CASE REPORT

A sudden paediatric death due to hand, foot and mouth disease: the importance of vigilance

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Abstract

Background: Hand, foot and mouth disease (HFMD) is caused by enteroviruses such as Coxsackie virus A16 (CVA16) and Enterovirus 71 (EV71). The diagnostic hallmarks are oral ulcers and maculo-papular or vesicular rash on the hands and feet. Severe form of this disease can lead to death due to neurological and cardiopulmonary complications. This case report aims to describe a fatal case of HFMD with minimal oral and skin manifestations.

Case report: A four-year-old girl was brought to a hospital after suddenly becoming unresponsive at home. She had a history of fever and lethargy for three days prior to her demise. The patient, and five other children in her neighbourhood had been diagnosed to have HFMD at a local health clinic; the other children had recovered without complications.

Results: Autopsy revealed a few punctate, sub-epidermal vesicles measuring 1 to 2 mm on the palm of her right hand and sole of the right foot, visible only with a magnifying glass. Internal examination revealed prominent nodularity at the oro- and hypopharynxes. The lungs were markedly congested and oedematous. Histopathology of the lung showed marked oedema and haemorrhage with mild pneumonic changes. Oedema with increase in macroglia and astrocytic proliferation were seen in the cerebral tissue, but no lymphocytic infiltration was evident. Enterovirus EV71 was detected by polymerase chain reaction in samples from the lung, cerebrospinal fluid and serum. The cause of death was given as HFMD complicated by pneumonia.

Conclusion: Fatal HFMD may have minimal signs. A complete history, careful physical examination and relevant investigations lead to a diagnosis at post mortem examination. Awareness of the subtle signs and rapid deterioration associated with a fatal case of HFMD is a challenge to clinicians who encounter these cases.

Keywords: Hand, foot and mouth disease, autopsy, Enterovirus 71, sudden death

INTRODUCTION

Hand, foot and mouth disease (HFMD) is characterized by oral ulcers and maculo-papular or vesicular rash on the hands and feet. It often occurs in large-scale outbreaks in countries such as Taiwan, Bulgaria, China and Malaysia but sporadic cases have also been reported. It is caused by non-polio enteroviruses such as Coxsackie A16 (CVA16) and Enterovirus 71 (EV71). EV71 has a wider spectrum of presentations, from mild, self-limiting illness to a more severe disease with neurological and cardiopulmonary complications leading to death. Aseptic meningitis, encephalitis, poliomyelitis-like paralysis, neurogenic pulmonary oedema and acute paralysis syndrome have been described in many fatal cases. We report a case of a four-year-old girl with minimal cutaneous manifestation of HFMD and an unexpected fatal outcome. We hope to raise awareness among health care practitioners of the necessity to follow-up HFMD cases to detect possible complications that could lead to death. In addition, this case demonstrates the importance of obtaining the relevant history to arrive at the correct diagnosis.

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CASE REPORT

A four-year-old girl was brought unconscious to the hospital Emergency Department. She died despite resuscitation efforts. Further enquiry revealed that she had been diagnosed with HFMD approximately one week earlier. Her younger brother (aged 2 years) and four other small children in the neighborhood had also been diagnosed with the same illness. According to her grandfather, who was her minder, the girl appeared generally unwell, in contrast to the other children who remained active. She had loss of appetite, fever, lethargy and vomiting for a few days before becoming unconscious.

Autopsy examination

The body of the girl was proportionate for age and was well-nourished. No obvious skin lesion was seen at the characteristic places. However, close examination with a magnifying glass, revealed a few punctate, sub-epidermal vesicles measuring 1 to 2 mm, on the palm of the right hand and sole of the right foot (Fig. 1). There was no surrounding erythema or inflammation. Internal examination showed prominent nodularity at the oro- and hypopharynxes. The lungs were markedly congested and oedematous (Fig. 2). The brain, heart, liver and kidneys were unremarkable grossly.

FIG. 1: (A) Traces of vomitus seen at the perioral area. No rash or vesicle at the peri- and intra-oral regions noted. (B) Palm of the right hand showing two minute subepidermal vesicles measuring 1-2 mm (arrow). No surrounding inflammation seen. (C) A subepidermal vesicle measuring 1 mm noted at the sole of the right foot (arrow)

FIG. 2: Gross and histopathological examination. (A) Markedly congested and oedematous lung. (B) Mild cerebral oedema. (C) Prominent nodularity at the oro- and hypopharynxes (arrows). (D) Low power (4x) and (E) high power views of a section taken from the nodular oropharynx showing lymphoid follicular hyperplasia with germinal centre formation
Representative sections from the brain, heart, lungs, liver, spleen, tonsils and hypopharynx were collected for histological examination. The lung showed marked oedema and haemorrhage with foci of neutrophilic aggregations within the alveolar space and mild interstitial lymphocytic infiltration. Cerebral oedema with increase in macroglia and astrocytic proliferation was noted, however no lymphocytic infiltration was evident. The myocardium was normal with no evidence of myocarditis. The oro- and hypopharynx nodularity was due to mucosal lymphoid follicular hyperplasia (Figs. 2D & E).

**Microbiology investigations**
Cerebrospinal fluid (CSF), blood and urine samples were sent for culture and sensitivity. All samples showed no growth. Microscopical examination of the CSF showed a white blood cell count of 20 cell/mm³. CSF, serum and lung tissue were sent for molecular detection of CV A16 and EV71, specific antigens associated with HFMD. The result showed presence of EV71 antigen in all samples. The cause of death was given as HFMD complicated by pneumonia.

**DISCUSSION**
A child who died shortly after being brought unconscious to the Emergency Department raised several grave concerns. In this case, a history of previous diagnosis of HFMD has allowed subtle receding hand and foot rashes to be detected and the appropriate investigations to be done, resulting in detection of the infective agent and arriving at the correct diagnosis.

Outbreaks of HFMD in Malaysia occur periodically. In Sarawak, an outbreak has been reported to occur every 3 years since 1997. In other Asian countries such as China, Taiwan, Singapore and Vietnam, outbreaks of this disease also occur, leading to a number of fatalities. A striking aetiological agent shared by these fatal HFMD was EV71. EV71 was also responsible for 84 of 169 deaths due to HFMD in Vietnam in the 2011 outbreak as well as all cases of severe disease in the 2009 outbreak in Shenzhen, China. It was also the main type involved in fatal cases in 1998 in Taiwan. In our case this was also the aetiological agent detected.

HFMD is characterized by oral vesicular exanthema/ulcers plus vesicular lesions on the hands and/or feet and/or buttocks. Atypical presentations of HFMD include maculo-papular rash over the hands, soles and/or buttocks with or without oral ulcers. This illness ensues over a short period of time, with subtle clinical features that can lead to ominous signs culminating into fatal pulmonary oedema and cardiac dysfunction. The majority of fatal cases involves children aged 3 years and younger, with fever, and vomiting among the principle presentations. The deterioration occurs after three to four days of illness. Multivariate analysis of fatal cases revealed that atypical physical findings, raised total white cell count, vomiting and lack of mouth ulcers are predictive of fatal outcome. The girl in this case had all of the above features.

In the 1997 outbreak in Sarawak, Malaysia, 29 previously healthy children died after a short illness similar to this case. In addition, 10 of the children showed no cardiac abnormalities. A few available brain tissues examined in the Sarawak fatalities showed inflammation with necrosis suggesting central nervous system involvement, especially at the brain stem. Fatal cases of HFMD have been reported to be associated with encephalitis with brain stem involvement. It was suggested that the cardiopulmonary failure may be of neurogenic origin. Sympathetic hyperactivity and inflammation in the central nervous system led to neurogenic pulmonary oedema and cardiac failure. The brain tissue in this case did not show significant inflammation, despite presence of increased lymphocytes in the CSF. This may be because the brain was sampled at the cerebral cortex instead of the brain stem. Pulmonary oedema and pulmonary haemorrhage were also findings in fatal cases in Taiwan in 1998. This was also the case in this child. Additional lung findings reported include interstitial pneumonitis. In this case, prominent pulmonary oedema and hemorrhage may be due to acute left heart failure. In all cases, deterioration occurred rapidly, and mortality remained high despite intensive treatment.

**Conclusion**
Fatal HFMD may have minimal signs. In this case, a complete history, careful physical examination and relevant investigations led to the diagnosis at post mortem examination. Awareness of the subtle signs and rapid deterioration associated with fatal HFMD is a challenge to clinicians who encounter these cases.

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