A New Complication of Stem Cell Transplantation: Measles Inclusion Body Encephalitis

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ABSTRACT. Measles inclusion body encephalitis (MIBE) is a disease of the immunocompromised host and typically occurs within 1 year of acute measles infection or vaccination. We report a 13-year-old boy who had chronic granulomatous disease and presented 38 days after stem cell transplantation with afebrile focal seizures that progressed despite multiple anticonvulsants. After an extensive diagnostic evaluation, brain biopsy was performed, revealing numerous intranuclear inclusion bodies consistent with paramyxovirus nucleocapsids. Measles studies including reverse transcriptase–polymerase chain reaction and viral growth confirmed measles virus, genotype D3. Immunohistochemistry was positive for measles nucleoprotein. Despite intravenous ribavirin therapy, the patient died. MIBE has not been described in stem cell recipients but is a disease of immunocompromised hosts and typically occurs within 1 year of measles infection, exposure, or vaccination. Our case is unusual as neither the patient nor the stem cell donor had apparent recent measles exposure or vaccination, and neither had recent travel to measles-endemic regions. The patient had an erythematous rash several weeks before the neurologic symptoms; however, skin biopsy was consistent with graft-versus-host disease, and immunohistochemistry studies for measles nucleoprotein were negative. As measles genotype D3 has not been seen in areas where the child lived since his early childhood, the possibility of an unusually long latency period between initial measles infection and MIBE is raised. In addition, this case demonstrates the utility of brain biopsy in the diagnosis of encephalitis of unknown cause in the immunocompromised host. *Pediatrics* 2004; 114:e657–e660. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0949; *measles, encephalitis, immunocompromised host.*

ABBREVIATIONS. MIBE, measles inclusion body encephalitis; CGD, chronic granulomatous disease; SCT, stem cell transplantation; CMV, cytomegalovirus; ATG, anti-thymocyte globulin; GVHD, graft-versus-host disease; CsA, cyclosporine; WBC, white blood cell; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; HSV, herpes simplex virus; RT-PCR, reverse transcriptase PCR.

In addition to acute encephalitis and subacute sclerosing panencephalitis in immunocompetent hosts, measles virus can cause measles inclusion body encephalitis (MIBE) in immunocompromised hosts.[1,2] MIBE presents typically with focal and intractable seizures within 1 year of initial measles infection. The mortality rate is high, and no effective treatment exists.[3] We report a patient who had chronic granulomatous disease (CGD) and developed fatal MIBE after nonmyeloablative cytoreduction and allogeneic stem cell transplantation (SCT). There was no history of recent or remote measles infection or exposure.

CASE REPORTS

The patient was a 13-year-old Mexican-American boy who received a diagnosis of X-linked CGD at 2 years of age after serratia lymphadenitis. The patient was born in the United States and lived in Chicago but traveled frequently to urban Mexico, most recently 4 years before this illness. He received 1 documented measles-mumps-rubella vaccine at one year of age, and had no history of a measles-like illness or measles exposure at any time. A second measles-mumps-rubella vaccine was not documented. Despite prophylactic therapy for CGD with trimethoprim-sulfamethoxazole and thrice-weekly γ-interferon, he had multiple staphylococcal liver abscesses that required extensive surgical drainage. Poor compliance with interferon was documented. Because of the severity of his repeated infections, SCT was performed. An unrelated, 6:6 HLA-identical, 41-year-old, cytomegalovirus (CMV)-negative woman was identified. The conditioning regimen comprised fludarabine (180 mg/m²), busulfan (6.4 mg/kg), and equine anti-thymocyte globulin (ATG).[4] Because of fever and chills after equine ATG, he received rabbit ATG for the last 3 days. On day −1, he began graft-versus-host disease (GVHD) prophylaxis with cyclosporine (CsA) and on day 0 with mycophenolate mofetil. He received anti-infective prophylaxis with oral acyclovir, itraconazole, intravenous vancomycin, and weekly CMV-immune globulin.

On SCT day +10, he was admitted for fever and neutropenia and treated with broad-spectrum antibiotics. On day +11, a pruritic, erythematous rash developed, and his CsA dose was increased to treat presumed GVHD. Rash and low-grade fever persisted, and conjunctivitis and photophobia developed. Skin biopsy was consistent with GVHD; oral steroids were started with improvement in the rash. By day +19, he had engrafted with 99% donor chimerism by variable N-terminal repeats. On day +23, he presented with fever, headache, and eye pain. Head computed tomography scan and ophthalmologic examination were normal. Lumbar puncture showed 13 white blood cells (WBCs; 30% neutrophils, 52% lymphocytes, and 18% monocytes), glucose of 50 mg/dL, and protein of 34 mg/dL. Bacterial, fungal, and viral cultures were negative; cryptococcal antigen was negative. His

symptoms improved, and he was discharged on day +27. By day +33, he had worsening erythematous rash on his face, arms, and trunk, and corticosteroids were increased to treat GVHD.

On day +38, he was admitted to Children's Memorial Hospital with afebrile focal seizures involving his left hand. Immunosuppressive medications on admission included CsA, mycophenolate mofetil, and prednisone. CsA was stopped and tacrolimus (FK506) was started for possible CsA-induced seizures. The seizures progressed to involve his chin and tongue despite anticonvulsant therapy with clonazepam and valproic acid. Electroencephalogram showed focal status epilepticus (epilepsia partialis continua) involving the right frontal cortex. No neurologic abnormalities were noted on brain magnetic resonance imaging (MRI). He was transferred to the intensive care unit, where a continuous infusion of midazolam followed by a phenobarbital coma were unsuccessful in completely controlling seizures. Subclinical seizures persisted despite phenobarbital levels >300 μg/mL.

Lumbar puncture on day +43 was significant for glucose of 43 mg/dL, protein of 77 mg/dL, 51 WBCs/mm^3 (88% lymphocytes, 8% monocytes, and 4% neutrophils), and 8 red blood cells/mm^3. A repeat lumbar puncture on day +49 showed less inflammation, with glucose 59 mg/dL, protein 54 mg/dL, 9 WBCs/mm^3, and 294 red blood cells/mm^3. Spinal fluid cultures for bacteria, fungi, mycobacteria, and viruses were negative. Cryptococcal antigen was negative. Polymerase chain reaction (PCR) for herpes simplex virus (HSV)-1 and 2, human herpesvirus-6, enterovirus, Epstein-Barr virus, and arboviruses were negative. CMV antigenemia was negative. No antibodies to measles, mumps, varicella, adenovirus, HSV-1/2, or lymphocytic choriomeningitis virus were detected in the spinal fluid. Brain MRI on day +45 showed bilateral patchy areas of cortical swelling and signal abnormality, predominantly involving the frontal and temporal lobes, compatible with meningoencephalitis (Fig 1). A right frontal lobe lesion showed restricted diffusion. In retrospect, the initial MRI showed a small focus of signal abnormality in the right frontal cortex. Subsequent brain MRIs on day +49 and day +55 showed progressive involvement of the cerebral cortex and the basal ganglia. Treatment dose intravenous acyclovir was started on day +44 and was changed to intravenous gancyclovir on day +47.

Brain biopsy on day +53 demonstrated numerous eosinophilic intranuclear inclusion bodies and minimal perivascular inflammatory reaction. Inclusions of varied sizes were seen in astrocytes, oligodendroglial cells, and neurons. Electron microscopic examination showed that the inclusions were clusters of relatively long, curved, tubular structures consistent with paramyxovirus nucleo-

capsids (Fig 2). Extensive demyelination of axons was seen. Immunohistochemistry for HSV-1/2, CMV, human immunodeficiency virus, adenovirus, and Epstein-Barr virus was negative. Measles studies of the brain tissue performed at the Centers for Disease Control and Prevention were positive by reverse transcriptase (RT-PCR) for wild-type measles virus, genotype D3, and by immunohistochemistry[5] for measles nucleoprotein. Measles virus was isolated using the B95a marmoset lymphoblastoid cell line, and genotype D3 was confirmed by nucleotide sequence analysis of RT-PCR products. In addition, repeat skin biopsy on day +61 was consistent with GVHD.

After demonstration of intranuclear inclusion bodies, intravenous ribavirin was initiated on day +57 (loading dose of 30 mg/kg, then 15 mg/kg every 6 hours for 16 doses, and then 7.5 mg/kg every 8 hours). Despite ribavirin and intensive supportive therapy, the patient's neurologic status continued to deteriorate, and brain death was determined on day +70. Ribavirin was discontinued. Life support was stopped with the family's agreement on day +92, and the patient died. No postmortem study was permitted. Immunohistochemistry and RT-PCR of the initial skin biopsy (day +15) were negative for measles virus. RT-PCR performed on the donor stem cells was negative for measles virus.

DISCUSSION

MIBE occurs typically in immunocompromised patients within 1 year of measles infection.[1,3,6] Patients usually present with afebrile focal seizures and altered mentation. The seizures tend to be refractory to anticonvulsant therapy, and electroencephalogram often shows epilepsia partialis continua. The clinical features of our patient were consistent with this picture. Laboratory studies in MIBE are nondiagnostic, as cerebrospinal fluid parameters are often normal and cerebrospinal fluid antibodies to measles are usually undetectable. Imaging studies such as brain MRI and computed tomography are often normal. Diagnosis requires brain biopsy. Characteristic neuropathologic changes are glial cell proliferation and focal necrosis, with varying degrees of perivascular inflammation. Intranuclear and/or intracytoplasmic inclusion bodies are often present, and electron microscopic studies demonstrate characteristic tubular structures consistent with the paramyxovirus nucleocapsid.[3] The diagnosis of MIBE can be confirmed by RT-PCR for measles virus RNA or by immunohistochemistry. The prognosis is poor, with a 76% mortality rate, and all survivors manifesting significant neurologic sequelae.[3]

This case is unusual given the absence of apparent recent measles exposure or vaccination. The patient had not traveled outside Chicago during the year before SCT, and the last documented case of measles in Chicago was in 1997 (Julie Morita, MD, Chicago Department of Public Health, personal communication). The D3 measles genotype that was demonstrated by RT-PCR was last widespread in the United States in the epidemic of 1989–1991.[7] It is currently endemic in the western Pacific and has occurred only in small outbreaks in the United States in California (December 2000), Maryland (January 2001),[7] and Alabama (October–November 2002),[8] all associated with imported measles cases. The Alabama outbreak occurred around the time of the patient's SCT and suggests the possibility that an undiagnosed contact carried measles to the Chicago area.

Neither our patient nor the stem cell donor had history of recent travel to areas with endemic measles or to areas of the United States with recent
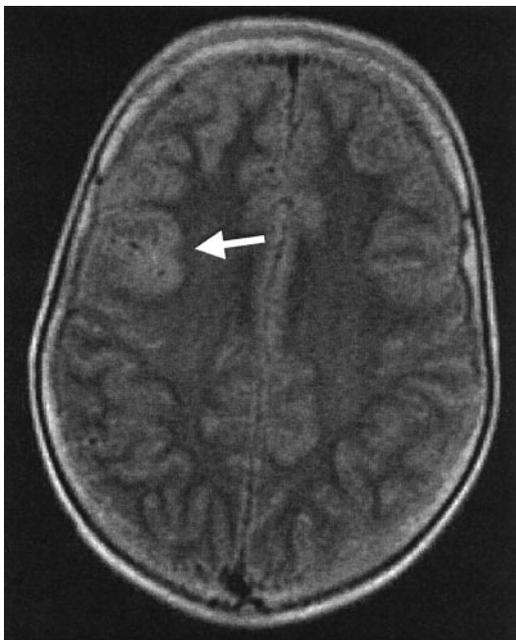

Fig 1. Brain MRI axial fluid attenuated inversion recovery image shows focal increased signal intensity and swelling in the right frontal gyrus (arrow). There is also diffuse subtle hyperintensity in the frontal cortex bilaterally, right greater than left.

Fig 2. Electron microscopy with uranyl acetate and lead citrate staining shows astrocytic nucleus with nucleocapsid structures that are evenly scattered at the center of the nucleus. They are seen as relatively long, curved, tubular structures measuring ~16 nm in diameter. Magnification ×12,000.
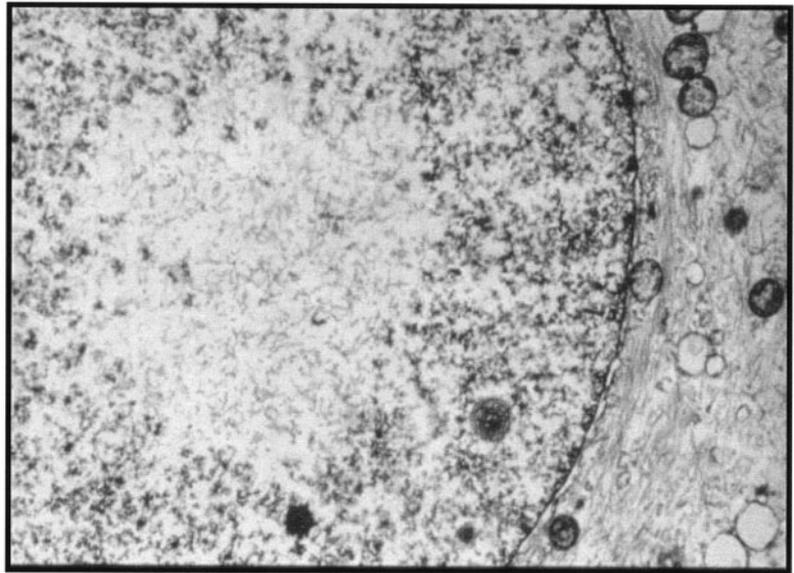
outbreaks. Our patient was born in Chicago during the epidemic of 1989-1991 (birth year 1989) and had traveled only to Mexico, where the D3 genotype has not been endemic in recent years.[9] An undiagnosed case of measles in the period 1989-1991 would suggest a latency period of 12 years, which is not typical of MIBE. The median length of time from acute measles infection or exposure to MIBE onset is 4 months.[3] A 21-year-old kidney transplant recipient with MIBE had measles infection at 10 months of age, but that diagnosis was not physician confirmed.[10] Two immunocompetent hosts with a disease course consistent with MIBE have been described with long periods (8 years and >10 years) from the time of clinical measles infection.[11,12] However, in those 2 cases, it is not clear whether the diagnosis was MIBE as seen in immunocompromised patients or was an unusual presentation of subacute sclerosing panencephalitis. It is unlikely that our patient's history of CGD placed him at increased risk for measles complications, but his SCT clearly did.

Our patient may have had a measles infection or exposure that was not recognized, although this is unlikely with his close medical supervision and prolonged hospitalizations the preceding year. Cases of MIBE without clear measles exposure or infection have been reported. In a review of MIBE, 18% of patients had no documented measles exposure or infection[3]; however, many of these cases occurred in years when measles was more prevalent. Our patient had a rash with conjunctival injection 27 days before the seizure onset, and skin biopsy suggested GVHD. Viral infections may precipitate skin GVHD, which has been described in a bone marrow recipient who contracted measles.[13] We believe that the rash and conjunctivitis were not manifestations of measles because the skin biopsy obtained soon after rash onset was consistent histologically with GVHD, and immunohistochemistry and RT-PCR both were negative for measles virus. We also doubt that the stem cell donor was the source of measles infection as she had no history of measles-like infection or travel to

an endemic area, and RT-PCR on the donor stem cells was negative for measles. MIBE has been reported 9 months after measles vaccination[14]; however, our patient received the measles vaccination many years before SCT, and the identification of genotype D3 is inconsistent with the well-established vaccine virus genotype (vaccine genotype is genotype A).

MIBE is a disease of immunocompromised hosts. Most cases have occurred in children with acute lymphoblastic leukemia, and there have been cases in patients with other malignancies, human immunodeficiency virus infection, kidney transplantation, and autoimmune illnesses.[1,3,6,15,16] MIBE has not previously been reported in patients after SCT. In a survey of 8 SCT recipients with measles infection, central nervous system disease was not seen, and in most patients, the disease was mild.[17] However, only 1 patient was within 1 year after transplantation, and the only patient who received steroids for GVHD (as did our patient) developed a measles complication (pneumonitis). Although measles infection is rare in many countries such as the United States, imported cases with secondary spread do occur and immunocompromised patients may have more atypical measles presentations. Therefore, with the increasing numbers of immunocompromised patients, practitioners need to be vigilant for both acute measles infection and MIBE in this population.

This case demonstrates the diagnostic utility of a brain biopsy in cases of encephalitis of unknown cause, particularly in immunocompromised individuals. Early brain biopsy may enable diagnosis and early institution of antiviral therapy. The utility of ribavirin or other therapies is unknown in MIBE. Ribavirin inhibits measles replication in vitro and has been used with some success to treat measles infections in immunocompetent hosts.[18,19] Ribavirin has been used in at least 4 cases (including our case) of MIBE,[3,14] with improvement in 1 case. In the last patient, intravenous ribavirin was initiated on hospitalization day 15, and improvement of symptoms

and imaging studies was seen[4]; however, significant long-term neurologic deficits remain (Naomi Winick, MD, personal communication). In the other cases, treatment was initiated on days 20 (current case), 18, and 17 of hospitalization, and all patients died. Early initiation of therapy with ribavirin is needed to be efficacious in other complications of measles; therefore, it is possible that ribavirin could improve symptoms with earlier diagnosis of MIBE. Interferon-α has been used in 3 patients; 2 had no improvement in neurologic symptoms, and 1 improved temporarily but died soon after from underlying acute lymphoblastic leukemia.[20,21]

One should maintain a high index of suspicion for MIBE in afebrile immunocompromised patients who present with focal status epilepticus. Typically, these patients have had recent measles infection or exposure; however, in our case, no history of either could be ascertained. MIBE has not been described previously in SCT patients, which may be attributable to the recent paucity of measles infections in developed countries. Our patient, as well as the reported kidney transplant recipient with measles infection 20 years before MIBE,[10] suggests the possibility of a long latency period between measles infection and onset of MIBE. Our case illustrates the importance of early brain biopsy in cases of obscure encephalitis or encephalopathy in the immunocompromised host.

ACKNOWLEDGMENT

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