

Acute petrified myocardium associated with meningococcal sepsis in childhood-onset systemic lupus erythematosus: a fatal case

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ABSTRACT

Acute petrified myocardium associated with septic shock, diagnosed by autopsy has rarely been described. A 15-year-old adolescent male was diagnosed with childhood-onset systemic lupus erythematosus. One year later, he was hospitalized with fever, myalgia, headache, arthritis, vomiting, dyspnea and was diagnosed with sepsis secondary to bronchopneumonia and meningitis. Blood culture identified *Neisseria meningitidis* serogroup Y. Despite antibiotics and intensive therapeutic measures, he died after 29 days of hospitalization. The autopsy revealed necrotic cardiomyocytes with dystrophic calcification and interstitial fibrosis.

KEYWORDS: Myocardial calcification. Sepsis. *Neisseria meningitidis*. Lupus. Intensive care.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with concomitant or additive involvement of various organs and systems. The childhood-onset systemic lupus erythematosus (cSLE) is more severe than adult SLE, with higher morbidity and mortality rates¹. Severe sepsis associated with cardiac dysfunction is a major predictor of poor prognosis in cSLE patients, particularly sepsis due to *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections².

The relationship between sepsis and myocardial calcification, also called “acute petrified myocardium”, “petrified heart of sepsis” or “heart of stone”, has been described in few animal models and case reports³⁻⁵. To our knowledge, no case report of petrified heart in cSLE currently exists. Therefore, we report herein a case of an adolescent male with cSLE who developed fatal meningococcal sepsis associated with severe acute petrified myocardium observed at a *postmortem* examination. The Ethical Committee of our University Hospital approved this study (Process N° CAAE 09231912.2.1001.0068).

CASE REPORT

An adolescent male aged 15 years and three months was diagnosed in another hospital with cSLE based on the presence of arthritis, proteinuria (1.2 g/day),

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lymphopenia, thrombocytopenia and 1:640 positivity of antinuclear antibodies (speckled pattern), as well as anti-double stranded DNA antibodies (ELISA, > 200 IU/mL [positive \geq 20 IU/mL]) and low complement levels (C3- 43 mg/dL [normal range 90-180 mg/dL]), C4- 4.5 mg/dL [normal range 10-40 mg/dL]).

Routine non live immunizations (tetanus, hepatitis B, seasonal influenza, pneumococcus and *Haemophilus*) had been previously administered. At 16 years and three months, he was hospitalized at our University Hospital with fever, myalgia, arthritis, vomiting, dyspnea and clinical signs of sepsis. There were no meningeal signs. On the same day, he developed a severe and acute headache, followed by generalized tonic-clonic seizures that required orotracheal intubation. The chest X-ray showed perihilar infiltrate on the right side. Laboratory exams revealed: hemoglobin 13.1 g/dL (normal range 14-18 g/dL), hematocrit 37%, white blood cell count 10,100/mm³ (1% metamielocytes, 15% bands, 68% segmented neutrophils, 6% lymphocytes and 10% monocyte), platelets 70,000/mm³, proteinuria (3.2 g/24 h), urinalysis (leukocytes 6,000 high-power field and erythrocytes 432,000 high-power field), urea 56 mg/dL (normal range 10-42 mg/dL), creatinine 3.59 mg/dL (normal range 0.5-0.9 mg/dL), C3- 25 mg/dL (normal range 90-180 mg/dL), C4- 2.1 mg/dL (normal range 10-40 mg/dL), and C-reactive protein 368 mg/dL (normal range <5 mg/dL). No abnormalities were observed on the cranial tomography and the echocardiography. A lumbar puncture was performed, and the cerebrospinal fluid (CSF) analysis showed the following: white cell count 36/mm³ (88% neutrophils, 8% lymphocytes), glucose 16 mg/dL (normal range 40-80 mg/dL) and protein 456 mg/dL (normal range 15-40 mg/dL). The initial clinical diagnoses were bronchopneumonia and meningitis, and the treatment included intravenous hydration, antibiotics (vancomycin, amikacin, meropenem and micafungin), vasoactive and inotropic drugs (norepinephrine, dobutamine and milrinone), mechanical ventilation and continuous renal replacement therapy.

Immunological tests revealed positive results for anti-dsDNA antibodies and IgG (58.79 GPL/mL) and IgM (31.45 MPL/mL) anticardiolipin antibodies. On the third day of hospitalization, peripheral blood culture identified *Neisseria meningitidis* serogroup Y with intermediate sensitivity to penicillin. The CSF culture was negative. Ten days after admission, the SLEDAI-2K⁶ was 21 and pulse therapy was administered without meaningful response. His oxygenation index and ventricular function progressively worsened. At this point, a second echocardiograph showed left ventricle ejection fraction of 49% (normal \geq 55%, by the Teichholz method) and mild enlargement

of the left ventricle and both atrium chambers. Despite all therapeutic and supportive measures, he died after 29 days of hospitalization. Serology tests for hepatitis (A, B and C), HIV, Epstein Barr virus, cytomegalovirus and toxoplasmosis were all negative.

The autopsy was performed after written consent was obtained from his next of kin. It revealed bilateral and extensive pneumonia, mild pleuritis and pericarditis, active diffuse proliferative nephritis and foci of chronic cerebral abscess in the left temporal cortical area. Remarkably, the heart was heavy, weighting 532 g (reference range 200-350 g) and stiff, and the cut surface had golden-yellowish rough areas scattered in both ventricles (Figure 1A-1C). Under microscopy, these yellowish and rough areas were necrotic cardiomyocytes with dystrophic calcification in their cytoplasm that were associated with interstitial myocardial edema and fibrosis, without myocardial vasculitis (Figure 1D, 1E, 1G, 1H). Von Kossa staining highlighted the calcifications in black (Figure 1F). The pericardium, coronary vessels and atrioventricular valves were preserved.

Myocardial analysis by electron microscopy showed severe damage to cardiomyocyte fibers and mitochondria, with intense myocytolysis (Figure 1J), edema, cristolysis and calcium accumulation in mitochondria (Figure 1M). In more intense lesions, calcification takes over the cellular content (Figure 1K, 1L). Interstitial and endothelial edema were other findings.

DISCUSSION

We reported the first case of acute petrified myocardium most likely induced by a meningococcal sepsis in an active cSLE patient.

Infections are a relevant cause of morbidity and mortality in cSLE patients. The most important risk factors associated with severe sepsis in cSLE populations are related to the disease itself (disease duration, lymphopenia, disease activity and hypocomplementemia) and treatment (glucocorticoid), as observed in our patient. Primary immunodeficiencies (particularly C2, C4, C1q and C1r-s deficiencies) could also contribute to severe infection in our patient; however, these abnormalities were not assessed during hospitalization².

Of note, sepsis was caused by a meningococcal disease (serogroup Y) in the present cSLE patient. In Brazil, this infection in children and young adults is predominantly caused by serogroups C (71%), B (19%) and W (6%), and rarely caused by serogroup Y⁷. Our patient had not been immunized with the anti-meningococcal vaccine (MenACWY conjugate vaccine) as the introduction of this

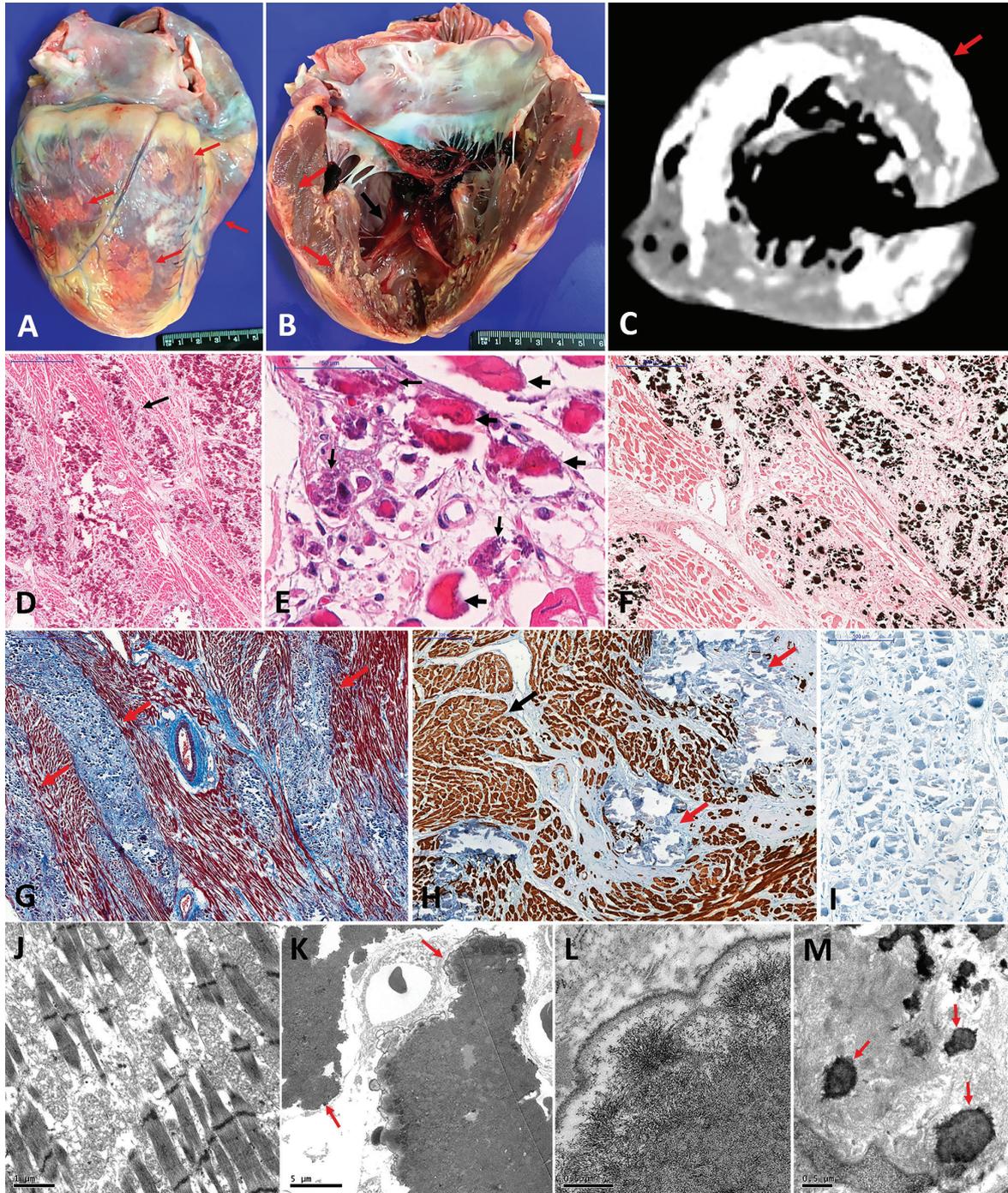


Figure 1 - Pathological findings in a heart with acute petrified myocardium: A) Gross exam of the heart (dorsal view) shows scattered yellowish subepicardial calcified plaques (arrow); B) scattered yellowish and calcified plaques (red arrows) in the myocardium on the left ventricle. An organized thrombus inside the cardiac left chamber (black arrow); C) postmortem, ex situ computerized tomography scan of the heart shows diffuse and coalescent hyperdense areas (calcification) in the entire myocardium on the ventricles, mainly in the left ventricle (arrow); D) necrotic cardiomyocytes with eosinophilic calcification and interstitial fibrosis (H&E); E) the calcification is within the cardiomyocyte cytoplasm and has lamellar (thick arrow) or granular (thin arrow) aspect (H&E); F) calcified cardiac fibers labeled in black with Von Kossa stain; G) interstitial collagen deposition (arrows) in the myocardium in the foci of necrotic and calcified cardiomyocytes (Masson trichrome stain); H) loss of desmin expression in necrotic and calcified cardiomyocytes (red arrows). Non-necrotic fibers maintain desmin expression and are labeled in brown (black arrow) (immunohistochemistry, anti-desmin, mouse monoclonal antibody, Cell Marque™); I) negative expression of Bcl2 in necrotic cardiomyocytes (immunohistochemistry, anti-Bcl2, mouse monoclonal antibody, Cell Marque™); J-M) electron microscopy analysis of thin sections of the myocardium shows diffuse and intense myocytolysis and mitochondrial cristolysis and edema (in J), calcification confined to cardiomyocyte cytoplasm (arrows in K), spicules of calcium with cottony aspect at the periphery of dense and lamellar calcification (in L), calcification in the entire mitochondrial matrix (arrows in M). Scale bars: L, M=0.5 µm; J=1 µm; K=5 µm; E=50 µm; I=100 µm; F, H=200 µm; D, G=500 µm.

vaccine was recent and it is not available in Brazilian public health care services. Thus, the presence of uncommon meningococcal serogroups not covered by the national vaccination program should be considered, and whenever possible, all prophylactic measures available should be implemented, especially in patients with risk factors.

Regarding the response to antibiotic treatment, in Brazil, there is no record of meningococcus resistance to penicillin, but 49% have an intermediate sensitivity profile⁷. The prevalence of penicillin resistance in serogroup Y is higher than that in the other groups. In the present case, the isolated meningococcal strain Y had intermediate resistance to penicillin.

Acute diffuse myocardial calcification is a rare sepsis-related phenomenon and has not been described in cSLE patients. Few cases associated with severe sepsis have been reported in the literature, and the majority of them had myocardial calcification in patients with neoplasia or severe hematological abnormalities^{4,5}.

There are two mechanisms that describe calcium deposition in cardiac myocytes: metastatic calcification and dystrophic calcification. Metastatic calcification is characterized by disturbances in calcium and phosphorus metabolism, leading to high serum calcium and phosphorus levels and deposition of calcium in previously normal tissue. Dystrophic calcification is the most common and occurs when there is a deposition of calcium in degenerated or dead cardiac myocytes⁸. This is usually associated with infarction and severe sepsis. Cell membrane damage leads to increased permeability, resulting in an uncontrolled influx of calcium ions. In sepsis, cells can be damaged by ischemia and increased levels of endogenous and exogenous catecholamine, as well as factors reducing membrane protection⁸.

A single or repeated excess of catecholamine is known to cause disseminated necrosis of cardiac myocytes⁹. In the present case, the patient used norepinephrine at low doses (up to 0.3 mcg/kg/min) for several days. However, he received dobutamine and milrinone for an extended time (\geq seven days).

Experimental animal models identified genes associated with myocardial protective effect on sepsis. Among them, *bcl-2*, with anti-apoptotic action, stands out as an inducer of mitochondrial resistance to injury caused by the intracellular calcium influx. In the present case, we performed immunohistochemistry to detect desmin and *bcl-2* antigens expression in the myocardium, with negative expression in areas with cardiomyocyte necrosis and dystrophic calcification (Figure 1H, 1I), suggesting a lack of involvement of *bcl-2* protein in acute petrified myocardial associated with sepsis¹⁰.

Proteins that influence cardiac contractility, such as UCP 2 (uncoupling protein 2), which has a protective myocardial effect, reduce mitochondrial edema and free radical release, and PARP (poly adenosine 5'-diphosphate-ribose polymerase), an enzyme responsible for accelerating the oxidative stress and the heart damage, has also been associated with the pathophysiology of myocardial injury in sepsis. Immunohistochemistry to detect the expression of these proteins in the cardiac muscle was not performed in the present case^{11,12}.

In our patient, the primary mechanism is likely to be dystrophic calcification due to septic shock, with calcium overload being the crucial pathogenic factor. Other factors, such as ischemia, acute kidney injury with renal replacement therapy, gene expression profile and vasoactive drug use, may have contributed to cell damage. The absence of myocardial vasculitis and other cardiac involvement associated with SLE in the autopsy suggests that the disease activity may be irrelevant to this acute myocardium calcification process.

Currently, there are no treatment for restrictive cardiomyopathy of acute petrified myocardium. Broad antibiotic therapy and inotropic and vasoactive drugs do not seem to change the fatal outcome, as was evident in this case. Prompt heart transplantation seems to be the only available treatment for patients in this condition⁵.

In conclusion, this is a rare case of acute restrictive cardiomyopathy with petrified myocardium associated with meningococcal sepsis in a cSLE patient with active disease.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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