



Case Report

Case report: Death caused by multi-organ metastatic calcifications as a result of intramuscular injections with paraffin oil

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ABSTRACT

In this forensic case report, we present autopsy findings from a young male in his thirties who had been self-injecting paraffin oil into his upper extremities 8 years prior to death. The injections induced an inflammatory response, leading to granuloma formation. This, in turn, resulted in severe hypercalcemia. The external autopsy examination revealed gross macroscopic ulcerations and enlargement of upper extremities, while calcifications of ligaments, heart, kidneys and dura mater was revealed on postmortem CT-scans. Histopathological examination showed extensive multiorgan metastatic calcifications in several tissues including the lungs, heart and kidney. Cause of death was estimated to be the extensive calcific deposits in the heart likely resulting in cardiac arrest. To our knowledge this is the first case reporting findings from an autopsy in which the cause of death was linked to cosmetic oil injections.

1. Introduction

In recent years, a dangerous trend among male bodybuilders has arisen where cosmetic oil is injected subcutaneously and intramuscularly with the purpose of increasing muscle volume. Several studies have described multiple complications occurring years after the injections, where some men develop severe hypercalcemia among a range of other serious organ effects such as nephrolithiasis and renal failure (Sølling et al., 2018; Tachamo et al., 2018; Eldrup et al., 2021). The clinical presentation is in most cases dominated by the symptoms of hypercalcemia with gastrointestinal symptoms, nausea and renal stones with the addition of pain and swelling from injection sites in the extremities (Eldrup et al., 2021; Sisti et al., 2020). The current understanding of the disease proposes that hypercalcemia can lead to end stage kidney disease (ESKD) (Walker and Shane, 2022),

Hypercalcemia is a consequence of the cosmetic oil injections, and predominantly paraffin oil has been used. The paraffin oil causes granulomas to develop at the sites of injection, which are in some literature described as paraffinomas (Lee et al., 1994). Paraffinomas develop during an inflammatory process in which inflammatory cells express high levels of the CYP27B1 gene, responsible for 1 α -hydroxylase, which

catalyzes synthesis of the active form of vitamin-D (1,25-dihydroxyvitamin D3) (Zehnder et al., 2001). The active vitamin-D mediates non-parathyroid hypercalcemia through increased calcium absorption from the intestines, reabsorption from kidneys, and release from bone.

Research on the subject is scarce and only few major studies on treatment have been published (Yahyavi et al., 2022; Schäfer et al., 2012). Treatment is mainly focused on lowering calcium levels and pain management, with no emphasis on other organs such as the lungs and heart. Current consensus is that surgical removal of the paraffinomas has limited or sparse effect on calcium levels and mainly prednisolone (a corticosteroid) has been demonstrated to have a significant effect (Yahyavi et al., 2022).

To the best of our knowledge, there have been no deaths reported in the literature to be directly linked to cosmetic oil injections or the complications hereafter. Since the increase in the usage of cosmetic-oil injections is relatively new, little is known of the long-term effects and mortality. Furthermore, there is limited knowledge on the histopathological distribution of the cosmetic oil and to which extent it infiltrates tissues other than the kidney. In this case report, we present autopsy, radiological and histopathological findings of a patient with multi-organ calcifications following years of elevated calcium levels.

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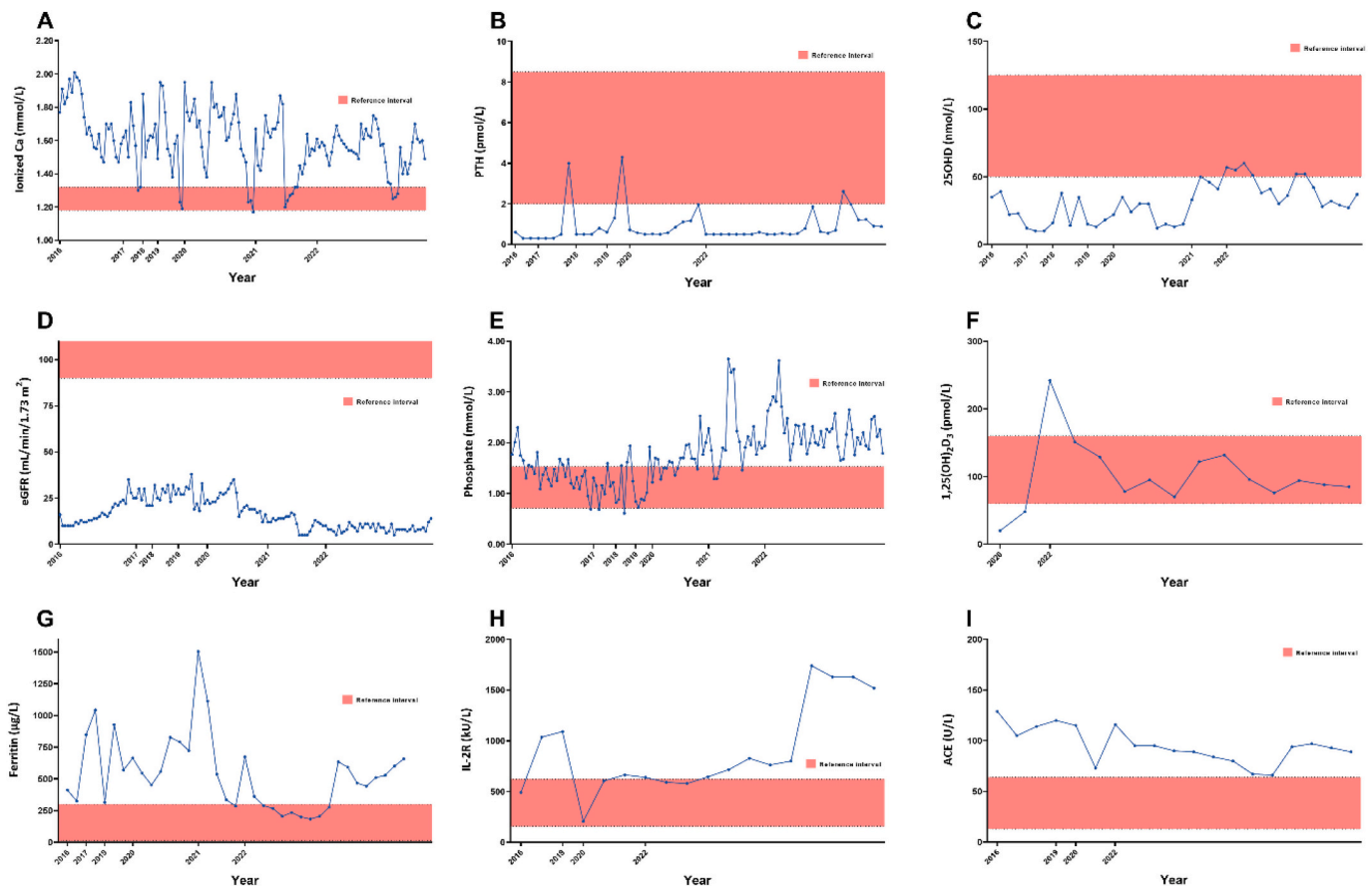


Fig. 1. A-I. Patient biochemistry from 2016 to 2022 including reference intervals indicated by red.

2. Case story

A young male in his thirties had 8 years prior to death self-injected an estimated total of 4000 mL paraffin oil into his biceps, triceps and deltoideus muscle on both upper extremities. Before the injections he had misused androgenic anabolic steroids (testosterone and testosterone derivatives), but this practice was completely abandoned. Initial contact with health care was approximately two years after the injections- due to nausea, dizziness and discomfort. Blood test showed severe hypoparathyroid hypercalcemia with ionized calcium in the range of 1.40–2.00 mmol/L with PTH 0,4–0,6 pmol/L and acute kidney failure, p-creatinine 400–600 $\mu\text{mol/L}$ (Fig. 1.). Granulomas had been formed at the injections site with a foreign body reaction causing severe vitamin-D driven hypercalcemia. Prednisolone treatment (12.5–50 mg) was applied with various effects on calcium levels over the years (Fig. 1). During treatment the patient had no specific symptoms from lungs or heart, nor was any extensive investigation into these organs made. The increased calcium levels ultimately led to end-stage kidney disease (ESKD), in which the male was treated with dialysis three times a week. The paraffinomas had been attempted surgically removed, leaving chronically infected open wounds, without any effect on elevated calcium levels.

In 2022, following planned hemodialysis (HD) treatment the patient felt a sudden onset of chest pain and shortly after was presented with cardiac arrest in which resuscitation had no effect.

3. Autopsy findings

External examination revealed bilateral chronic open wounds on upper extremities with deficits in muscle and soft tissue and visible necrosis (Fig. 2A-B). The wounds edges were rounded and elevated with palpable hard tissue beneath. Internal examination revealed

calcifications along dura mater (Fig. 2C), congested lungs and kidneys both with coarse and “sandpaper-like” sectional surface, enlarged heart with universal white spotty calcifications on the surface and a similar “sandpaper-like” sectional surface through the entirety of the myocardium (Fig. 2D.) Coronary arteries had moderate atherosclerosis, while no atherosclerosis was present in other major vessels.

4. Radiological findings

A whole-body computed tomography (CT) scan was performed prior to the autopsy and described by a board-certified radiologist. In addition to beforementioned autopsy findings, the scan further revealed universal and extensive calcium deposits among fascia, tendons and joints including falx cerebri as illustrated in Fig. 3A. Due to the size of the upper extremities these could not be fully scanned.

5. Histopathological findings

5.1. Histological tissue assessment

Lung and heart tissue sections from the deceased were histologically examined and compared with that of a sex-, age- and BMI-matched control case without paraffin oil involvement. A biopsy of the paraffinoma was also histologically evaluated. Briefly, all tissues were formalin-fixed, paraffin-embedded and cut into serial 4- μm thick sections. Three serial sections per tissue were deparaffinized through a gradient of xylene, 99 %, 96 % and 70 % ethanol, and subjected to Alizarin Red.

For alizarin red staining, slides were washed in demineralized water, submerged in alizarin red solution (9436, VWR Chemicals) and serially washed in acetone, a 1:1 dilution of acetone and xylene, and pure

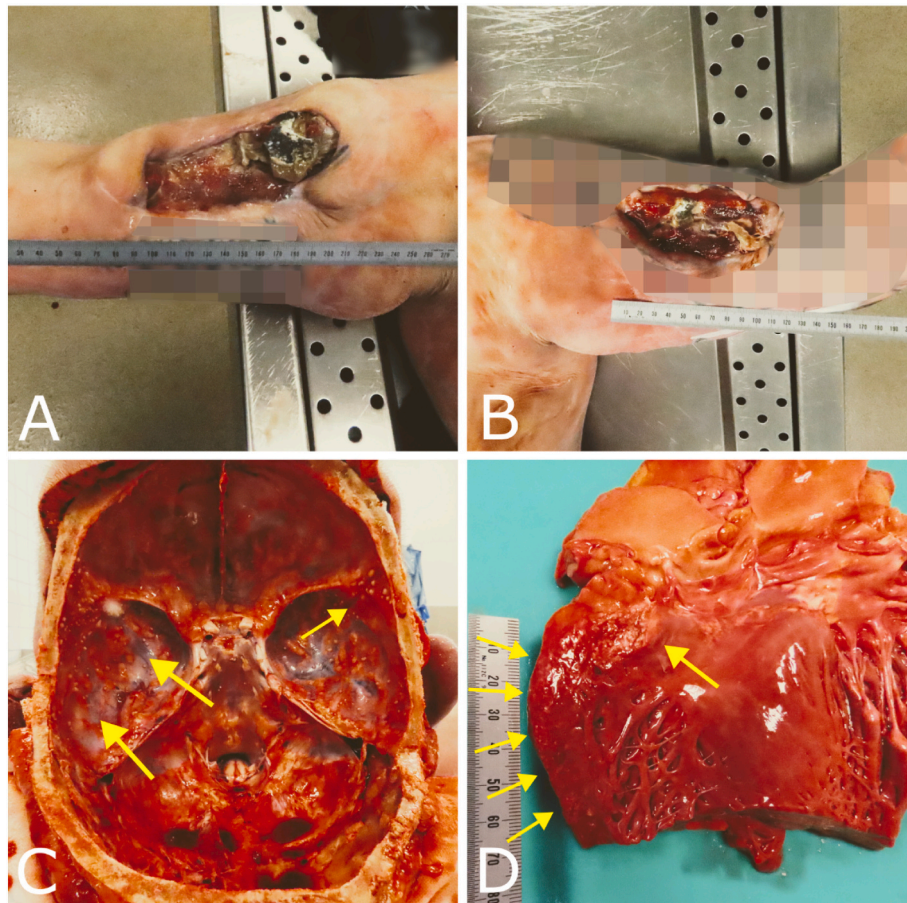


Fig. 2. (A-D): Open necrotic wound at injection sites on upper right (A) and left extremity (B). Dot like calcifications (cerebral calculi) on dura mater universally distributed on the basis of the skull (C). Left ventricle of the heart with spotty calcifications on longitudinal sectional cut of the myocardium (D). Yellow arrows indicate sites of calcification.

xylene. All reagents were purchased from Merck (Søborg, Denmark), unless otherwise specified. Sections were 40× brightfield scanned in a VS200 slide scanner (Olympus Microscopy, Tokyo, Japan).

5.2. Paraffinoma and lung

Samples from the paraffinoma at the upper extremities (Fig. 4A-B) showed numerous variable-sized vacuoles surrounded by a fibrotic stroma indicating scar tissue formation after chronic inflammation. Within the fibrotic tissue were signs of foreign body reaction with presence of immune cells including macrophages, lymphocytes, and a few multinucleated giant cells. On the calcium specific staining's (Fig. 4B) there were large calcium-phosphate deposits around the border of the vacuoles. In the taken samples there were no remaining muscle tissue.

Lung tissue (Fig. 4C-D) on H&E staining revealed alveolar wall thickening and alveolar walls with particle like calcium-phosphate deposits (Fig. 4C). CD68 staining on the lung tissue (Fig. 4D) showed several foamy alveolar macrophages in the alveolar space.

5.3. Heart findings

Spread through the myocardium in the left and right ventricle and septum were multifocal calcium-phosphate deposits with surrounding scar tissue formation and fibroblast proliferation (Fig. 5A-B). The deposits were more prevalent in relation to intramural arteries (Fig. 5C). Few areas had scarce myocytolysis but no areas of acute infarction were found. The unaffected myocardium appeared normal. Microscopic

examination of the kidneys was in line with the already diagnosed ESKD with nephrosclerosis, chronic inflammation and calcifications.

6. Discussion

This unique case describes the complications and direct link from paraffin-oil injections to death of a young man without any other comorbidities. Autopsy findings showed as expected kidney calcifications, but in addition multiple other organs were affected due to the severe and prolonged hypercalcemia. Cause of death in our case was estimated to be cardiac arrest due to the extensive calcium-phosphate deposits in the heart, with contributing factors from ESKD. While chronic kidney failure and nephrocalcinosis have been reported to be associated with paraffin oil disease previously, lung, heart and soft tissue calcifications in this severe form have not been reported before.

The increased use of paraffin oil injections for cosmetic reasons is a worldwide trend (Tachamo et al., 2018). Several case reports have been published (Ahn et al., 2013; Kozeny et al., 1984; Gyldenløve et al., 2014; Di Benedetto et al., 2002), but few studies have made larger observations on etiology, pathogenesis and morbidity (Sølling et al., 2018; Tachamo et al., 2018; Eldrup et al., 2021). A 2020 study with 88 males found a significant association between higher amounts of oil injected (>1000 mL) and level of hypercalcemia (Eldrup et al., 2021). In the 88 men, the average level of oil injected was 1080 mL, but our case had reportedly injected a total of 4000 mL indicating this was an extreme case. A 2018 systematic review concluded a mean duration of 7.96 years from initial injection to diagnosis of hypercalcemia (Tachamo et al., 2018). This review reported that 2 of 23 cases died due to renal

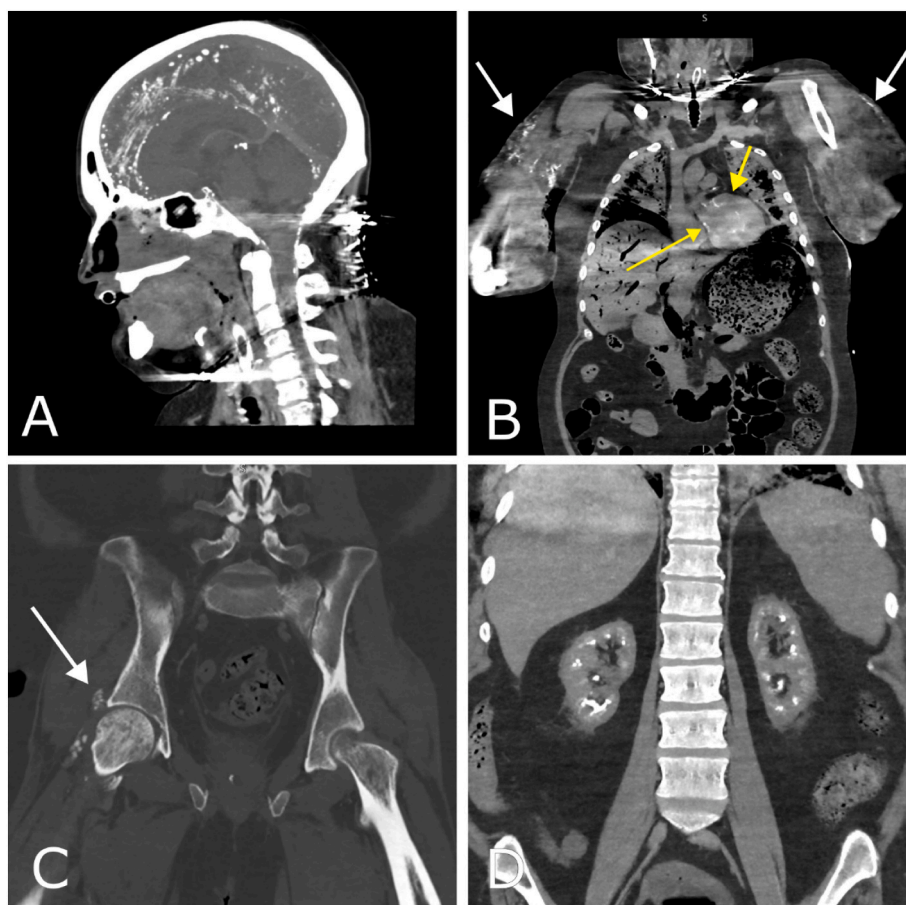


Fig. 3. (A-D) CT-scans: (A) Head in sagittal plane showing extensive calcifications of falx cerebri (B) Paraffinoma with calcifications in upper extremities at injection sites (white arrows) and calcifications in left ventricle wall (yellow arrows). (C) Calcifications of tendons at right hip (white arrows). (D) Abdomen in coronal plane illustrating nephrocalcinosis.

complications (Tachamo et al., 2018) and since then no other studies have reported on mortality in this disease.

Sudden cardiac death is responsible for approximately one quarter of the patients treated with HD for ESKD (O'Shaughnessy et al., 2014). Recent studies on the subject suggest the mechanism to be attributed to fatal arrhythmias caused by electrolyte imbalances rather than structural changes to the heart (Genovesi et al., 2021). However, HD patients are rarely selected for forensic autopsy and the mechanism leading to SCD is not fully understood. Studies suggest that among fatal arrhythmias, ventricular fibrillation or ventricular tachycardia was observed in 78,6 % of the cases (Wan et al., 2014). Whether the fatal arrhythmia was caused by an electrolyte imbalance or as a direct product of the pathological metastatic calcium-phosphate deposition was not possible to clarify.

Myocardial calcifications are usually categorized as either dystrophic or metastatic. Dystrophic myocardial calcifications are often seen following years after infarction or after infection as a response to tissue necrosis (Nance Jr et al., 2015). However, metastatic myocardial calcifications can present itself after any disturbance in calcium homeostasis including ESKD (Nance et al., 2015). In this case the disturbance in calcium homeostasis was due to the inflammatory response within the paraffinomas. The exact mechanism which leads to calcium-phosphate deposit in the heart is not fully understood.

The metastatic calcification in the pulmonary tissue is a known complication to chronic renal failure and other disturbances to calcium metabolism, and can lead to a restrictive respiratory pattern (Madtes, 2016). In our case there were no known respiratory symptoms and lung function was never examined.

Many etiologies can result in cerebral calculi, especially malignant extra- and intra-axial tumors, none of which was found during autopsy indicating these were due to hypercalcemia (Celzo et al., 2013).

The histological samples taken from the injection sites did not contain any muscle cells. This we believe was due to the extensive inflammation and fibrotic tissue within the paraffinoma. From an unpublished case within our department, with non-lethal cosmetic oil injections, the histopathological samples showed inflammation and fibrotic tissue invasion within muscle tissue, indicating intramuscular spreading of the granulomatous tissue which could severely complicate surgical removal.

7. Conclusion

Complications from cosmetic oil injections can be severe. The effect of severe hypercalcemia on kidney function has been well described, but this case suggests clinicians should address pulmonary and cardiac complications when treating patients for paraffinoma induced hypercalcemia, especially if calcium levels cannot be adjusted to normal and/or high volumes of oils have been injected. Furthermore, this case presents important information on mortality, which might urge future bodybuilders to not engage in this dangerous self-harming activity. Further studies are needed, notably on extrarenal complications.

Abbreviations

PMCT	postmortem computed tomography
HD	hemodialysis

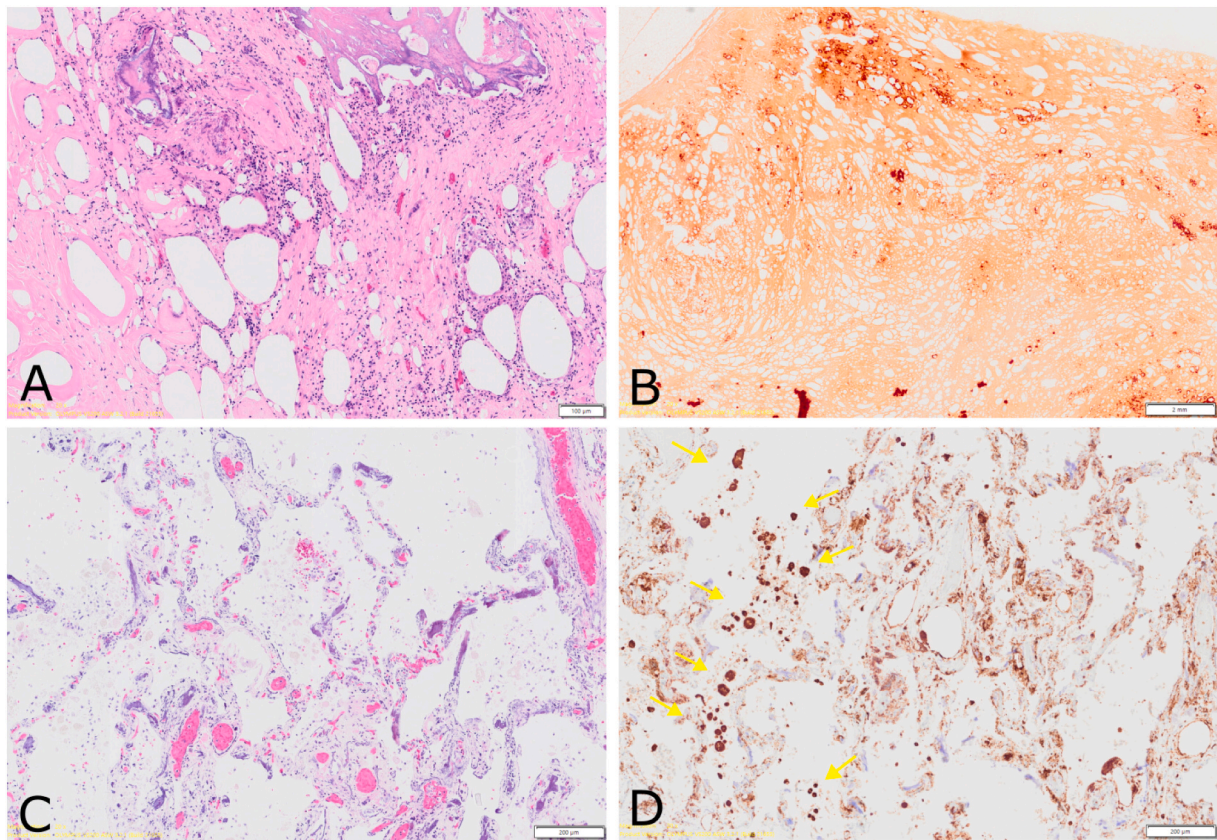


Fig. 4. (A-B) Paraffinoma showing variable-sized vacuoles surrounded by calcium deposits in a fibrotic stroma with acute and chronic inflammation (H&E, left; Alizarin Red, right). (C-D) Lung tissue showing thickened alveolar septa with calcium deposits and CD68 positive foamy alveolar macrophages indicated by yellow arrows (A + C: H&E, B; Alizarin Red, D; CD68).

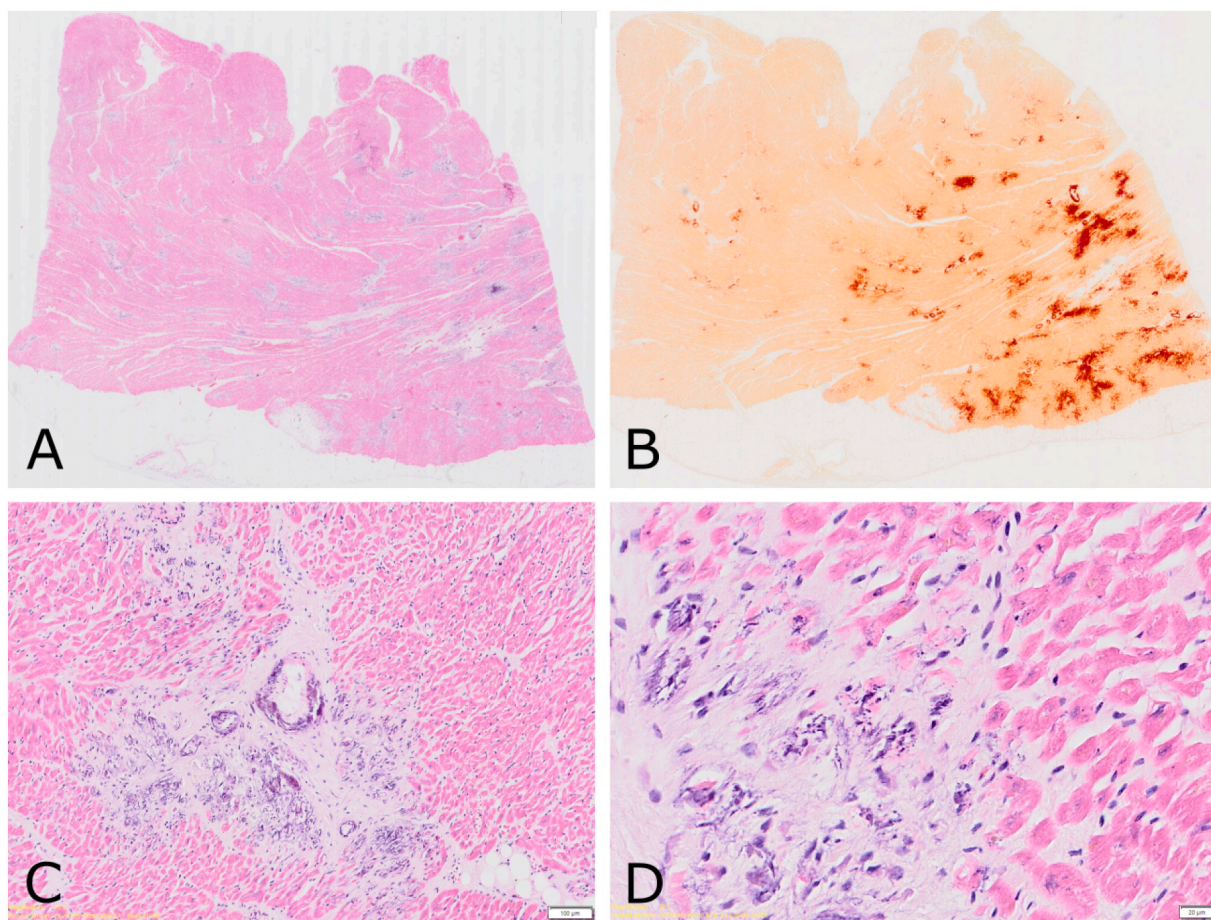


Fig. 5. (A-B) Myocardium with multiple areas of calcification (H&E, left; Alizarin Red, right). (C-D) Higher magnifications showing interstitial calcium deposits in the myocardium and around the blood vessels surrounded by fibrosis. Within the fibrosis are a few inflammatory cells (H&E).

SDC sudden cardiac death
ESKD end-stage kidney disease

CRediT authorship contribution statement

Søren Reinhold Jakobsen: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Marta Diaz-delCastillo:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Martin Blomberg Jensen:** Writing – review & editing, Visualization, Supervision, Data curation. **Thomas Levin Andersen:** Writing – review & editing, Methodology, Formal analysis. **Ebbe Eldrup:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Trine Skov Nielsen:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None to declare. No external funding was received.

Data availability

The data that has been used is confidential.

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