

A Case of Atypical Hand-Foot-and-Mouth Disease (Enterovirus Exanthema) from Clinical Practice

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A clinical case of atypical hand-foot-and-mouth disease in a previously healthy girl was presented. The disease had atypical course with vesiculobullous lesions located mainly on the buttocks, dorsal surfaces of the feet, shins, knees, and less pronounced on the elbows and dorsal surfaces of the hands; purpuric lesions on the feet, palms and soles; minimal oral lesions; and streptococcal co-infection. Timely hospitalization and appropriate treatment of the patient led to her fast and complete recovery and showed effectiveness of therapy prescribed.

Key words: ENTEROVIRUS INFECTIONS; HAND, FOOT AND MOUTH DISEASE; CHILD

INTRODUCTION

In recent years, there has been a significant increase of infectious diseases caused by non-polio enteroviruses. An epidemic outbreak occurs every 3-4 years because new serotypes of viruses (e.g., Coxsackie A6, Enterovirus D68, Enterovirus 71) appear. All enteroviruses are antigenically heterogeneous and have wide geographical distribution. Enterovirus infections (EVI) show a clear seasonal pattern and the incidence is highest in summer and autumn, but in the tropics the infection is registered throughout the year. They are associated with a great variety of manifestations, from mild respiratory form, gastrointestinal infections, herpangina, hemorrhagic conjunctivitis, and exanthema (hand, foot and mouth disease, HFMD, is one of them) to more severe diseases such as pleurodynia, hepatitis, myopericarditis, pancreatitis, aseptic meningitis, encephalitis, paralysis, and neonatal sepsis leading to mortality (1, 2). Aggregated data provided by representatives from 24 of 31 EU and European Economic Area countries between 2015 and 2017 demonstrate that 66% of EVI were in children younger than 5 years, and 45% had neurological symptoms. Other symptoms were nonspecific fever (23%), respiratory symptoms (17%), HFMD (7%) and myocarditis (1%). Sixty-eight deaths were temporally associated with EVI. Typing of 67% of specimens revealed 66 enterovirus types. Coxsackievirus A6 was the most frequently detected enterovirus type (13% of 11,559

typed enteroviruses), and 65% of patients with coxsackievirus A6 infection with available clinical data presented with HFMD (3).

The typical course of HFMD is generally mild and self-limited. We present a case of atypical severe HFMD from our practice.

CASE REPORT

A girl aged 6 years and 4 months presented to the infectious department on day 6 of the disease. On admission, she presented with big blisters with serous-hemorrhagic content, maculopapular lesions on her lower limbs (mainly on dorsal surface of the feet, shins and knees), buttocks, elbows, single lesions on dorsal surface of her hands and ears, accompanied with pain and itching, immobility, malaise and poor appetite.

Present history: the disease started six days before with low grade fever and cough. Temperature was normalised on day 3 of the disease, but three maculopapular lesions

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FIGURE 1. Atypical hand-foot-and-mouth disease: vesiculobullous lesions on lower limbs on admission.



FIGURE 2. Atypical hand-foot-and-mouth disease: minimal oral lesions on the day of admission; streptococcal cheilitis.



FIGURE 3. Atypical hand-foot-and-mouth disease: purpuric lesions on lower limbs on day 12 of the disease.



FIGURE 4. Atypical hand-foot-and-mouth disease: onychomadesis one month after discharge.

appeared on her buttocks and transformed to vesicles on day 4, along with new maculopapular lesions on the buttocks, legs, elbows, hands and ears. The next day, all these elements changed to vesiculobullous lesions. She was hospitalised to a district hospital and transferred to the infectious department on day 6.

Her past history was unremarkable. The girl was immunised according to the Immunization Calendar of Ukraine. Her mother denied any contacts with infectious patients in the previous three weeks.

On admission, the patient's general condition was moderately serious because of skin and toxic syndromes. She was conscious, lying on her back with partly flexed hips and knees. Vital signs: heart rate 124, RR 22 *per* minute, SpO₂ 98%. The skin was pale, and papular and vesiculobullous rashes 0.4-6.0 cm with serous-hemorrhagic content were seen predominantly on the buttocks and lower limbs (on the knees, shins and feet) (Figure 1). Single maculopapular lesions were on the left ear, elbows and dorsum of the hands, and purpura on the dorsum of the feet. A small 'honey' crust was seen in the left corner of the mouth. Rash was absent on the head, neck and trunk. The conjunctivas were reddened. Visible oral mucosa was pinkish with single aphthae 0.3-0.4 cm on the tongue (Figure 2). Submandibular lymphatic nodes up to 0.7 cm in diameter were painless, elastic, and movable on palpation. Meningeal symptoms were negative. Breathing was vesicular, heart tones were loud and rhythmic. Abdomen was soft and painless, with mild hepatomegaly (+2 cm) on palpation. Urination was regular, but constipation was present for three days.

Laboratory tests on admission: mild lymphocytosis (49%) and accelerated erythrocyte sedimentation rate (35 mm/h), high ASL-O titer (1818 IU/mL). The patient's coagulation factors were normal. ELISA for varicella zoster IgM was negative. Real-time polymerase chain reaction detected enteroviral RNA in foecal samples. Thus, the diagnosis was atypical vesiculobullous HFMD.

The patient's treatment included polyvalent intravenous immunoglobulin 100 mL for two days and intravenous detoxication therapy, local antiseptics ('brilliant green' that makes specific appearance of patient's skin). Cefazolin in average doses was administered for 14 days intravenously because of streptococcal co-infection.

Diseases dynamics: on days 9-11 of the disease, there were no new rashes, vesicles and bullae started healing, but abdominal pain appeared. Acute surgical disease was excluded. Fresh purpuric maculopapular lesions (1-1.5 mm) appeared on the feet dorsum, soles and palms on day 12 of illness (Figure 3) and increased on the next day. Therefore, prednisolone 2 mg/kg daily was administered parenterally for five days with gradual withdrawal within five days. The patient was successfully discharged two weeks after admission. The girl was examined one month later; she was generally healthy, the skin at the sites of previous lesions had normal colour and structure without pigmentation or scarring, onychomadesis was noted on her index and ring fingers of the left hand (Figure 4).

DISCUSSION

The hand, foot and mouth disease is one of characteristic clinical presentations of EVI that occurs all around the world,

exhibiting seasonal variation in temperate climates. In these locations, individual cases and regional outbreaks usually occur in spring, summer and fall. In Asian and Pacific nations, HFMD has been a significant public health concern since 1997, with recurrent epidemics. The reported incidence rate of HFMD in East and Southeast Asia is higher in Singapore (6%-14% at age 1) than in other areas (3-5 times higher than in China). The rate of symptomatic case hospitalization for HFMD in this region is 6%, of which 18.7% are expected to develop complications, severe in some cases, including central nervous system disease, pulmonary oedema, and death. Five percent of such cases are fatal, yielding the overall case fatality ratio of 52.3 *per* 100 000 symptomatic infections (4, 5). Most symptomatic cases are recorded in children under the age of 10. Because the virus is shed in stools for many weeks, some studies indicate that family members and close contacts are also at risk of developing HFMD (6-12). The most common pathogens are Coxsackie A16 virus and enterovirus 71. In Ukraine, there is no specific surveillance for EVI, and the level of their diffusion is not known as no information exists on the circulation of these viruses.

The hand, foot and mouth disease is a distinct, specific, monomorphic exanthema, enabling identification of specific serotypes. In 'classical' HFMD, the exanthema is preceded by a prodromal stage (lasting 1-4 days) with subfebrile temperatures, loss of appetite, sore throat, cough, rhinitis, and abdominal pain before the onset of oral and cutaneous findings (prodromal stage with high fever and cough for three days was seen in our patient). The most common presenting symptom is usually mouth or throat pain secondary to the enanthema. The characteristic feature of HFMD enanthema is the presence of vesicles mainly on soft palate, uvula, cheeks, and lips mucosa, surrounded by a thin halo of erythema, eventually rupturing and forming superficial ulcers with a grey-yellow base and erythematous rim (enanthema has the character of herpangina). This was absent in our patient. The exanthema usually appears in one day (but in our patient it appeared in two days with purpuric lesions occurring on days 12-13 of illness). It can be macular, papular or vesicular, starting as small (1-5 mm) erythematous maculopapular lesions that rapidly enlarge and progress to vesicular eruption that is characterized by 2-8 mm oval, gray blisters on dorsal aspects and sides of the fingers, as well as on palmoplantar surfaces, which are often arranged parallel to the dermatoglyphs and surrounded by a red halo. Classical exanthema involves buttocks. The lesions can be either asymptomatic or tender and painful. Mild to moderate itching may be present, mostly during healing. Desquamation can follow the exanthema, and lesions usually resolve without scarring or secondary infection. Clearance may be expected after 5-10 days of the disease with full recovery within 7-21 days (1, 12-14).

Severe, atypical cases of HFMD have been reported worldwide since 2008. They are caused by a new lineage of Coxsackie virus A6 (7,15). Atypical HFMD has distinct presentations that include high fever, widespread vesiculobullous lesions, even confluent blisters (that were seen in our patient), localized not only on the palms, soles and buttocks, but on the dorsum of hands and feet, perineum, external surfaces of shins, and forearms, knees and elbows (as seen in our patient), with involvement of the perioral region, neck and trunk considered as widespread exanthema (10, 16, 17). So, atypical HFMD could be confused with varicella, bullous impetigo, vasculitis (as in the case presented) (10, 18, 19). Patients with atypical, Coxsackievirus A6-associated HFMD may not have oral lesions typical for HFMD (as in our patient). Additional cutaneous findings of Coxsackievirus A6 infection may include onychomadesis, Beau lines 1-3 months after disease onset (also seen in our patient), or nail discoloration.

The diagnosis of HFMD is usually made clinically. In patients with a high probability of having the disease based on their clinical characteristics and sick contacts, laboratory testing is not necessary. If there is doubt or possible complications, the presumptive diagnosis is confirmed by direct detection of the virus from blister material, nasopharyngeal secretions, stools, cerebrospinal fluid, blood, or biopsy materials. Reverse-transcriptase real-time quantitative polymerase chain reaction (RT-qPCR) has been shown to be more sensitive than viral culture in detecting EV RNA and has become the gold standard for diagnosing EVI (1, 2, 20). In the case presented, EVI was diagnosed by this method. IgM-capture enzyme-linked immunosorbent assays are inexpensive and detect IgM antibodies early and in a high percentage of patients (12).

We could also make a conclusion on the role of streptococcus species in the development of bullous lesions in our patient, as she demonstrated high titres of ASL-O and had typical signs of streptococcal cheilitis. *Staphylococcus aureus* or *Streptococcus pyogenes* are considered to play the main role in the aetiology of atypical bullous varicella zoster infection (21, 22), though development of big blisters in HFMD could be caused by streptococcus species.

No proven antiviral treatment exists for HFMD. Pleconaril is an oral viral capsid inhibitor with activity against picornaviruses. Results on clinical outcome vary considerably from complete recovery to fatalities (2), and it is not registered in Ukraine. Thus, the goals of treatment are typically supportive, as for any self-limited viral disease. The only option available for treatment is the administration of intravenous immunoglobulin (IVIG). A combination of high doses of corticosteroids and IVIG are administered to patients with neurological disease in case of EVI and show its efficiency, as

autoimmune phenomenon triggered by the enterovirus plays a role in the pathophysiology of the disease (12). Thus, IVIG and high doses of prednisolone were prescribed to our patient successfully. Pain and fever can be managed with nonsteroid anti-inflammatory drugs and acetaminophen. The most important part of supportive treatment is to relieve the pain associated with the lesions affecting oral mucosa. Appropriate measures include local anaesthetics or lozenges (14). Secondary bacterial infection of skin lesions, usually due to *Staphylococcus aureus* or *Streptococcus pyogenes*, is possible in case of large bullae erosion, in spite of antibiotic therapy (1). The administration of cefazolin in our patient is justified by the presence of large confluent bullae and the possible role of streptococcal species in their development, specific cheilitis and high level of ASL-O.

CONCLUSION

Atypical HFMD is caused by a new lineage of Coxsackie virus A6. It has some clinical and morphological peculiarities such as more severe course, larger surface of skin lesions, centrifugal localization of lesions, possibility of another type of lesions except for traditional maculopapular and vesicular, minimal or absent oral lesions. Bacterial co-infection is not rare, so appropriate treatment should be initiated on time.

REFERENCES

1. Anokhin VA, Sabitova AM, Kravchenko IE, Martynova TM. Enterovirus infections: modern features. *Pract Med.* 2014;85:52-9. (in Russian)
2. De Crom SCM, Rossen JWA, van Furth AM, Obihara CC. Enterovirus and parechovirus infection in children: a brief overview. *Eur J Pediatr.* 2016;175:1023-9. doi: 10.1007/s00431-016-2725-7
3. Bubba L, Broberg EK, Jasir A, Simmonds P, Harvala H; Enterovirus study collaborators. Circulation of non-polio enteroviruses in 24 EU and EEA countries between 2015 and 2017: a retrospective surveillance study. *Lancet Infect Dis.* 2020;20(3):350-361. doi:10.1016/S1473-3099(19)30566-3
4. Koh WM, Badaruddin H, La H, Chen MI-Ch, Cook AR. Severity and burden of hand, foot and mouth disease in Asia: a modelling study. *BMJ Glob Health.* 2018;3:e000442. doi:10.1136/bmjgh-2017-000442
5. Gao LD, Hu SX, Zhang H, Luo KW, Liu YZ, Xu QH, et al. Correlation analysis of EV71 detection and case severity in hand, foot, and mouth disease in the Hunan Province of China. *PLoS One.* 2014;9:e100003. doi:10.1371/journal.pone.0100003
6. Osterback R, Vuorinen T, Linna M, Susi P, Hyypää T, Waris M. Coxsackievirus A6 and hand, foot, and mouth disease, Finland. *Emerg Infect Dis.* 2009;15:1485-8. doi:10.3201/eid1509.090438
7. Ramirez-Fort MK, Downing C, Doan HQ, Benoist F, Oberster MS, Khan F, et al. Coxsackievirus A6 associated hand, foot and mouth disease in adults: clinical presentation and review of the literature. *J Clin Virol.* 2014;60:381-6. doi: 10.1016/j.jcv.2014.04.023
8. Puenpa J, Chiochansin T, Linsuwanon P, Korkong S, Thongkomplew S, Vichaiwattana P, et al. Hand, foot, and mouth disease caused by coxsackievirus A6, Thailand, 2012. *Emerg Infect Dis.* 2013;19:641-3. doi:10.3201/eid1904.121666
9. Fonseca MC, Sarmiento L, Resik S, Martínez Y, Hung LH, Morier L, et al. Coxsackievirus A6 and enterovirus 71 causing hand, foot

- and mouth disease in Cuba, 2011-2013. Arch Virol. 2014;159:2451-5. doi:10.1007/s00705-014-2071-x
10. Hubiche T, Schuffenecker I, Boralevi F, Léauté-Labrèze C, Bornebusch L, Chiaverini C, et al. Dermatological spectrum of hand, foot and mouth disease from classical to generalized exanthema. Pediatr Infect Dis J. 2014 Apr;33:e92-8. doi:10.1097/INF.000000000000120
 11. Cisterna DM, Lema CL, Martinez LM, Verón E, Contarino LP, Acosta D, et al. Atypical hand, foot, and mouth disease caused by coxsackievirus A6 in Argentina in 2015. Rev Argent Microbiol. 2019;51:140-3. doi: 10.1016/j.ram.2018.05.003.
 12. Repass GL, Palmer WC, Stancampiano FF. Hand, foot, and mouth disease: identifying and managing an acute viral syndrome. Cleveland Clin J Med. 2014;9:537-43. doi: 10.3949/ccjm.81a.13132.
 13. Sarma N, Sarkar A, Mukherjee A, Ghosh A, Dhar S, Malakar R. Epidemic of hand, foot and mouth disease in West Bengal, India in August, 2007: a multicentric study. Indian J Dermatol. 2009;54:26-30. doi: 10.4103/0019-5154.48982.
 14. Fölster-Holst R, Kreth HW. Viral exanthems in childhood – infectious (direct) exanthems. Part 2: Other viral exanthems. J Dtsch Dermatol Ges. 2009;7:414-9. doi: 10.1111/j.1610-0387.2008.06869.x.
 15. Feder HM Jr, Bennett N, Modlin JF. Atypical hand, foot, and mouth disease: a vesiculobullous eruption caused by Coxsackie virus A6. Lancet Infect Dis. 2014;14:83-6. doi: 10.1016/S1473-3099(13)70264-0.
 16. Buttery VW, Kenyon C, Grunewald S, Oberste MS, Nix WA. Atypical presentations of hand, foot and mouth disease caused by coxsackievirus A6 – Minnesota, 2014. MMWR Morb Mortal Wkly Rep. 2015;64:805.
 17. Kuntz T, Koushk-Jalali B, Tigges C, et al. Atypische Hand-Fuß-Mund-Krankheit [Atypical variant of hand-foot-mouth disease]. Hautarzt. 2019;70(12):964-968. doi:10.1007/s00105-019-4452-2
 18. Mathes EF, Oza V, Frieden IJ, Cordoro KM, Yagi S, Howard R, et al. "Eczema coxsackium" and unusual cutaneous findings in an enterovirus outbreak. Pediatrics. 2013;132:e149-57. doi: 10.1542/peds.2012-3175
 19. Lott JP, Liu K, Landry ML, Nix WA, Oberste MS, Bologna J, et al. Atypical hand-foot-and-mouth disease associated with coxsackievirus A6 infection. J Am Acad Dermatol. 2013;69:736-41. doi: 10.1016/j.jaad.2013.07.024. Epub 2013 Sep 10.
 20. Blomqvist S, Klemola P, Kajjalainen S, Paananen A, Simonen ML, Vuorinen T, et al. Co-circulation of coxsackieviruses A6 and A10 in hand, foot and mouth disease outbreak in Finland. J Clin Virol. 2010 May;48:49-54.
 21. Singh A, Mandal A, Seth R, Sheriff A. Recurrent varicella complicated with staphylococcal scalded skin syndrome in an immunocompromised child. Indian J Child Health. 2016;3:359-61.
 22. Wong KJ, Osowicki J, Seaby E, Curtis N, Gwee A. Bullous herpes zoster. J Pediatr. 2014;164:667. doi: 10.1016/j.jpeds.2013.10.026.

SAŽETAK

Atipičan slučaj bolesti ruku, nogu i usta (Enterovirusni egzantem) iz kliničke prakse

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Prikazujemo atipičan slučaj bolesti ruku, nogu i usta u prethodno zdrave djevojčice. Bolest je imala atipičan tijek s vezikulobuloznim lezijama smještenima uglavnom na stražnjici, dorzalnim površinama stopala, goljenica, koljena, manje izražene na laktovima i dorzalnim područjima šaka; purpurnim lezijama stopala, dlanova i tabana; minimalnim oralnim lezijama; i streptokoknom infekcijom. Pravodobna hospitalizacija i odgovarajuće liječenje bolesnice rezultirali su njezinim brzim i potpunim oporavkom te pokazali djelotvornost primijenjene terapije.

Ključne riječi: ENTEROVIRUSNA INFEKCIJA; BOLEST RUKU, NOGU I ISTA; DIJETE