l), hyperphosphatemia (1.89 mmol/l, ref. 0.80–1.50 mmol/l) and hyperparathyroidism (31 pmol/l, ref. 1.6–6.9 pmol/l) that were treated with sevelameer (phosphate binder; 80mg once a day) and cinacalcet (90mg once a day). Again it was decided to increase the dialysis frequency with addition of 25g sodium thiosulfate during each dialysis session. Intensive wound care was started as well as administration of pain medication (paracetamol 4dd1000mg, pregabalin 2dd25mg, fentanyl nasal spray 3dd100ug, oxycodone controlled release 2dd40mg, oxycodone 4–6dd10mg) and antibiotics (piperacilline/tazobactam 4000/500mg i.v. twice a day). The dose of prednisolone was diminished from 5mg/day to 2.5mg/day and the alfacalcidol (from 0.25 ug/day)(vitamin D) was stopped. A bilateral surgical breast ablation and hyperbaric oxygen treatment were considered but were abandoned due to clinical deterioration

as a result of a aspiration pneumonia. Progressive sepsis followed and the patient died shortly thereafter supported by palliative sedation in September 2017.

3. Discussion

Calciphylaxis is predominantly observed in patients with end stage renal disease [3,10]. Interestingly, occasionally it is also described in non-dialysis patients, for instance in individuals with an active malignancy, alcoholic liver disease or connective tissue disease [5,10–12]. Risk factors predisposing to calciphylaxis are female sex, Caucasian race, obesity (BMI>30kg/m²), hypertension, diabetes mellitus, long history of dialysis (>6 years), active malignancy, chronic inflammatory state (e.g. Crohn's disease, hyperparathyroidism, hypoalbuminemia, hypercoagulable state, vitamin D administration, corticosteroids and vitamin K antago-

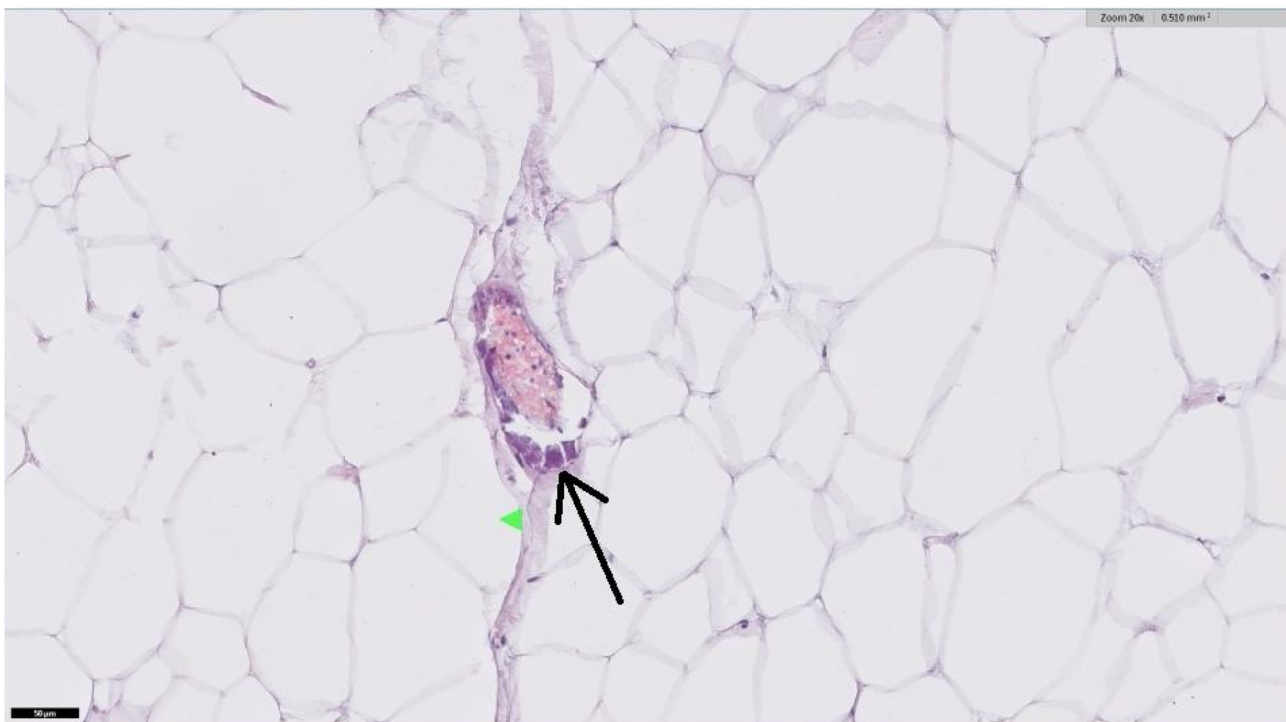


Fig. 2. Calcification of a small cutaneous artery.



Fig. 4. Calciphylaxis of the right breast (2017).



Fig. 5. Calciphylaxis of the left breast (2017).

nists [1–4,10,13–15]. On histology, calciphylaxis is characterized by mural calcification, microthrombi and fibroblastic intima proliferation of the cutaneous arterioles leading to tissue necrosis.

Several pathophysiological theories are proposed [4,7]. Some suggest that the syndrome must be considered as the far end of a continuum of systemic vascular calcification. Calcium deposits is a common finding in patients with end-stage renal disease, but the fact that not all of these patients develop calciphylaxis supports a multifactorial cause [4,13,14]. Other theorised that calciphylaxis is an active, cell-mediated process including matrix remodelling and deposition [8]. It is thought to be the end result of a deficiency of several calcification inhibiting proteins, for example matrix Gla protein which is vitamin K dependent. Therefore, any therapy with vitamin K antagonist is discouraged.

Calciphylaxis should be considered in each hemodialysis patient having painful subcutaneous nodules, non-healing ulcers and/or soft tissue necrosis. Diagnosis can be confirmed via skin biopsy, but also through ultrasound, mammography, X-rays or a three-phase technetium 99 m methylene diphosphate bone scan (organs) [1,3–5,7].

Randomized controlled trials or guidelines considering the most efficient treatment of calciphylaxis are currently lacking. If calciphylaxis is likely, the mainstays of treatment are adequate wound care, pain killers, antibiotics for sepsis control and intensifying dialysis frequency with sodium thiosulfate addition [10,16]. This

agent promotes vasodilatation and increases the solubility of the calcium-phosphate deposits by forming highly soluble calcium-thiosulfate complexes [14]. It is also advised to discontinue vitamin K antagonists, steroids and vitamin D use. Phosphate binders such as sevelamer or a hyperparathyroidectomy may be discussed, possibly supported by cinacalcet or etelcalcitide addition. These medications regulate serum calcium levels by increasing the sensitivity of the calcium receptors on the parathyroid gland.

The role of wound debridement is controversial. Literature shows that wound debridement may be necessary in patients exhibiting extensive infected wounds. Many patients with calciphylaxis have a poor peripheral perfusion and therefore poor healing potential. As a consequence, surgical debridement can induce further necrosis and associated complications. If a dry eschar covers a stable noninfected wound, surgical debridement is contraindicated. Surgical treatment however is required once wounds are infected or an abscess is present [17–19]. Hyperbaric oxygen may be helpful if the areas of skin necrosis are limited.

4. Conclusion

Calciphylaxis must be considered in patients on long term haemodialysis reporting painful, (non-)ulcerating subcutaneous nodules or skin necrosis. A multidisciplinary treatment approach includes wound care, pain relief, antibiotics, increasing dialysis frequency with addition of sodium thiosulfate and optimizing serum calcium and phosphate levels. The role of surgery and hyperbaric oxygen for tissue necrosis is limited. Early diagnosis and treatment might be successful in selected cases.

Conflicts of interest

All authors declare no conflicts of interest relevant to this report.

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Ethical approval

Given that this case report isn't a research study, and the patient did not get any other/extra treatment for the purpose of the case report, this case report has been exempted from ethical approval conform the law on medical research involving human subjects (WMO).¹ Patient gave written informed consent before she passed away.

Consent

Written informed consent to use the case and the images was obtained from the patient before passing away. Written informed consent was also obtained from the family before the publication of this case report and its accompanying images. A copy of the written consent form is available for review.

Author contribution

E. Verstappen: (corresponding author) Collection of information, Writing of the manuscript;
A. Maaskant-Braat: Contributing to idea and valuable criticisms;

¹ Medical Research (Human Subjects) Act. Ministry of Foreign Affairs. Available via <http://www.ccmo.nl/en/your-research-does-it-fall-under-the-wmo>.

M. Scheltinga: Photography, obtaining informed consent, writing of the manuscript.

Registration of research studies

Given that this is a retrospective case report where no research was conducted.

Guarantor

E. Verstappen and M. Scheltinga

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