# Clinical profile and virology analysis of hand, foot and mouth disease cases from North Kerala, India in 2015–2016: A tertiary care hospital-based cross-sectional study

Sir,

Hand, foot and mouth disease manifests with low-grade fever along with vesicles or papules on oral mucosa, palms, soles and buttocks.[1,2] Rash affecting face, perioral area and trunk and rash more than 0.5 cm in size are considered as features of atypical hand, foot and mouth disease.[3-5]

We conducted a study to describe the clinical features and etiology of hand, foot and mouth disease in patients attending the Dermatology Department of Government Medical College, Kozhikode, Kerala, India.

The first 60 patients who attended the Dermatology Outpatient Department of our institution from September 1, 2015 with clinically diagnosed hand, foot and mouth disease were included in the study, after obtaining written informed consent from individual patient (or the guardian in case of children below 18 years). Ethical clearance was obtained from Ethics Committee of our institution and Manipal Academy of Higher Education where the viral study was carried out.

Patients who were diagnosed to have probable or definite drug reaction as per World Health Organization causality assessment and patients showing multinucleated giant cells in Tzanck smear analysis were excluded from the study.[6]

Using a predesigned proforma, data on patient profile and clinical manifestations were collected from each patient. The subjects were classified into those with limited rash, extensive rash and generalized rash [Table 1]. Those who manifested with rash affecting face, perioral area or trunk and those who presented with skin lesions of size 0.5 cm or more were categorized as atypical hand, foot and mouth disease.[4]

Swabs collected by rupturing intact vesicle with a sterile needle or from oral erosion or posterior pharynx (in the absence of intact vesicle) were transported in viral transport medium for virology workup.[7-9*] The data were analyzed. Thirty eight patients (63.3%) tested positive for enterovirus by real-time polymerase chain reaction [Table 1]. Serotyping identified Coxsackievirus A16 (4, 6.7%), Coxsackievirus A6 (31, 51.7%) and untyped enteroviruses (3, 5%) as the causative agents [Table 1]. Age of the study group ranged from 8 months to 34 years with slight male predilection (32 males and 28 females, 1.1:1).

Clinical manifestations documented in the study group were tabulated as shown in Tables 1-3 [Figure 1]. Adults manifested more pronounced constitutional symptoms when compared to children. Three patients gave previous history suggestive of hand, foot and mouth disease in the same season. Three children (5%) manifested

[*] A pan enterovirus real-time reverse transcriptase polymerase chain reaction with Fast-Track Diagnostics Respiratory Pathogens 21-Kit (Fast Track Diagnostics, Luxembourg) was performed for the detection of enterovirus. The positive cases were tested for specific serotypes of enteroviruses such as Coxsackievirus A6 by a nested reverse transcriptase polymerase chain reaction[7] and Coxsackievirus A16 [8] and Enterovirus 71 by real-time reverse transcriptase polymerase chain reaction assay.[9] Pan enterovirus positive cases that were not Coxsackie A6, A16 or Enterovirus 71 were subjected to pan enterovirus conventional polymerase chain reaction and the resulting positive amplicons were DNA sequenced by ABI-3500 Sequencer (Applied Biosystems®, USA). DNA sequences were matched with NCBI GenBank database and considered as positive if it showed similarity more than 96% with corresponding enterovirus strains in NCBI GenBank. Samples which were negative for pan enterovirus conventional polymerase chain reaction and other serotype specific polymerase chain reaction (Coxsackievirus A6, Coxsackievirus A16, Enterovirus 71) for enterovirus detection have been categorized as untyped. Those tested negative were considered as polymerase chain reaction negative group.

**Table 1: Clinical characteristics of hand, foot and mouth disease patients attending the dermatology department**

| Type of enterovirus causing HFMD* | Age | | | | Sex | | Fever | Extent of rash | | | | Mucosal lesions | Atypical HFMD | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <2 years | 2-12 years | 13-18 years | >18 years | Male | Female | | Palms, soles and oral cavity alone | Limited | Extensive | Generalized | | Male | Female | Total |
| CVA6 (31) | 21 | 8 | 0 | 2 | 18 | 13 | 29 | 4 | 10 | 5 | 12 | 12 | 11 | 9 | 20 |
| CVA16 (4) | 1 | 1 | 0 | 2 | 3 | 1 | 2 | 1 | 2 | 1 | 0 | 1 | 0 | 1 | 1 |
| Untyped (3) | 2 | 1 | 0 | 0 | 1 | 2 | 3 | 0 | 0 | 0 | 3 | 0 | 1 | 2 | 3 |
| PCR negative for enterovirus (22) | 14 | 6 | 1 | 1 | 10 | 12 | 19 | 2 | 2 | 5 | 13 | 8 | 7 | 7 | 14 |
| Total (60) | 38 | 16 | 1 | 5 | 32 | 28 | 53 | 7 | 14 | 11 | 28 | 21 | 19 | 19 | 38 |

*Number in bracket shows the number of patients. Extent of rash - limited: Lesions involving one body region alone (scalp and face or upper limbs or trunk or lower limbs) with or without involvement of palms, soles and/or oral cavity. Extensive: Rash affecting two body regions. Generalized: Rash affecting more than two regions of body. HFMD: Hand, foot and mouth disease, PCR: Polymerase chain reaction, CVA6: Coxsackievirus A6

**Table 2: Distribution of rash in hand, foot and mouth disease cases**

| Type of enterovirus* | Perioral area (%) | Face sparing perioral area (%) | Trunk (%) | Upper limbs (%) | Buttocks (%) | Lower limbs (%) | Palms (%) | Soles (%) |
|---|---|---|---|---|---|---|---|---|
| Coxsackie A16 (4) | 1 (25) | 0 | 0 | 1 (25) | 2 (50) | 2 (50) | 3 (75) | 2 (50) |
| Coxsackie A6 (31) | 11 (35.5) | 3 (29.7) | 8 (25.8) | 11 (35.5) | 22 (71) | 19 (61.3) | 29 (93.5) | 27 (87.1) |
| Untyped enterovirus (3) | 3 (100) | 0 | 3 (100) | 2 (66.7) | 2 (66.7) | 2 (66.7) | 2 (66.7) | 2 (66.7) |
| PCR negative for enterovirus (22) | 7 (31.8) | 5 (22.7) | 10 (45.5) | 15 (68.2) | 10 (45.5) | 16 (72.7) | 20 (90.9) | 19 (86.4) |
| Total (60) | 22 (36.7) | 8 (13.3) | 21 (35) | 29 (48.3) | 36 (60) | 39 (65) | 54 (90) | 50 (83.3) |

*Number in bracket shows the number of patients. PCR: Polymerase chain reaction

**Table 3: Type of rash in hand, foot and mouth disease cases**

| Type of enterovirus* | Vesicle (%) | Crusted lesion (%) | Erosion (%) | Macule (%) | Papule (%) | Plaque (%) | Bulla (%) | Pustule (%) |
|---|---|---|---|---|---|---|---|---|
| Coxsackie A16 (4) | 4 (100) | 0 | 0 | 0 | 1 (25) | 0 | 0 | 0 |
| Coxsackie A6 (31) | 31 (100) | 9 (29) | 4 (12.9) | 10 (32.3) | 22 (71) | 1 (3.2) | 1 (3.2) | 2 (6.4) |
| Untyped enterovirus (3) | 3 (100) | 2 (66.7) | 1 (33.3) | 2 (66.7) | 2 (66.7) | 0 | 0 | 0 |
| PCR negative for enterovirus (22) | 22 (100) | 10 (45.5) | 2 (9.1) | 7 (31.8) | 10 (45.5) | 0 | 1 (4.5) | 3 (13.6) |
| Total (60) | 60 (100) | 21 (35) | 7 (11.7) | 19 (31.7) | 35 (58.3) | 1 (1.7) | 2 (3.3) | 5 (8.3) |

*Number in brackets shows the number of patients. PCR: Polymerase chain reaction

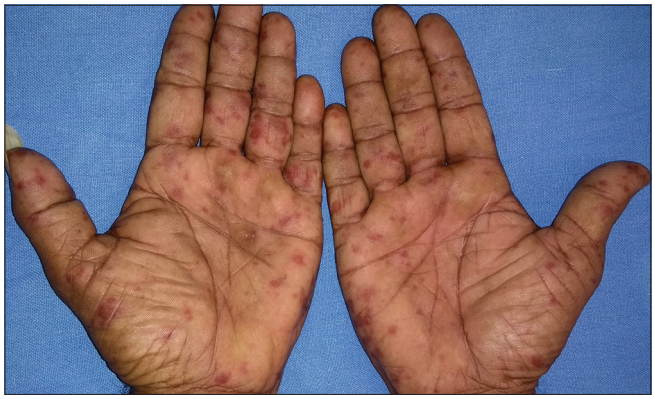

**Figure 1:** Erythematous macules in the palms in hand, foot and mouth disease

with hand, foot and mouth disease without any involvement of palms, soles or oral cavity. Generalized rash was documented in 28 patients (46.7%) [Table 1].

Thirty eight patients (63.3%) had features of atypical hand, foot and mouth disease [Tables 1-3 and Figures 2a and b].

Detailed workup including polymerase chain reaction-based study of cerebrospinal fluid for viral infection was within normal limits in two patients who developed seizures, and febrile seizure was diagnosed in the above cases. All patients received symptomatic treatment. The two children who had seizures received clobazam as antiepileptic drug. Complete recovery in 7–10 days was recorded in each case.

This study reports co-circulation of Coxsackievirus A6 and Coxsackievirus A16, with Coxsackievirus A6 being the predominant cause of hand, foot and mouth disease in North Kerala during 2015–2016 which is in variance with the two previous studies from Kerala.[10,11]

Our finding of Coxsackievirus A6 showing a predilection for children was consistent with other reports from Asia, but contrary to Western data.[1,4,12-15] Though recurrence of hand, foot and mouth disease in the same season is reported earlier (attributed to infection with a different strain formed by genetic recombination), we cannot comment whether the three patients who gave history of previous hand, foot and mouth disease in our study suffered from same virus infection or not because the earlier diagnosis in these cases was not confirmed by virology workup.[16]

Rash sparing palms, soles and oral cavity as observed in some of our patients is reported earlier.[4,5] The higher percentage of atypical hand, foot and mouth disease in this study could be attributed to the study being conducted in a tertiary care institution.[17]

Nearly one-third of the clinically suspected cases testing polymerase chain reaction negative for pan enterovirus could be due to delay in sample collection, inadequate material for virology workup, the failure to maintain the cold chain during viral transport and inability to detect a new or uncommon enterovirus RNA by the assay. Not collecting throat swab and stool sample in included cases would have contributed to the negative result.

Small sample size and lack of follow-up were the main limitations of our study. By conducting the study in a tertiary referral center, we were unable to gather information on the epidemiological aspects.

To conclude, absence of rash in hands, feet and mouth at the time of presentation does not rule out hand, foot and mouth disease. We recommend continuous monitoring to understand the changing patterns of hand, foot and mouth disease.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent

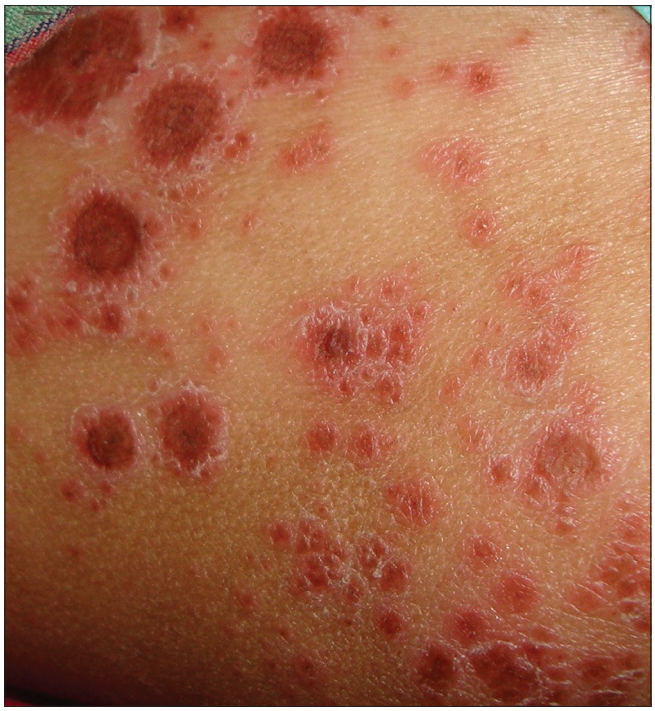

**Figure 2a:** Rash of size >0.5 cm size in hand, foot and mouth disease

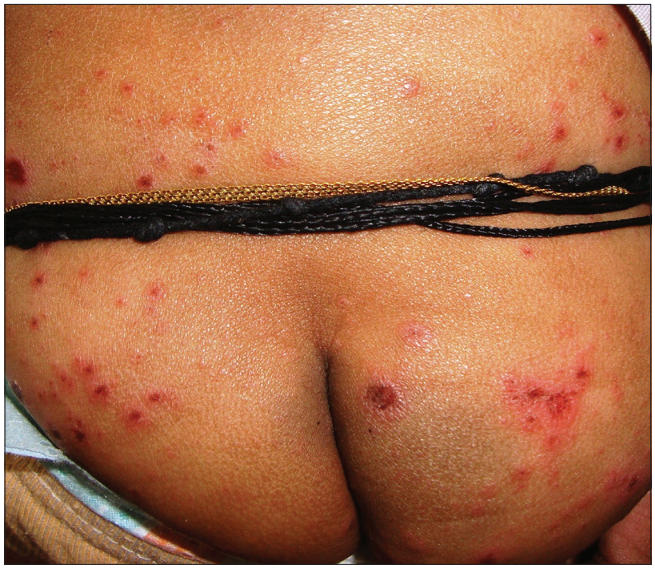

**Figure 2b:** Rash of size >0.5 cm size in the buttocks

for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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