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Clinical Manifestations of Coxsackievirus A6 Infection Associated with a Major Outbreak of Hand, Foot, and Mouth Disease in Japan

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A serious outbreak of hand, foot, and mouth disease (HFMD) occurred in Japan in the summer of 2011 (1,2). A major cause of this epidemic was coxsackievirus A6 (CA6), and the clinical manifestations of the disease differed from those of typical HFMD. The Infectious Diseases Control Law mandates medical doctors in Japan to officially report cases exhibiting the following symptoms immediately after diagnosis: fever with sore throat and appetite loss, followed by the appearance of reddish vesicles on the hands and feet approximately 2 days after the onset of fever. The vesicles usually disappear within 7 to 10 days without specific treatment. Reported cases should satisfy both of the following clinical criteria: (i) vesicles measuring 2–5 mm with blisters on the palm of the hand and sole or dorsum of the foot and oral mucosa and (ii) vesicles that heal without crust formation.

During the 2011 outbreak, it was challenging for pediatricians to judge whether the majority of HFMD cases should be diagnosed as a subtype of conventional HFMD or a new type caused by CA6 infection. We recommend that pediatricians should be alert while making diagnosis because the rashes caused by CA6 are similar to those caused by chickenpox. Establishing differential diagnoses is necessary in order to prevent misdiagnosis and inappropriate treatment. The critical point in differentiating CA6 from other infections is the specific clinical course and spread of eruptions with scabbing. For this purpose, in 2011, we summarized the detailed clinical features of HFMD caused by CA6 infection (CA6-associated HFMD).

On the basis of laboratory confirmation (1), we reviewed 28 cases of CA6-associated HFMD that occurred in Japan between June 2011 and July 2011. CA6 strains were detected in samples of feces and/or pharyngeal swabs and tested using reverse transcription (RT)-PCR and sequencing of the VP1 region (AB649286-AB649291). Clinical samples were collected during the course of medical care in hospitals and laboratory tests were performed for the purpose of diagnosis and treatment. Informed consent for this study was obtained from all the patients’ guardians, and the clinical samples were diagnosed for national surveillance.

Patient age ranged from 9 months to 9 years (mean, 29.1 months), and 75% of patients were aged under 3 years. There was no statistically significant gender difference. All HFMD cases were associated with a fever (38.0–40.2°C; mean, 39.0°C) that lasted for 1.5 days on average. The appearance of rashes on the oral mucosa was noted from the second day of onset of fever, similar to that observed in cases of herpangina with less oral pain and reluctance to eat. The appearance of reddish vesicles on the extremities and buttocks was noted on the third day of onset; these vesicles were mostly found on the upper arms, thighs, lips, neck, and buttocks, while they were found less frequently on the hands and soles of the feet. The vesicles were flat and umbilicated. Some lesions grew to be more than 10 mm in diameter, and scabbing was observed within several days (Fig. 1).

As described above, the criteria for notification in Japan require that the vesicles associated with HFMD heal without crust formation. However, in this study, crust formation was observed within several days of disease onset in all 28 cases. The notification criteria for HFMD include vesicles that heal without crust formation. Our results showed that CA6-associated HFMD did not fulfill the notification criteria for HFMD. However, it was impossible to find crust formation in the early stage of the illness. In some cases, a careful differential diagnosis from chickenpox, impetigo contagiosa, herpes simplex disease, and varicella-zoster disease was required. The critical features of CA6-associated HFMD were the successive appearance of herpangina-like oral mucosal lesions, widely spread rashes, and crust formation during the healing process.

We followed 16 recovered cases for 2–8 weeks and found that 6 (37.5%) experienced onychomadesis, which was a significant finding. All cases healed without severe sequelae, except for the 6 cases that developed onychomadesis. The incidence of CA6-associated HFMD with crust formation is thought to be high (almost 100%), with the rate of onychomadesis estimated to be over 30%. Further studies are therefore needed.
Rashes associated with CA6-associated HFMD are spread more widely on the extremities and trunk, unlike those associated with typical HFMD where they are mostly localized on the palms of the hands and soles of the feet. One notable clinical symptom of CA6-associated HFMD is onychomadesis, an outbreak of which was reported in Finland in 2008 (3). Similar cases were reported from Ehime Prefecture in Japan in 2009 (4), Taiwan in 2011 (5), the United States in 2012 (6), and from other countries. Although the number of patients with CA6-associated HFMD decreased in Japan in 2012, the clinical manifestations of CA6 infection should be continuously and carefully monitored in the national surveillance program. Comparisons of the clinical manifestations of CA6-associated HFMD with those of other types of enterovirus-associated HFMD are in progress, including studies on CA16 and enterovirus 71, in a large number of patients.


**Conflict of interest** None to declare.

**REFERENCES**