Acute Flaccid Paralysis Syndrome Associated with Echovirus 19, Managed with Pleconaril and Intravenous Immunoglobulin

Richard Starlin,1 Nevada Reed,1,4 Beth Leeman,3 Joseph Black,5 Elbert Trulock,2 and Linda M. Mundy1

Divisions of 1Infectious Diseases and 2Pulmonary Medicine, 3Department of Neurology, Washington University, and 4School of Medicine and 5Department of Neurology, Barnes-Jewish Hospital, St. Louis

We describe a 39-year-old woman who had undergone bilateral lung and renal transplantation and who was admitted to the hospital with acute onset of flaccid paralysis of the left leg due to echovirus 19 infection. The patient was treated with pleconaril and intravenous immunoglobulin, which correlated with clinical and laboratory evidence of improvement.

Enteroviruses are members of the picornavirus family. This family includes coxsackieviruses A and B, echoviruses, enteroviruses 68 to 71, and polioviruses. These viruses cause a wide array of diseases, the bulk of which are benign childhood illnesses, including nonspecific febrile syndromes, and some of which are distinct clinical entities, such as hand-foot-and-mouth disease and herpangina. However, in immunocompromised hosts, these viruses can cause severe infections, including encephalitis, myocarditis, neonatal sepsis, and myelitis. Enteroviral infections predominate during the summer and fall (May–October) in North America, but sporadic cases occur year-round [1].

The prototypic severe enteroviral infection is poliomyelitis. Symptomatic poliovirus infections (which account for <10% of poliovirus infections) typically have an initial phase with nonspecific symptoms, such as fever, headache, and sore throat, that resolve in 1–2 days. Fewer than 1% of patients with polio infection develop CNS involvement, which is frequently heralded by abrupt onset of fever, headache, vomiting, and meningismus. Fortunately, polio has been eradicated from the Western Hemisphere. Sporadic poliomyelitis-like syndromes, however, continue to occur [2]. We describe a case of acute flaccid paralysis associated with echovirus 19 in a profoundly immunosuppressed transplant recipient.

Case report. The patient was a 39-year-old woman with cystic fibrosis who had undergone bilateral lung transplantations in 1991 and again in 1997. She had experienced multiple episodes of rejection and had also received a renal transplant from a living related donor in 1999. She was admitted to Barnes-Jewish Hospital in St. Louis on 19 June 2000 because of acute flaccid paralysis of the left leg. Her medical history was significant for hospitalization in April 2000 for lung transplant rejection, for which she was treated with a 6–day course (11–16 April) of rabbit antithymocyte globulin (total dose, 485 mg). Her immunosuppressive regimen was also intensified by the addition of sirolimus to tacrolimus and prednisone. She was hospitalized again in May because of pneumonia, and she was treated with cefepime and inhaled tobramycin.

After the patient was discharged from the hospital, she traveled to the Ukraine to adopt a child. The child had a “cold” at the first meeting. The patient subsequently developed a diarrheal syndrome and she treated herself for presumptive Clostridium difficile colitis with orally administered metronidazole. Her symptoms resolved, and the family returned home on 8 June 2000. The patient had a routine clinic visit 14 June, and routine blood cultures were sent for cytomegalovirus surveillance. She was asymptomatic at the visit. On 17 June, she developed low-grade fever, sore throat, and malaise that prompted a visit to the emergency department. A viral syndrome was diagnosed, and she was discharged home. On 19 June, she developed acute flaccid paralysis of the left leg and returned to the emergency department. She also reported severe headache with photophobia, fever, and vomiting. She was admitted to the hospital for further evaluation.

Physical examination indicated that the patient had a fever (temperature, ≤38.2°C) and meningismus. Mental status and cranial nerves were intact. Strength and reflexes in the upper extremities were normal. The left leg had flaccid paralysis except for minimal plantar flexion. Strength in the right leg had decreased to 2/5–3/5. Ankle and patellar reflexes were absent in the left leg, but they were preserved in the right leg. Plantar reflexes were flexor bilaterally. Sensation was intact throughout the affected limb, and no bowel or bladder symptoms were evident.

Laboratory evaluation revealed a peripheral WBC count of 4400 cells/mm³, with an absolute lymphocyte count of only 300 cells/mm³. CSF analysis revealed 71 nucleated cells (of 79
The patient’s respiratory failure was attributed to nosocomial pneumonia. Additional viral cultures of blood samples were performed on 10 July and 31 July; the results were negative for enterovirus. Despite having received aggressive treatment for pseudomonas pneumonia and candida glabrata sepsis, the patient’s clinical condition worsened, and she died of respiratory failure on 26 August 2000.

**Discussion.** Echoviruses and other enteroviruses have been linked to many isolated cases and outbreaks of meningococcal meningitis [3, 4] and to fulminant neonatal infection [5]. Enteroviruses have also been implicated in other acute CNS processes, most frequently transverse myelitis and flaccid paralysis [6–8]. The occurrence of acute flaccid paralysis caused by viral infection in the United States has largely been controlled by the polio vaccination program [2]. We believe that this patient represents the first reported case of acute flaccid paralysis due to nonpolio enterovirus in a solid-organ transplant recipient. There have been occasional cases and outbreaks of infection due to nonpolio enteroviruses and vaccine-related polioviruses. Several reports of fatal disseminated enteroviral infections have been reported in adult bone marrow transplant recipients (table 1) [9–11]. In addition, there have also been reports of outbreaks of infectious gastroenteritis caused by coxsackie A viruses on bone marrow transplant units that have caused significant mortality [12]. One fatal case of infection with coxsackievirus B and cytomegalovirus in a heart-lung transplant recipient was reported [13].

Enteroviral infection in humans induces both a humoral immune response and a cell-mediated immune response [14]. Avoidance of most viral infections requires intact cell-mediated immunity as the primary host defense. Enteroviruses are an important exception to this rule; neutralizing antibody is required to control infection with these microorganisms [15]. Patients with agammaglobulinemia cannot produce neutralizing antibodies and are known to develop life-threatening, chronic enteroviral infections, which underscores the importance of the humoral response in control of these viral pathogens [14, 15]. Because the patient that we describe had been treated with potent immunosuppressive agents that can have lasting effects on lymphocyte production and function, we speculate that she could not mount a specific immune response.

This patient was treated with IVIG in an attempt to provide...
neutralizing antibody against echovirus 19. This strategy has been used successfully for patients with chronic enteroviral meningencephalitis, and suppression of enteroviral replication and negative results of cultures of CSF specimens have been achieved [16]. However, in these patients, enteroviral infections were not cured; without exception, the patients relapsed [15]. In addition, the patient that we described was treated with pleconaril on an open-label, compassionate-use basis. Pleconaril is an agent with activity against the enterovirus family [17]. It works by inhibiting the uncoating and release of infectious viral RNA. This inhibits the production of progeny virions [18]. The orally administered drug has very good bioavailability and excellent CNS penetration. It has been difficult to demonstrate the efficacy of pleconaril, because enteroviral infections are typically self-limiting. In small studies in which it was administered on a compassionate-use basis, pleconaril has been shown to be well tolerated, and its use has been known to coincide with clinical and laboratory improvement in patients with X-linked agammaglobulinemia and chronic enteroviral meningencephalitis, neonatal sepsis, acute-chronic poliovirus infection, and severe enteroviral infection after bone marrow transplantation [19].

Although the patient that we describe had a negative viral blood culture before initiation of therapy, her progressive neurologic syndrome was suggestive of an evolving CNS process. Of interest, the objective clinical improvement in neurologic function that was noted by multiple observers coincided with the initiation of treatment with pleconaril and IVIG. Such improvement could be attributable to either the natural resolution of echovirus 19 infection or the therapeutic effect of the prescribed regimen. Nonetheless, the patient tolerated the pleconaril and IVIG well and without any adverse events.

Given the increasing diversity of immunosuppressed hosts due to immunosuppressive regimens available today, this clinical presentation of severe enteroviral infection may become more common in the years to come. The role of pleconaril and of combined therapy with IVIG for management of enteroviral infections needs further evaluation, because it may become the treatment of choice for both primary treatment of immunosuppressed hosts with severe enteroviral infections and secondary prophylaxis for immunocompromised patients who are at high risk for relapse of chronic enteroviral infection.

Acknowledgments

We thank Neil Goldstein at Viropharma, Exton, Pennsylvania, for the coordinated access to pleconaril; Drs. Richard Bullock and Greg Storch at Washington University, St. Louis, for the identification of the echovirus and for their thoughtful discussion; M. Steven Oberste, Ph.D., of the Enterovirus Reference Laboratory, Centers for Disease Control and Prevention, Atlanta, for further characterization of the echovirus; and Mr. Jordana Stewart, for manuscript preparation.

References