Cardiac Tamponade and Heart Failure Due to Myopericarditis as a Presentation of Infection with the Pandemic H1N1 2009 Influenza A Virus[▽]

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We describe a fatal case of myopericarditis presenting with cardiac tamponade in a previously healthy 11-year-old child. Pandemic H1N1 2009 influenza A virus sequences were identified in throat and myocardial tissues and pericardial fluid, suggesting damage of myocardial cells directly caused by the virus.

CASE REPORT

Here, we report a fatal case of myopericarditis presenting with cardiac tamponade associated with infection with the pandemic A/H1N1 2009 influenza virus in a previously healthy 11-year-old girl with no known risk factors, including obesity, for severe, complicated pandemic influenza.

The patient developed a high fever (39.2°C) with coughing and vomiting on the evening of 28 October. The next morning, she was visited by a general practitioner, who prescribed antipyretic, antibiotic, and cortisone treatments. About 36 h after the onset of symptoms, the girl presented to the emergency unit of the district hospital with asthenia and dizziness. She was pale and afebrile at 35°C, with tachycardia of 140 beats/min and tachypnea of 32 breaths/min. Routine blood samples were analyzed. The white blood cell count was elevated at 23.8×10^9 cells/liter, and C-reactive protein was elevated at 21.6 mg/liter. Her creatine kinase (CK) level was elevated at 5,814 IU/liter (normal range, 26 to 140 IU/liter), the troponin level was 4.24 ng/ml (normal range, 0 to 0.060 ng/ml), the myoglobin level was 1,849.4 ng/ml (normal range, 12 to 76 ng/ml), and the lactate dehydrogenase level was 1,408 IU/liter (normal range, 266 to 500 IU/liter). Her chest X-ray was reported to be clear. An electrocardiogram (ECG) showed sinus tachycardia with

diffuse ST segment elevation. An urgent echocardiogram was performed, which demonstrated normal ventricle size, severely compromised pump function (ejection fraction, 20 to 30%), diffuse hypokinesia, and a small pericardial effusion, consistent with myopericarditis with a predominant myocarditic component. Metabolic lactic acidosis was also detected and treated with intravenous administration of $\text{Na}^+\text{-HCO}_3^-$.

Because of the need for specialized care and treatment, the patient was transferred to a regional pediatric hospital, but during ambulance transport she had loss of consciousness and needed respiratory assistance. Clinical conditions worsened during transfer to the pediatric intensive care unit (ICU): a peripheral pulse was absent, the central pulse was weak, and the capillary refill time was >5 s. Cardiac frequency (CF) detected by the monitor was 110 beats/min with a wide QRS interval. CF rapidly decreased. Atropine was administered, and cardiopulmonary resuscitation (CPR) maneuvers were performed. The central pulse became absent, and the echocardiogram showed no contractile activity.

The pathological exam showed macroscopic changes such as increased ventricular size (left ventricle thickness, 2.2 cm; right ventricle thickness, 0.35 cm); the left/right ventricle size ratio was 6.28, versus a normal value of 3.1. Pericardial effusion (150 ml) was detected. Pulmonary congestion leading to pneumonic hepatization was also found.

Microscopic changes revealed mild inflammation: modest infiltration of histiocytes (CD68 positive) and myocellular necrosis were detected (Fig. 1 and 2).

PCR analysis of a nasopharyngeal swab collected at the ICU was positive for the pandemic H1N1 2009 influenza virus. The sample was grown in MDCK-SIAT1 cells (hemagglutinating units [HAU], 64). Molecular analyses of several samples of tissues and fluids collected during the autopsy were performed. The pandemic influenza virus was detected in bronchi, in the myocardial tissue, and in both the pericardium and pericardial fluid, whereas it was not found in the lungs or in other tissues or fluids, such as the pharynx, tonsils, and spleen (Table 1). The virus was isolated from myocardial tissue but not from

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FIG. 1. Myocardium sample showing moderate myocarditis and the presence of histiocyte infiltration and focal necrosis. The sample was stained with hematoxylin and eosin. Original magnification, $\times 250$.

other tissues (the pharynx, tonsils, spleen, mesenteric lymph nodes, and liver).

The patient was also examined for other common bacterial and viral respiratory agents (e.g., pneumococcus, mycoplasma, and respiratory syncytial virus [RSV], etc.), and the results were all negative.

Sequence analysis of the hemagglutinin (HA) showed a D222E mutation (H1 numbering), which has been detected in many countries at frequencies of <0.01 to 31.7% (13). It is unclear whether and to what extent change at amino acid position 222, which is located in the receptor binding domain of the HA, influences receptor binding specificity and, ultimately, virus pathogenicity. With regard to neuraminidase (NA) genes, no significant mutations were detected, and the virus was found to be susceptible to NA inhibitors.

The study findings suggest that cardiac tamponade and heart failure following myopericarditis in this young patient were

FIG. 2. Cluster of histiocytic cells (CD68 positive) in the neighborhood of damaged myocytes. Cells were stained with peroxidase. Original magnification, $\times 250$.

TABLE 1. Laboratory results

Clinical sample or tissue type	Result ^a from:	
	Real-time RT-PCR analysis ^b for pandemic A/H1N1	Isolation in MDCK-SIAT1 cells (HAU)
Rhinopharyngeal swab	Positive	Positive (64)
Pharynx	Negative	Negative
Tonsil	Negative	Negative
Bronchus	Positive	Negative
Lung	Negative	Negative
Spleen	Negative	Negative
Heart	Positive	Positive (16)
Pericardium	Positive	Negative
Pericardial fluid	Positive	Negative

^a Positive results are listed in bold.

^b Real-time reverse transcriptase PCR (RT-PCR) analysis was performed using the CDC pandemic kit.

due to direct tropism and damage caused by the 2009 H1N1 influenza virus. Cardiac involvement is not an uncommon complication of seasonal influenza. Elevated CK levels in 12% of patients affected by influenza but without cardiac symptoms and in up to 15% of patients with abnormal ECG patterns suggestive of myocarditis have been reported previously (4, 7). Myocardial damage or clinical myocarditis has also been reported in studies from Japan (6) and Canada (9). In molecular studies conducted in the United States and in Italy, influenza virus accounted for 2 to 10% of all viral agents isolated from myocardial tissues (1, 3).

Viruses are the most important infectious cause of myocarditis. Molecular studies of cardiac samples obtained through cardiac catheterization of patients presenting with acute viral myocarditis resulted in the identification of viral genomes in 38 to 53% of the cases (1, 3). Enteroviruses, especially group B coxsackieviruses, appear to be the major agents implicated (11), but other viruses may also be involved. Influenza viruses A and B may play a role in myocarditis and/or pericarditis, and sporadic cases of myocarditis due to the influenza virus have been reported over the past few decades (8). Overall, there is consistent evidence that influenza viruses may trigger cardiovascular death and that influenza vaccines reduce the risk of cardiac events in subjects with established cardiovascular disease. However, most of the evidence comes from observational and interventional studies of adults and the elderly in whom a cardiac event generally consists of a clinical sequela of primary respiratory infection (8, 12).

Cardiac involvement in influenza is usually reported to occur between 4 and 9 days after the onset of influenza symptoms and is characterized by worsening dyspnea, ECG abnormalities (i.e., ST elevation and Q waves), elevation of cardiac enzymes (e.g., the M [muscle type] and B [brain type] subunits of CK [CK-MB]), and impaired left ventricular function (10). Fulminant myocarditis is characterized by profound left ventricular dysfunction and cardiogenic shock, which requires inotropic support. In some cases, pericardial effusions may result in cardiac tamponade. Myocyte damage may be due to a direct cytolytic effect of the virus or to the host immune response (5); the former mechanism usually plays the major role in cases

with early myocardial involvement, whereas immune response-mediated damage is most likely to occur in later phases of infection (8). In our case, cardiac involvement occurred early in the course of infection, on the third day after the onset of fever, and was associated with fever decrease by crisis. The timing of cardiac involvement, in combination with virus detection in myocardial and pericardial tissues and fluid, strongly suggests a direct effect of the 2009 pandemic influenza virus on the myocardium and pericardium. Importantly, increased virus tropism for myocardial tissue may be favored by the cytokine cascade, enhancing or modifying virus receptor exposure on endothelial cells lining the myocardial tissue (12). A recent study has already reported a severe form of acute myocarditis in four children confirmed to be positive for the 2009 pandemic virus (2). Our work further demonstrates that cardiac tamponade resulting from myopericarditis may occur during pandemic H1N1 influenza virus infection in young subjects, without known predisposing factors. All these observations suggest the possibility that the novel H1N1 virus is more commonly associated with severe forms of myocarditis than previously circulating influenza virus strains. Furthermore, the above data strongly highlight the importance of early diagnosis and treatment in these cases to reduce the risk of severe cardiac events in children.

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