Differentiating the wild from the attenuated during a measles outbreak

Lindsay Nestibo BN RN[1], Bonita E Lee MD FRCPC MSC (Epi)[2], Kevin Fonseca PhD D(ABMM)[3], Jennifer Beirnes[4], Marcia M Johnson MD MHSc FRCPC[5], Christopher A Sikora MD MSc MPH CCFP FRCPC[6]

L Nestibo, B Lee, K Fonseca, J Beirnes, M Johnson, C Sikora. Differentiating the wild from the attenuated during a measles outbreak. Paediatr Child Health 2012;17(4):e32-e33.

In the midst of a local measles outbreak, a recently immunized child was investigated for a new-onset measles-type rash. Nucleic acid testing identified that a vaccine-type measles virus was being shed in the urine. Clinically differentiating measles from a nonmeasles rash is challenging, but can be supported by a thorough medical history evaluation. Rashes are expected to occur after immunization; nucleic acid testing can be used when it is difficult to differentiate between wild and attenuated strains.

Key Words: *Measles; PCR; Secondary transmission; Vaccine*

La différenciation entre les souches sauvages et atténuées pendant une flambée de rougeole

Pendant une flambée locale de rougeole, un enfant récemment vacciné a subi des examens en raison d'une éruption rougeoleuse *de novo*. Le test d'acide nucléique a établi qu'un virus rougeoleux de type vaccinal était excrété dans l'urine. Il est difficile d'obtenir la différenciation clinique de la rougeole et d'une éruption non rougeoleuse, mais on peut l'étayer par une évaluation approfondie des antécédents médicaux. Des éruptions peuvent se produire après la vaccination. Le test d'acide nucléique peut être utile lorsqu'il est difficile de différencier les souches sauvages des souches atténuées.

In the spring of 2010, several imported cases of measles were reported within the province of Alberta (population of 3.5 million in 2009). Most cases of measles in Alberta, like the rest of Canada and the Americas, are linked to an imported illness or exposure during travel. Given the infrequent occurrence of measles in Alberta, and the high potential for transmission, an advisory was issued notifying all physicians to be on high alert for patients exhibiting symptoms consistent with measles infection. We describe a case of rash illness in a patient whose nasopharyngeal (NP) swab and urine sample tested positive for the measles virus using a nucleic acid amplification test following mumps-measles-rubella (MMR) immunization. The present case illustrates the difficulty in clinically differentiating various causes of childhood exanthemas, and serves as a reminder of the expected effects associated with the administration of the MMR vaccine. It also reinforces the expected limitations that should be placed on laboratory testing for measles.

CASE PRESENTATION

In the spring of 2010, there was heightened awareness of measles infection in the physician community as a result of a public health notification related to several imported measles cases in Alberta. During this period, a 15-month-old child presented to his paediatrician's office with irritability, a fever (38.8°C), a cough and conjunctivitis. The child had a five-day history of illness that began with an elevated temperature and a raised, sandpaper-like rash that originated at the occiput, and eventually spread to and covered the torso. There was mild cervical lymphadenopathy, and no rhinitis or Koplik spots. The child was not immunocompromised and had no significant medical history. Just 12 days before presentation to his paediatrician, the child was immunized with the M-M-R II vaccine (Merck Canada Inc). A thorough investigation by the Division of Population and Public Health, Alberta Health Services, revealed no significant travel history and no contact with any known measles patients in the preceding four weeks. All other members of the household were healthy and previously immunized with an MMR vaccine.

Clinical specimens were collected and submitted for laboratory testing, which included a throat swab for *Streptococcus pyogenes* (group A streptococcus), a serum sample for measles immunoglobulin (Ig) M and IgG antibodies (Enzygnost Anti-Measles Virus IgM and IgG ELIZA, Siemens Healthcare Diagnostics, Germany), a urine sample and an NP swab for a measles reverse transcription polymerase chain reaction (RT-PCR) test at the Provincial Laboratory for Public Health (ProvLab) in Alberta (1). The child's serum tested positive for both measles IgM and IgG antibodies. Both the urine sample and the NP swab tested positive for measles by RT-PCR at ProvLab, and the samples were referred to the National Microbiology Laboratory in Winnipeg, Manitoba, for genotyping (2). At the community laboratory, the throat swab tested positive for group A streptococcus, and because the clinical presentation was consistent with scarlet fever, amoxicillin was prescribed. Two weeks after the resolution of symptoms, the National Microbiology Laboratory reported the measles virus in both samples as being genotype A – 100% identical to Genbank entry #FJ2111583 (the Edmonston-Enders vaccine strain).

DISCUSSION

The MMR vaccine contains live attenuated measles virus. It is estimated that administration of this vaccine is associated with moderate (39.4°C) fever in as many as 5% of recipients, and a rash in approximately 2% of those receiving immunization (3). These events typically occur approximately five to 12 days following immunization and often resolve without medical intervention. These systemic effects are likely caused by replication of the attenuated strains and host immune reaction. It has been shown that following the immunization of healthy children, the measles virus can be detected in urine as early as one day and as late as 14 days (4). Similarly, during acute infection by wild-type measles, the virus could be detected by

[1]*Communicable Disease Control, Alberta Health Services;* [2]*Paediatric Infectious Disease, University of Alberta;* [3]*Provincial Laboratory for Public Health;* [4]*National Microbiology Laboratory, Public Health Agency of Canada;* [5]*Population and Public Health Division, Alberta Health Services;* [6]*School of Public Health, University of Alberta, Edmonton, Alberta*

Correspondence: Dr Christopher A Sikora, University of Alberta, Suite 104 West Tower, Coronation Plaza, 14310–111 Avenue, Edmonton, Alberta T5M 3Z7. Telephone 780-342-0252, e-mail csikora@ualberta.ca

Accepted for publication July 19, 2011

RT-PCR for up to 14 days in >50% of healthy children (5) and up to one month in >90% of HIV-infected children (6). With the high sensitivity of an RT-PCR assay for measles virus and the lower detection limit at approximately 10 to 100 copies per reaction (7), recently immunized patients could test positive for an attenuated vaccine strain for two weeks or longer. In addition to shedding the vaccine strain for a prolonged period of time, administration of the vaccine to an individual with HIV infection and, in particular, those with AIDS, can rarely result in disseminated illness (8). In the original study by Katz et al (9), the measles virus could not be cultured from throat swabs or blood samples in the postimmunization period in a cohort of 31 children. While the attenuated virus can be detected in clinical specimens following immunization, it is understood that administration of the MMR vaccine to immunocompetent individuals does not carry the risk of secondary transmission to susceptible hosts (10). There is a case report suggesting the transmission of vaccine strain between immunocompetent siblings, but the conclusion was based only on clinical presentation, with no laboratory confirmation of infection (11,12).

In jurisdictions where measles is uncommon, a measles-like rash may be mistaken for other viral agents such as adenovirus, enterovirus or parvovirus B19 (13). The successful genotyping and identification of the measles virus as a vaccine strain in the present child serves to remind clinicians of potential signs and symptoms following the administration of live attenuated viral vaccines (14). In the immediate postimmunization time period, testing patients for the specific viral agents in the attenuated vaccine by molecular assays needs to be accompanied by characterization of the detected virus because it is expected that the serological tests will be positive and not indicative of acute wild-type infection (15). In true wild-type measles infection, measles IgM may be negative during the first few days of the rash and in susceptible individuals with waning immunity – an observation also reported in mumps cases (16,17). Testing for measles should only be considered in specific circumstances for which there is a possible exposure history to wild-type virus. This could include travel to an endemic area and/or exposure to a confirmed case of disease. An exposure history may be complicated by international travel and undetected exposures in airport terminals (18). The detection and characterization of the measles virus is important for Public Health purposes and in environments where such clinical illness is rare but wild-type virus is circulating (18,19). For suspected measles cases, laboratory tests should include measles IgM and IgG serology, as well as an NP swab and a urine sample for the detection of the measles virus. This testing should only be considered if exposure to the wild-type (not vaccine-strain) virus is strongly suspected.

ACKNOWLEDGEMENTS: The authors acknowledge Ms Joy Jaipaul, Dr Alberto Severini and Dr Graham Tipples for their invaluable assistance in the investigation of the measles cluster in Alberta and the preparation of this manuscript.

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