Hand-foot-and-mouth disease: a new look at a classic viral rash

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Purpose of review
Hand-foot-and-mouth disease (HFMD) is a common cause of viral rash in children with classic skin findings which are easily recognized by pediatricians. Recently, several atypical cutaneous manifestations of HFMD have been described. Awareness of these patterns may lead providers to appropriate diagnosis and management. This review also highlights the epidemiological patterns of more virulent strains and emerging research in disease prevention.

Recent findings
Classic HFMD presents with tender lesions on the hands, feet, and oral mucosa. Atypical skin findings in HFMD may be seen in children with atopic dermatitis. These include 'eczema coxsackium', in which eczematous skin is superinfected with coxsackie virus, resembling herpes infection. Nail changes, such as shedding, may follow HFMD after a latency period. Enterovirus 71 is responsible for epidemic outbreaks of HFMD in Asia, with systemic manifestations and occasionally neurological sequelae. Research is underway to develop a vaccine which could curb epidemics, but for the present, supportive care and hygiene measures are the standard of care.

Summary
Atypical manifestations of HFMD in children with atopic dermatitis may mimic herpetic superinfection. In a child presenting with nail changes, consider antecedent HFMD in the differential diagnosis. The mainstay of treatment for HMFD remains supportive care.

Keywords
Beau's lines, eczema coxsackium, hand-foot-and-mouth disease, onychomadesis

INTRODUCTION

Hand-foot-and-mouth disease (HFMD) is a viral illness which has received a significant amount of attention in the past two decades because of its ability to cause recurrent outbreaks worldwide. The syndrome is caused by various strains of enterovirus type A, most commonly coxsackie virus A16 and enterovirus 71 (EV71). Infection predominantly occurs in children less than 10 years of age.

This review will present the recent literature pertaining to HFMD, emphasizing atypical cutaneous manifestations of illness, virulence patterns, recognition of severe life-threatening disease, and new directions in prevention and management.

EPIDEMIOLOGY

The classical cutaneous findings of HFMD were first described in 1958, with Robinson *et al.* [1] reporting an outbreak of 60 people (including 47 children) in Toronto, from which coxsackie A16 was isolated. Since that time, HFMD has been linked to EV71 and coxsackie virus types A16, A6, A5, A7, A9, A10, B2, and B5 [2]. In the United States, CVA16 and EV71 are historically the most common cause of HFMD [3]; however, there has been a recent emergence of CVA6-associated outbreaks worldwide, including outbreaks in four US states over a 4-month period in 2011–2012 [4]. In 2014 alone, reports of CVA6-associated HFMD outbreaks were reported in China, Thailand, Spain, Cuba, New Zealand, and the United Kingdom [5–10]. Humans are the only reservoir for these enteroviruses, and epidemics often occur among young children in school and daycare

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KEY POINTS

- Atypical manifestations of HFMD in children with atopic dermatitis may mimic herpetic superinfection.
- In a child presenting with nail ridging or shedding, consider antecedent HFMD in the differential diagnosis.
- In the Asian continent, virulent enterovirus strains are responsible for epidemic HFMD with significant morbidity.
- Currently, measures for prevention include proper hygiene; in the future, vaccine development may prevent epidemic spread of disease.

settings. Cyclical epidemics occur every few years in a given geographic region once a critical number of new unexposed children is reached. Transmission occurs via fecal-oral contact and respiratory secretions, and the usual incubation period is 3–6 days. Strong seasonal trends are seen in temperate regions, with peak outbreaks in spring and summer months.

PRESENTATION

HFMD classically presents as a self-limited febrile illness with malaise, oral ulcerations causing throat or mouth pain, and a vesicular exanthem found on the hands and feet. The illness begins with fever, malaise, poor appetite, and sore throat. Fever is typically low grade and resolves in 48 h. Painful oral lesions begin to appear within 1–2 days of fever onset, and are usually located on the tongue, palate, and buccal mucosa (Fig. 1). Erythematous oral macules evolve into vesicles which rupture and cause painful ulcerations [2]. Patients may present with dehydration because of significant discomfort with eating and drinking. A rash subsequently develops most often on the palms and soles (Fig. 2), and also commonly on the buttocks and genital region. Skin lesions are typically vesicles with surrounding erythema, but may also manifest as small erythematous macules, papules, clustered vesicles, and even bullae. Cutaneous lesions are nonpruritic, but often painful. Complete resolution typically occurs within 7–10 days. It is not uncommon for a patient to exhibit only one or two of these findings, such as the oral-cutaneous findings without fever or systemic symptoms [11].

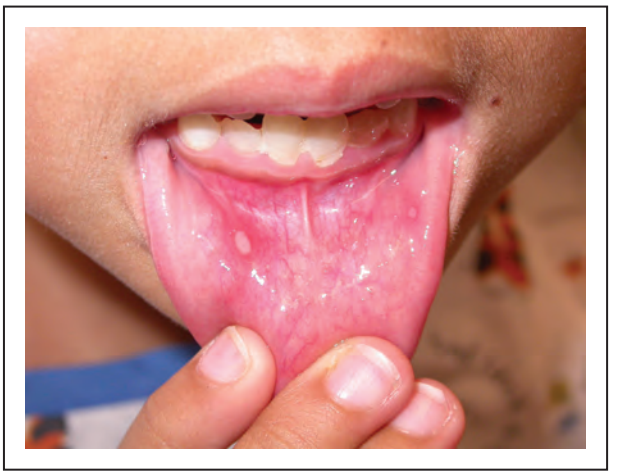

FIGURE 1. Oral enanthem: painful oral erosions on the lower labial mucosa. These typically appear within 24–48 h of fever onset.

ATYPICAL CUTANEOUS MANIFESTATIONS

Although classic manifestations of HFMD are often easily recognized by pediatricians, there are several atypical presentations of disease which should prompt consideration of HFMD. A recent comprehensive review of atypical HFMD exanthema was published by Mathes *et al.* [12▪▪]. This article highlights four unusual clinical phenotypes based on a retrospective case series of 80 patients with

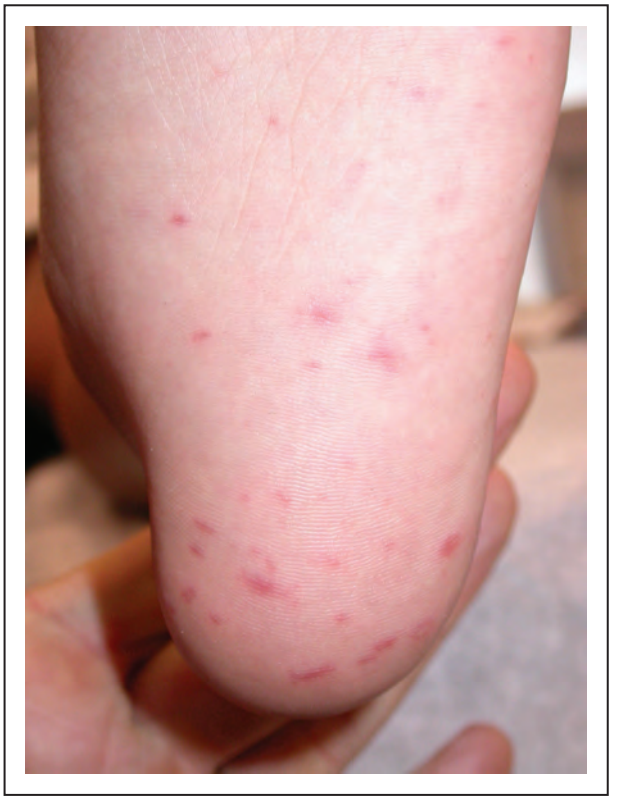

FIGURE 2. Exanthem: typical appearance of classic HFMD on the plantar surface. Note that the long axis of the lesion is parallel to dermatoglyphs (ridges on palms and soles or 'fingerprints'). This is a classic distribution.

CVA6 infections [12▪▪]. The four atypical cutaneous syndromes include: typical lesions with more extensive distribution involving trunk and extremities; 'eczema coxsackium' which resembles eczema herpeticum with erosions localized to areas of previous or active atopic dermatitis (Fig. 3a–c); Gianotti–Crosti-like eruptions with acrally distributed lesions on the face, arms, and legs, but with relative sparing of the trunk; and hemorrhagic findings of petechiae or purpura. Bullae was a more common finding in infants below 1 year, petechiae/purpura and nail changes were more common in older children above 5 years, and 'eczema coxsackium' was the most common in those with a history of atopic dermatitis. These findings were also observed in CVA6-associated HFMD outbreaks in Boston and Edinburgh [10,13].

Efforts made to correlate viral serotype with disease phenotype have had conflicting results. Hubiche *et al.* [14▪] characterized the dermatological spectrum of HFMD in a prospective, cross-sectional study in 2014 of 82 patients with confirmed and serotyped disease. These patients were recruited from seven dermatology units across France, and, while this likely caused an overrepresentation of atypical exanthema due to referrals, their findings provide assistance in the diagnosis of HFMD in patients with atypical rashes. Of the two predominant viral strains represented (CVA6 51.2% and CVA16 34.1%), CVA6 caused more perioral lesions, but widespread exanthem was produced with similar frequency by both strains. This conflicts with a report from a past outbreak in Taiwan, in which CVA6 caused more severe skin findings than other strains [15]. Overall, differentiation between CVA6 and CVA16 does not have much clinical utility, as both are typically self-limited and are not associated with the severe neurological or cardiopulmonary illness that occurs with the EV71 strain. In addition, 100% of patients in the Hubiche cohort did have involvement of at least two of the three classic sites (hands, feet, and/or mouth); highlighting that even an atypical presentation will adhere to the classic distribution.

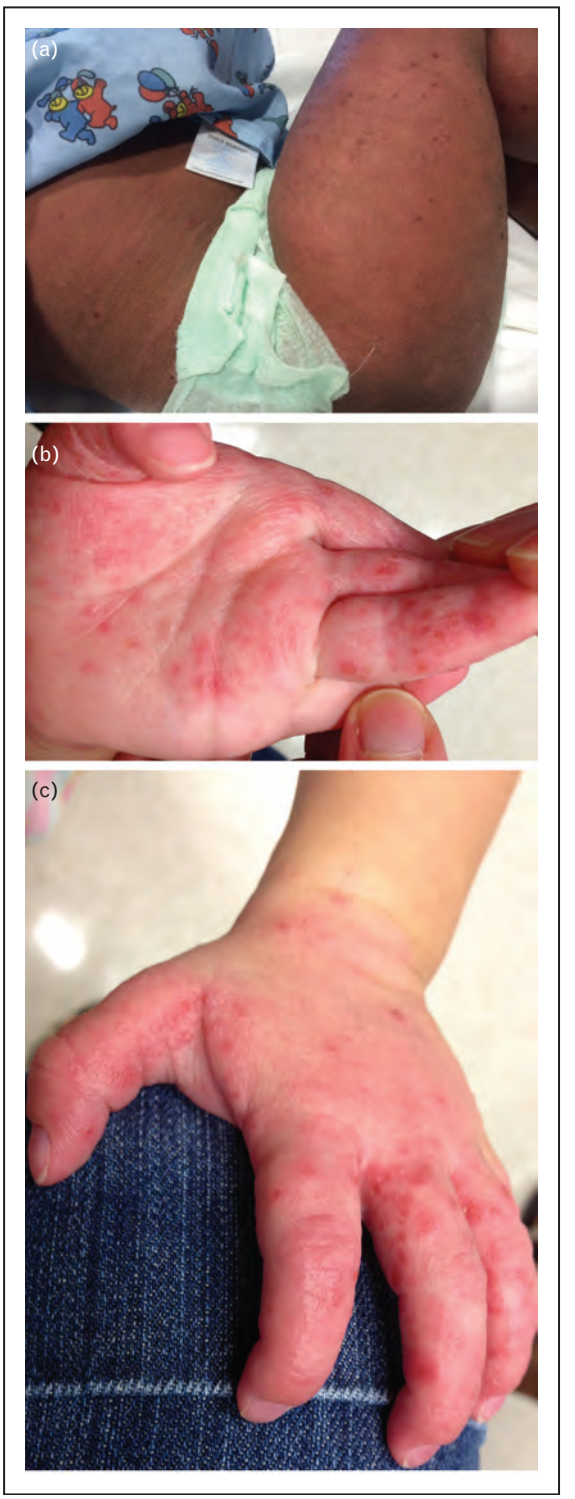

FIGURE 3. (a–c) 'Eczema coxsackium': eruption of painful vesicular lesions in a background of atopic dermatitis of legs (a) and hands (b and c).

NAIL INVOLVEMENT

In some cases, a chief complaint of nail changes may suggest antecedent HFMD infection. Beau's lines and onychomadesis can both occur following infection, and reflect temporary nail matrix arrest. Beau's lines manifest as horizontal ridges or grooves of the nail plate (Fig. 4a); whereas onychomadesis is characterized by complete separation of the proximal nail from the nail bed (Fig. 4b). This phenomenon was first described in 2000 by Clementz and Mancini, and has since been corroborated by multiple reports [16]. The mean latency of nail changes from onset of HFMD illness is about 40 days, and it has been associated with multiple enterovirus strains [17]. The incidence of nail changes is variable

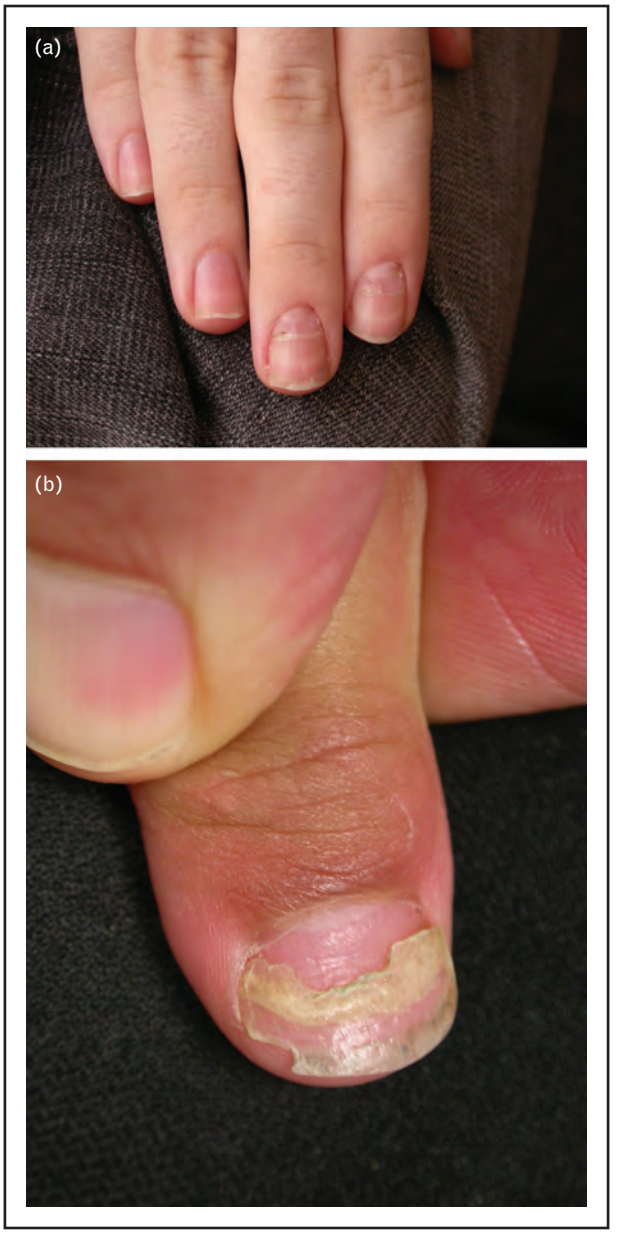

FIGURE 4. (a–b) Nail changes associated with HFMD. (a) Beau's lines, or horizontal ridging of nails which should grow out with nail plate. With onychomadesis (b), there is complete separation of proximal nail from the underlying nail bed. Both are caused by temporary nail matrix arrest.

and likely underreported because of delayed onset. It can be a common finding in specific epidemics, such as an HFMD outbreak in a Spanish nursery school in which 12 of 17 children with HFMD (70.5%) went on to have nail shedding [18]. The prognosis is good in most cases, with return of normal nail growth over 6–12 months following shedding. The exact mechanism of nail growth cessation in HFMD is not fully understood; however, PCR isolation of enterovirus in nail fragments suggests damage from direct viral replication [19].

LABORATORY TESTING

The diagnosis of classical HFMD is made from clinical presentation alone and does not require laboratory confirmation. However, viral testing in cases of suspected atypical HFMD can be useful in guiding management. As eczema coxsackium is clinically indistinguishable from eczema herpeticum, herpes simplex virus (HSV) testing should be performed to rule out herpes infection requiring treatment with acyclovir [20]. For severe cases in which confirmation of HFMD is indicated, reverse transcriptase PCR can identify the presence of enterovirus in vesicle fluid, oropharyngeal swab, or stool specimen. Identification of a specific enterovirus strain requires gene sequencing, and is only performed by public health laboratories in the setting of an epidemic.

SEVERE DISEASE

Severe illness from HFMD, with the exception of severe dehydration from poor oral intake and late access to care, is mostly due to direct infection of the central nervous system. Neurological manifestations include aseptic meningitis, acute focal paralysis, and brainstem encephalitis. Most fatalities are due to autonomic dysregulation caused by brainstem encephalitis, which leads to cardiopulmonary failure in rare cases. Acute focal paralysis resembles poliomyelitis, but has a better prognosis with complete resolution in most cases.

In recent decades, most reports of severe illness and death related to HFMD stem from EV71 epidemics in the Asia Pacific region. Last year, Xing *et al.* [21▪▪] published the largest epidemiological study of HFMD to date, using 2008–2012 data from China's HFMD surveillance system to document over 7.2 million cases of HFMD (combining laboratory-confirmed cases and those diagnosed by clinical criteria alone). The rate of severe disease, defined as involving neurological or cardiopulmonary complications, was 1.1% (82 486). There were 2457 deaths (0.03%) recorded, with EV71 identified in 93% of laboratory-confirmed fatalities (1617/1773).

In another large study from China, Zhang *et al.* [22] reported 26 829 children with symptoms concerning for EV71 infection, including HFMD in the Shanghai region during an EV71 epidemic 2010–2012. During that time, 767 (2.9%) children were admitted to the hospital, 89 (39.7% of the admitted) of them had signs of neurological involvement, and seven died. Neurological involvement included altered mental status, aseptic meningitis, brainstem encephalitis, myoclonus, ataxia, and acute focal paralysis. Of the 82 survivors with neurological

involvement, five had deficits at the time of discharge, and all had returned to normal by 2-month follow-up. MRI findings correlated with neurological examination findings in some, but not all, cases of neurological impairment, and may be helpful for understanding the extent of disease and estimating prognosis [23▪,24].

RISK STRATIFICATION

In Asian countries seeing more virulent epidemics of HFMD, researchers are attempting to find better ways to risk stratify patients who may be more likely to rapidly progress to severe or fatal disease. A meta-analysis by Fang *et al.* [25▪▪] aggregated data from 19 observational studies to identify variables that conferred risk for rapid progression to severe disease (neurological, respiratory, or circulatory complications, or death). These included fever duration of 3 or more days, temperature 37.5°C or greater, young age, increased neutrophil count, hyperglycemia, vomiting, and EV71 infection.

Other groups have sought to correlate clinically useful biomarkers with disease severity. Multiple cytokine profiles have been associated with severe disease, although no consistent profile has emerged as clinically predictive [26–28].

Genetic susceptibility to HFMD infection is also being explored. The identification of several single-nucleotide polymorphisms has correlated with both disease susceptibility and progression to severe disease [29,30], but this basic science research has not yet translated into clinical practice.

MANAGEMENT

The majority of patients with HFMD are managed in an outpatient setting with supportive care measures only. There are currently no effective antiviral therapies. Maintaining adequate hydration and nutrition is the primary challenge, and the use of cool liquids, syringe feeding, and systemic analgesics can be helpful. The use of topical oral anesthetics is not recommended in young children, as it has not been shown to improve oral fluid intake and carries the risk of systemic absorption and toxicity [31].

The use of intravenous immunoglobulin (IVIG) for the treatment of severe HFMD has become common practice in regions with prevalent EV71, with some studies suggesting apparent benefit [32]. However, recent research has raised concerns over the ability of certain immunoglobulin G (IgG) subclasses (IgG3) to actually potentiate EV71 infection *in vitro*, whereas other subclasses neutralize infection [33]. More research is needed to better characterize the potential benefits and harms of IVIG therapy for severe HFMD.

The use of systemic glucocorticoids early in illness has been associated with an increased risk of developing severe disease [34▪,35]. This clinical pattern is supported by data from mouse models, in which administration of glucocorticoids on day 1 or 3 of illness was associated with increased tissue viral loads and increased mortality [36]. Often in an ill-appearing child presenting with an eruption, systemic glucocorticoids are considered as empiric treatment. If HFMD is suspected, steroids should be avoided.

PREVENTION

Currently, the most effective prevention measures for HFMD are hand washing, disinfecting common areas/shared toys, and limiting exposure by keeping ill children out of school or daycare. There is no approved vaccination for the causative viruses of HFMD, but several vaccines are currently under development. There are three different inactivated EV71 vaccines which have completed phase 3 clinical trials in China [37]. Each has shown at least 90% efficacy against EV71-associated HFMD, but none offers protection against other common HFMD-causing viral strains such as CVA16, CVA6, or CVA10. A bivalent EV71/CVA16 vaccine has shown efficacy in mouse trials, but has not yet reached clinical trials [38▪]. Given the ability of enterovirus A to cause outbreaks involving more than one strain concurrently or to alternate dominant strains year-to-year, the most desirable method of prevention would be a safe, effective, and affordable polyvalent vaccine targeting all of the leading causes of HFMD. A major barrier to the production of such a vaccine is the lack of usable cross-country epidemiological surveillance data.

CONCLUSION

HFMD is a common viral illness well known to the general pediatrician. Awareness of atypical manifestations of this common illness can aid in diagnosis and appropriate counseling. In particular, we highlight the recently described 'eczema coxsackium' – a herpetic-like superinfection in patients with atopic dermatitis. In addition, if a patient presents with nail changes suggesting nail matrix arrest, a clinician should be prompted to ask about febrile illness or skin eruption occurring in the previous 1–3 months.

Thus far, outbreaks with the most severe neurological sequelae have occurred in the Asian continent; however, a more virile strain could lead to

similar morbidity in the United States. As such, we may expect to see emerging research focused on vaccine development and distribution worldwide.

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Conflicts of interest

There are no conflicts of interest.

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