Coxsackievirus B5 associated with hand-foot-mouth disease in a healthy adult

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INTRODUCTION

Hand-foot-mouth disease (HFMD) is an acute and highly contagious viral exanthem that commonly affects children younger than 5 years.1 The infection can be symptomatic and the clinical manifestations include mild fever with a characteristic vesicular eruption on the hands, feet, and oral cavity.2 Historically, HFMD is known as a self-limited disease process. However, recurrent outbreaks over the last 2 decades in the Asian and Pacific populations have caused severe illness and debilitating complications, even death. In addition, North American outbreaks were recently documented and have affected unexpected numbers of healthy adults and children.1 The purpose of this case report is to present an atypical case of HFMD in a healthy adult caused by coxsackievirus B5 and to recognize the potential danger of HFMD epidemics.

CASE REPORT

A 34-year-old white man was referred to our dermatology center with a chief complaint of a painful rash. Six days before arrival at our clinic, the patient stated he began to have low-grade fever and painful sores in his mouth. Subsequently, painful, burning blistering of the hands, feet, and face developed along with crusting of the scalp. He denied any significant medical or surgical history, takes no medications, and has no allergies. However, social history revealed the patient's 1-year-old son recently had HFMD from an outbreak at his daycare.

Physical examination found dusky erythematous macules on the tips and medial and lateral aspects of the digits and on the palmar surfaces bilaterally (Fig 1). Similar lesions were noted on the medial plantar surfaces on both feet but in lesser quantity. Erythematous crusted macules were noted diffusely on the scalp (Fig 2). In addition to the few vesicles that were noted on the superior helices of the ears, left and right nasal side walls, and in the nasolabial folds, there were also vesicles and erythematous, eroded and crusted papules noted in the perioral area (Fig 3). The oral mucosa had extensive erythematous macules (Fig 4).

A complete blood count and blood chemistry test found no abnormalities. Acute coxsackievirus antibody serum panel found positive titers for coxsackievirus B5 and coxsackievirus B2 at 1:16 and 1:8, respectively, with the remaining coxsackievirus A (CVA) and coxsackievirus B (CVB) titers being negative. In addition, enterovirus panels were negative. Titers of 1:8 or 1:16 may be indicative of either past or present infection, because these complement-fixing antibodies persist for only a few months. Shave biopsy on the right superior helix showed interface vacuolar dermatitis with numerous suprabasal necrotic keratinocytes, early intraepidermal vesicle formation, and few eosinophils (Fig 5, A-C).3

Based on the history and physical examination, HFMD was diagnosed. The elevated CVB5 titer and pathology results were also strongly suggestive of this diagnosis. Other diagnoses to be considered...
were herpangina, aphthous ulcers, varicella, gingivostomatitis, erythema multiforme, and drug eruption. Symptomatic treatment was discussed, and the patient was given prescriptions for viscous and topical lidocaine for the painful oral and scalp lesions, respectively. In addition, as-needed analgesics, such as Tylenol and ibuprofen, and maintaining adequate oral fluid intake were discussed. At 1 week of follow-up, the patient stated his sore throat had decreased slightly, and the lesions on his scalp had already begun to resolve. At 1 month, the patient stated his fingernails had begun to shed from the nail base (onychomadesis). In addition, the skin and mucosal lesions almost completely resolved at this point. He reached his normal state of health with regrowth of new fingernails by 2 months postinfection.

DISCUSSION

HFMD is a highly contagious childhood exanthem caused by viruses that belong to the genus Enterovirus in the Picornaviridae family. It is classically characterized by a papulovesicular eruption on the hands and feet and within the oral cavity. Enteroviruses are spread by direct vesicular contact and fecal-oral and respiratory routes. Prodromal symptoms may consist of fever, malaise, abdominal pain, poor appetite, sore throat, and myalgias. After a 3- to 7-day incubation period, painful oral ulcers are usually the first clinical signs of the disease, with skin manifestations occurring concurrently or shortly after. Complete resolution of symptoms typically occurs by 7 to 10 days and treatment is mainly supportive.

Fig 1. Dusky erythematous macules on palms.

Fig 2. Erythematous crusted macules diffusely on scalp.

Fig 3. Tense bullae noted on the superior helices of ears, left and right nasal side walls, and in nasolabial folds. Few vesicles and erythematous, crusted macules noted in perioral area.

Fig 4. Erythematous, macular eruptions present on the posterior and lateral oropharyngeal structures and with erosions present on the posterior portion and the anterior tip of tongue.
After reviewing the literature, it is unclear whether there are significant differences in the disease course and outcome of HFMD depending on the pathogen responsible. The most common causes of HFMD are CVA16 followed by Enterovirus 71 (HEV71). Recent data show that CVA6, CVA10, and CVB5 are becoming common as well. In 2014, Hubiche et al set out to characterize the dermatologic spectrum of HFMD in 82 patients with confirmed and serotyped disease and found most patients were infected with CVA6 (51.2%) and CVA16 (34.1%). Patients infected with CVA6 exhibited more perioral lesions, but both strains caused similar rates of generalized skin findings and resulted in a benign disease course. These data can infer that differentiation between CVA6 and CVA16 does not have much clinical utility. In addition, all of the patients in the Hubiche et al sample did have involvement of at least 2 of the 3 classic sites (hand, feet, and/or mouth), highlighting that even an atypical presentation will adhere to the classic distribution. Onychomadesis is a minor complication of the nail beds that has been most commonly seen after infection with CVA6 and CVA10, although reports of nail shedding after CVA5, CVA6, CVB1, and CVB3 infection have been reported.

In contrast, China and surrounding countries have increasingly reported a significantly greater frequency of serious complications and fatalities resulting from HEV71 infection when compared with CVA16 and CVA6. Xing et al published the largest epidemiologic study to date and showed the rate of severe disease and death in patients affected by HFMD. The rate of severe disease was 1.1% (82,486), and the rate of death was 0.03% (2,457) with HEV71 being identified in 93% of laboratory-confirmed fatalities. As briefly mentioned, most of these complications and fatalities are occurring in Asia’s pediatric population; however, adults in these regions are affected as well.

What does this mean for us? In the United States and worldwide the most common cause of HFMD is CVA16. As with the other serotypes, this strain primarily affects children but can also affect adults by similar routes of transmission. Recent outbreaks of HFMD throughout multiple states have been reported and described an increasing percentage of affected adults. CVA6 is thought to be responsible for the increase in adult infection rate because it is capable of affecting a broader demographic. Although it has also been known to cause an atypical clinical presentation and onychomadesis, most of the reported CVA6 cases still followed a benign disease course and resolved without severe or life-threatening complications. As such, the frequency of severe complications and fatalities from HFMD in the United States is much less when compared with those seen in the Asia Pacific region.

Our patient’s clinical picture and nail shedding was suggestive of an atypical presentation of HFMD. Initially, we suspected our patient to be infected by CVA6 because of his atypical presentation and post-infectious complication of onychomadesis. Another possibility considered was an atypical case of herpangina owing to extensive involvement of the posterior mucosa. However, our patient’s serologic tests came back positive with a CVB5 titer at 1:16. Of the 6 CVB serotypes, CVB5 is one of the most common serotypes in humans with infection being common, but usually asymptomatic. It is commonly known for causing viral myocarditis and sporadic cases of cardiomyopathy. However, increasing reports exist in China of CVB5 infection causing severe HFMD, sporadic cases of central nervous system disease, and epidemics of aseptic meningitis. In 2009, Hu et al took throat swabs and serum specimens from 110 Chinese children who had confirmed HFMD and detected CVB5 infection in 14 patients (12.7%), of whom, 11 patients exhibited signs of neurologic disease. Another study by Yang...
et al\textsuperscript{16} found serologic differences in HFMD infection based on geographic distribution and found that 14.4\% of children in Shandong province were infected with CVB5. Although multiple studies show large groups of CVB5-infected individuals exhibiting signs of severe disease in China, this is not the case in the United States. In addition, there are no reports in the literature describing onychomadesis occurring secondary to CVB5 infection, thus making our patient’s disease course unique to any geographic location.

Because treatment is mainly supportive, recognition and prevention play a vital role in limiting spread of HFMD and decreasing outbreaks. One way physicians can help is to identify affected patients and educate them on preventive measures. Enteroviruses are shed in the stool for many weeks after initial infection, so good hand hygiene should be made a mandatory practice, especially in health care settings, daycare centers, and other places where outbreak is common.\textsuperscript{3} The Centers for Disease Control and Prevention\textsuperscript{17} recommend all affected patients and their close contacts to practice the following: frequent hand washing, especially after changing diapers and using the restroom; frequent disinfection of commonly used surfaces and objects; avoiding close contact with infected individuals. These recommendations are simple tasks that play an important role in preventing further spread of infection.

Multiple viruses in the Picornaviridae family are responsible for causing HFMD in persons of all ages. Although infection and illness is most commonly seen in young children and immunocompromised adults, there has been an unexpected increase in the amount of affected healthy adults. This could be because of reinfection with an unusual or more virulent strain as well as improper utilization of preventive measures by affected patients and close contacts. Because HFMD has the potential to reach epidemic levels in the United States, dermatologists and primary physicians need to be aware of the potential complications that can result. In addition, identification of the signs and symptoms of HFMD in a broader demographic should be a goal set by all physicians to prevent further disease spread, and thus, decrease the risk of future epidemics.

**REFERENCES**

1. Repass GL, Palmer WC, Stancampiano FF. Hand, foot, and mouth disease: identifying and managing an acute viral syndrome. Cleve Clin J Med. 2014;81:537-543.
2. Ramirez-Fort MK, Downing C, Doan HQ. Coxsackievirus A6 associated hand, foot and mouth disease in adults: clinical presentation and review of the literature. J Clin Virol. 2014;60:381-386.
3. DermNet New Zealand. Hand, foot and mouth pathology. http://www.dermnetnz.org/topics/hand-foot-and-mouth-disease-pathology/. Accessed November 7, 2016.
4. Nassef C, Ziemer C, Morrell DS. Hand-foot-and-mouth disease: a new look at a classic viral rash. Curr Opin Pediatr. 2015;27:486-491.
5. Park SK, Park B, Ki M. Transmission of seasonal outbreak of childhood enteroviral aseptic meningitis and hand-foot-mouth disease. J Korean Med Sci. 2010;25:677-683.
6. Kaminska K, Martini G, Lucchini R. Coxsackievirus A6 and hand, foot, and mouth disease: three case reports of familial child-to-immunocompetent adult transmission and a literature review. Case Rep Dermatol. 2013;5:203-209.
7. Centers for Disease Control and Prevention (CDC). Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus A6 — Alabama, Connecticut, California, and Nevada, November 2011—February 2012. MMWR Morb Mortal Wkly Rep. 2012;61:213-214.
8. Blomqvist S, Klemola P, Kaajalainen S, et al. Co-circulation of coxsackieviruses A6 and A10 in hand, foot and mouth disease outbreak in Finland. J Clin Virol. 2010;48:49-54.
9. Hubiche T, Schuffenecker I, Boralevi F, et al. Dermatological spectrum of hand, foot and mouth disease from classical to generalized exanthema. Pediatr Infect Dis J. 2014;33:e92-e98.
10. Davia JL, Bel PH, Ninet VZ, et al. Onychomadesis outbreak in Valencia, Spain associated with hand, foot, and mouth disease caused by enteroviruses. Pediatr Dermatol. 2011;28:1-5.
11. Alexander JP Jr, Baden L, Pallansch MA, Anderson LJ. Enterovirus 71 infections and neurologic disease — United States, 1977—1991. J Infect Dis. 1994;169:905-908.
12. Xing W, Liao Q, Viboud C, et al. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study. Lancet Infect Dis. 2014;14:308-318.
13. Jiang M, Wei D, Ou WL, et al. Autopsy findings in children with hand, foot, and mouth disease. N Engl J Med. 2012;367:91-92.
14. Hu YF, Yang F, Du J, Zhang T, Xue Y, Jin Q. Coxsackievirus B5, associated with neurological hand, foot and mouth disease, China. J Infect. 2012;65:189-191.
15. Chen P, Tao Z, Song Y, et al. A coxsackievirus B5-associated aseptic meningitis outbreak in Shandong Province, China in 2009. J Med Virol. 2013;85(3):483-489.
16. Yang F, Zhang T, Hu Y, et al. Survey of enterovirus infections from hand, foot and mouth disease outbreak in China, 2009. Virol J. 2011;8:508.
17. Centers for Disease Control and Prevention (CDC). Hand, foot, and mouth disease: prevention & treatment. www.cdc.gov/hand-foot-mouth/about/prevention-treatment.html. Accessed June 10, 2014.