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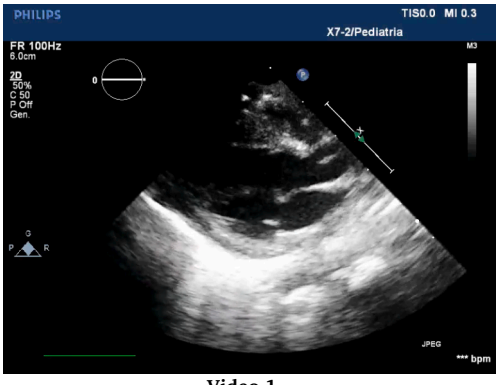
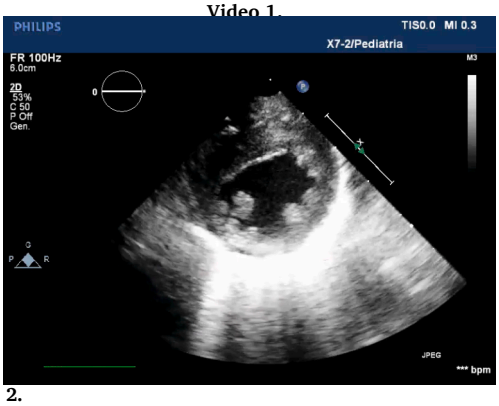
Enterovirus fulminant myocarditis as cause of acute heart failure in a newborn

In November 2019, a 6-day-old male newborn was admitted with fever, conjunctivitis, and cervical lymphadenopathy. He was initially treated with antibiotics for suspected bacterial sepsis. Despite resolution of fever and C-reactive protein (from 4.8 to 1.5 mg/dL) decrease, he developed progressive severe lactic acidosis with liver injury, coagulopathy, thrombocytopenia ($36*10^9$/L), lethargy with seizures that were responsive to phenobarbital, and progressive acute heart failure (high-sensitivity troponin-T of 24,274 ng/L [normal value below 15], CK-MB 53.7 μg/L) complicated by recurrent episodes of ventricular tachycardia. ECG revealed Q waves and ST-segment changes in the antero-lateral leads (Fig. 1**A**), and echocardiography showed a dilated and thickened left ventricle (LV) with severe systolic dysfunction (LV ejection fraction [EF] of 10 %, **Videos 1–2**), left coronary artery dilatation with a focal aneurysm (Fig. 1**B**), and pericardial effusion. High enterovirus RNA load was detected by real-time polymerase chain reaction (RT-PCR) from a pharyngeal swab (20,655 copies/mL) and from blood (979,920 copies/mL). Further characterization of the isolated enterovirus identified a coxsackievirus B3. On day 11 after birth, due to refractory cardiogenic shock, despite mechanical ventilation and inotropic support, a central venous-arterial extracorporeal membrane oxygenation (VA-ECMO) was positioned, and a surgical right ventricular myocardial biopsy was performed. Histology revealed diffuse acute lymphocytic myocarditis. Viral genome analysis of the myocardial biopsy detected enterovirus at a viral load of 642,620 RNA copies/μg. Intravenous immunoglobulins (2 g/kg/die once a day for 2 days) and high-dose corticosteroids (methylprednisolone 30 mg/kg qd for 3 days) were administered as therapy for viral myocarditis with significant lymphocytic infiltrate. No specific antiviral therapies were available [1]. On VA-ECMO support and after immunosuppressive therapy, high-sensitivity troponin-T and CK-MB levels dropped to 4,701 ng/L and 3.7 μg/L respectively. The patient was supported with VA-ECMO for 8 days, and then discontinued. The difficult decision of VA-ECMO removal was taken after parental discussion because of an associated irreversible disseminated intravascular coagulation (DIC) causing uncontrolled bleeding, several surgical revisions, and multiple transfusions, without any sign of ventricular functional improvement. Furthermore, the expected neurologic prognosis was poor in this setting. The patient died of multiorgan failure on day 19 after birth. An autopsy restricted to the heart confirmed massive lymphomonocytic infiltration mainly involving the LV with an enterovirus load of 334,990 RNA copies/μg (Fig. 1**C-E**), a value that was almost halved compared with the first detection on biopsy. No evidence of coronary dilation or coronary vasculitis was documented. The newborn, who was delivered vaginally without complications, likely acquired the enterovirus intrapartum.



Video 1.



Video 2.

1. Discussion

Enteroviral infection in the neonatal period may present as a mild self-limited disease, sepsis-like illness, or in more severe cases as a fatal multi-system disease with myocarditis, meningoencephalitis, hepatitis, and coagulopathy. A high viral load in the blood is associated with a more severe disease [2,3]. The neurological signs and symptoms that the patient developed can be attributable either to the cerebral hypoperfusion due to cardiogenic shock or meningoencephalitis associated with multi-system enterovirus infection. A spinal tap was not performed due to a dramatic and rapid onset of cardiogenic shock; thus, meningoencephalitis cannot be ruled in or out. Furthermore, electroencephalogram was poorly diagnostic because of ongoing pharmacological therapy including phenobarbital, midazolam, and fentanyl. Nevertheless, brain ultrasound of the newborn excluded intracranial hemorrhage before and after VA-ECMO institution. The survival rate in neonatal enterovirus acute fulminant myocarditis is approximately 60 % and decreases to 36 % in patients requiring VA-ECMO support [4,5]. Known

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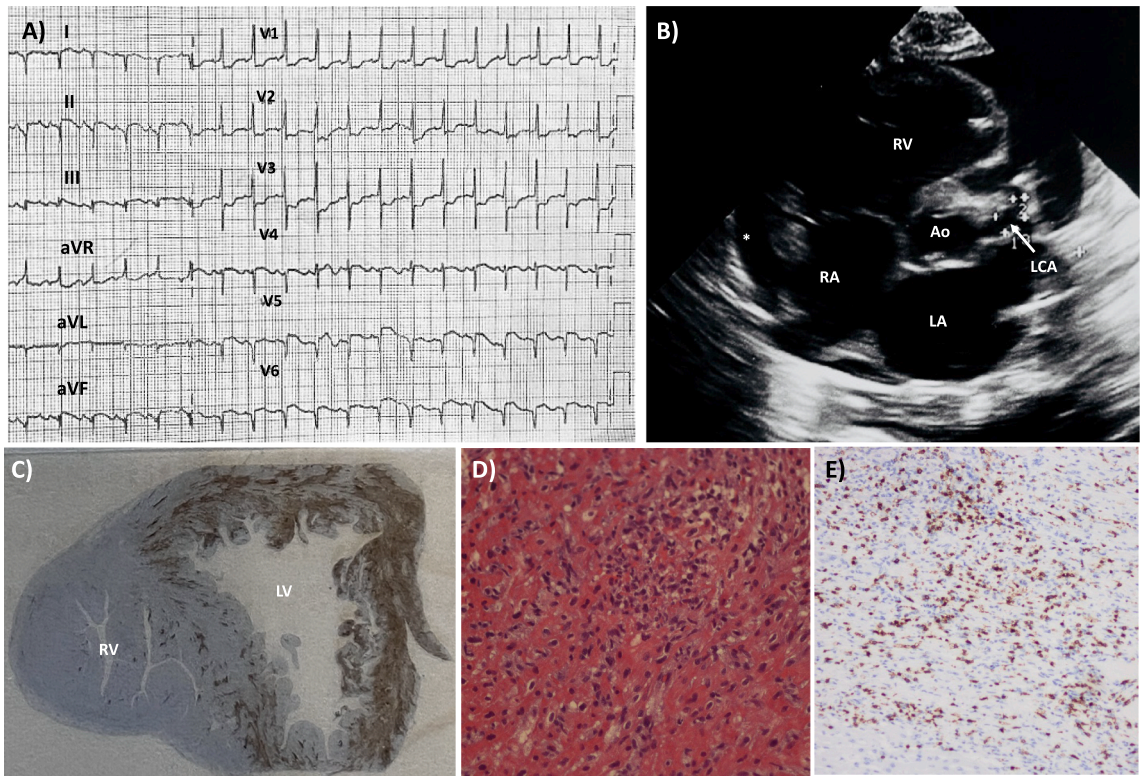

Fig. 1. Enterovirus acute myocarditis. (A) ECG revealed sinus rhythm of 150 beats per minute, Q waves, ST elevation in lateral leads, and ST depression in anterior leads **(B)** Echocardiography showed a dilated and thickened left ventricle (LV) with severe systolic dysfunction, left coronary artery dilatation (LCA, arrow) with a discrete aneurysm, and pericardial effusion (*). **(C)** The staining of the whole heart at autopsy revealed diffuse staining for leukocyte common antigen (CD45) indicating a massive lympho-monocytic infiltration mainly involving the LV. **(D)** Hematoxylin-eosin showed inflammatory infiltrates with areas of myocardial necrosis; (original magnification 200x). **(E)** The staining for CD3 revealed the presence of *T*-lymphocytes in the inflammatory infiltrate further confirming the diagnosis of active myocarditis (original magnification 200x). LA indicates left atrium; RA, right atrium, RV, right ventricle.

predictors of poor prognoses, such as age below 2 years, LVEF < 30 %, and ventricular arrhythmias were present [5].

Although immunosuppression is generally not recommended for enterovirus myocarditis [1,6,7], a significant reduction in copies of the enteroviral genome in the heart, and a decrease in cardiac markers of injury were observed. This unique observation opens the question as to whether administration of passive antibodies and targeting the enterovirus-induced inflammatory response may be effective [8]. Finally, even if no specific drugs can be used against enterovirus sepsis, there a clinical trial assessing the effect of pleconaril suggested a survival benefit in patients assigned to this treatment [9].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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