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## Atypical Hand-Foot-Mouth Disease Associated with Coxsackievirus A6 Infection

Jason P. Lott, MD MSHP<sup>\*,†</sup>, Kristina Liu, BA<sup>\*</sup>, Marie-Louise Landry, MD<sup>‡</sup>, W. Allan Nix, BS<sup>§</sup>,  
M. Steven Oberste, PhD<sup>§</sup>, Jean Bolognia, MD<sup>\*</sup>, and Brett King, MD PhD<sup>\*</sup>

<sup>\*</sup>Department of Dermatology, Yale University School of Medicine (SOM)

<sup>†</sup>Robert Wood Johnson Foundation Clinical Scholars Program, Yale University SOM

<sup>‡</sup>Departments of Laboratory Medicine and Internal Medicine, Yale University SOM

<sup>§</sup>Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention

### Abstract

**Background**—Hand, foot, and mouth disease (HFMD) is an acute viral illness commonly caused by coxsackievirus A16 (CV-A16) and enterovirus 71 infections. Recently, atypical HFMD has been reported in association with CV-A6, an uncommon enterovirus strain.

**Objective**—To describe the clinical features of atypical HFMD associated with CV-A6 infection and its diagnostic laboratory evaluation.

**Methods**—Patients presenting to our institution with history and examination suggestive of atypical HFMD from January 2012 to July 2012 were identified. Morphology and distribution of mucocutaneous lesions were recorded. Enterovirus infection was assessed by reverse transcriptase polymerase chain reaction of biologic specimens. Enterovirus type was determined by viral capsid protein 1 gene sequencing.

**Results**—Two adults and 3 children with atypical HFMD were identified. Four of 5 patients exhibited widespread cutaneous lesions. In 2 patients with a prior history of atopic dermatitis, accentuation in areas of dermatitis was noted. Associated systemic symptoms prompted 4 of 5 patients to seek emergency care, and both adults were hospitalized for diagnostic evaluation. Infection with CV-A6 was confirmed in all patients.

**Limitations**—This study is a case series from a single institution.

**Conclusion**—Consideration of the expanded range of cutaneous findings in atypical HFMD caused by CV-A6 infection may assist clinicians in diagnosis and management.

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**Corresponding Author (send reprint requests here):** Brett King, MD PhD, 333 Cedar St, LCI 501, PO Box 208059, New Haven, CT 06520-8059, Phone: 203-785-4091, Fax: 203-785-7637.

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## Keywords

Hand-foot-mouth disease; coxsackievirus A6; enterovirus; exanthem; atypical; diagnosis; evaluation

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## Introduction

Hand-foot-mouth disease (HFMD) is an acute viral illness characterized by fever, intraoral vesicles and erosions, and papulovesicles that favor the palms and soles.<sup>1</sup> Typically, the most common causative agents are coxsackievirus A16 (CV-A16) and enterovirus type 71 (EV-71). HFMD ordinarily occurs from spring to fall, usually affecting children 5 years of age and younger.<sup>2</sup>

Recently, the Centers for Disease Control and Prevention (CDC) reported HFMD with atypical features in several states, including Connecticut, caused by the uncommon strain coxsackievirus A6 (CV-A6).<sup>3</sup> We report 5 patients with HFMD secondary to CV-A6 with atypical, widespread cutaneous manifestations. Given the increasing incidence of this distinct form of HFMD, clinicians should become familiar with its clinical presentation and laboratory confirmation.

## Patient 1

A 43-year-old male was hospitalized in January 2012 with a 2-day history of headache, fever, chills, night sweats, odynophagia, myalgias, and a painful palmoplantar eruption impairing his ability to grasp and ambulate.<sup>3</sup> His wife and son had been ill with fever, nausea, and vomiting the week before, and several children at the son's daycare center had been recently diagnosed with HFMD.

Physical examination revealed 2–9 mm pink-red papules and papulovesicles on the left forearm, dorsal hands, palms, fingers, and on one toe (Fig. 1A). Several 1–2 mm vesicles and erosions were present on the hard and soft palates. One 4 mm painful subungual macule was present on the left thumb.

An initial evaluation including a complete blood cell count was normal and polymerase chain reaction (PCR) of serum for parvovirus B19 was negative. Reverse transcriptase-polymerase chain reaction (RT-PCR)<sup>4</sup> of plasma for enterovirus was positive. Histologic examination of a papule on the right hand showed scattered necrotic keratinocytes, exocytosis of lymphocytes, minimal interface change, and a perivascular lymphocytic infiltrate within the dermis. Viral typing performed by the CDC confirmed CV-A6 infection via viral capsid protein (VP) 1 gene sequencing.<sup>5</sup>

He received supportive care only and had a full recovery.

## Patient 2

A 21-year-old male was hospitalized in March 2012 with fever and shaking chills after having been recently diagnosed with Graves' disease. The day after admission he

complained of odynophagia, and the following day he developed a “rash” on his hands, prompting a dermatologic consultation.

Physical examination revealed 2 mm vesicles in the posterior pharynx and numerous 1–2 mm pink-red papules and papulovesicles on the lips, ears, upper extremities (antecubital fossae, dorsal hands, palms, fingers), and lower extremities (thighs, shins, dorsal feet, soles) (Fig. 1B–C).

Histologic examination of a papule on the right forearm showed orthokeratosis, mild spongiosis, focal vacuolar degeneration, and a perivascular lymphocytic infiltrate with rare neutrophils, suggestive of a viral exanthem. Enterovirus RT-PCR of plasma, stool, and vesicular fluid was positive, and the virus in vesicular fluid was identified as CV-A6 by the CDC.

The eruption began to resolve spontaneously, and the patient was discharged from the hospital.

### Patient 3

In February 2012, a 22-month-old girl with a history of atopic dermatitis (AD) and recurrent otitis media was referred to the dermatology clinic for a tender cutaneous eruption of two days’ duration. One day before the onset of the rash, she had presented to the ED because of a fever and was given oral amoxicillin for presumed otitis media.

Physical examination revealed numerous, 3–5 mm, pink-red papulovesicles involving the lips, anterior axillary line, upper extremities (antecubital fossae, forearms, dorsal hands, palms), gluteal cleft, and lower extremities (thighs, popliteal fossae, shins and soles). There was an obvious predominance of lesions in her antecubital fossae (Fig. 1D), a site where she commonly manifested AD. A stool sample was positive for enterovirus by RT-PCR and was typed as CV-A6 by the CDC.

The child’s illness resolved within one week without treatment, although she subsequently developed onychomadesis (also described in other CV-A6 HFMD outbreaks).<sup>6,7</sup> The patient’s older sister and several children in the patient’s daycare center were subsequently reported to have developed HFMD.

### Patient 4

A 4-year-old boy with a history of asthma and an ileal resection for intussusception presented to the ED in March 2012 because of fever, diarrhea, and a tender cutaneous eruption. He had been hospitalized overnight seven days prior for a fever, cough, and abdominal pain and had been discharged home on oral amoxicillin for presumed pneumonia.

Physical examination revealed 2 mm erosions on the soft palate and 2–4 mm pink-red papulovesicles on the mucosal and cutaneous lips (Fig. 1E). Similar lesions were present on the ears, back, flexor wrists and palms, buttocks, flexor lower extremities, and soles (Fig.

1F–G). Enterovirus RT-PCR of stool and vesicular fluid was positive. Subsequently, virus in the vesicular fluid was typed as CV-A6 by the CDC.

The patient was discharged from the ED with supportive care only, and his illness resolved without sequelae.

## Patient 5

A 19-month-old girl with a history of atopic dermatitis presented to the ED in July 2012 for a 3-day history of a fever and a “rash.” Her mother stated she had had contact with other children diagnosed with HFMD several weeks prior.

Physical examination revealed 4–5 mm erosions on the anterior and lateral aspects of the tongue, erythema of the posterior oropharynx, and edema of the tonsillar pillars. There were 1–5 mm pink-red papulovesicles on the cheeks, perioral area, upper and lower extremities, back, buttocks, and mons pubis. At sites of previous atopic dermatitis, especially the dorsal hands and fingers, the papulovesicles coalesced into plaques. The palms and soles were spared.

Scrapings from a lesion on the left foot were negative for herpes simplex virus (HSV) and varicella-zoster virus (VZV) by direct fluorescent antibody assay and cell culture. Oral and rectal swabs were positive for enterovirus by RT-PCR. Subsequently, the enterovirus in the oral sample was typed as CV-A6 by the CDC.

The patient was discharged from the ED with supportive care only, and her illness resolved without sequelae.

## Discussion

Hand, foot, and mouth disease is an acute vesicular exanthem and enanthem caused by enteroviruses and seen primarily in young children.<sup>8,9</sup> Cutaneous lesions vary from erythematous papules to oval-shaped vesicles; they may be asymptomatic or tender and favor the palms and soles.<sup>3,10</sup> The dorsal aspects of the hands and feet as well as the buttocks may also be involved.<sup>10</sup> A vesicular enanthem involving the hard and soft palates, tongue, gingiva, and buccal mucosa is present in nearly 100% of patients.<sup>11,12</sup> Typically, HFMD resolves spontaneously within one week without therapeutic intervention.<sup>10</sup> Most epidemics of HFMD have been caused by serotypes CV-A16 and EV-71. Less commonly associated serotypes include coxsackieviruses A5, A7, A9, A10, B1, B3, and B5.<sup>10,13–15</sup> Whereas CV-A16 infection is almost always mild, EV-71-associated HFMD may be more severe with encephalitis, acute flaccid paralysis, myocarditis, pulmonary edema, and even death, though the more severe manifestations are rare.

CV-A6 infection usually presents as herpangina, not HFMD.<sup>16</sup> Since 2008, however, outbreaks of CV-A6-associated HFMD have occurred in Singapore,<sup>17</sup> Japan,<sup>18</sup> Finland,<sup>6,19</sup> and Taiwan.<sup>20,21</sup> A recent report highlighted 63 cases of atypical and severe HFMD that occurred in the U.S. from November 2011 to February 2012,<sup>3</sup> and infection with CV-A6 – a strain not commonly identified in the U.S. – was confirmed in 25 of 34 patients whose

clinical specimens were tested.<sup>3</sup> Although all 25 CV-A6 strains were closely related genetically (based on partial VP1 gene sequences) to CV-A6 strains circulating internationally, no epidemiologic evidence (e.g. travel history) directly linked any of the U.S. cases to importation. Among the features that made CV-A6 HFMD atypical and more severe were the disease occurrence in late fall and winter<sup>22</sup> and a greater than expected proportion of affected adults (24%) and hospitalizations (19%).<sup>3</sup>

The patients described here highlight the atypical clinical presentation of CV-A6 HFMD (Table 1). Three of the five patients presented during winter months, two of the patients were adults, and the eruption in four of the five patients was widespread. Prominent involvement of sites of dermatitis – the antecubital and popliteal fossae in Patient 3 and the dorsal hands and fingers in Patient 5 – was seen in two patients with atopic dermatitis. Notably, another patient (Patient 2) with no personal or family history of atopy had involvement of the antecubital fossae. Systemic symptoms, e.g. fever, chills, diarrhea, and myalgias, together with tender mucocutaneous lesions, led 4 of 5 patients to seek emergency hospital care; both adults were hospitalized for diagnostic evaluation.

The predilection of lesions of CV-A6 HFMD for areas of atopic dermatitis resembles eczema herpeticum (Kaposi varicelliform eruption). Honing of other viral exanthems to sites of inflammation or cutaneous injury has also been described, e.g. localization of varicella to an area of sunburn<sup>23</sup> or diaper dermatitis,<sup>24</sup> and accentuation of CV-A16 HFMD in an area of diaper dermatitis.<sup>24</sup> Viremia in the setting of increased vascular permeability at sites of inflammation may underlie this phenomenon.

The differential diagnosis for typical HFMD varies depending on the presence or absence of cutaneous involvement. When only the oral mucosa is involved, the differential diagnosis includes primarily herpangina, orolabial herpes simplex infection, and aphthous stomatitis. However, the differential diagnosis includes eczema herpeticum, varicella, disseminated zoster, and erythema multiforme major if there is widespread cutaneous involvement.

Whereas the diagnosis of typical HFMD relies primarily on physical examination and history, confirmation of atypical cases may require additional laboratory evaluation (Table 2). Molecular amplification methods such as RT-PCR are the most sensitive for detecting enteroviruses. RT-PCR assays used in diagnostic laboratories are “type-common”, detecting all enterovirus serotypes, which number over 100, without differentiation. Viral typing requires nucleic acid sequencing of the viral capsid protein 1 and is only performed at specialized research or public health laboratories such as the CDC.

Detecting virus by RT-PCR from vesicular fluid is preferred for HFMD, but throat swabs and stool samples are also acceptable. Testing blood samples is not recommended since enterovirus viremia occurs early, seeds the skin, then recedes and, with the exception of young infants, is often negative when patients present with disease.<sup>25</sup> The real-time RT-PCR assay used in our laboratory is very sensitive, allowing for the detection of very low level viremia, as in Patients 1 and 2 described above.<sup>4</sup>

Virus isolation is suboptimal for HFMD since group A coxsackieviruses and EV-71 often require specialized cell systems such as rhabdomyosarcoma cell lines or inoculation of

suckling mice,<sup>25</sup> neither of which are available in most laboratories. Routine cultures of skin lesion samples from three of our patients were negative (Patients 1, 2, and 4), yet two of these were tested by enterovirus RT-PCR and were strongly positive (Patients 2 and 4).

Commercially available enterovirus antibody assays utilize outdated complement fixation methodology, require acute and convalescent serum samples for diagnosis, are limited to 6 to 12 serotypes, and do not include enterovirus types commonly associated with HFMD. For these reasons, they are not recommended for use.

The emergence of CV-A6 has led to atypical presentations of HFMD. Clinicians need to be aware of the expanded range of cutaneous findings in CV-A6 HFMD in order to consider the diagnosis, initiate appropriate laboratory evaluation (Table 2), and recommend supportive care.

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**Figures 1.**

Cutaneous lesions of atypical HFMD. Erythematous papulovesicles involving the fingers of Patient 1 (A). Erythematous papules involving the ear and antecubital fossa of Patient 2 (B, C). Significant involvement of the antecubital fossa, a common site of involvement of AD in Patient 3, in addition to scattered papules on the forearm and thigh (D). Papulovesicles involving the perioral area and lips (E), sole (F), and palm (G) in Patient 4.



Table 1

Patient demographics, clinical presentations and laboratory results. RT-PCR, reverse transcriptase-polymerase chain reaction.

Patient	Age (years)	Enterovirus Detection by RT-PCR	Body Sites Involved	Clinical Features	History of Atopic Dermatitis	Presented to the Emergency Department
1	43	*Plasma +	<ul style="list-style-type: none"> <li>• Oropharynx</li> <li>• Left forearm</li> <li>• Dorsal hands, palms, fingers (including subungual thumb)</li> <li>• Toe</li> </ul>	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Chills</li> <li>• Night sweats</li> <li>• Headache</li> <li>• Odynophagia</li> <li>• Myalgias</li> </ul>	No	Yes, subsequently hospitalized
2	21	Stool + Plasma + *Fluid from a cutaneous vesicle +	<ul style="list-style-type: none"> <li>• Oropharynx, lips</li> <li>• Ears</li> <li>• Antecubital fossae</li> <li>• Dorsal hands, palms, fingers</li> <li>• Thighs, shins</li> <li>• Dorsal feet, soles</li> </ul>	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Chills</li> <li>• Odynophagia</li> </ul>	No	Yes (for fever), subsequently hospitalized
3	2	*Stool +	<ul style="list-style-type: none"> <li>• Lips</li> <li>• Peri-axillary chest, antecubital fossae (AD site), forearms</li> <li>• Dorsal hands, palms</li> <li>• Gluteal cleft</li> <li>• Thighs, popliteal fossae (AD site), shins</li> <li>• Soles</li> </ul>	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Onychomadesis (subsequently)</li> </ul>	Yes	Yes
4	4	Stool + *Fluid from a cutaneous vesicle +	<ul style="list-style-type: none"> <li>• Oropharynx, lips</li> <li>• Ears</li> <li>• Flexor wrists</li> <li>• Palms</li> <li>• Back</li> <li>• Buttocks</li> </ul>	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Diarrhea</li> </ul>	No	Yes

Patient	Age (years)	Enterovirus Detection by RT-PCR	Body Sites Involved	Clinical Features	History of Atopic Dermatitis	Presented to the Emergency Department
5	4	Stool + *Oral +	<ul style="list-style-type: none"> <li>• Flexor aspect of the lower extremities</li> <li>• Soles</li> <li>• Oropharynx, tongue</li> <li>• Perioral face, cheeks</li> <li>• Upper extremities</li> <li>• Dorsal hands and fingers (AD sites)</li> <li>• Back, buttocks, mons pubis</li> <li>• Lower extremities</li> <li>• Dorsal feet</li> </ul>	<ul style="list-style-type: none"> <li>• Fever</li> </ul>	Yes	Yes

\* Virus in sample sequenced as CV-A6 at the Centers for Disease Control and Prevention (CDC).

**Table 2**

Laboratory evaluation of suspected atypical hand-foot-mouth disease (HFMD). CDC, Centers for Disease Control and Prevention; DFA, direct fluorescent antibody assay; HSV, herpes simplex virus; PCR, polymerase chain reaction; RT, reverse transcriptase; VZV, varicella-zoster virus.

Atypical HFMD should be considered when either papulovesicles extend beyond the typical distribution pattern, lesions favor sites of atopic dermatitis as in eczema herpeticum, the disease presents in the winter, or adults are affected. In such cases, the following diagnostic laboratory evaluation is recommended:

- DFA or PCR of keratinocytes from the floor of an intact vesicle to exclude HSV or VZV infection
- RT-PCR of vesicle fluid\* to confirm enterovirus infection. If vesicle fluid is unavailable, then RT-PCR of oropharyngeal or stool specimen\*. In the latter case, a stool specimen rather than a swab of the perianal area should be obtained.
- If an epidemic is suspected, contact a specialized research or public health laboratory such as the CDC for additional testing, i.e. viral capsid protein (VP) 1 gene sequencing.

Differential diagnosis

- Eczema herpeticum, varicella, disseminated zoster, erythema multiforme major

\* Culture and serology are not recommended (see text)