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When the heart gets the flu
Fulminant influenza B myocarditis: A case-series report and review of the literature

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ABSTRACT

Purpose: To describe patients with refractory cardiogenic shock related to influenza B virus myocarditis rescued by venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO).
Material and methods: Consecutive patients hospitalized in our unit for influenza-associated myocarditis were prospectively included. We also conducted a systematic MEDLINE database literature review through the PubMed search engine, between 1946 and 2017.
Results: We report the cases of 4 young patients with fulminant myocarditis requiring VA-ECMO for 6 [5–8] days. Influenza B virus was detected in all patients, either in nasopharyngeal sampling or bronchoalveolar lavage fluid. The 4 patients received oseltamivir. Heart function recovery allowed ECMO device removal without cardiac sequelae in all 4 patients. Systematic review retrieved 184 cases of influenza-associated myocarditis, most cases associated with H1N1 type-A infection during the 2009 pandemic. Forty eight cases of influenza myocarditis-associated cardiogenic shock requiring mechanical circulatory support including 3 cases due to influenza B virus were described. Mean duration of mechanical circulatory support was 8.5 ± 6 days and mortality rate was 33%.
Conclusions: Influenza myocarditis is a rare but reversible cause of cardiogenic shock amenable to VA-ECMO rescue. Early antiviral therapy and ECMO support should be considered for patients with fulminant myocarditis during an influenza epidemic.

1. Introduction

Acute myocarditis is an inflammatory disease of the heart most often caused by common viral infections. Its spectrum of clinical manifestations includes chest pain, arrhythmia and heart failure. The circulatory failure can be life-threatening and requires high doses catecholamine and mechanical circulatory support [1]. Molecular techniques, e.g. reverse transcriptase-PCR, can identify viruses in endomyocardial biopsies, blood or respiratory samples, with enterovirus, adenovirus, parvovirus B19 and human herpesvirus-6 (HHV6) being the most frequently detected. Influenza myocarditis has been reported more rarely and is usually associated with influenza A virus. We describe four cases of influenza B virus myocarditis engendering cardiogenic shock, successfully managed with the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO).

For our literature review, the MEDLINE database was searched using "myocarditis" and "influenza" as key words. Articles were screened and those in English reporting clinical cases of influenza myocarditis were selected.

2. Case reports

2.1. Case 1

A 28-year-old woman, with a 3-day history of fever, myalgias, cough and diarrhea was hospitalized in March 2013 for sudden-onset chest pain. Her only remarkable medical history was two ectopic pregnancies. At admission, she was tachycardic, her physical examination was

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otherwise normal. The initial EKG revealed low-voltage, Q waves and 1-mm ST-segment elevation in lateral leads. Chest X-ray was normal. Echocardiogram showed severely impaired left ventricular (LV) function with ejection fraction (LVEF) estimated at 30% with diffuse hypokinetic wall motion, aortic time-velocity integral (TVI) at 9 cm, diffuse myocardial hypertrophy and small pericardial effusion. Oseltamivir was prescribed after collection of respiratory samples. Twelve hours post-admission, the patient's blood pressure decreased and she complained of nausea and abdominal pain. Echocardiographic LVEF was 20% and TVI decreased to 7 cm. Inotropic support with dobutamine (10 μg/kg/min) was initiated. Six hours later, mean arterial pressure brutally dropped to 40 mmHg, the patient had nausea and vomiting, lactate level increased to 9,8 mmol/L and aortic TVI decreased to 5 cm. Peripheral femorofemoral VA-ECMO was surgically implanted at bedside under general anesthesia without complication, achieving rapid correction of signs of circulatory failure. Respiratory sample analyses identified Influenza B virus and other myocarditis causes were excluded. Oseltamivir was continued for 5 days. Five days after ECMO implantation, heart function had fully recovered and the circulatory support was removed without any complications. The patient was discharged from the ICU the next day in good condition.

2.2. Case 2

In January 2013, a 35-year-old woman was admitted to our hospital's Emergency Department (ED) with a 3-day history of diffuse myalgias, headaches, and severe abdominal and lumbar pain. On examination, she was tachycardic, tachypneic, and her abdomen was sensitive without rebound tenderness or muscular defense. Chest X-ray showed cardiomegaly. Electrocardiogram revealed sinus tachycardia with PQ-segment depression. Thoracic computed tomography revealed pericardial effusion. Myocarditis was suspected and the patient was transferred to our ICU. Her clinical status rapidly worsened and she developed signs of circulatory failure. Echocardiogram showed biventricular failure with LVEF at 25%, LVOT TVI at 7 cm, and a large pericardial effusion without signs of compression. Dobutamine infusion was initiated at 10 μg/kg/min, combined with oseltamivir, cefotaxime and clarithromycin. Four hours later, LVEF continued to worsen, falling to 10% with TVI at 7 cm despite a 1 mg/h epinephrine infusion. After new echocardiographic evaluation of the pericardial effusion which did not seem to be responsible for tamponade, peripheral femorofemoral VA-ECMO was surgically implanted at bedside under general anesthesia with an intra-aortic balloon pump without complications, and achieved rapid regression of signs of circulatory failure. Virologic analysis of bronchoalveolar lavage (BAL) isolated B influenza virus and oseltamivir was continued for 5 days. Her course on ECMO was complicated by rhabdomyolysis, capillary-leak syndrome, acute renal failure requiring renal replacement therapy and disseminated intravascular coagulation with diffuse distal ischemia. All complications resolved and her clinical status improved rapidly. Five days after ECMO implantation, LVEF was 40% with TVI at 16 cm, allowing ECMO withdrawal. She was discharged from the ICU 1 week later.

2.3. Case 3

A 43-year-old woman with multiple sclerosis was admitted to the ED of another hospital in March 2013 for acute-onset chest pain. Five days before admission, she developed asthenia, cough, 39 °C fever and inspiratory chest pain. At ED admission, her physical examination was normal except for a regular tachycardia at 120 bpm. Electrocardiogram documented sinus tachycardia and microvoltage. Her first echocardiogram showed severe LV dysfunction (LVEF at 30% and LVOT TVI at 9 cm) and minor pericardial effusion. The next day, she developed cardiogenic shock, with blood pressure at 70/40 mmHg and signs of circulatory failure. Despite a 10 μg/kg/min dobutamine infusion, her clinical condition failed to improve and she was transferred to our ICU. She received oseltamivir, clarithromycin and dobutamine was switched to epinephrine (up to 1.5 mg/h). Her hemodynamic status deteriorated over the following hours with estimated LVEF at 10% and TVI at 6 cm (see transthoracic echocardiography). Femorofemoral VA-ECMO was surgically implanted at bedside under general anesthesia without complications, and rapidly corrected her circulatory failure. BAL virology found B influenza virus and oseltamivir was continued for 10 days. Seven days after ECMO implantation, LVEF returned to normal, allowing device removal and the patient was discharged from the ICU a few days later.

2.4. Case 4

In early January 2015, a 39-year-old previously healthy man with 5-day history of flu-like syndrome, consulted at the ED with chest pain and worsening dyspnea. EKG at admission showed diffuse ST-segment depression suggesting myopericarditis. Transthoracic echocardiography revealed LV dysfunction (LVEF at 20%, TVI at 8 cm) with pericardial effusion. The high sensitive troponin Ic level was 6000 ng/L. Because of hypotension, elevated lactate levels and acute renal failure, dobutamine (10 μg/kg/min) was infused and he was transferred to our ICU. Upon arrival we found severe biventricular dysfunction with LVEF < 10% and TVI at 5 cm, which required increasing inotropic support. He had a circumferential pericardial effusion without signs of tamponade. Peripheral VA-ECMO was surgically implanted at bedside under local anesthesia without complication, and considering his medical history, empiric antibiotic therapy was started with oseltamivir and clarithromycin. The next day, PCR analysis of respiratory secretions was positive for influenza B virus. His clinical course was uneventful, except for acute renal failure requiring continuous renal replacement therapy, and pulmonary edema that resolved. Seven days post-admission, his hemodynamic state normalized, as did his myocardial function. ECMO was removed 9 days after implantation and dobutamine support was discontinued 2 days later.

The main characteristics of the 4 patients were reported in the Table 1.

3. Literature review

We conducted a systematic MEDLINE database literature review through the PubMed search engine, between 1946 and 2017, using the following criteria: myocarditis and influenza. We also searched the references of identified studies. Observational studies and case series reporting on adult or pediatric patients having proven or highly suspected influenza myocarditis were eligible. Those with limited clinical information were excluded. Two authors (G.H. and N.B.) independently reviewed the retrieved abstracts and assessed eligibility. A third author (C.E.L.) determined eligibility in the case of disagreement. The following data were extracted: study design, participants' characteristics (including echocardiographic data), need for and type of mechanical circulatory support, outcome data (hospital mortality).

One hundred and eighty four cases of patients suffering from influenza myocarditis were reported in the literature (supplementary table), including 165 cases since the 2009 pandemic: 144 related to A/H1N1 virus, 5 to A/H3N2 virus, 25 to A virus (serotype not reported), and 10 to B virus. Fifty one percent of cases were women, and their mean ± SD age was 33 ± 17 years. Main clinical presentations were cardiogenic shock, new onset heart failure, chest pain mimicking acute coronary syndrome, tamponade, electric storm, atrioventricular block and sudden death. Two thirds of patients received antiviral therapy, mainly oseltamivir and few received peramivir, zanamivir or ribavirine. Left ventricular dysfunction was severe in most of cases with a mean LVEF of 29% ± 14%. Mechanical circulatory support was used in 48 patients including 3 patients with B Influenza infection: mechanical circulatory support without precision in 14 patients, ECMO in 21 patients, intra-aortic balloon pump in 11, Impella devices in 3, and long term ventricular assist device in 6 patients. 83% of these patients had MCS in the first