Post-vaccine measles in a child with concomitant influenza, Sicily, Italy, March 2015

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We describe the occurrence of measles in an 18 month-old patient in Sicily, Italy, in March 2015, who received the first dose of a measles-containing vaccine seven days before onset of prodromal symptoms. Measles virus infection was confirmed by PCR and detection of specific immunoglobulin; viral genotyping permitted the confirmation of a vaccine-associated illness. The patient had a concurrent influenza virus infection, during a seasonal epidemic outbreak of influenza.

Case description

In early March 2015, measles-mumps-rubella-varicella zoster (MMRV) vaccine was administered to an apparently healthy 18-month-old child living in Sicily, Italy. Seven days later, the child presented to the family paediatrician with fever (40.1°C), catarrhal cough, runny nose and eyelid oedema. Macular rash appeared over the body two days later, starting on the trunk and then spreading to the neck and face. By day 13, the rash was fading, but due to the persistence of symptoms, the child was admitted to a children's hospital and reported as a possible case of vaccine-related measles to the Epidemiology Department of the Regional Public Health.

The local health authority carried out an epidemiological investigation: a standard measles notification form was sent to the regional health authorities and immediately forwarded to the Ministry of Health and to the Infectious Diseases Epidemiology Unit of the National Institute of Health. No direct link was identified with other measles cases in the community and the family had no history of travel outside Sicily. Moreover, contact investigation revealed no household members or pre-school contacts with symptoms consistent with measles. One of the child's parents developed influenza-like illness (ILI) symptoms (fever (›38°C) and cough, which lasted for three consecutive days) one day after administration of MMRV vaccine to the patient.

Urine and throat swab specimens were collected from the child and submitted to the Regional Reference Laboratory in Palermo for nucleic acid-based testing for measles, mumps, rubella and varicella zoster viruses and genotyping of any detected viruses. Given that this patient with suspected vaccine-associated measles developed symptoms during a seasonal epidemic outbreak of influenza viruses, and taking into account reports of morbilliform rash associated in patients with influenza B who tested negative for measles virus infection [1,2], testing was also requested for influenza and other respiratory viruses.

While no viruses could be detected in the urine specimen, measles, influenza A(H3N2) and respiratory syncytial viruses were detected in the throat swab.

On day 17, the patient's symptoms resolved without complications and the patient was discharged from hospital (Figure).

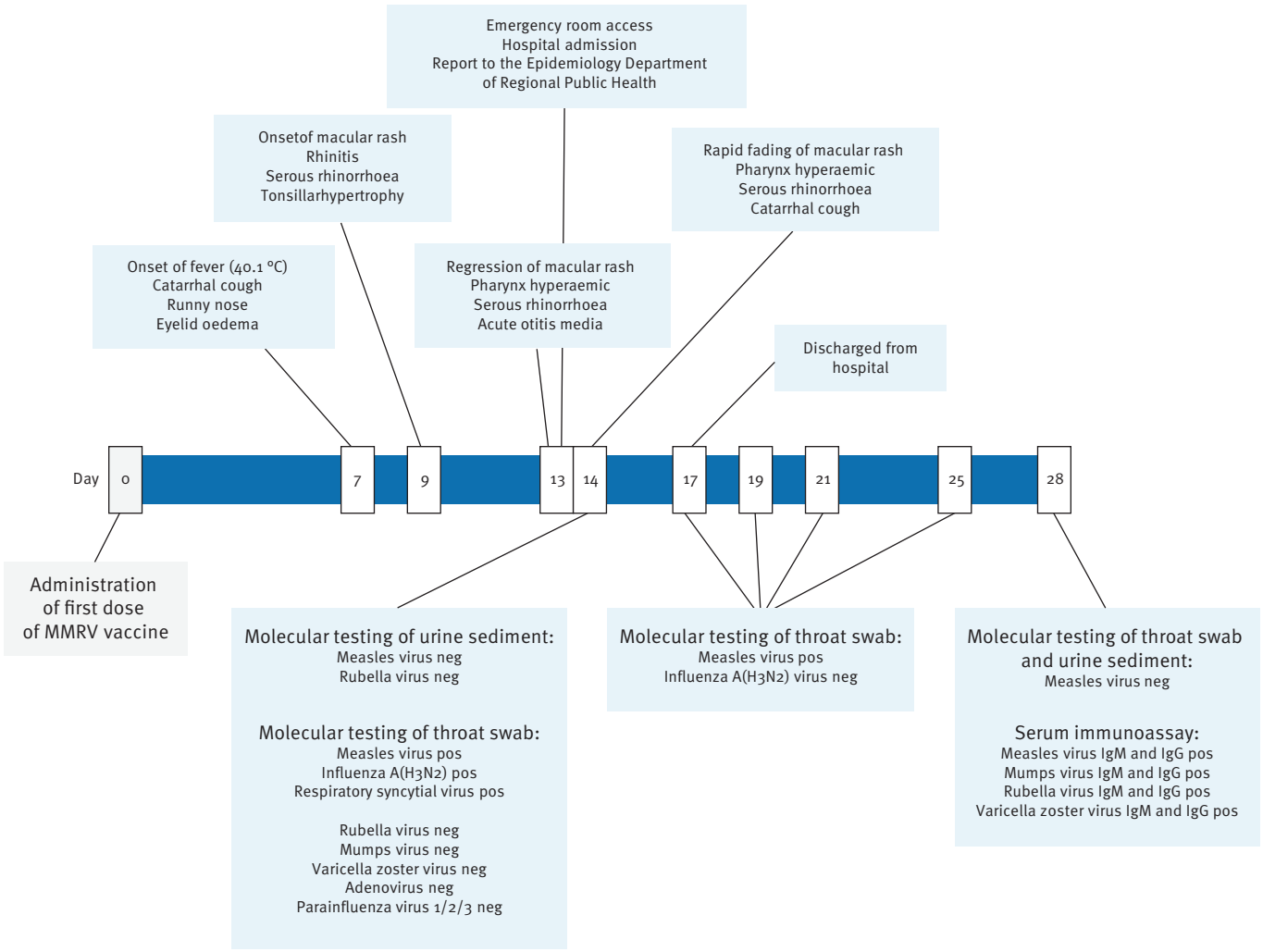
Measles virus was detected in throat swabs taken on days 17, 19, 21 and 25, but no influenza or other respiratory viruses were detectable in these specimens.

Measles virus was not detected on day 28 from a throat swab and urine specimen. A blood sample was taken at this time for serological testing for measles, mumps, rubella and varicella zoster viruses. A time line of events is shown in the Figure.

Seroconversion following MMRV immunisation was evaluated through the detection of specific measles, rubella, mumps and varicella zoster IgM and IgG antibodies by chemiluminescent immunoassay (CLIA) (measles virus: IgM = 3.1 arbitrary units (AU)/mL, IgG ›300

Figure

Time line of symptoms and physical signs in a child with post-vaccine measles and concomitant influenza, case management, specimen collection and laboratory results, Sicily, Italy, March 2015



MMRV: measles-mumps-rubella-varicella zoster; neg: negative; pos: positive.

AU/mL; mumps virus: IgM = 1.3 AU/mL, IgG = 78.9 AU/mL; rubella virus: IgM = 1.97 AU/mL, IgG = 18.0 international units (IU)/mL; varicella zoster: IgM = 0.71 AU/mL, IgG = 271.8 mIU/mL).

The measles virus was determined to be the Schwarz vaccine strain, genotype A, MVs/Palermo.ITA/12.15 [A] (VAC) [3] by sequence analysis of the genome.

Laboratory investigations

Serological and nucleic acid-based tests were performed for surveillance of measles and rubella, and genotype determination at the Regional Reference Laboratory of Palermo, formerly a member of the national network for influenza surveillance and genotyping (INFLUNET).

For the detection of specific measles, rubella, mumps and varicella zoster IgM and IgG antibodies, commercial CLIA tests were used (LIAISON (DiaSorin) and VITROS (Ortho Clinical Diagnostics)), which have the following cut-off values: measles IgM ≥ 1.0; measles IgG ≥ 13.5; mumps IgM ≥ 1.0; mumps IgG ≥ 10.0; rubella IgM ≥ 1.2; rubella IgG ≥ 15.0; varicella zoster IgM ≥ 1.0; varicella zoster IgG ≥ 100.0.

Throat swabs and the sediment of urine samples were tested using a real-time PCR instrument (QuantStudio 7 Flex Real-Time PCR system, Applied Biosystems), using specific primer/TaqMan probe sets for measles [4], mumps [5], rubella [4] and varicella zoster [6,7] viruses after extraction of total RNA using QIAmp Viral RNA Mini Kit (Qiagen).

Measles genotyping was conducted to distinguish wild-type from vaccine-associated measles viral strains. PCR products, targeting either the N gene or the H gene [8], were obtained from throat swab and sequenced using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems).

SuperScript One-Step RT-PCR kit with Platinum Taq (Invitrogen) were used for both endpoint reverse transcription RT-PCR and real-time RT-PCR reactions.

Sequences were confirmed as measles virus following comparison with the BLAST algorithm and they were phylogenetically analysed to assign genotype and cluster. The sequences were identified as Schwarz vaccine strain (genotype A) and were submitted to GenBank (accession numbers KR262162 (gene N) and KR262161 (gene H)).

Background

In Italy, vaccination against measles is included in the national vaccination schedule. Two doses of measles-mumps-rubella (MMR) vaccine have been recommended in all regions since the early 1990s [9], sometimes in association with varicella vaccination. The first dose is given at 13–15 months-old and the second at the age of 5–6 years [10].

In accordance with the national measles elimination plan [11], an enhanced surveillance system was introduced in 2007 [12] with the aim of improving timeliness, completeness of case reporting and case investigation, including laboratory confirmation of diagnosis and viral genotyping.

As the incidence of wild-type measles decreases in countries with high levels of vaccination coverage, vaccine-associated cases could be misreported [13,14], suggesting that there is a need to improve the ability to distinguish between vaccine-associated measles and 'true' wild-type measles virus infection [15].

Post-marketing surveillance of vaccines is mandatory in Italy and adverse reactions observed after the administration of vaccines are reported through the national pharmacovigilance network. According to the latest data available [16], these are mainly represented by fever, skin rash and febrile seizures, while post-vaccination viral shedding is a very uncommon event, which has been rarely documented so far [17,18].

Discussion

With an estimated more than 500 million doses administered in over 60 countries since the 1970s, the benefit of measles vaccination in preventing illness, disability and death appear unchallengeable [19,20].

Moreover, vaccine safety is annually validated by accurate post-marketing surveillance of adverse reactions conducted by the Italian Medicines Agency (AIFA). As for other live attenuated vaccines, adverse reactions following MMR or MMRV immunisation rarely present with clinically significant illness [16]: such illness is indistinguishable from wild-type measles. In this context, the reference laboratory for molecular surveillance plays a fundamental role in measles virus characterisation, through viral sequencing and genotyping, in order to promptly differentiate between wild-type and vaccine-related strains [14,18].

In this report, we documented the pharyngeal excretion of the Schwarz measles vaccine virus in an apparently healthy child with a febrile rash after measles vaccination and with laboratory-confirmed influenza A(H3N2) coinfection.

On the basis of our data, some points can be noted.

Firstly, although unlikely, measles after MMRV vaccination is possible, and this can mimic wild-type infection, leading to potential measles case misclassification. The application of molecular techniques for viral genotyping is helpful to correctly classify a case and to drive the decisions of public health authorities at the local level.

Secondly, this is the first report of a measles case with concurrent influenza and respiratory syncytial virus detection: we cannot exclude the possibility that the co-presence of other viral natural infections in a very young child, showing a slight hypogammaglobulinaemia in serum protein electrophoresis, may have favoured, or even determined, the occurrence of vaccine-related measles virus in pharyngeal secretions. Unfortunately, the parent showing ILI symptoms was not tested for influenza virus, making us unable to assess, although very likely, an intrafamilial transmission of influenza virus infection.

Notably, virus excretion was demonstrated over a 25-day period after vaccination, which is longer than previously reported [17,21,22]. Interference with other coinfecting viruses or a defective host immune response could play a role in this unexpected persistence of measles virus, although this hypothesis will require further investigation.

Thirdly, virus excretion was repeatedly detected in the throat, but not in urine sediment. This finding partially contrasts with World Health Organization (WHO) guidance for laboratory diagnosis for measles virus infection, which suggests to test preferentially for the virus in the sediment of urine samples that have been collected within at least five days after the onset of rash [23]. In the case presented here, in accordance with WHO guidance, matched urine and throat specimens were collected on the fifth day after the onset of macular rash.

Detection of measles virus in respiratory samples up to 16 days after the onset of rash suggests that other host cell pathways or viral mechanisms, potentially related to other concomitant viral infections, might be responsible for such an event. However, also in this case, further studies are necessary to better explain such an anomaly.

In conclusion, development of measles in individuals who have received MMR or MMRV vaccine is a possible,

although extremely rare, event. Therefore, especially in geographical areas with a low incidence of measles, maintenance of efficient molecular surveillance systems and the improvement of the timeliness of both case reporting and virus genotyping is of paramount importance, to ensure correct differentiation between vaccine-related illness and natural measles infection [24].

Conflict of interest

None declared.

Authors' contributions

Conceived and designed the study: FT, FV. Collected clinical and epidemiological data: PD, CD, NC. Analysed data: FT. Wrote the paper: FT, FV.

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