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A Case of Atypical Hand-Foot-and-Mouth Disease Caused by Coxsackievirus A6: Differential Diagnosis from Varicella in a Pediatric Intensive Care Unit

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In 2011, a large outbreak of hand-foot-and-mouth disease (HFMD) caused by coxsackievirus A6 (CV-A6) occurred in Japan and other countries. The cutaneous manifestations of CV-A6-associated HFMD (CV-A6-HFMD) are more extensive and variable than those of classic HFMD (1–3). Differential diagnosis of HFMD from chickenpox is occasionally challenging because of its unusual clinical characteristics. For example, the spread of rashes in CV-A6-HFMD is more toward the extremities and body trunk, a manner different from that in typical HFMD in which the rashes are mostly localized to the hands and soles of the feet (1,2).

A 24-month-old girl was hospitalized in the pediatric intensive care unit (PICU) on May 16, 2013 (23 days before day 0) due to hypoxemia. The patient had an underlying diagnosis of Down syndrome with a ventricular septal defect and pulmonary hypertension but no history of varicella infection or vaccination against varicella. Before discharge on June 8, 2013 (day 0), she developed a reddish papular rash with some vesicles on her hip, which rapidly spread throughout her entire body and face; she was afebrile.

On June 10, 2013 (day 2), the Infection Control Team (ICT) of the Saiseikai Nakatsu Hospital (Osaka, Japan) was notified of this patient as a suspected case of chickenpox in PICU. Assessment of this case was complicated because the rash spread to her upper and lower extremities; however, it was also observed to a lesser extent on her body trunk but not on the head. Although the papules were comparable to varicella in terms of their size (approximately 5 mm), HFMD was considered to be more likely because there were fewer vesicles than that expected for varicella, and the rash was neither crusted nor pigmented.

Infection control policies and measures for varicella-zoster virus (VZV) and enterovirus are different. VZV is transmitted via droplet nuclei, whereas enterovirus is transmitted from person to person via direct contact with the virus shed from the gastrointestinal or upper respiratory tract. To prevent enteroviral transmission, hand hygiene is particularly important (4). Although there was no other case of suspected chickenpox in PICU, the Department of Pediatrics was concerned about the high transmissibility of varicella, which is airborne. ICT in collaboration with the pediatric staff immediately initiated varicella infection control in the pediatric ward and performed laboratory diagnosis for treatment of the present case. ICT decided to implement the following responses: (i) immediate isolation of the infected patient from other children in PICU from June 10, 2013; (ii) immediate restriction on PICU use from June 10, 2013; and (iii) drafting a plan of broad prophylactic administration of antivirals against VZV for children who were housed in the same room depending on the laboratory result for VZV.

In addition to a specific laboratory examination for VZV, specimens of pharyngeal swabs, vesicular fluid, and feces were collected during the course of medical care, and laboratory tests were performed for diagnosis and treatment. Informed consent for this study was obtained from the patient’s guardian, and the clinical samples were tested to devise a treatment plan and infection control measures.

On June 12, 2013 (day 4), the results of VZV tests including analysis of IgM, IgG, and specific viral antigen, were negative. On the same day, specimens (vesicle fluid, nasopharyngeal swabs, and feces) were collected, and reverse transcription (RT)-hyper PCR (5) was performed to screen for enterovirus in all samples (day 4). RT-hyper PCR was employed because it is faster than previously available PCR methods (5,6).

Based on the results obtained by RT-hyper PCR, ICT immediately terminated varicella surveillance and discontinued the restriction on PICU use and antiviral therapy to the patient. The team also withdrew the broader prophylactic antiviral administration throughout the unit and instead endorsed precautions against contact infections.

On June 14, 2013 (day 6), RT-PCR was performed to determine the partial nucleotide sequence of the capsid protein VP1 cording region. Primer pairs were designed
to amplify the VP1 (partial) to VP2 (partial) coding region of CV-A6 (AB678778) and used for sensitive detection of the viral genome. We used specific primers for CV-A6 because the clinical picture was similar to the unique clinical characteristics of the CV-A6-HFMD outbreak in 2011 (2). The primers used were Ca6seq1_5 (5'-AAATGCAGTGGAAAGTGCTGTGAGC-3') and Ca6seq1_3 (5'-TTTACCACCTCTAAAGTTACCCAC-3'). The size of the PCR product was 957 bp, and the sequence was determined by the Sanger method. All three samples (vesicle, nasopharyngeal swab, and feces) had the same sequence length of 909 bp, which had 95% similarity to AB678778 and was subsequently identified as CV-A6 (deposited to the DDBJ under the accession no. AB827357). Thus, the case was finally diagnosed as CV-A6-HFMD.

Several types of enteroviruses may cause HFMD. Although the dominant pathogens of HFMD are considered to be CV-A16 and enterovirus 71, a growing number of HFMD cases due to CV-A6 have been reported in Japan since 2009, followed by the largest nationwide outbreak in 2011. CV-A6 causes atypical HFMD, which is characterized by a large rash that spreads over the entire body trunk, as occurred in the present case. However, ICT planned measures against varicella control that included ruling out varicella, which has potential to severely impact on the patients housed together (7). Therefore, because of a rapid laboratory diagnosis, unnecessary prophylactic administration was avoided and PICU was reopened as soon as possible. The patient was carefully followed-up for onychomadesis, which typically results after CV-A6-HFMD (2,3).

CV-A6-HFMD was the most common cause of HFMD as of June 2013. Considering that CV-A6 strains have caused a larger number of atypical HFMD cases since 2011, our experience should provide useful information regarding infection control in PICUs. Early PCR testing was useful in this case. For the clinical differentiation of CV-A6-HFMD from varicella, CV-A6 cases show eruption more frequently on the limbs, buttocks, and peristome than those found in varicella cases. In several cases, the eruptions can spread to the trunk (2), similar to the eruptions associated with varicella infections (Fig. 1). Differential diagnosis by PCR should be particularly useful to differentiate CV-A6-HFMD from varicella.


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Conflict of interest None to declare

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