A case report: extensive myocardial calcification and non-ischaemic cardiomyopathy related to past sepsis

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Background
Diffuse myocardial calcification following severe sepsis is a rare complication whose long-term effects are not well-understood.

Case summary
A 51-year-old man presented with a 6-month history of worsening dyspnoea on a background of sepsis 9 years prior. His initial echocardiogram showed moderate systolic dysfunction and a mildly dilated left ventricle. Cardiac computed tomography showed signs of mild coronary artery disease without significant stenosis, but the diffuse extensive left ventricular (LV) mid-myocardial calcification was visible. Cardiac magnetic resonance imaging showed diffuse extensive LV mid-myocardial late gadolinium enhancement in keeping with the calcification. He was diagnosed with non-ischaemic cardiomyopathy. He was commenced on appropriate anti-failure medical therapy, maintains New York Heart Association functional class II functional status, and has received a prophylactic implantable cardioverter-defibrillator.

Discussion
Diffuse myocardial calcification might be associated with long-term development of non-ischaemic cardiomyopathy. The benefit of monitoring such patients for long-term effects is not routine, but should be considered.

Keywords
Case report • Sepsis • Cardiomyopathy • Cardiac magnetic resonance imaging • Computed tomography • Transthoracic echocardiography

Introduction
Sepsis is a relatively common life-threatening condition caused by an overwhelming host immune response to infection1 that can affect every organ, including the heart. One uncommon complication is septic myocardial calcification, which is the appearance of new-onset diffuse myocardial calcifications in the absence of disturbance in calcium homeostasis.2 The cause of such calcification is unknown, although it may be associated with catecholamine exposure in response to sepsis or exogenous administration.3

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Myocardial calcifications can be appreciated on imaging modalities such as computed tomography (CT) or cardiac magnetic resonance imaging (CMRI). CT serves as the best non-invasive test for visualization and quantification of myocardial calcifications.2 CMRI with late gadolinium enhancement technique is the gold standard non-invasive test for quantification of left ventricular (LV) systolic function and fibrosis which is a useful tool in predicting heart failure and arrhythmia risk.4

The long-term effects of diffuse myocardial calcifications are poorly understood. It is theorized that diffuse myocardial calcifications can lead to ventricular systolic dysfunction or scar-related arrhythmia,2 although late-onset cardiomyopathy and associated ventricular arrhythmias due to diffuse myocardial calcifications has not been reported.

We report a case of non-ischaemic cardiomyopathy 9 years following sepsis-associated myocardial calcification.

**Timeline**

| Time          | Events                                                                 |
|---------------|------------------------------------------------------------------------|
| Admission     | Present with dyspnoea associated with abdominal pain and distension. |
| March/April   | Diagnosed with pyelonephritis requiring haemofiltration.               |
| 2009          | Computed tomography (CT) scan at diagnosis (Figure 1A): no cardiac changes. |
|               | Subsequent imaging with CT scan on Day 12 (Figure 1B): showed cardiomegaly, moderate-sized pericardial effusion, and diffuse mid-wall myocardial calcification. |
|               | Transthoracic echocardiogram on Day 32 showed mildly dilated left ventricular (LV) and moderate systolic dysfunction. |
|               | The pericardial effusion was deemed haemodynamically not significant. LV ejection fraction (LVEF) not objectively quantified. |
|               | Presented with cerebrovascular event.                                  |
| Admission     | Transthoracic echocardiogram showed severe LV dysfunction LVEF 22% and an apical thrombus measuring 1.5 cm x 0.9 cm. Treated with anticoagulation. |
| April 2018    | Presented with 6-month history of worsening dyspnoea and peripheral pitting oedema. |
|               | Electrocardiogram (Figure 2) showed left atrial enlargement and inferior pathological Q waves, identical to findings in April 2018. |
|               | Transthoracic echocardiogram showed severe LV dysfunction with LVEF of 20%. |
| November 2018 | Cardiac CT (Figure 1C): mild coronary artery disease with no evidence of significant stenosis. Dilated LV was in keeping with known non-ischaemic cardiomyopathy. Diffuse LV mid-myocardial calcification was noted. |
| October 2019  | Cardiac magnetic resonance imaging (Figure 1D and E): Diffuse extensive mid-myocardial late gadolinium enhancement involving almost the entire LV myocardium associated with moderately dilated LV and LVEF of 34%. |
| April 2020    | Continued on appropriate anti-failure medical therapy; maintained stable New York Heart Association class II functional status, and received a prophylactic implantable cardioverter-defibrillator implantation. |

**Case presentation**

In November 2018, a 51-year-old Caucasian male presented with worsening dyspnoea over 6 months, and lower leg oedema, orthopnoea, and paroxysmal nocturnal dyspnoea. His exercise tolerance was limited to 40–50 m. He denied any chest or abdominal pain, palpitations, or syncope. He did not report history of smoking, excessive alcohol consumption, or drug use including marijuana, cocaine, and amphetamines.

His past history included urosepsis nine years prior (March/April 2009) and a cerebrovascular event 6 months prior (April 2018). In March 2009, the patient presented with right upper quadrant pain, abdominal distension, and worsening dyspnoea. He was subsequently diagnosed with pyelonephritis. A CT scan (Figure 1A) identified a 4 mm calculus within the bladder near the left vesicoureteric junction. Notably, this CT scan (Figure 1A) did not show any cardiac changes. It was complicated by renal failure which required short-term haemofiltration. His serial blood films showed neutrophilia and a leucoerythroblastic appearance with marked left shift. A follow-up CT scan in April 2009 (Figure 1B) showed cardiomegaly, moderate pericardial effusion, and unusual diffuse LV mid-myocardial calcification. His transthoracic echocardiogram showed mildly dilated LV and moderate systolic dysfunction without significant pericardial effusion; LV ejection fraction (LVEF) was not objectively quantified. Due to preoccupation to attend his urosepsis during the admission, the abnormal cardiac findings were not followed up. He had no cardiac symptoms until he presented with a cerebrovascular event in April 2018. A large LV apical thrombus was detected on his transthoracic echocardiography.
His main abnormal physical examination finding during his heart failure presentation in November 2018 was bilateral below-knee pitting oedema. There were signs of respiratory distress. He had a heart rate of 80 beats/min, blood pressure of 140/90 mmHg, respiratory rate of 18 breaths/minute, SpO₂ 98% on room air, temperature of 37.0°C. He was not overweight. There were no peripheral signs of infective endocarditis, respiratory disease, or hepatic disease. His prae- cordial examination revealed a non-displaced apex beat, with no palpable thrills or right ventricular heave. His auscultation revealed S₁ and S₂ heart sounds, with no added sounds, murmurs, or lung crepitations.

His electrocardiogram (ECG) on admission (Figure 2) showed evidence of left atrial enlargement, pathological inferior Q waves, and no acute T wave or ST segment changes. It was unchanged compared to his earlier ECG in April 2018 (Figure 3). The serial cardiac troponin levels were normal. His cardiac CT (Figure 1C) showed signs of mild coronary artery disease without significant stenosis, but diffuse LV mid-wall myocardial calcification. His LVEF was quantified at 20% based on his transthoracic echocardiogram.

Secondary causes of non-ischaemic cardiomyopathy were investigated for and were found to be normal. Serological tests for sarcoidosis showed normal serum angiotensin converting enzyme level, calcium, and phosphate levels. Serological screens for autoimmune pathologies with known cardiac complications were normal. These include extractable nuclear antigens, antineutrophil cytoplasmic antibodies, lupus, and antiphospholipid antibodies. Investigations for microbes including *Legionella pneumophila/longbeachae* antibodies, *Mycoplasma pneumoniae* antibodies, *Chlamydia* antibodies, hepatitis B virus (HBsAg), hepatitis C virus (HCV antibodies), HIV antibody/antigen combo were negative.

The patient was diagnosed with non-ischaemic cardiomyopathy and commenced on valsartan/sacubitril 24.3/25.7 mg BD, spironolactone 12.5 mg OD, frusemide 40 mg OD, atorvastatin 40 mg OD, bisoprolol 5 mg OD, and warfarin. His subsequent CMRI in October 2019 (Figure 1D and E) showed LVEF of 34% and diffuse LV mid-myocardial late gadolinium enhancement suggestive of scarring in the corresponding wall with myocardial calcification as visualized on his CT images from March/April 2009 (Figure 1A and B).
Since the November 2018 admission, he has adhered to appropriate antifailure medical therapy and maintained New York Heart Association class II functional status. In April 2020, he still maintains New York Heart Association class II functional status, and because of his persistent reduced LVEF, he received a prophylactic implantable cardioverter-defibrillator.

**Figure 2** November 2018 ECG on admission. Electrocardiography showing no acute ST or T wave changes. There are pathological Q waves seen in the inferior leads II, III, aVF. There is evidence of left atrial enlargement best seen as terminal p wave lengthening in lead V1.

**Figure 3** April 2018 electrocardiogram, 6 months before November 2018 admission. Unfortunately, there is left atrial/right atrial electrode reversal, but this is the only recent electrocardiogram before November 2018 admission. There are no acute ST or T-wave changes. There are pathological Q waves seen in the inferior leads II, III, aVF. There is evidence of left atrial enlargement best seen as terminal p-wave lengthening in lead V1.
Discussion

We report a case of a 51-year-old man with delayed-onset non-ischaemic cardiomyopathy 9 years post his presentation with sepsis associated with extensive myocardial calcification. Septic myocardial calcification has rarely been reported in the medical literature. Myocardial calcification has been documented since long ago and is further classified into two categories, dystrophic (calcium deposited in areas of necrosis) and metastatic (hypercalcemia-associated conditions, e.g. renal disease, hyperparathyroidism, sepsis). The mechanism of myocardial calcification, particularly in renal disease and hyperparathyroidism, has been attributed to abnormal serum levels of calcium and phosphorus. The mechanism of septic myocardial calcification (Figure 4) remains poorly understood, although catecholamine excess, nitric oxide and inducible nitric oxide synthase, and microvascular ischaemia have been implicated. Most case studies did not report long-term complications, while one patient did not survive the initial complication. There was one similar case in which prolonged administration of high-dose catecholamines was implicated as the cause for subsequent development of heart failure within three months of the patient’s admission. In our case, the patient developed non-ischaemic cardiomyopathy, 9 years after his presentation with sepsis and associated myocardial calcification. He had not been known to have deranged calcium homeostasis or exogenous catecholamine exposure.

Secondary causes of cardiomyopathy such as granulomatous disease (e.g. sarcoidosis), autoimmune diseases, vasculitis, and microbes which can be associated with myocardial calcification or cardiomyopathy were excluded by serological testing.

The presence of pathological inferior Q waves in his ECGs was indicative of previous myocardial infarction or scar development. However, coronary artery disease was ruled out based on a CT coronary angiogram.

The absence of secondary causes on screening and the presence of myocardial calcification and LV dilatation preceded the subsequent presentation of heart failure, further corroborates our diagnosis of late-onset non-ischaemic cardiomyopathy related to past sepsis. His sub-clinical structural heart disease predates the presentation of heart failure by 9 years. Indeed, he would be the first reported case of delayed-onset non-ischaemic cardiomyopathy associated with extensive myocardial calcification. Other potential risks related to myocardial calcification or scarring are atrioventricular conduction disorders or ventricular arrhythmias. Our patient received a prophylactic automated implantable cardioverter-defibrillator due to his risk of ventricular arrhythmia in the setting of persistent reduced LV systolic function and extensive myocardial calcification.

In conclusion, the development of septic myocardial calcification is a rare phenomenon but carries long term implications in inducing cardiomyopathy and a potential nidus for cardiac arrhythmia. As sepsis and infection are common phenomena worldwide, it is possible myocardial calcification is under recognized. Our case demonstrates a potential link to subsequent cardiomyopathy. Cardiac imaging such as CT and magnetic resonance imaging are being used more widely and it is important to highlight any myocardial calcification or abnormal tissue characteristics so that patients can be monitored closely and therapeutic interventions can be instituted early to prevent complications in the long term. It is important to consider past sepsis and septic myocardial calcification as a potential cause of irreversible non-ischaemic cardiomyopathy.

Figure 4 Proposed mechanism involving the current literature on mediators in septic myocardial calcification. Note, there may be unexplored relationships between elements in the mechanism.
Lead author biography

Anthony Martin Lim is a medical student under the mentorship of Associate Professor Chiew Wong. Anthony hopes to train in cardiology, and perhaps enter the new field of cardiac intensivist medicine (cardiology + critical care). Main cardiology interests include the diagnosis and treatment of valvular heart disease, heart failure, and arrhythmias.

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 authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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