Life-Threatening Parvovirus B19–Associated Myocarditis and Cardiac Transplantation as Possible Therapy: Two Case Reports


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Parvovirus B19 infection can cause a wide spectrum of disease syndromes. Two cases of parvovirus B19 infection were identified that resulted in life-threatening myocarditis shortly after acute infection in immunocompetent individuals. The diagnosis was made with serological and polymerase chain reaction techniques. One patient was successfully treated by heart transplantation. Sequence analysis showed that the parvovirus B19 cloned from the patients’ sera had 99% homology with the prototype sequence. Clinicians should be alerted to the possible role of parvovirus B19 in myocarditis presenting in immunocompetent patients.

Polymerase Chain Reaction

PCR analysis was performed by a single-round PCR amplification reaction that coamplifies VP1 and VP2 sequences in a single step using the following primers: VP1 5’ AGG AAG TTT GCC GGA AGT TC 3’ and 5’ GTG CTG AAA CTC TAA AGG TG ACT 3’; VP2 5’ GAC ATG GAT ATG AAA AGC CTG AAG 3’ and 5’ GTT GTT CAT ATC TGG TTA AGT TAA AGG TG 3’.

Materials and Methods

Serology

IgG and IgM antibodies to the parvovirus B19 capsid protein VP2 were sought with use of commercial EIA kits (DAKO, Gostrup, Denmark; Biotrin, Dublin) in accordance with the manufacturers’ instructions. Quantification of IgG antibodies (IU/mL) was facilitated with reference to the International Parvovirus Standard Serum for IgG [5]. IgM results were expressed as index values, whereby values >1.0 were considered positive.

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Informed consent was obtained from the parents of the patients, and the guidelines of the authors’ institutions were followed in the conduct of the clinical research.

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Table 1. Case 1: summary of data from serological and PCR testing for parvovirus B19.

<table>
<thead>
<tr>
<th>Days after onset</th>
<th>Sample</th>
<th>PCR, genomes/mL</th>
<th>Anti-capsid IgG (IU/mL)</th>
<th>Anti-capsid IgM index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Serum</td>
<td>Positive, $5 \times 10^7$</td>
<td>&lt;2</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>42</td>
<td>Serum</td>
<td>Positive, $1 \times 10^7$</td>
<td>46</td>
<td>5.2</td>
</tr>
<tr>
<td>70</td>
<td>Serum</td>
<td>Negative</td>
<td>49</td>
<td>2.0</td>
</tr>
<tr>
<td>85</td>
<td>Serum</td>
<td>Negative</td>
<td>62</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>70 Left ventricle</td>
<td></td>
<td>Positive</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>70 Right ventricle</td>
<td></td>
<td>Positive</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

* Index values >1.0 were considered positive.

\(^2\) After transplantation.

\(^3\) Of removed heart.

Case Reports

**Patient 1.** A previously healthy 13-year-old boy was admitted in April 1994 following progressive fatigue over a period of 2 weeks and syncope associated with congestive heart failure with tachycardia (160 beats/min), tachypnea, hepatomegaly, and radiographic cardiomegaly. In addition, severe abdominal spasms and diarrhea occurred that did not respond to treatment. Electrocardiogram showed T-wave inversion and elevated S-T segments. The left ventricle was dilated and contracted poorly.

Laboratory analysis revealed a hemoglobin level of 14.6 g/dL, C-reactive protein level of 171 mg/L, and a leukocyte count of 11,000/mm³. The intravenous administration of diuretics, catecholamines, and inodilators did not stabilize the patient’s condition. The patient therefore underwent orthotopic cardiac transplantation 2 months after admission and recovered well. More than 2 years later, in March 1997, the patient was reported to be in excellent health.

Before admission, the patient had no typical clinical symptoms of parvovirus B19 infection. A serum sample was taken shortly after admission in order to search for an infectious cause of disease. The serological findings, which were as follows, showed no indication of infection with the infectious agents tested: enterovirus (coxackievirus and echovirus pool antigen) CF test (CFT), 1:16; Coxiella burnetii CFT, <1:16; Chlamydia pneumoniae immunofluorescence, IgG of <1:8 and IgA of <1:8; cytomegalovirus CFT, <1:8, and EIA for IgM, <1:32; adenovirus CFT, 1:16; Mycoplasma pneumoniae CFT, <1:16; respiratory syncytial virus, 1:8; influenza virus A CFT, 1:16; influenza virus B CFT, 1:16; and parvovirus B19 EIA, IgG of <2 IU/mL and IgM of <1.0. Nonetheless, parvovirus B19 DNA was detected in this serum by PCR. A sample drawn 3 weeks later revealed seroconversion for IgG and IgM antibodies to parvovirus B19. The serological findings with regard to all the other infectious agents corresponded to those found in the first serum sample.

Parvovirus B19 DNA was also detected in numerous biopsy specimens of the patient’s removed heart (table 1). Serum samples and biopsy material were also sent to a second laboratory (Public Health Laboratory Service [Dr. B. Cohen], London) for independent analysis. The serological results were confirmed by a parvovirus B19 IgG antibody assay (DAKO) and an in-house monoclonal antibody capture radioimmunoassay for IgM. Parvovirus B19 DNA could also be detected in the biopsy specimens by single-round and nested PCR methods.

Microscopic analysis of the removed heart revealed hypertrophic heart-muscle tissue with enlarged and irregular nuclei, particularly in the region of the left ventricle. The interstitium had many fibrous dilations and contained discrete lymphocytic infiltrations. The rear wall had a transmural scar. Analysis of the other sections revealed fine, netlike fibrin of varying degrees with discrete lymphocytic infiltration in places. In addition, mild endocarditis as well as slight chronic and fibrous pericarditis were evident in papillary muscle close to the scar. The findings were considered to be in accordance with an almost completely healed perimyocarditis.

**Patient 2.** In April 1995 a 7-year-old girl was admitted to the hospital because of a 5-day history of high fever, vomiting, and joint and abdominal pain. She also had a truncal rash with erythematous macules on the abdomen and upper chest, purpuric lesions on the back, and urticarial lesions on the flexor surfaces of both arms. On admission the child was severely ill with a fever (temperature, 40.2°C), pulse rate of 120/min, blood pressure of 80/50 mm Hg, some subcutaneous bleeding of the trunk, edema of joints and backs of the hands, and minimal lymphadenopathy (cervical lymph nodes, 1 cm in diameter). Laboratory analysis revealed hypoproteinemia, thrombocytopenia, elevated transaminase levels, a leukocyte count of 12,800/mm³, an erythrocyte count of 4.5 × 10⁶/mm³, a hematocrit of 37.1%, a C-reactive protein level of 3.1 mg/dL, and a hemoglobin level of 11.8 g/dL. Blood gas analysis was normal, and blood and urine cultures were negative. Cardiac arrest occurred suddenly on the 7th day of illness; resuscitation efforts (intubation, ventilation, i.v. catecholamine and adrenaline, and electrical and manual stimulation of the heart) were successful only for a short time, and the patient died after 45 minutes.
Table 2. Case 2: summary of data from serological and PCR testing for parvovirus B19.

<table>
<thead>
<tr>
<th>Days after onset</th>
<th>Sample</th>
<th>PCR, genomes/mL</th>
<th>Anti-capsid IgG (IU/mL)</th>
<th>Anti-capsid IgM index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Serum</td>
<td>Positive, $5 \times 10^4$</td>
<td>$&gt;100$</td>
<td>7.5</td>
</tr>
<tr>
<td>$7^*</td>
<td>Serum</td>
<td>Positive, $5 \times 10^3$</td>
<td>$&gt;100$</td>
<td>4.1</td>
</tr>
<tr>
<td>$7^*</td>
<td>Pericardial fluid</td>
<td>Positive, $5 \times 10^3$</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>$7^*</td>
<td>Ascites</td>
<td>Positive, $5 \times 10^3$</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>$7^*</td>
<td>Heart septum</td>
<td>Positive</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>$7^*</td>
<td>Lung</td>
<td>Positive</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

* Index values $>1.0$ were considered positive.

Some of the data for the second case is as follows:

- Serum sample: positive for B19, with 5 x 10^4 genomes/mL.
- Anti-capsid IgG: >100 IU/mL, index 7.5.
- Anti-capsid IgM: 4.1

Serological analysis of sera collected on the 4th and 7th days of illness showed no evidence of recent infection with the following viruses: enteroviruses (per CFT using enterovirus pool antigen as well as individual antigens of coxsackieviruses B1–5, echoviruses 11 and 30, and coxsackieviruses A5, 7, 9, 10, and 16; and in-house EIAs for IgM and IgA using coxsackie-echovirus pool antigen), herpes simplex, varicella zoster, cytomegalovirus, measles, rubella, mumps, influenza A and B, and parainfluenza. However, acute infection with parvovirus B19 was demonstrated in two independent laboratories by the presence of parvovirus B19–specific IgG and IgM antibodies and by the detection of parvovirus B19 DNA by PCR in both serum samples. Parvovirus B19 DNA was also detected in ascites and pericardial fluid, as well as in lung and heart muscle (table 2). Attempts to isolate virus in cell culture of ascites, pericardial fluid, and lung tissue were unsuccessful, and detection of enterovirus RNA by PCR was also negative [8].

Histology of the heart revealed diffuse lymphocytic infiltration in all sections but particularly around the right ventricle, as well as cardiomyocytes with enlarged nuclei. In addition, fresh parenchymal bleeding was seen that may have resulted from resuscitation attempts.

Discussion

The patients described herein suffered severe myocarditis following acute parvovirus B19 infection. Although neither patient was known to have been in contact with the virus, both were infected in the month of April, when parvovirus B19 infections are prevalent. Infections with enteroviruses, which are frequently associated with myocarditis, tend to occur in the late summer months and were not prevalent in the patients’ communities at the time.

Taken together, these two cases provide convincing evidence of the involvement of parvovirus B19 in cardiac disease. Remarkable here is the ability of parvovirus B19 to cause severe perimyocarditis in a patient far beyond infancy, i.e., in a fully immunocompetent individual. In the majority of cases, however, parvovirus B19 infection runs a subclinical course or produces only mild symptoms.

The mechanisms influencing the severity of infection are as yet poorly understood. One possibility may be the existence of particularly virulent parvovirus B19 strains. However, nucleotide sequence analysis of parvovirus B19 DNA (>2,000 nt from case 1 and >600 nt from case 2), which was cloned from the patients’ sera, showed 99% homology with the published sequence [9], which argues against strain variation. The cellular receptor for parvovirus B19, blood group P antigen or globo-B19 was demonstrated in two independent laboratories by the presence of parvovirus B19–specific IgG and IgM antibodies.

Histology of the heart revealed diffuse lymphocytic infiltration in all sections but particularly around the right ventricle, as well as cardiomyocytes with enlarged nuclei. In addition, fresh parenchymal bleeding was seen that may have resulted from resuscitation attempts.

The clinician should be aware of the possible role of parvovirus B19 in myocarditis presenting in immunocompetent patients. In cases of life-threatening disease, cardiac transplantation can provide an adequate form of treatment, as seen here in patient 1. However, even if a suitable donor heart had been available, transplantation probably would not have saved the life of patient 2. The intravenous administration of immune globulin (IVIG) has been proposed as a treatment for severe persisting anemia associated with parvovirus B19 infection in immunocompromised individuals. However, the patients described herein were able to mount a satisfactory immune response, as demonstrated by the increase in both IgG and IgM antibodies.

Although we consider it unlikely that IVIG would have helped the patients described herein, who suffered acute rather than chronic parvovirus B19 infection, it may benefit patients with parvovirus-associated myocarditis who are immunocompromised. The role of parvovirus B19 in both fetal and childhood myocarditis warrants further studies.

References


