CASE REPORT

Myocardial calcification secondary to toxic shock syndrome: a comparative review of 17 cases

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SUMMARY

Myocardial calcification is a rare and life-threatening condition. It has been associated with a myriad of causes, including ischaemic heart disease, cardiac surgery, rheumatic fever, and myocarditis. However, this entity is less well recognised in the setting of toxic shock syndrome. Published medical literature is scarce with regard to the pathogenesis and clinical implications of this potential association. We chronicle here the case of a patient with myocardial calcification secondary to toxic shock syndrome from our clinical experience. Furthermore, a systematic literature search of the medical databases PubMed and Google Scholar was conducted. A total of 17 cases fulfilled the inclusion criteria. The data on patients' characteristics, epidemiology, clinical features, comorbid conditions, diagnosis, clinical course and outcome were collected and analysed. The present review outlines our current understanding of the epidemiology of and risk factors for sepsis-related myocardial calcification, the pathophysiology of this condition and currently available approaches to diagnosis.

degeneration or contraction-band necrosis is considered as the major underlying mechanism in patients with sepsis. An initial insult to myocardial cell membrane causes influx of calcium with myofibrillar hypercontraction, intracellular phosphate depletion and ultimately, leading to cell death and necrosis.³ The initial cell membrane injury in septic shock is attributed to circulating micro-organisms and their toxins with excessive endogenous catecholamine release following septic shock as well as due to the exogenous catecholamine administration during resuscitation. In a vast majority of cases, it is first identified as an incidental finding on cross-sectional chest imaging or echocardiography. No definitive management guidelines exist for this disease.

We describe here the case of a young woman who developed septic shock due to endomyometritis, which led to myocardial calcification found on CT chest. Furthermore, we performed a structured literature review of this entity summarising patients' demographics, clinical presentation, diagnostic modalities, clinical course and outcome.

BACKGROUND

In 1990, septic shock-related myocardial calcification was first reported by Catellier *et al* as an incidental finding noticed at necropsy.¹ After a decade, this condition was described as a premortem finding encountered incidentally on chest radiograph of a patient who was admitted to critical care unit with septic shock requiring intensive resuscitation after 42 days of admission.² Since then, many case reports and small case series have been documented in the medical literature. In terms of pathogenesis of this entity, a unique histological attribute of myofibrillar

CASE PRESENTATION

A 21-year-old woman (gravida 2, para 2) presented to an outside medical centre with fever, severe abdominal pain, myalgia and diarrhoea for 2 days. The patient was discharged from the hospital after a normal spontaneous vaginal delivery 5 days ago. On admission, she was hypotensive to 65/30 mm Hg, tachycardic to 110 beats per minute and febrile to 38°C. On physical examination, she appeared to be in severe distress. Bimanual pelvic and abdominal examinations revealed marked uterine tenderness. The patient was initiated on intravenous norepinephrine, vasopressin and broad-spectrum antibiotics. Thereafter, she was transferred to our hospital for further management.

On day 1 of admission, ultrasonography and CT of the abdomen and pelvis revealed findings compatible with endomyometritis. Subsequently, the patient underwent exploratory laparotomy and an uneventful total abdominal hysterectomy with right salpingectomy was performed. On day 2 of admission, a bedside echocardiogram revealed a persistently depressed left ventricular function. Due to worsening haemodynamic status, epinephrine was also started in addition to the above-mentioned therapy. On day 3 of admission, transthoracic echocardiogram revealed a left ventricular ejection fraction of approximately 10% with mildly reduced right ventricular function. As her condition further

Figure 1 CT scan of the chest on day 19 of admission showing calcification of the left ventricle.

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Figure 2 Chest CT on day 1 of admission demonstrating the normal appearance of the myocardium.

deteriorated, venoarterial extracorporeal membranous oxygen support (ECMO) and continuous renal replacement therapy for worsening renal function were initiated. After haemodynamic support, her condition improved. On day 9 of admission, she was successfully decannulated.

Although she completed her course of antibiotics, spiking constant fever did not subside. On day 19 of admission, a repeat CT scan of the chest was performed, which revealed diffuse punctate myocardial calcifications, involving interventricular septum, left ventricle and the anterior margin of right atrium and ventricle ([figure 1](#)). Review of cardiac images from prior CT, performed on day 1 of admission, was negative for these findings ([figure 2](#)). Furthermore, echocardiogram performed on day 16 and day 21 of admission showed normalisation of the cardiac function. On day 28 of admission, a follow-up chest CT also revealed the persistent calcifications ([figure 3](#)).

OUTCOME AND FOLLOW-UP

She was decannulated from the ECMO but continued to require renal replacement therapy. After resolution of the acute phase of illness, patient's depressed left ventricular function normalised as reflected by her echocardiographic data (E/e' lateral ratio, 8.4; E/A ratio, 1.8; LA diameter, 34 mm; and E/Em ratio: 8.08). However, the myocardial calcifications persisted. She went to

Figure 3 CT scan of the chest on day 28 of admission showing persistent calcification of the left ventricle.

post-acute rehabilitation unit, with no signs or symptoms suggestive of cardiomyopathy to date.

DISCUSSION

Myocardial calcification is categorised as dystrophic or metastatic. The metastatic calcification is commonly found in patients with chronic renal failure due to alterations in calcium and phosphate metabolisms. In these patients, it may also lead to calcified deposits in various other organs, including cardiovascular system. However, the dystrophic calcification is relatively uncommon and it has been associated with myocardial infarction, trauma, surgery, or myocarditis.¹ The average time for the development of this type of calcification ranges from days to months in areas of myocardial necrosis, haemorrhage or fibrosis.¹ Although dystrophic calcification has previously been reported in patients with severe sepsis and septic shock, it is an extremely rare clinical association. Previously, sepsis-related myocardial calcification has only been described in a handful of case reports thus far.

We systematically searched the published medical literature to retrieve the available data for myocardial calcification secondary to toxic shock syndrome. The articles were collected as of September 2018 using the medical databases, PubMed (National Library of Medicine, Bethesda, Maryland, USA) and Google Scholar. Different Medical Subject Headings (MeSH) terminologies, including 'myocardial calcification', 'septic shock' and 'nonischemic calcification' were combined using the Boolean operators 'AND' and 'OR' with the terms 'dystrophic myocardial calcification', 'sepsis' and 'treatment'. Furthermore, a few articles were accessed through a manual search using the reference list of the search results. The inclusion criteria for the final comparative analysis comprised of the studies available in the full-text form in the English-language literature.

A total of 93 articles consisting of but not limited to original articles, case series and case reports were initially obtained using the above-mentioned search strategy. The titles and abstracts of all these articles were carefully reviewed for their relevance to our study. A total of 26 articles were first enlisted for re-review whereas 67 studies were excluded as they were not related to our topic, were in a language other than English and/or full-text versions were not available. After removing duplicate and redundant articles, 15 papers were included in the present study for the final review and analysis. A thorough reading of these articles yielded a total of 17 cases of septic shock-related myocardial calcification.^{1–15} The data of the patients, including demographics, clinical features, comorbid conditions, diagnostic tools, prognosis and outcomes are summarised ([table 1](#)).

A comprehensive review of these cases revealed slight male predominance (men, $n = 10$; women, $n = 7$). The age ranged broadly from 6 to 71 years (mean age: 40 years). All patients required admission to the critical care unit during their course of illness. The aetiology of sepsis was varied, with pneumonia being the major cause. Calcification was detected from as early as 11 days to as late as 70 days from admission (mean duration: 27 days). All patients required vasopressors for haemodynamic support at some point during the course of the hospital stay. Three patients were already on dialysis whereas a few patients required renal replacement therapy during the acute phase of illness. In the past, the cases were diagnosed incidentally on necropsy. In the present times, the use of imaging has become widespread and most calcifications are found incidentally on CT scan of the chest, but most patients die after initial phase of underlying illness. Therefore, the role of myocardial calcification

Table 1 Literature review on myocardial calcification secondary to toxic shock syndrome

Authors	Publication year	Country	Age/gender	Clinical presentation	Comorbid conditions	Calcification detection time after admission (days)	Diagnostic testing	Clinical course and outcome
Catellier <i>et al</i> ¹	1990	USA	38/F	Peritonitis, sepsis	ESRD, hyperparathyroidism	11	Necropsy findings	Patient died after parathyroidectomy due to sepsis
Catellier <i>et al</i> ¹	1990	USA	6/M	Endocarditis, sepsis	Pulmonic valve atresia, cyanotic heart disease	NA	Necropsy findings	Patient died postoperative corrective cardiac surgery complicated by renal failure, respiratory failure and sepsis
Lapatto-Reiniluoto <i>et al</i> ²	2000	Finland	34/M	Ectopic eczema, sepsis leading to renal failure requiring dialysis	None	42	Chest X-ray, TTE, CT chest, autopsy	MODS leading to death
Schellhammer <i>et al</i> ³	2002	Germany	20/F	Septic shock	None	31	CT chest, TTE	Not reported
Rossi and Santos ⁴	2003	Brazil	27/M	Septic shock	None	27	Necropsy	Patient was discharged on day 25 of admission and was found dead in bed 2 days later
Simmons <i>et al</i> ⁵	2007	USA	58/M	Septic shock secondary to pneumonia	Acute lymphoblastic leukaemia	24	CT chest, TTE with global LV dysfunction and EF of 20%	Patient recovered. LVEF normalised to 55% though still some wall-motion abnormalities persisted
Van Kruijsdijk <i>et al</i> ⁶	2011	Netherlands	56/M	Septic shock following <i>Shigella</i> bacteraemia	Hairy cell leukaemia	31	CT chest, TTE	Not reported
Tominaga <i>et al</i> ⁷	2014	Japan	71/M	Septic shock due to pneumonia	ESRD on dialysis	13	CT chest, TTE, myocardial biopsy on follow-up imaging	Patient recovered but systolic and diastolic dysfunction persisted with calcifications
Akbas <i>et al</i> ⁸	2014	Turkey	36/F	Severe sepsis secondary to pneumonia	Acute myeloblastic leukemia	25	CT chest	MODS and death after 37 days of admission
Torfs <i>et al</i> ⁹	2016	Belgium	56/F	Sepsis	Not reported	13	CT chest	Follow-up CT on day 44 of admission showed persistent calcifications and TTE showed diffuse LV hypokinesia with EF of 20%
Vermeulen <i>et al</i> ¹⁰	2017	Belgium	53/F	Staphylococcal pharyngitis leading to toxic shock syndrome	Not reported	14	CT chest	Echocardiography on day 25 and 39 of admission showed EF of 50% and 45%, respectively. Long-term follow-up not reported
Kunz <i>et al</i> ¹¹	2017	Germany	60/M	Sepsis secondary to pneumonia	Progressive multiple myeloma	70	CT chest	Not reported
Torracchi Carrasco ¹²	2017	Ecuador	28/F	Septic shock following pneumonia	Not reported	20	CT chest	Patient discharged in a stable condition but with persistent tachycardia and pleuritic chest pain. Long-term follow-up not reported
Pak <i>et al</i> ¹³	2018	USA	29/F	Postpartum toxic shock syndrome requiring ECMO support	Not reported	Several weeks	CT chest	Discharged to extended acute-care facility on ventilator support
Ng <i>et al</i> ¹⁴	2018	Australia	15/M	Neutropenic septic shock	Klinefelter syndrome, B-cell acute lymphoblastic leukaemia	21	TTE, CT chest	Not reported
Kapandji <i>et al</i> ¹⁵	2018	France	66/M	Septic shock secondary to pneumonia leading to ARDS and requiring ECMO support	None	32	CT chest, TTE, cardiac MRI	Patient recovered. TTE 18 months postdischarge with LVEF of 55% and persistent diastolic dysfunction

Continued

Table 1 Continued

Authors	Publication year	Country	Age/gender	Clinical presentation	Comorbid conditions	Calcification detection time after admission (days)	Diagnostic testing	Clinical course and outcome
Kapandji <i>et al</i> ¹⁵	2018	France	26/F	Septic Shock secondary to pneumonia leading to ARDS and requiring ECMO support	Intravenous drug user	27	CT chest, autopsy	Patient died 94 days after admission. She progressively developed RCM and LV failure
The present report	2018	USA	21/F	Postpartum toxic shock syndrome requiring ECMO and dialysis	None	19	CT chest	Patient recovered. Follow-up echocardiogram showed normal cardiac function. Discharged to post-acute care facility for dialysis needs

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; LVEF, left ventricular ejection fraction; MODS, multiple organ dysfunction syndrome; RCM, restrictive cardiomyopathy; TTE, transthoracic echocardiography.

as a contributing factor to the mortality has been obscured by severe acute illness.

In this review, the calcification was discovered as an incidental finding on chest imaging in a vast majority of cases and no particular management was undertaken. An interesting observation was made in the present review that most patients recovered from the acute phase of illness. However, they were discharged from the hospital with no specific follow-up instructions for this condition. It is theorised that the persistent calcifications may decrease elasticity of the myocardium that can eventually lead to restricting the ventricular filling. In this study, restrictive cardiomyopathy was noted in one of the reported cases, which is in line with the afore-mentioned hypothesis.¹⁵ However, the data on the long-standing effects of these calcifications are scarce. With the advances in haemodynamic support such as ECMO and widespread use of renal replacement therapy, the chances of surviving the acute phase of illness have considerably increased. Therefore, the patients who recover from the acute phase of illness should be monitored for signs of cardiomyopathy secondary to such calcifications. Regardless, in patients admitted to the critical care unit for management of septic shock and requiring haemodynamic support, myocardial calcifications can also be detected incidentally on chest imaging after a few days of illness.

The clinical significance of myocardial calcification has not been extensively studied thus far. Furthermore, there are no specific treatment and follow-up guidelines for patients who survive the acute phase due to the paucity of the reported cases. According to the outcome analysis of cases included in this review, six of the 17 patients died shortly after the acute phase of illness, five during the hospital stay and one shortly after discharge. With regard to the long-term follow-up of the reported cases, one patient died due to progressive restrictive cardiomyopathy and left ventricular failure. Two patients were monitored for over 18 months; one showed persistent diastolic dysfunction and the other had persistent wall-motion abnormalities, but demonstrated otherwise normal cardiac function.

Learning points

- ▶ Myocardial calcifications can be detected incidentally on chest imaging in critically ill patients with toxic shock syndrome.
- ▶ The role of this condition in patients who die during or shortly after the acute phase of illness is not clear due to concurrent presence of comorbidities.
- ▶ The long-term effects of this abnormality on cardiac function have not been gauged due to the paucity of the reported cases.
- ▶ There are no standard management options for the myocardial calcifications. For patients who survive, there is no long-term follow-up plan. Patients who recover from acute phase of illness should be monitored for signs of cardiomyopathy.
- ▶ This paper prompts clinicians to undertake meticulous research on this topic, especially on the pathogenesis, risk factors, clinical implications and potential treatment options.

Contributors TalA: designed the study, performed the literature review, drafted the manuscript, formulated the data table and reviewed the manuscript. FI: performed the literature review, drafted the manuscript, revised the manuscript critically for important intellectual content and gave the final approval for the version published. TahA: contributed to the case presentation and discussion. MH: reviewed the manuscript and suggested pertinent modification.

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