Measles Inclusion-Body Encephalitis Caused by the Vaccine Strain of Measles Virus

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We report a case of measles inclusion-body encephalitis (MIBE) occurring in an apparently healthy 21-month-old boy 8.5 months after measles-mumps-rubella vaccination. He had no prior evidence of immune deficiency and no history of measles exposure or clinical disease. During hospitalization, a primary immunodeficiency characterized by a profoundly depressed CD8 cell count and dysgammaglobulinemia was demonstrated. A brain biopsy revealed histopathologic features consistent with MIBE, and measles antigens were detected by immunohistochemical staining. Electron microscopy revealed inclusions characteristic of paramyxovirus nucleocapsids within neurons, oligodendroglia, and astrocytes. The presence of measles virus in the brain tissue was confirmed by reverse transcription polymerase chain reaction. The nucleotide sequence in the nucleoprotein and fusion gene regions was identical to that of the Moraten and Schwarz vaccine strains; the fusion gene differed from known genotype A wild-type viruses.

Neurological abnormalities associated with measles range from nonspecific electroencephalographic changes and CSF pleocytosis at the time of acute uncomplicated measles to more serious manifestations such as postinfectious encephalomyelitis, subacute sclerosing panencephalitis (SSPE), and the more recently described measles inclusion-body encephalitis (MIBE). MIBE, also referred to as subacute measles encephalitis, acute encephalitis of the delayed type, and immunosuppressive measles encephalitis, is associated with immunodeficiency and typically develops within months of measles virus infection [1–4]. In this report we describe a case of MIBE associated with the vaccine strain of measles in a patient not previously known to be immunocompromised.

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Case Report

A previously healthy 21-month-old boy presented to the emergency department of a community hospital in status epilepticus. Irritability and occasional episodes of vomiting had occurred during the preceding 2 weeks. There was no history of fever, cough, coryza, conjunctivitis, or rash, and no exposure to measles could be documented. On presentation he had a temperature of 39.5°C, with no meningeal signs. A cranial CT scan demonstrated abnormal attenuation and swelling of the left temporal lobe, with narrowing of the ipsilateral lateral ventricle. Because of this finding, a lumbar puncture was deferred, administration of intravenous ceftriaxone and acyclovir was initiated, and the child was transferred to The Hospital for Sick Children, in Toronto.

The child's medical history was unremarkable and included no recurrent or unusual infections but normal growth and development. Measles-mumps-rubella vaccine (MMR, Merck Sharp & Dohme, West Point, PA), had been administered at 12 months of age. Diphtheria-tetanus-pertussis and inactivated polio vaccines had also been given, as routinely recommended in Canada. There was no family history of immunodeficiency or unusual or recurrent infections.

Physical examination revealed an unconscious boy whose height and weight were at the 90th and 70th percentiles, respectively. There was no conjunctivitis, enanthema, or exanthem. Bilateral mild optic-disk edema was observed. No focal neurological deficits were found. Minimal oral thrush and a monilial diaper rash were noted. The peripheral blood leukocyte count was 4.7×10^9/L, with 1.97×10^9/L granulocytes, 1.32×10^9/L lymphocytes, and 1.41×10^9/L monocytes. The

hemoglobin level was 10.9 g/L, the platelet count was 295 $\times$ 10^9/L, and the erythrocyte sedimentation rate was 32 mm/h. Serum electrolytes, glucose, urea, creatinine, and liver function values were normal. Electroencephalography demonstrated focal left-temporal and parasagittal polymorphic delta waves. A presumptive diagnosis of encephalitis was made; administration of acyclovir and ceftriaxone was continued.

On the day after admission, the patient's level of consciousness improved, and although he was somewhat lethargic, he was easily aroused and later in the day became fully conscious and active. Despite this initial improvement, his clinical status deteriorated over the next 7 days. Seizures, primarily affecting the right face and limbs, continued despite anticonvulsant therapy. After 7 days' incubation, *Campylobacter upsaliensis* was isolated from a blood culture performed at the community hospital. Stool and repeated blood cultures performed at the time of admission to our hospital remained negative. A 7-day course of oral erythromycin was administered.

On the 8th day of hospitalization, a deteriorating level of consciousness (Glasgow coma scale, 3–5), weak gag reflex, collapsed left-lower lobe with increasing oxygen requirements, and syndrome of inappropriate secretion of antidiuretic hormone prompted his transfer to the intensive care unit, where ventilatory support was instituted. A lumbar puncture, performed on the 9th day of hospitalization, revealed an opening pressure of 20 cm H_2O. CSF analysis demonstrated a leukocyte count of <3/mm^3, erythrocyte count of <3/mm^3, protein level of 0.1 g/L, and glucose level of 4.6 mmol/L. Gram stain and cultures were negative. PCR assays for herpes simplex virus 1 and 2, Epstein-Barr virus, cytomegalovirus, and *Mycoplasma pneumoniae* were negative, as was reverse-transcription PCR (RT-PCR) for enteroviruses.

On day 9, a large area of abnormal signal intensity in the left temporal lobe and patchy changes in the right temporal and frontoparietal lobes were found on MRI. Electroencephalography demonstrated bilateral periodic lateralizing epileptiform discharges. Measles-specific IgM and IgG were detected in the serum but not in the CSF. An extensive serological evaluation was negative for other potential causes of encephalitis (enteroviruses, influenza A and B, adenoviruses, herpes simplex viruses 1 and 2, human herpes virus-6, Epstein-Barr virus, St. Louis encephalitis, Powassan encephalitis, eastern equine encephalitis, western equine encephalitis, *Bartonella henselae*, and *M. pneumoniae*). On the 11th day of hospitalization a brain biopsy was performed.

Following the presumptive diagnosis of MIBE on day 18, a 3-week course of intravenous ribavirin (20 mg/[kg · d]) was initiated. A single dose of vitamin A (100,000 U) and two courses of intravenous immune globulin (1 and 2 g/[kg · dose]) were given. Despite these interventions, neurological deterioration continued. Seizures became progressively worse and difficult to control. Epilepsia partialis continua developed. Profound coma and loss of brainstem function ensued. On hospital day 51, the patient died after ventilatory support was withdrawn. Permission to perform an autopsy was denied.

Laboratory Methods

Pathology. Biopsy tissue for microscopic examination was fixed in 10% neutral buffered formalin, paraffin-embedded, sectioned, and stained with hematoxylin/eosin according to standard protocols. Immunohistochemical staining for measles antigens was performed with use of a mix of monoclonal antibodies to the measles virus hemagglutinin and matrix proteins (Chemicon, Temecula, CA) at a 1:600 dilution, after microwave antigen retrieval and overnight incubation at 4°C, and was developed with the Vector Elite system (Vector Laboratories, Burlingame, CA). 3,3′-Diaminobenzidine was used as chromogen.

Tissue for ultrastructural examination was fixed in 1% glutaraldehyde, post-fixed in osmium tetroxide, and embedded in Epon Araldyte resin (Cedarlane Laboratories, Hornby, Ontario, Canada). Sixty-nanometer sections were mounted on copper grids, stained with lead citrate, and examined with a Philips 201 electron microscope (Philips, Scarborough, Ontario, Canada) at 60 kV.

Nucleic acid extraction. Fresh brain tissue was obtained at biopsy and frozen immediately at −70°C. For measles RT-PCR, tissue was placed immediately into 500 μL of guanidinium isothiocyanate buffer and minced with a sterile 22-gauge needle. Insoluble material was removed by centrifugation at 2,500 rpm for 15 minutes at 40°C. The supernatant was then acidified and extracted with phenol-chloroform (modified from [5]). The RNA pellet was resuspended in 30 μL of RNAse-free water, and the RNA concentration was determined by ultraviolet spectroscopy.

For enterovirus RT-PCR, RNA was extracted from brain tissue with the TRIzol reagent (GIBCO BRL, Burlington, Ontario, Canada) and from CSF with use of the Amplicor enterovirus test kit (Roche, Toronto, Ontario, Canada); RNA was resuspended in the provided buffer. For herpes group viruses PCR, DNA was extracted from brain tissue with the Qiagen blood and tissue kit (Qiagen, Toronto, Ontario, Canada) and from CSF as previously described [6].

RT-PCR and sequencing. Measles virus RNA and beta-actin mRNA (as a control) were detected by RT-PCR as described previously [7] with some modifications. For each RT-PCR reaction, only a single set of primers without 5′ digoxygenin was used for both the RT and PCR reactions, and 35 cycles of PCR were performed. Primer sets were designed to amplify the 450 nucleotides coding for the COOH-terminal 150 amino acids of the nucleoprotein (N) and the entire coding region of the fusion (F) protein [7–9]. PCR products were purified with use of the Promega (Madison, WI) PCR cleanup kit and sequenced with a cycle-sequencing reaction with fluorescent dye terminators (Perkin-Elmer, Applied Biosystems Division, Foster City, CA), and the reaction products were

analyzed using an ABI 373 automatic sequencer (Perkin-Elmer). The sequencing primers have been described previously [8, 9].

Sequence data from multiple reactions were analyzed with version 9.1 of the Genetics Computer Group package [10], PHYLIP version 3.4 [11], and PAUP [12]. Reference sequences from vaccine and wild-type viruses have been described previously [13–15]. RT-PCR for enteroviruses was performed with the Amplicor enterovirus test kit. PCR for herpes group viruses was performed as previously described [6].

Immunologic evaluation. Tetanus toxin, mumps, rubella. and HIV antibody titers were measured by ELISA. Polio antibody titers were determined by virus neutralization assay [16]. Isohemagglutinin titers were measured with a standard agglutination technique. Peripheral blood mononuclear cell proliferation assays were performed by standard techniques with [H^3] thymidine incorporation [17]. Lymphocyte markers were determined by flow cytometry [17].

Results

Pathology. Light microscopy revealed moderate neuronal and oligodendroglial loss and reactive astrocytosis within the cortex and underlying white matter, as well as sparse lymphocytic meningoencephalitis. Immunohistochemical staining for measles hemagglutinin and matrix proteins (with a mix of antibodies against both proteins) demonstrated the expected cytoplasmic pattern (figure 1). Electron microscopy revealed the presence of intracytoplasmic and intranuclear inclusions with the characteristic appearance of paramyxovirus nucleocapsids within neurons, oligodendroglia, and astrocytes (figure 2).

Measles serology. Antibodies to measles virus were detected by CF at a titer of ≥1:1,024. Enzyme immunoassays demonstrated the presence of antimeasles IgG (optical density [OD]$_{450}$, 1.766; cutoff, 0.542 [Rubeola IgG ELISA, Gull, Salt Lake City, Utah]) and IgM (OD$_{450}$, 0.754; cutoff, 0.2 [Enzygnost measles IgM ELISA, Dade Berhring Canada, Mississauga, Ontario, Canada]).

RT-PCR and sequencing. Measles RNA was detected by RT-PCR in the brain tissue sample from the patient.

The 450 nucleotides coding for the COOH-terminal 150 amino acids of the measles N protein contain the greatest amount of sequence variability present on the measles genome [18]. Nucleotide heterogeneity in this region can exceed 12% [14]. The sequence obtained from the N gene PCR product from our patient was identical to that of the Moraten and Schwarz vaccine strains [9], indicating that this isolate is a member of genotype A [14, 19]. In contrast, the sequence differed from wild-type genotype D3, D5, D6, C1, B1, B2, D4, H, and D2 viruses by at least 5.7%.

Measles genotype A contains the prototype Edmonston strain and all of the vaccine strains; it also includes wild-type viruses isolated during the prevaccine era [8, 14, 19] and
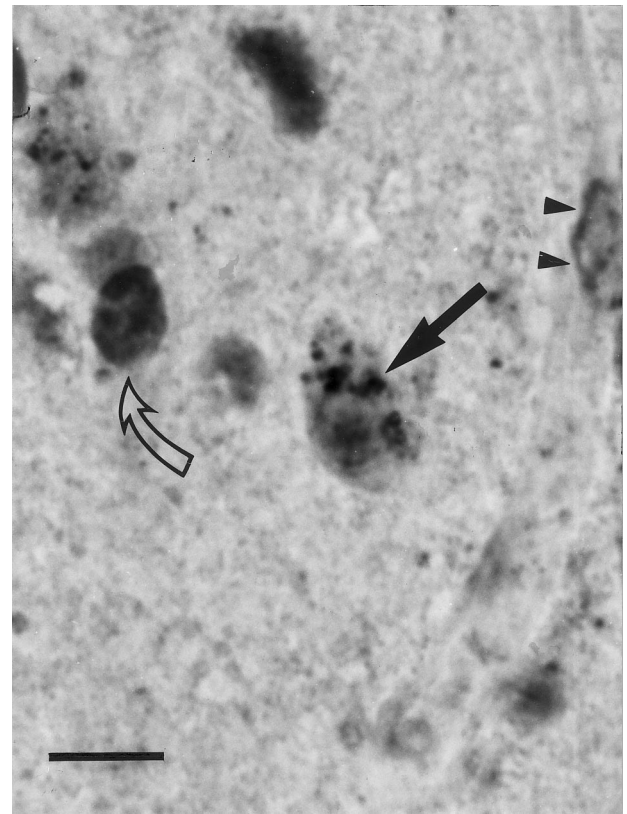

Figure 1. Positive immunohistochemical staining for measles hemagglutinin and matrix proteins within neuronal cytoplasm (*solid arrow*), glial cell nucleus (*open curved arrow*), and endothelial nucleus (*arrowheads*) (scale bar = 15 μ).

several more recently isolated wild-type viruses [15, 19, 20]. Because vaccine and wild type genotype A viruses cannot be distinguished on the basis of their N gene sequences, it was necessary to sequence a region of the F gene. The F gene contains four unique nucleotide substitutions that are found only in the Moraten and Schwarz vaccine strains and have not been found in any of the genotype A wild-type viruses analyzed so far ([9] and P. A. Rota and W. J. Bellini, unpublished observations). The 800 nucleotides of the F gene sequence obtained from the patient's sample were identical to the sequences of Moraten and Schwarz strains.

Immunologic evaluation. Markers of the patient's humoral immunity were assayed for in serum samples obtained prior to administration of intravenous immune globulin. Evaluation of cellular immunity was limited and complicated by the treatment with intravenous immune globulin, steroids, and ribavirin [21, 22].

The IgM level (0.8 g/L) was within the normal range (0.2–1.5 g/L), whereas that of IgG was slightly reduced (3.7 g/L; normal, 4.5–14.3 g/L) and that of IgA was slightly elevated (1.2 g/L; normal, 0.2–1.0 g/L). Levels of C3, C4, and total hemolytic complement were normal, as was the anti-B isohemagglutinin titer (blood group A). Serological tests for various
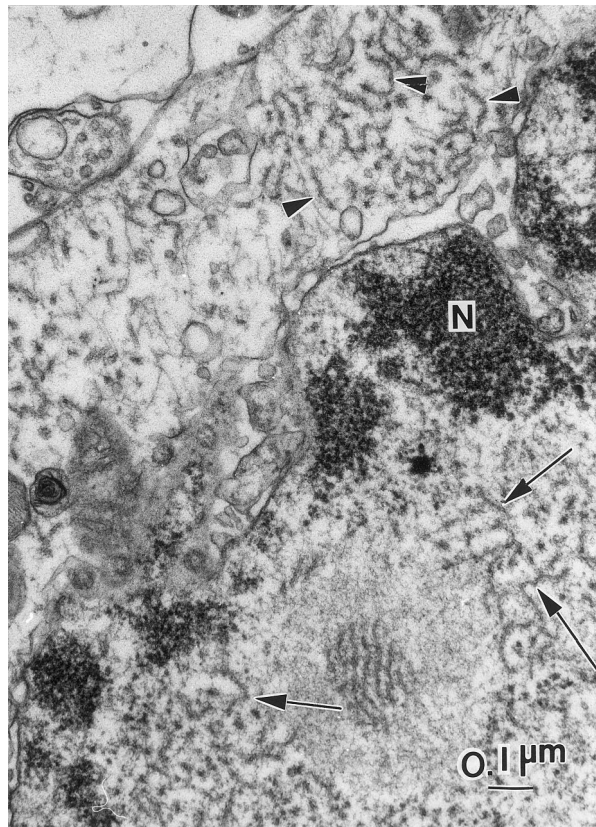
Figure 2. Transmission electron micrograph demonstrating tubular paramyxovirus particles within oligodendroglial cell nucleus (*arrows*) and cytoplasm (*arrowheads*) (original magnification, × 48,600).

sentinel markers demonstrated antibodies to mumps and poliovirus types 1 and 2, whereas antibodies to rubella virus, poliovirus type 3, and tetanus toxin could not be detected.

Proliferative responses of peripheral blood mononuclear cells to mitogens showed low-level responses to stimulation with staphylococcal protein A (SpA and STA) and no response to stimulation with concanavalin A, phytohemagglutinin, and pokeweed mitogen. Findings of lymphocyte subpopulation marker studies were remarkable for a profoundly depressed $CD8^+$ cell population (1/μL), with a CD4:CD8 cell ratio of 317. Antibodies to HIV and HIV p24 antigen were not detected by ELISA.

Immunologic evaluation of both parents and a younger female sibling was performed. All were immunologically normal (data not shown).

Discussion

The clinical course of this patient, including the initial presentation with seizures, the development of epilepsia partialis continua, and the rapid progression to coma and death, as well as the brain biopsy histopathology, was consistent with a diagnosis of MIBE. The diagnosis was estab-

lished by demonstrating the presence of intranuclear and intracytoplasmic paramyxovirus particles by electron microscopy, measles hemagglutinin and matrix proteins by immunohistochemical staining, and measles virus RNA by RT-PCR. The sequencing data provided convincing evidence of the presence of a vaccine strain virus within the patient's brain. Unless he was infected with an as-yet-undescribed wild-type genotype A virus, the vaccine strain was indeed the causative agent in this case.

MIBE usually develops 1–7 months after acute measles, although occasional cases have been described as occurring in the absence of clinical illness or documented measles exposure [3]. Seizures and altered level of consciousness are the most common initial manifestations and are typically followed by rapid clinical deterioration marked by worsening seizures, development of epilepsia partialis continua, deepening coma, and death in the majority of cases [1–4]. CSF analysis is usually normal, although mild pleocytosis and an elevated protein level may be observed [3]. In contrast to SSPE, the presence of high antibody titers to measles in the CSF is rare.

Electroencephalographic changes are nonspecific and include diffuse slowing and spike wave activity [1, 3, 4]. Neuroimaging is usually normal at the time of presentation, but nonspecific abnormalities such as edema, atrophy, and ventricular dilation can occur [1, 4]. Brain biopsy is necessary to establish a definitive diagnosis. Neuronal loss, proliferation of astrocytes and microglia, perivascular cuffing by lymphocytes, and minimal inflammation are characteristically seen on histopathology. In the majority of cases, intranuclear and intracytoplasmic inclusions are seen within glial cells and neurons. On electron microscopy, intranuclear and intracytoplasmic long, tubular structures consistent with paramyxovirus nucleocapsids are seen. Measles virus can occasionally be recovered in cell culture, but since the viruses in MIBE are usually replication-defective, their presence can best be demonstrated by RT-PCR [1–3].

The mortality ascribed to MIBE is ~75%, with a high incidence of neurological sequelae among survivors [3]. No effective treatment is available for MIBE. Two patients treated with intravenous ribavirin have been reported, one of whom apparently responded to prolonged therapy with this agent [3]. Our patient did not show any improvement during a 3-week course of ribavirin, although this may, at least in part, be related to the late initiation of therapy. Intrathecal and intramuscular IFN-α has been used in a small number of cases without any clear benefit [23, 24].

Our understanding of the pathogenesis of MIBE is incomplete. It has been proposed that the virus gains entry into the CNS through the cerebral endothelial cells [25] or infected monocytes [26] and spreads slowly within the CNS, infecting neurons and glial cells [1, 2]. As in SSPE, measles viruses implicated in MIBE are usually replication-defective, their genomes possessing numerous mutations and mRNAs coding

for many viral proteins being transcribed and translated at abnormal rates. The nucleocapsid and phosphoprotein are consistently detected by immunohistochemistry, whereas hemagglutinin is only occasionally found, and the membrane and fusion proteins are undetectable [27–31]. In fact, it has been suggested that MIBE is fundamentally similar to SSPE but that clinical symptoms appear earlier and are more rapidly progressive in the absence of an adequate immune response [27, 29].

An immunologic evaluation of this patient was prompted by the diagnosis of MIBE. While we cannot ascribe his condition to any classic immunodeficiency syndrome, our findings support the presence of a primary immunodeficiency. Most significantly, a profoundly depressed CD8 cell population was demonstrated. Cell-mediated immunity is essential for clearance of the measles virus, as illustrated by the uneventful recovery of hypogammaglobulinemic patients from measles [2]. Among the T-cell populations, CD8 cells are primarily expanded after measles infection [32] and are presumed to be an important component of the lymphocytic infiltrate at the sites of virus replication [33]. In the rat model, persistence of measles virus in the brain is promoted by CD8 depletion [34].

Thus, the depressed CD8 cell count identified in this patient may have permitted the persistence of measles and the eventual development of MIBE. The absence of specific antibody responses to several vaccine antigens, despite the presence of specific antibodies to other antigens, including measles, suggests an abnormality in the humoral arm of the immune system as well.

Measles vaccine has been implicated previously in two immunocompromised patients with MIBE [35, 36]. The first was a 2-year-old child with acute lymphoblastic leukemia who developed delayed prolonged atypical measles with pneumonitis 1 month after vaccination, from which he partially recovered but relapsed and subsequently developed encephalitis [35]. Measles virus was recovered from the throat and conjunctivae but was not further characterized. The second patient was a 7-year-old child with acute lymphoblastic leukemia who presented with a clinical picture consistent with MIBE 54 days after vaccination [36]. The presence of measles virus in the CSF was established by immunofluorescence assay of an inoculated Vero cell culture, but no further characterization was done. The possibility of infection with wild-type measles virus cannot be ruled out in either of these cases.

The capacity of measles vaccine viruses to cause severe neurological disease in immunocompetent individuals remains controversial [37]. On the basis of temporal association, numerous case reports have attempted to implicate the vaccine as a cause of acute encephalitis. In one of these cases a "vaccine-like virus" was isolated from CSF [38]. Epidemiological data demonstrate that the rate of acute encephalitis within 15–30 days of measles vaccination [38, 39] is comparable to the expected background encephalitis

rate [37, 38, 40]. However, a clustering of cases on days 8 and 9 postvaccination suggests a possible causal relationship [39].

While the proportion of SSPE cases among vaccinated children has increased since the introduction of universal vaccination, the overall incidence has declined considerably [37, 41]. Furthermore, given the very long incubation period of SSPE, it has been impossible to rule out infection with a wild-type virus in any of the reported cases [42]. To date, there have been no reports of genetic sequences characteristic of measles vaccine strains in cases of acute encephalitis or SSPE.

Measles vaccine has been successfully used, without serious complications, in many immunocompromised patients. Among children with acute lymphoblastic leukemia in remission and allogeneic bone marrow transplant recipients ≥2 years after transplantation, no serious adverse events were documented following receipt of MMR vaccine [43, 44]. Measles vaccine is well tolerated in HIV-infected persons [45–47], is recommended for those who are asymptomatically infected with HIV, and should be considered for symptomatic HIV-infected patients who do not have evidence of severe immunosuppression [48].

The recent report of a case of measles pneumonitis caused by a vaccine strain in a patient profoundly immunosuppressed by HIV has prompted the interim advice to withhold measles vaccination from severely immunocompromised HIV-infected patients [48, 49]. Measles vaccine strain virus has also been demonstrated as a cause of giant cell pneumonia in two patients with severe combined immunodeficiency [50]. MIBE has been reported in HIV-infected patients, but the vaccine strain has not been implicated [3, 51, 52].

We believe that the present report is the first to clearly demonstrate that severe neurological disease can be caused by the vaccine strain of measles virus. The risk of such a serious adverse event must be balanced by the rarity of such an event and the overwhelming evidence supporting the efficacy of the vaccine in reducing the morbidity and mortality associated with measles. It is significant that our patient was found to suffer from a profound deficiency of CD8 cells as well as dysgammaglobulinemia, which were not suspected clinically at the time of vaccination.

Most significant primary immunodeficiency states in children will be detected before the age of MMR vaccination, and for such children live virus vaccines should be avoided. Clearly, a serious outcome such as occurred for this patient is an exceedingly rare event, and this report should not lead to changes in current immunization practices.

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