Myocarditis Caused by Human Parainfluenza Virus in an Immunocompetent Child Initially Associated with 2009 Influenza A (H1N1) Virus

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The association between respiratory viruses and myocarditis has hardly ever been described. We report a case of acute myocarditis in an immunocompetent child associated with the presence of parainfluenza virus type 3 infection, in a context of recent influenza illness, confirmed by molecular and serological studies.

CASE REPORT

A 12-year-old girl presented in October 2009 with a 10-day history of fever, cough, and coryza. She had no past medical history of note, there was no family history of cardiac illness, and she did not receive any medications. On 19 October, a nasopharyngeal swab (NPS) sample was taken for microbiological studies. A PCR examination was positive for pandemic influenza A/H1N1 (A/H1N1 pdm) virus by using the CDC protocol for real-time reverse transcription-nested PCR (RT-PCR) for influenza A (H1N1) virus (http://www.who.int/csr/resources/publications/swineflu/realtimemtptcr/en/index.html). She was admitted to a regional hospital in Ciudad Real, Spain, with a diagnosis of viral pneumonia caused by influenza A virus, in the context of pandemic influenza A/H1N1 pdm circulation. She was discharged with antiviral treatment (oseltamivir [3 mg/kg body weight/dose twice daily for 5 days]). Two weeks later, she was readmitted to the hospital with dyspnea and signs of heart failure. She needed intravenous (i.v.) perfusion of inotropic drugs, and a diagnosis of severe left ventricular dysfunction was made. After stabilization, the patient was treated with carvedilol (3.12 mg/12 h), enalapril (5 mg/12 h), furosemide (10 mg/12 h), and acenocumarol (Sintrom). On 3 December, a new NPS sample was taken and PCR examination was negative for influenza A/H1N1 pdm virus by using the same CDC real-time RT-PCR protocol.

On 12 January 2010, after progressive deterioration in cardiac function, the patient was readmitted to the regional hospital and transferred to a university hospital in Madrid, Spain. On admission, the patient’s blood pressure was 91/52 mm Hg, pulse rate was 112 bpm, temperature was 37.0°C, and O2 saturation measured 99% while the patient was breathing room air. The level of C-reactive protein (CRP) was 4.6 mg/dl. The red cell count and hemoglobin level were normal, and the white cell count was 10,700 cells/mm³, with 51.8% polymononuclear cells, 41% lymphocytes, and 5.7% macrophages. Liver enzymes were 50 U/liter aspartate aminotransferase (AST) and 56 U/liter alanine aminotransferase (ALT). The levels of creatine kinase and troponin T were 31 U/liter and 0.01 ng/ml, respectively.

On 21 January, the patient was transferred to our hospital to be listed for heart transplantation, with a diagnosis of refractory heart failure. On admission, the patient was hemodynamically unstable (blood pressure, 70/55 mm Hg; pulse rate, 105 bpm; temperature, 37.1°C). Chest X ray revealed a severe cardiomegaly, and two-dimensional (2D) Doppler echo showed severe left ventricular systolic with ejection fraction of 32% and severe dilatation of left ventricle. The hemoglobin level was normal (12.7 g/dl), as were platelets (305,000/mm³). The girl had no evidence of sepsis or bacterial infection (negative blood, urine, and tracheal aspirate cultures). All serological investigations for herpes simplex virus (HSV)-1, HSV-2, varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV-6) provided negative results, and a PCR examination of an NPS sample was negative for influenza A/H1N1 pdm virus.

There was progressive heart failure, with impending renal failure. The patient required venoarterial extracorporeal membrane oxygenation (ECMO) for stabilization, with cannulation of the carotid artery and jugular vein. A donor heart was available within 24 h, and transplant was successful. Pericardial fluid, a cardiac biopsy specimen, blood, and serum were sent for histological studies, microbiological culture, and molecular diagnosis. Multiplex PCRs in blood, pericardial fluid, and cardiac biopsy samples were negative for HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, and enterovirus (EV). The multiplex
RT-PCR (Clart Pneumovir version 3.0; Genomica, Madrid, Spain) in pericardial fluid and cardiac biopsy specimens was found to be positive for human parainfluenza virus type 3 (HPIV-3). A new NPS sample was sent to the National Centre of Microbiology (ISCH) for microbiological studies. With this sample, the PCR examination was positive for rhinoviruses only.

The histological studies of the cardiac biopsy specimen showed a moderate interstitial infiltration of lymphocytes as well as neutrophils and eosinophils in myocardial and pericardial tissues.

In order to complete the virological findings, both the NPS sample taken on 19 October and pericardial fluid, cardiac biopsy specimen, and serum samples taken on 22 January were sent to the National Centre of Microbiology. The nasopharyngeal swab sample taken on 19 October was positive for influenza A/H1N1 pdm virus, HPIV-3, and coronavirus 229E. The presence of HPIV-3 in pericardial fluid and the cardiac biopsy specimen was confirmed by using two different molecular tests: multiplex RT-PCR assay (1) and the Luminex xTAG respiratory viral panel (RVP) assay. Other viruses studied by these methods were negative (enterovirus, rhinovirus, coronavirus, influenza A, B, and C viruses, respiratory syncytial virus [RSV], adenovirus, bocavirus, and metapneumovirus).

The serological tests used for analysis of antibodies against respiratory virus were indirect immunofluorescence assay (IFA), neutralization test (NT), inhibition of hemagglutination (IHA), and complement fixation (CF). The influenza A virus-, HPIV-1, -2, and HPIV-3-specific antibody titers in the initial serum sample were significantly elevated (Table 1). The NT showed a 1.5-fold increase in neutralizing antibodies against influenza A/H1N1 pdm virus (A/California/07/2009) virus. The high titers of antibodies against HPIV-1 and -3 can be explained by marked cross-reactivity between anti-HPIV antibodies. Previous studies have documented the cross-reactivity of antibodies against HPIV-1 and -3, for the envelope glycoproteins HN and F of these viruses (6). Titers of antibodies against influenza A virus, HPIV-1, and HPIV-3 remained elevated 2 months after the diagnosis of viral pneumonitis.

The postoperative period was uneventful, and the patient was discharged from the intensive care unit (ICU) at day +7 and discharged from the hospital at day +15. She was in functional class I 10 months after transplant, without episodes of rejection.

The etiology of myocarditis is multifactorial (infections, immunological, toxins, drugs, and physical agents such as radiation) (5, 13). Molecular studies of cardiac samples obtained through cardiac catheterization of patients presenting with acute viral myocarditis resulted in the identification of viral genomes in a range of 38 to 53% of the cases. Coxsackieviruses, especially those of group B, appear to be the major agents implicated, but other viruses, such as adenoviruses (12), cytomegalovirus (8), echovirus (11), influenza virus (3), Epstein-Barr virus (9), HHV-6 (10), hepatitis C virus (7), and parvovirus B19 (2), may be involved.

The present case illustrates an unusual presentation of myocarditis caused by HPIV-3 after an upper respiratory tract infection. Other respiratory viruses (influenza A/H1N1 pdm virus and coronavirus 229E) were detected in the NPS samples, but only HPVI-3 was detected in the cardiac tissues. Recent studies showed high rates of codetection of two or more respiratory viruses in children admitted with acute respiratory tract infection (4).

Clinical myocarditis and secondary pericarditis due to HPIV-3 have been reported previously, although the diagnosis has been established on the basis of serology findings (13). However, serology for HPIVs is difficult to interpret, due to the high degree of cross-reactivity among them, as previously reported (6). In our case, HPIV-3 was found during diagnoses with the nasopharyngeal swab, cardiac tissues, and pericardial fluid; thus, the diagnosis was confirmed by molecular tests.

TABLE 1. Serological tests for antibody titers

<table>
<thead>
<tr>
<th>Date of sample collection (mo-day-yr)</th>
<th>Influenza A virus (per CF)</th>
<th>IHA</th>
<th>NT</th>
<th>IIF</th>
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<tr>
<td></td>
<td></td>
<td>A/California/07/2009 (H1N1 pdm)</td>
<td>A/Brisbane/59/2007 (H1N1 seasonal)</td>
<td>A/California/07/2009 (H1N1 pdm)</td>
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<tr>
<td></td>
<td></td>
<td>HPIV-1</td>
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<tr>
<td>12-3-2009</td>
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<td>1-25-2010</td>
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REFERENCES