Novel pH1N1 viral cardiomyopathy requiring veno-venous extracorporeal membrane oxygenation

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**Objective:** To report a case of pH1N1 viral infection presenting as heart failure requiring mechanical extracorporeal life support.

**Design:** Case report.

**Setting:** Pediatric intensive care unit at a regional children’s hospital.

**Patient:** Obese 14-yr-old boy who presented with pH1N1-related cardiomyopathy and respiratory failure that required extracorporeal membrane oxygenation.

**Interventions:** Extracorporeal membrane oxygenation, echocardiography, high-frequency oscillating ventilation.

**Measurements and Main Results:** Discovery of severe dilated cardiomyopathy and respiratory failure.

**Conclusions:** Patients with pH1N1 may present in profound heart failure in addition to respiratory failure. Extracorporeal membrane oxygenation may play an important role in managing these complex patients. (Pediatr Crit Care Med 2011; 12: 000–000)

**Key Words:** pH1N1; swine flu; cardiomyopathy; extracorporeal membrane oxygenation; obesity; children

Since the first North American cases of novel pH1N1 influenza A were described in April 2009 (1), the Centers for Disease Control estimates that, as of December 2009, there have been between 39–80 million cases in the United States. The clinical spectrum of novel pH1N1 infection ranges from mild upper respiratory tract symptoms to fatal pneumonia. An estimated 8,880 to 16,460 pH1N1-related deaths have occurred in the United States (2), whereas it is believed that >14,000 deaths have occurred worldwide. Although the global number of novel pH1N1 cases is not known, >440,000 laboratory confirmed cases had been reported to the World Health Organization by October 2009 (3).

Although fever, sore throat, and upper respiratory tract symptoms are the predominate features of most patients presenting with novel pH1N1 infection, vomiting and diarrhea have been reported in up to 25% of patients (4). In this report, we describe the unusual case of a child with novel pH1N1 infection presenting in acute heart failure due to novel viral myocarditis.

**Case Summary**

The Institutional Review Board of Seattle Children’s Hospital approved this project and provided exemption to the requirement of informed consent.

A previously healthy, mildly obese (body mass index, 28.3 kg/m²) 15-yr-old boy presented to his primary care provider with a 2-wk history of fever, productive cough with blood-tinged sputum, and shortness of breath. Review of symptoms was remarkable for abdominal pain with coughing, fatigue, and exposure to siblings with upper respiratory tract infection symptoms. After a brief trial of conservative therapy for presumed viral upper respiratory tract infection, he was empirically treated with oral amoxicillin and clavulanate for the presumptive diagnosis of pneumonia. Worsening symptoms over the next 24 hrs prompted an emergency department visit, at which time he was noted to be in febrile and in profound respiratory distress with systemic oxygen saturation of 71%. After a failed trial of noninvasive positive pressure ventilation, he underwent endotracheal intubation and required significant mechanical ventilatory support with 0.8 FiO₂ and 20 cm H₂O of positive end-expiratory pressure to maintain adequate oxygenation. The patient was subsequently transferred to a regional medical center where patchy infiltrates and cardiomegaly were noted by chest radiography. These findings prompted transthoracic echocardiography, which revealed severe dilated cardiomyopathy with an estimated 15% to 20% left ventricular ejection fraction. Laboratory studies were significant for elevated serum creatinine (1.3 mg/dL), B-type natriuretic peptide (1031 pg/mL; normal, <100 pg/mL), and white blood count (6900; 68% neutrophils, 13% bands). In the setting of possible viral myocarditis, the patient was empirically treated with intravenous immunoglobulin. Direct fluorescent antibody testing of nasopharyngeal fluid did not reveal adenovirus, respiratory syncytial virus, influenza A or B, parainfluenza viruses, or human metapneumovirus. Additionally, coxsackie, enterovirus, cytomegalovirus, Epstein-Barr virus, parvovirus, and herpes simplex viruses were not detected by polymerase chain reaction (PCR) of airway secretions.

The patient was then transferred to Seattle Children’s Hospital for further management and evaluation for cardiac transplantation candidacy. On admission to the intensive care unit, he was febrile, diaphoretic, tachycardic, and mildly hypotensive. Diffuse hazy airspace opacities were noted on chest radiography (Fig. 1). A second echocardiogram revealed left ventricle dilation without hypertrophy and an estimated body mass index with an ejection fraction of 18%. Working on a presumed diagnosed of severe respiratory failure, viral pneumonia, and a viral cardiomyopathy, he was empirically treated with ceftriaxone and intravenous immu-
noglobulin. He required intravenous dopamine, dobutamine, and milrinone infusions to maintain adequate blood pressure and lidocaine infusion to control frequent premature ventricular contractions. PCR analysis of nasal washings identified coronavirus and influenza A that was subsequently subtyped as novel pH1N1. Enteral oseltamivir and rimantadine were administered for influenza A. However, poor intestinal absorption prompted conversion to intravenous peramivir, an investigational antiviral agent which has received Emergency Use Authorization from the Food and Drug Administration for the treatment of novel pH1N1 influenza (5). Respiratory cultures did not detect a bacterial source of respiratory failure or evidence of bacterial superinfection. Because of the inability to achieve adequate ventilation and oxygenation using conventional ventilation with high pressure at 36 hrs, he was converted to high-frequency oscillatory ventilation. Using ventilatory settings of 0.1 FIO2, 35 cm H2O mean airway pressure of, 5 Hz frequency, and 80 cm H2O amplitude, he was only able to achieve an oxygenation index of 60 and a PaO2/FIO2 ratio of 58.

To improve oxygenation and maximize gas exchange, he was placed on veno-venous extracorporeal membrane oxygenation (ECMO), using a wire-reinforced cannula (31F, Avalon Laboratories, LLC, Rancho Dominguez, CA) placed via the right internal jugular vein. Veno-arterial ECMO was considered in the setting of poor cardiac systolic function; however, the patient had evidence of adequate perfusion with the assistance of pharmacologic inotropic support. In addition, his serum B-type natriuretic peptide was relatively low (136 pg/mL), and his serum troponin I was in the normal range. Veno-venous ECMO flows of approximately 3.6 L/min were achieved, providing mixed venous oxygen saturations of 75% to 80%. He was transitioned to a conventional ventilator (40% FIO2, 28 cm H2O peak inspiratory pressure, 15 cm H2O positive end-expiratory pressure, and 13 cm H2O pressure support). His pulmonary status improved over the next 5 days. ECMO was weaned and successfully discontinued after 6 days of support. Four days after ECMO decannulation, the patient experienced an acute episode of ventricular tachycardia, which responded to electrical cardioversion and intravenous amiodarone therapy. In addition, the patient experienced an episode of severe pulmonary hemorrhage, necessitating reinstitution of high-frequency oscillatory ventilation. A subsequent echocardiogram demonstrated evidence of ongoing severe dilated cardiomyopathy with an estimated ejection fraction of 15% and moderate mitral regurgitation. Serum B-type natriuretic peptide increased to 1600 pg/mL. Repeat PCR of nasal washings did not detect influenza A. Based on worsening echocardiographic findings in the setting of presumed viral myocarditis, a course of high-dose corticosteroid therapy was initiated. Endomyocardial biopsy was not performed at that time because of the risks associated with transferring the patient to the catheterization suite.

The patient’s respiratory and cardiovascular status improved over several days, and he was successfully extubated but still required inotropic support. A subsequent echocardiogram demonstrated slightly improved cardiac function with moderate left ventricle and left atrium dilation, moderate mitral regurgitation, and estimated ejection fraction of 23%. He underwent diagnostic cardiac catheterization, which revealed normal coronary anatomy, 7 mm Hg transpulmonary gradient, and 34 mm Hg left ventricular end-diastolic pressure. Endomyocardial biopsy obtained at that time revealed myocyteolysis and myofibers with hypertrophic changes. Electron microscopy demonstrated clearing of the cytoplasm and autophagic vacuoles, suggestive of basophilic degeneration consistent with novel pH1N1 viral infection 4 wks before the time of biopsy. In light of ongoing myocardial dysfunction, he is being evaluated for possible cardiac transplantation.

**DISCUSSION**

Between April and December 2009, 793 patients with confirmed or suspected novel pH1N1 viral infection were evaluated or treated at Seattle Children’s Hospital. Thirty-eight of the 233 hospitalized patients with novel pH1N1 infection, including the patient described in this report, were admitted to the intensive care unit. Seventeen of these patients required mechanical ventilation, with the average length of intensive care unit care being 6.1 days. In addition to the patient described in this case report, ECMO support was initially considered for an immuno-suppressed bone marrow transplant recipient with aspergillus infection and severe pH1N1 respiratory failure. However, because data from the Extracorporeal Life Support Organization (ELSO) registry indicated no immunocompromised bone marrow transplant recipient ECMO survivors (6), ECMO was not offered and this patient subsequently died of respiratory failure. With the exception of this patient, all novel pH1N1 patients treated at our institution have survived to extubation or hospital discharge.

The Centers for Disease Control and Prevention has identified several risk fac-
tors for novel pH1N1-related complications, including age <2 yrs and >65 yrs, pregnancy, chronic medical or immunosuppressive conditions, and long-term aspirin therapy in persons <19 yrs of age (7). There is growing evidence that obesity may be an independent risk factor for novel pH1N1-related complications (8). Initial data from the ELSO registry indicate that 38% of patients placed on ECMO for novel pH1N1-related illness had a body mass index of >30 (9). Although the etiological relationship between obesity and severe novel pH1N1 illness has not been fully elucidated, there is evidence that increased body mass index is associated with significantly increased influenza-related mortality in an animal model of obesity (10). In the subject of our report, obesity is the only potential risk factor for increased complications from novel pH1N1 influenza.

Initial myocardial biopsy was not performed to confirm viral myocarditis in this patient due to risks associated with transporting an ECMO-supported patient to the cardiac catheterization suite. However, the patient’s clinical course, viral load, and findings on subsequent myocardial biopsy strongly suggest pH1N1-induced cardiomyopathy. It may be argued that the patient’s nasal wash PCR was also positive for coronavirus; therefore, the observed myocarditis may have been caused by coronavirus infection. Although coronavirus infection has been utilized in an animal model of viral myocarditis (11), coronavirus has not been identified by PCR of myocardial tissue specimens from patients suspected of having viral myocarditis in a large reported series (12, 13). The only previously described association between coronavirus infection and myocarditis was described in a letter to the editor published in Lancet 30 yrs ago (14). Myocardial biopsies were not obtained in that case, and the relationship between coronavirus and myocardial dysfunction was based on circulating coronavirus antibodies. It is unlikely, therefore, that coronavirus was the etiological agent of the myocarditis observed in our patient. Most cases of viral myocarditis are due to infection with enteroviruses or adenovirus (12, 15), whereas myocarditis is an uncommonly reported complication of influenza A infection (16). The clinical presentation of acute viral myocarditis ranges from mild impairment of myocardial function to cardiac to severe heart failure and cardiogenic shock. Dysrhythmia, impaired systolic and diastolic function, or pericardial effusion contribute to myocardial dysfunction. Mortality approaches 20% with full recovery of ventricular function seen in 45% of cases with acute viral myocarditis (17).

The treatment of viral myocarditis largely remains supportive, with hemodynamic instability being managed with vasoressors and inotropic agents. Additionally, intravenous immunoglobulin and corticosteroid therapy may play a role in managing these patients. We did not observe any appreciable improvement in myocardial function after initiation of peramivir therapy in the patient described in this report. However, it is possible that the observed improvement in pulmonary function was related to the use of this investigational agent. Mechanical circulatory support, including intraaortic counterpulsation, ventricular assist device, or ECMO, may be required to support patients with severe, refractory heart failure until recovery of ventricular function or heart transplantation. Although extracorporeal biventricular mechanical support has been successfully used to bridge an adult patient with influenza A myocarditis to recovery (18), many of these patients ultimately die of multiple organ system failure (19). Similarly, published reports (20) of the use of ECMO to support pediatric patients with acute fulminate viral cardiomyopathy include successes and failures. A unique feature of the case described in this report is the successful use of veno-venous ECMO to support a patient with combined cardiopulmonary failure rather than veno-arterial ECMO, which is the most common modality (20). A recent review (20) of international ELSO registry data did not identify any infants, children, or young adults with acute myocarditis who have been supported with veno-venous ECMO. We believe the use of veno-venous ECMO was appropriate in this case, because it reduces deoxygenated coronary blood flow associated with cervical veno-arterial ECMO cannulation. In addition, delivering oxygenated blood to the pulmonary circulation may facilitate pulmonary vasodilation, thereby reducing myocardial stress of the right ventricle. Combined, these may improve myocardial recovery.

Over 2,000 children with nonbacterial pneumonia or acute respiratory failure have been supported by ECMO, with overall survival ranging from 50% to 63% (21). A recent review (20) of the ELSO registry revealed that 155 (61%) of 225 of pediatric patients who received ECMO support for severe, acute myocarditis survived to hospital discharge. These reports clearly demonstrate that ECMO can be an important and lifesaving therapy for children with either viral respiratory failure or myocarditis. As of September 2009, 36 patients with novel pH1N1 viral illness who required ECMO support had been reported to the ELSO registry (9). The median age of these patients is 19 yrs, with half of the patients being <18 yrs of age. Six (27%) of the 22 women in this group were pregnant. Overall survival was approximately 59%, which is similar to that recently reported for adults who were supported by ECMO for severe acute respiratory failure (22). A comprehensive review (23) of the initial clinical experience on using ECMO to support patients with novel pH1N1 influenza respiratory failure in Australia and New Zealand was recently reported. The report is notable for the large percentage (34%) of mechanically ventilated pH1N1 patients who required ECMO support. The median age of ECMO patients was 34 yrs, with only three children requiring support. The median duration of ECMO support was 10 days, with an overall survival of approximately 75% at the end of the study period.

The rapid global spread of novel pH1N1 influenza has forced healthcare officials and providers to carefully review infection control policies, treatment strategies, and alternative hospital staffing models. The burden of disease is so significant that, in many settings, patients being evaluated for symptoms of acute respiratory illness are assumed to be infected with novel pH1N1 influenza, and formal testing for definitive confirmation of novel pH1N1 illness is not being performed. Fortunately, severe life-threatening complications of novel pH1N1 illness are uncommon and seem to be largely limited to specific high-risk groups. The patient described in this case presentation underscores the importance considering unusual presenting symptoms, such as heart failure when evaluating patients at greatest risk for novel pH1N1 complications. Furthermore, ECMO support for novel pH1N1 patients with refractory respiratory failure seems to improve survival and should, therefore, be considered early during clinical course of these challenging patients.
REFERENCES


