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Atypical presentation of hand, foot, and mouth disease caused by enterovirus serotype coxsackievirus A6, in India

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ABSTRACT

A 27-year-old male presented in the OPD of Naval Hospital in Port Blair, Andaman Islands, India, in 2011 with a history of low-grade fever associated with malaise and a pruritic skin rash. Case 2 – A 17-year-old male student reported to the OPD at Naval Hospital, Kochi Kerala, India, in August 2015. He presented with eruptions on both the palm and soles with a history of high-grade fever for the past 3–4 days. Clinically, both the cases were diagnosed as hand, foot, and mouth disease (HFMD). Both samples were tested against measles virus and varicella-zoster IgM antibodies by enzyme immunoassay and found negative. Stool sample (case 1) and lesion swab (case 2) were processed by enterovirus reverse transcription polymerase chain reaction and phylogenetic analysis, and both were positive for enterovirus human coxsackievirus A6 (CVA6) (untranslated region [UTR]). Phylogenetic analysis also confirmed that both the CVA6 etiology belonged to the genotype F. HFMD in adults often asymptomatic and very few patients get atypical symptoms. Clinical diagnosis is often troublesome to identify HFMD in such cases. An epidemiological surveillance/vigilance is essential to document these atypical cases in near future in developing countries like India.

Key words: HFMD; enterovirus; coxsackievirus A6; Andaman Islands; India

INTRODUCTION

Human coxsackievirus A6 (CVA6) belongs to the enterovirus A species (genus *Enterovirus*, family *Picornaviridae*) and causes hand, foot, and mouth disease (HFMD). Huge outbreaks in the Asia-Pacific region have been identified since 1997, and HFMD becomes common epidemic disease globally. Human enterovirus A comprises coxsackievirus A 2–8, 10, 12, 14, and 16 and enterovirus 71. The clinical features associated with HFMD caused by CAV6 differ from classic HFMD caused by other strains. Newly emerging novel recombinant forms (A-H) of the CVA6 were identified in 2014 (1) based on 3D polymerase phylogeny (2) and were

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responsible for unusual HFMD in Edinburgh, UK (2,3). We report the detection of CVA6, subgenotype F in two young adults, causing HFMD for the 1st time in India (Figure 1).

CASE REPORT

Case 1

In September 2011, a 27-year-old male presented in the OPD of INHS Dhanvantri, Naval Hospital in Port Blair, Andaman Islands, India, with a history of low-grade fever associated with malaise and a pruritic skin rash. Clinical examination revealed reddish purpuric macular spots on the hard palate and congested exanthemas at the posterior pharyngeal wall (Figure 2a). His eruption progressed to the knees, feet, and buttocks. The palms and soles had maculopapular eruptions (Figure 2b). He was a school bus driver by profession and had a history of exposure to affected children with febrile illness with rash. From his background and symptoms, the patient was diagnosed with HFMD. Routine blood investigations were in normal limits except for the marginal increase in the total count with lymphocytes. Since it was not possible to collect lesion swab, stool sample was collected and was tested for enterovirus by nucleic acid amplification test. He was treated with oral broad-spectrum antibiotics, analgesics, and mupirocin ointment for local application on the skin lesion and removed within 2 weeks.

Case 2

A 17-year-old male student reported to the OPD at Naval Hospital, INHS Sanjivani, Naval Base, Kochi Kerala, India, in the month of August 2015. He presented with eruptions on both palm and soles with a history of high-grade fever for the past 3–4 days. His eruptions started with a maculopapular lesion in the oral cavity and progressed on both palms and soles into purpuric macular and papulovesicular with clear fluid (Figure 2c and d). Clinically, the case was diagnosed with HFMD.

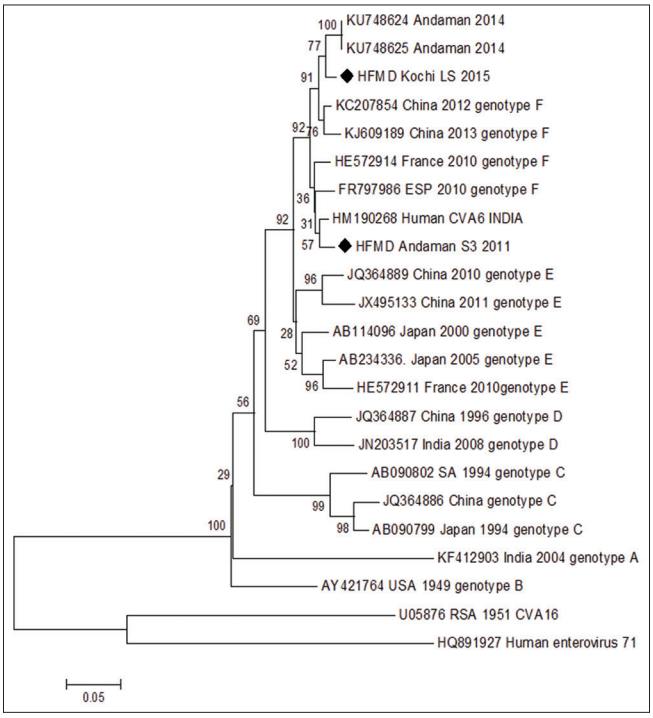

FIGURE 1. Phylogenetic tree analysis of enterovirus coxsackievirus A6 associated with atypical hand, foot, and mouth disease in Andaman and Kochi. The tree was constructed through the Neighbor-joining method using Kimura's two parameter (K2P). Bootstrap resampling was used to determine robustness of groupings; values of ≥70% are shown. Scale bar indicates the percentage of K2P distance.

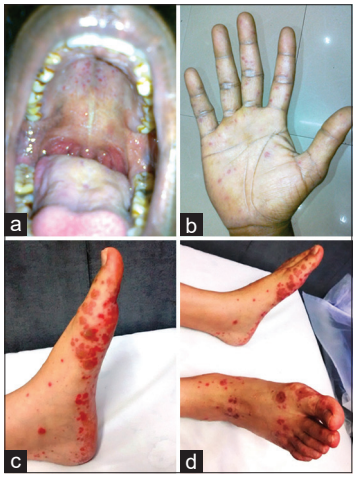

FIGURE 2. (a-d) Clinical examination revealed multiple purpuric macules as well as a few erythematous papules and vesicles on the hands and legs of the both patients.

The routine blood investigation showed increased TLC to 13,800 with polymorphs increased to 84%. ESR was raised 36 mm/h, and the SGOT and SGPT were also marginally elevated to 78 and 64, respectively. A lesion swab was taken from the vesicle fluid in viral transport medium and was tested for enterovirus by nucleic acid amplification test (4). The patient was first treated as an outpatient and put on oral broad-spectrum antibiotics. Subsequently, rashes flared up and fever also continued, and the patient was admitted to the hospital and started on parenteral broad-spectrum antibiotics twice a day for 5 days. Initially, the lesions were cleaned and treated with topical application of mupirocin ointment; fever was managed by oral analogies. A chlorhexidine mouth was given for oral ulcers. He was discharged after 5 days and advised to use local application of mupirocin ointment on the skin lesion. The fever continued till 7 days and subsequently subsided while the rashes took around 2 weeks to subside.

Both samples were tested against measles virus and varicella-zoster IgM antibodies by enzyme immunoassay (Abcam's anti-Measles virus IgM Human *in vitro* ELISA; Abcam's anti-Varicella-Zoster virus IgM Human *in vitro* ELISA) and found negative. Stool sample (case 1) and lesion swab (case 2) were processed by enterovirus reverse transcription polymerase chain reaction and phylogenetic analysis and both were positive for enterovirus CVA6 (UTR). cDNA sequences of CVA6 from both cases and intra-serotype reference sequences were aligned using MEGA 6 software (MEGA: version 6.01). Phylogenetic analysis revealed that both the study sequences from Port Blair Andaman (S3 2011) and Kochi, Kerala (LS 2015) were in the same cluster. The pairwise genetic distance between HFMD LS 2015 from Kochi and CVA6 isolate obtained during the 2015 HFMD outbreak in Andaman (KU748624) was very small (K2P=0.024), and the CVA6 caused atypical HFMD in Andaman (S3_2011) during 2011 showed small genetic distance with the isolate HM190268 from mainland India during the outbreak in 2009. The phylogenetic analysis also confirmed that both the CVA6 etiology belonged to the genotype F. Elsewhere, studies have been identified the association between recombination groups and clinical presentation of HFMD, suggest that CVA6 genotype F is associated with atypical HFMD (2).

Through it was established that CVA6 causing HFMD in India (5), however, our reports emphasize the CVA6 genotype F causing atypical manifestation of HFMD in adults. Frequent report of HFMD among adults and adolescents was with the common etiology of CVA6 and also reported that CVA6 associated with various atypical manifestations (6). Seeing as, CVA6 is the pathogen rising as a threat to cause atypical HFMD with unusual manifestations. Therefore, there is a need to rule out etiology causing CVA6 among the patients suspected with HFMD. HFMD in adults often asymptomatic and very few patients get atypical symptoms. Clinical diagnosis is often troublesome to identify HFMD in such cases. An epidemiological surveillance/vigilance is essential to document these atypical cases in near future in developing countries like India.

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CONFLICTS OF INTEREST

All authors have no conflicts of interest to declare.

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