Fatal Myocarditis Associated with Acute Parvovirus B19 and Human Herpesvirus 6 Coinfection

JACQUES ROHAYEM, JÜRGEN DINGER, RAINER FISCHER, KARIN KLINGEL, REINHARD KANDOLF, AND AXEL RETHWILM

Institut für Virologie, Klinik für Kinderheilkunde, and Institut für Pathologie, Medizinische Fakultät “Carl Gustav Carus,” Technische Universität Dresden, 01307 Dresden, and Abteilung für Molekulare Pathologie, Institut für Pathologie, Universität Tübingen, 72076 Tübingen, Germany

Received 3 August 2001/Returned for modification 4 September 2001/Accepted 11 September 2001

We report on the case of a healthy young boy who developed a fulminant myocarditis due to acute coinfection with erythrovirus (parvovirus B19) and human herpesvirus 6 (HHV-6) in the absence of an antiviral immune response. We suggest that the HHV-6-induced immunosuppression enhanced dissemination of parvovirus B19, which led to fatal myocarditis.

CASE REPORT

An 11-year-old boy was admitted with a 3-day history of fever that progressed within a few hours to acute distress. He had no notable medical history; in particular, there were no signs of a preexisting immunodeficiency. On examination he was lethargic and cyanotic with tachypnea and had a fever (41.3°C). His blood pressure was 73/31 mm Hg, and his pulse was 201 beats/min. Erythema and exudates on the tonsils were noted, as were cervical lymphadenopathies and a rash involving both arms and the neck. Examination of the head, lungs, and abdomen was normal. There were no focal neurological signs. He was intubated. Intravenous dopamine and dobutamine were given. Arterial blood gas analysis showed a pH of 7.26 and partial O2 pressure of 3.48 kPa, with an O2 saturation of 43.4%. Cardiac arrest occurred suddenly; resuscitation efforts were successful only for a short time, and the patient died of congestive heart failure 55 min later.

Biochemical laboratory findings were normal except for C-reactive protein (64.5 mg/liter; normal level, <10 mg/liter), creatinine kinase (6.60 μkat/liter; normal level, 0.10 to 3.17 μkat/liter), and troponin T (0.59 ng/ml; normal level, <0.1 ng/ml) levels. The white blood cell count was 5 × 10⁹/liter, with lymphocytopenia (lymphocyte count, 0.35 × 10⁹/liter) and thrombocytopenia (platelet count, 36 × 10⁹/liter).

Postmortem examination of the heart revealed enlargement of both ventricles, with pericardial and subpleural petechial hemorrhage. Histopathological examination showed a diffuse myocarditis with interstitial infiltrates of mononuclear cells (predominantly CD8⁺ lymphocytes). Histological examination of the pharynx revealed diffuse interstitial infiltrates of mononuclear cells.

Serological results did not indicate acute infection with adenovirus, herpes simplex virus type 1 or 2, Epstein-Barr virus, cytomegalovirus, influenza type A or B virus, coxsackievirus type A or B, echovirus, or hantavirus. Testing for parvovirus B19-specific antibodies was performed by a commercially available enzyme immunoassay (Medac) with baculovirus-expressed VP1 and VP2 proteins as antigens. Testing for human herpesvirus 6 (HHV-6)-specific antibodies was performed by an indirect immunofluorescence technique with MT4 cells infected with HHV-6 variant B (HHV-6B), strain Z29, and HSB-2 cells infected with HHV-6 variant A (HHV-6A), strain GS. Testing for immunoglobulin G (IgG) and IgM antibodies to parvovirus B19 and HHV-6A and HHV-6B was negative. Bacteriological cultures of blood specimens and cerebrospinal fluid were negative. Attempts to isolate virus from the patient’s blood, cerebrospinal fluid, lung, spleen, and brain tissue were unsuccessful.

Nucleic acid isolation was performed with the QiaAmp viral kit (Qiagen) for body fluids or by the method of Chomczynski and Sacchi (5) for samples recovered postmortem. All samples that tested positive were extracted a second time and reanalyzed. On the basis of the parvovirus B19 DNA sequence (GenBank accession number AB030694), a nested PCR was performed to amplify a region of the gene for capsid proteins VP1 and VP2. Primers P1 (5′-GTA CAG GAG GTA CAG CAT C; base pairs 3728 to 3746) and P2 (5′-ACC CAC TCC TTG CTG ATA C; base pairs 4176 to 4158) were used for the first-round PCR, and primers P3 (5′-AGA GGG CTG CAG CAT C; base pairs 3786 to 3804) and P4 (5′-GTT GGT ATG GCT GAG GTA CAG TCA ACA C; base pairs 3786 to 3804) and P4 (5′-GTT GGT ATG GCT GAG ACA C; base pairs 4075 to 4057) were used for the nested reaction. Parvovirus B19 DNA was detected in the patient’s spleen tissue, lung tissue, brain tissue, and myocardium (Table 1). For the detection of HHV-6 DNA by nested PCR, primers that amplify a region of the gene for the putative large tegument protein gene were used (2, 10). HHV-6 DNA was detected in the pharynx, spleen tissue, and lung tissue (Table 1). Amplimers were molecularly cloned with the TOPO-TA cloning kit (Invitrogen). DNA sequences were determined on an ABI PRISM 377 DNA sequencer with an ABI PRISM dye terminator cycle sequencing kit (Applied Biosystems). The parvovirus B19 DNA sequence detected in spleen tissue and the myocardium showed 99% similarity to that of parvovirus B19 isolate Rm (GenBank accession number AB030694). The HHV-6 DNA sequences detected in the pharynx, spleen tissue, and lung tissue showed 99 and 97% similar-
Abbreviations and symbols: CSF, cerebrospinal fluid; ISH, in situ hybridization; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; CMV, cytomegalovirus; EBV, Epstein-Barr virus; +, positive; −, negative; ND, not determined.

Discussion. Both parvovirus B19 and HHV-6 are ubiquitous viruses that usually cause mild diseases in childhood. Parvovirus B19 is the causative agent of erythema infectiosum, also called fifth disease. Parvovirus B19 infection has been reported to be a rare but severe cause of myocarditis in infants and children (7, 11, 13). HHV-6 is the causative agent of exanthema subitum, also called sixth disease. On the basis of its biological properties and genomic sequences, HHV-6 has been divided into two subgroups, defined as HHV-6A and HHV-6B (1). Primary HHV-6 infections are caused almost exclusively by HHV-6B (6).

To our knowledge, this is the first report of a patient with fatal myocarditis due to parvovirus B19 in the course of a concomitant HHV-6 infection. Our patient presented with clinical symptoms compatible with both primary parvovirus B19 and primary HHV-6 infections, i.e., a 4-day history of fever, cervical lymphadenopathy, erythema, and exudates of the tonsils, as well as a cutaneous rash involving both the arms and the legs. A diffuse pharyngitis is compatible with a viral infection transmitted by the respiratory route. The lymphocytopenia is compatible with an immunosuppression caused by an acute viral infection. Thrombocytopenia is compatible with a primary parvovirus B19 infection (3, 12). The postmortem examination of the heart showed a histology typical of that caused by viral myocarditis, and in situ hybridization analysis confirmed myocardial invasion with parvovirus B19. Amplified HHV-6 sequences showed the highest degrees of homology to HHV-6B.

All these findings and the patient’s clinical history provide strong evidence for a primary coinfection with parvovirus B19 and HHV-6, although no serological response to either virus was detected. The absence of serological markers is not surprising. IgM responses to HHV-6 can be detected only 5 to 7 days following the onset of symptoms, and many infected children may not develop detectable IgM responses (4). IgM responses to parvovirus B19 can be detected only 3 to 4 days following the onset of symptoms. The clinical history of our patient was only 4 days.

We suggest that HHV-6 induced a severe immunosuppression that enhanced the dissemination of parvovirus B19, leading to fulminant myocarditis. HHV-6 is thought to exhibit a unique spectrum of biological properties that make it an immunosuppressive agent of its own (8). To date, two reports have described severe HHV-6-associated illnesses: one in an 11-month-old child (14) and another in a 37-year-old man (15), both of whom were immunocompetent. In both patients, an immunosuppression caused by HHV-6 was hypothesized. Our patient was rather old to have a primary HHV-6 infection, which may have resulted in more severe complications.

Although quite unusual, this case report underlines the importance of recognizing a primary coinfection with two viruses, each of which by itself usually causes a benign infection.

We thank Tino Schwarz and Hans Nitschko for communicating the parvovirus B19-specific primer sequences and Claudia Seiler for technical assistance.

REFERENCES

