Clinical Case Report

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Case report: painful exanthems caused by enterovirus D68 in an adolescent

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Abstract

Rationale: Unlike other enteroviruses which can cause herpangina or hand-foot-and-mouth disease, enterovirus D68 (EV-D68) has usually been linked to respiratory and neurological problems in young children. Skin manifestations had rarely been described in current literatures.

Patient concerns: We report a 17-year-old girl with fever and painful skin rash over legs and soles for 9 days. Pitting edema was also noted below the knees. There was no respiratory tract or neurological symptoms in this patient.

Diagnoses: EV-D68 was detected from a throat swab by RT-PCR and confirmed to be subclade B3 by sequencing.

Interventions: Supportive management.

Outcomes: The patient was afebrile after 9 days and got full recovery on the 23rd day at outpatient follow-up.

Lessons: To the best of our knowledge, this is the first report of EV-D68 infection with skin manifestations, clinical images, and detailed clinical course. Our findings in this particular case extend the understanding of the disease spectrum.

Abbreviation: EV-D68 = enterovirus D68.

Keywords: enterovirus D68, painful exanthem, skin manifestations

1. Introduction

Enterovirus D68 (EV-D68) is a non-enveloped, single-stranded positive-sense RNA virus belonging to Picornaviridae family. It was discovered in 1962 from children with respiratory tract infections and reemerged in 2014. Some epidemics were also reported worldwide. Two types of clinical presentations of EV-D68 infection are usually described. One is respiratory tract infection symptoms, including cough, wheeze and sometimes asthma attack, which are often present in young children. Another one is polio-like illness or flaccid myelitis, being a less prevalent but more severe and important clinical presentation.[1] Skin manifestations, including hand-foot-and-mouth disease and simple viral exanthem, are infrequently described during EV-D68 outbreaks. We report a case of unusual presentation of EV-D68 infection with skin rash.

2. Case report

This 17-year-old senior high school girl is a previously healthy Taiwanese native who adhered to the Taiwan national immunization schedule, with no sexual experience, and no recent travel history. Prior to her illness, 3 of her classmates had fever, cough, and rhinorrhea. She presented with fever up to 39 °C, accompanied by chills, general malaise, and intermittent headache. There was no cough, rhinorrhea, or sore throat. She took mefenamic acid and betamethasone on the second day of illness. However, fever persisted and pink maculopapular rashes appeared on the 3rd day, beginning mainly on the lower legs and gradually spreading to the thighs (Fig. 1). The rash was not scaly or palpable but was painful, pruritic, and blanchable. Pitting edema was also noted below the knees.

She was admitted on the 6th day due to prolonged fever. There were no oral ulcers or joint pain. Muscle strength was full and physical examinations were unremarkable. Her initial laboratory findings indicated leukocytosis with a white-cell count of 11,560 per cubic millimeter (69% neutrophils) and elevation of C-reactive protein (4.73 mg/dl). Urinalysis and glomerular filtration rate were within normal limits. No organic lesion was found by abdominal sonography. On the next day of admission (day 7), rashes scattered on the arms and face, and faintly erythematous papules on the soles were noted (Fig. 1). A throat swab was positive for enterovirus with a high copy number (3.0×10^6 copies/ml) by real-time RT-PCR. After obtaining the informed consent from the parent for publication and specimen analysis, the RT-PCR and nested PCR were performed with primer sets as described earlier[2] followed by auto-sequencing with the forward primer using an ABI 3730XL automatic sequencer. Sequences of the VP1 and VP3 regions were aligned using BLAST against reference sequence databases in GenBank. Enterovirus D68 subclade B3 was confirmed. Other tests including blood culture, *Streptococcus pyogenes* culture, parvovirus B19 PCR, virus

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Informed written consent was obtained from the patient parents for publication of this case report and accompanying images.

The authors have no conflicts of interest to disclose.

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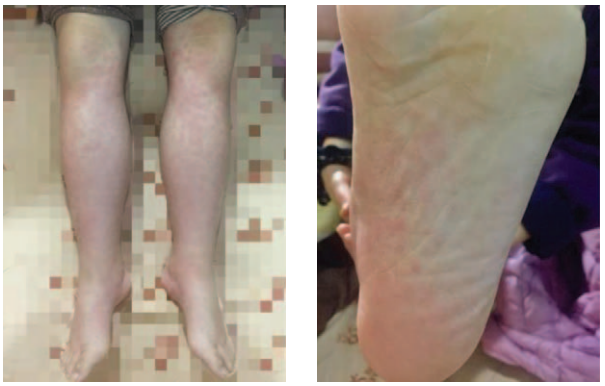

(a) (b)

Figure 1. (A) Painful, blanchable, and non-palpable maculopapular rash appeared on the legs and thighs. (B) Scattered faint erythematous papules on the soles.

isolation from throat swabs, cytomegalovirus, and Epstein-Barr virus serologic tests were all negative. Rashes on the lower extremities gradually disappeared on the 9th day and fever resolved. At outpatient follow-up on day 16, there was no skin rash but both of her ankles were mildly swollen. Her white blood cell count and C-reactive protein returned to normal. The leg swelling was resolved completely on the next week.

3. Discussion

Exanthem is rapid onset of rash with specific diagnostic features. Coxsackieviruses, Echoviruses, and enterovirus A71 are frequently associated with viral exanthem.[3] Enterovirus should be considered in febrile children with skin rash. The enteroviral exanthem may appear as maculopapular, vesicular rash or petechial or bullous lesions with or without a distinct distribution. EV-D68 with exanthem had rarely been reported and there is a lack of detailed description.[4,5] Skin rash with leg edema as the sole clinical manifestation of EV-D68 infection has never been described in the literature. Our findings in this particular case extend our understanding of the disease spectrum caused by EV-D68.

Epstein-Barr virus, parvovirus B19, secondary syphilis, drug eruption, or autoimmune diseases are also possible etiologies in febrile children with skin rash, but they were all excluded in our case. The rash on the soles, a more common site of enterovirus infection, changed our perspectives. In a previously healthy girl without sexual experience and travel history who received full course of routine immunizations, enterovirus infection is at the top of the differential diagnosis list.[6] This is the reason why the enterovirus PCR was ordered soon after admission.

Isolation of EV-D68 from samples is difficult. The viruses prefer cooler temperatures and thus lower incubation temperatures than those for other enteroviruses have to be applied.[7] Besides, unlike other enteroviruses, shedding of EV-D68 is low and rarely detected in stools. PCR is a preferred method for identifying EV-D68.

Pathogenesis of infectious exanthem caused by EV-D68 is not understood. A rational hypothesis is that the viruses enter from a distant site via direct inoculation or dissemination. The immune response against the virus leads to vessel damages, endothelium swelling, hemorrhage, and edema.

In Taiwan, the first case of acute flaccid myelitis caused by EV-D68 was described in a 5 years old boy in 2016,[8] though circulation and cluster of EV-D68 has been reported since 2007 according to the enterovirus surveillance system established by Taiwan Centers for Disease Control.[9] Subclade A1, A2, and B1 were the prevalent genotypes from 2007 to 2013 in Taiwan. However, most EV-D68 strains detected after 2014 were subclade B3.[10] By comparing the partial VP1 and VP3 sequences with current database, the EV-D68 subtype identified in our case belongs to subclade B3.[11] On the basis of the above analysis, the possibility of mutation or an emerging subclade was less likely in our case.

4. Conclusion

Here, we report an otherwise healthy adolescent with unusually painful exanthems and edema on the lower extremities. Such a presentation of EV-D68 infection might have been overlooked. By sharing our experience, we hope to raise a higher index of suspicion and ensure thorough investigations using proper molecular methods for timely identification of EV-D68 infections in patients presented with painful exanthems of the extremities.

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Author contributions

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