Deaths of Children during an Outbreak of Hand, Foot, and Mouth Disease in Sarawak, Malaysia: Clinical and Pathological Characteristics of the Disease

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From April through June 1997, 29 previously healthy children aged <6 years (median, 1.5 years) in Sarawak, Malaysia, died of rapidly progressive cardiorespiratory failure during an outbreak of hand, foot, and mouth disease caused primarily by enterovirus 71 (EV71). The case children were hospitalized after a short illness (median duration, 2 days) that usually included fever (in 100% of case children), oral ulcers (66%), and extremity rashes (62%). The illness rapidly progressed to include seizures (28%), flaccid limb weakness (17%), or cardiopulmonary symptoms (of 24 children, 17 had chest radiographs showing pulmonary edema, and 24 had echocardiograms showing left ventricular dysfunction), resulting in cardiopulmonary arrest soon after hospitalization (median time, 9 h). Cardiac tissue from 10 patients showed normal myocardium, but central nervous system tissue from 5 patients showed inflammatory changes. Brain-stem specimens from 2 patients were available, and both specimens showed extensive neuronal degeneration, inflammation, and necrosis, suggesting that a central nervous system infection was responsible for the disease, with the cardiopulmonary dysfunction being neurogenic in origin. EV71 and possibly an adenovirus, other enteroviruses, or unknown cofactors are likely responsible for this rapidly fatal disease.

From 14 April through 30 June 1997, a total of 29 previously healthy children were brought to various hospitals in Sarawak, Malaysia; within a short period, they died of rapidly progressive cardiac failure and pulmonary edema that was refractory to supportive therapy. Several case patients had echocardiographic evidence of left ventricular dysfunction and radiological features consistent with pulmonary edema. The children had a prodromal febrile illness that sometimes included extremity rashes, oral ulcers, or both, consistent with hand, foot, and mouth disease (HFMD). The majority also had neurological manifestations, but these symptoms were overshadowed by the prominent cardiac and pulmonary problems. Concurrently, there was a widespread community outbreak of HFMD caused primarily by enterovirus 71 (EV71). This outbreak began in early April, and, from 1 June through 30 August, a total of 2628 cases were reported to the Sarawak State Department of Health, 889 children were hospitalized for observation, and 39 patients had aseptic meningitis or acute flaccid paralysis.

Although numerous epidemics of HFMD caused by EV71 have been reported throughout the world and although some of these have been associated with neurological complications [1–12], a cluster of deaths of patients with this clinical presentation of HFMD has occurred only in the context of another outbreak of HFMD in Taiwan during April–June 1998 [13–18]. In this report, we describe the clinical and pathological manifestations of the unusual, rapidly fatal disease in the 29 case patients in Sarawak.

Methods

Review of medical records. As soon as the outbreak was recognized, doctors in Sarawak were requested to report to the State Department of Health all children who presented with a short history of fever, who did or who did not have mouth ulcers or rashes, and whose condition progressed rapidly to refractory shock, resulting in death. All patients who met the above criteria and who did not have an identifiable cause of death (e.g., bacterial septicemia or Japanese encephalitis) were included in the study. Two reviewers abstracted information on demographics, clinical features, and laboratory and radiographic findings from the medical records, by use of a standard data-collection form. Later, a third independent reviewer checked the accuracy of the abstracted information.

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Table 1. Symptoms of the 29 case patients at the time of hospitalization.

Symptom	Patients, *n* (%)
Fever	29 (100)
Oral ulcer	19 (66)
Extremity rash[a]	18 (62)
Vomiting	17 (59)
Cough or cold	10 (35)
Seizure	8 (28)
Diarrhea	6 (21)
Limb weakness/paralysis	5 (17)

[a] The extremity rashes varied among the case patients and were papular, vesicular, or both.

Pathological studies. Postmortem examinations were performed on 4 of the deceased patients at hospitals in Sarawak, and the histopathological slides were reviewed by 3 laboratories (Centers for Disease Control and Prevention [CDC] in Atlanta, GA; Sarawak General Hospital in Kuching, Malaysia; and University Hospital in Kuala Lumpur, Malaysia). Percutaneous cardiac biopsies were performed on 6 other case patients, including one from whom biopsy specimens of the brain, liver, and lung were also obtained. Tissue specimens were examined for EV71, flavivirus, adenovirus, hantavirus, Colorado tick fever virus, spotted fever and typhus group rickettsii, and leptospira, by use of in situ hybridization and immunohistochemical methods. Immunohistochemical assays were performed by use of a labeled streptavidin-biotin method, as described elsewhere [19]. The primary antibody used was an anti-EV71 mouse monoclonal antibody.

Microbiological studies. Various specimens were obtained from CSF, sera, throat swabs, rectal swabs, stool, and vesicle fluid from case patients and were cultured for viruses on cell culture lines that would support the growth of many enteroviruses, adenoviruses, flaviviruses, and reoviruses. The cell lines used included rhabdomyosarcoma cells, human pulmonary adenocarcinoma (A549) cells, African green-monkey kidney (Vero) cells, human lung fibroblast cells, and *Aedes albopictus* (C6/36) cells. Agents causing cytopathic effect in the cultures were characterized by agent-specific antigen detection, virus neutralization, or PCR. A sample of available serum specimens was tested for antibodies to enteroviruses, flaviviruses, yellow fever virus, dengue virus, Japanese encephalitis virus, herpes simplex virus types 1 and 2, cytomegalovirus, mumps virus, adenoviruses, *Mycoplasma pneumoniae,* scrub typhus, murine typhus, tick typhus, and leptospira. Because most patients died shortly after hospitalization, generally only a single serum specimen was available for testing. Reference laboratories included those at the Institute of Medical Research and University of Malaya in Kuala Lumpur, Malaysia; the University of Malaysia Sarawak in Sarawak, Malaysia; and the CDC in Atlanta, GA.

Results

Demographic characteristics. Twenty-nine patients met the case definition. The median age of the case patients was 1.5 years (mean, 1.7 years; range, 0.5–5.9 years); 19 (66%) were boys. Sixteen case patients (55%) were of Chinese ethnicity, 6 (21%) were Iban, 5 (17%) were Malay, and 1 (3%) each were Melanau and Bidayuh. Eleven case patients (38%) resided in Sibu, 7 (24%) in Sarikei, 6 (21%) in Kuching, 3 (10%) in Miri, and 1 (3%) each in Bintulu and Sri Aman. The following case report illustrates the typical clinical course and findings of the case patients.

Case report. A 22-month-old previously healthy boy presented to the hospital with a 2-day history of fever and cough and weakness of the left upper limb of 1 day's duration. At admission, he had a temperature of 37.8°C, a heart rate of 175 beats/min, a respiratory rate of 60 breaths/min, and a blood pressure of 103/50 mm Hg. He was drowsy, with evidence of peripheral hypoperfusion (capillary refill time, 5 s), and had a papular rash on the feet and a hypotonic and areflexic left upper limb.

The chest radiograph showed diffuse interstitial and alveolar infiltrates, compatible with pulmonary edema. An echocardiogram showed a dilated left ventricle with an ejection fraction of 29%. The WBC was 28,400 cells/mL, with 58% neutrophils, 34% lymphocytes, and 8% monocytes; the hematocrit level was 37%, and the platelet count was 495,000 cells/mL. Other values were as follows: serum sodium, 136 mmol/L; serum potassium, 6 mmol/L; serum chloride, 106 mmol/L; blood urea level, 63 mg/dL (10.5 mmol/L); serum bilirubin, 0.4 mg/dL (6.8 μmol/L); serum albumin, 4.6 g/dL; serum alkaline phosphatase, 161 U/L; serum alanine aminotransferase, 48 U/L; serum aspartate aminotransferase, 228 U/L; serum lactate dehydrogenase, 1312 U/L; and serum creatine kinase level, 1218 U/L, with an MB fraction of 130 U/L (11%).

The patient was intubated at admission; frothy pink secretions were noted from the endotracheal tube. Despite therapy with diuretics, inotropic agents, and intravenous immunoglobulin, the patient developed progressive hypotension, resulting in death 3.5 h after admission.

Clinical presentation. Among the 29 case patients, the median duration of symptoms before hospitalization was 2 days (range, 1–10 days). The most common symptoms at the time of hospitalization were fever, oral ulcers, papular or vesicular

Table 2. Physical findings at the time of admission to the hospitals, for the 29 case patients.

Finding	No. (%) of patients	Median value (range)
Temperature ≥37°C	20 (69)	37.4 (32.8–40.0)
Cyanosis	19 (66)	—
Crackles or rales on lung examination	18 (62)	—
Heart rate ≥180 beats/min	12 (41)	170 (104–245)
Respiratory rate ≥40 breaths/min[a]	13 (45)	50 (30–60)
Systolic blood pressure, mm Hg[b]	29 (100)	108 (0–156)
Diastolic blood pressure, mm Hg[b]	29 (100)	70 (0–94)
Extremity rashes[c] or oral ulcers	21 (72)	—
Capillary refill time >2 s	12 (41)	—
Mottling of the skin	7 (24)	—
Decreased movement of ≥1 limb	4 (14)	—

[a] Data were available for only 18 case patients.
[b] Data were available for only 14 case patients.
[c] The extremity rashes varied among the case patients and were papular, vesicular, or both.

Table 3. Results of laboratory studies during hospitalization for the 29 case patients.

Test	No. tested	Median (range)
Hematologic		
WBC, $\times 10^3$ cells/mm^3	24	24.7 (5.1–28)
Polymorphonuclear cells, %	20	63 (17–96)
Hematocrit, %	20	38 (26–52)
Platelets, $\times 10^3$ cells/mm^3	24	454 (20–844)
Prothrombin time, s	11	16 (14–36)
Partial thromboplastin time, s	11	46 (32–132)
Electrolyte and serum chemistry		
Sodium, mmol/L	26	136 (125–144)
Potassium, mmol/L	26	4.7 (3.4–7.5)
Chloride, mmol/L	25	104 (93–108)
Calcium, mg/dL[a]	10	9.2 (8.0–11.6)
Glucose, mg/dL[b]	14	211 (88–404)
Blood urea, mg/dL[c]	24	29 (17–78)
Creatine kinase, U/L	15	259 (99–2400)
Lactate dehydrogenase, U/L	14	643 (381–2405)
Liver function		
Alanine aminotransferase, U/L	15	23 (10–139)
Aspartate aminotransferase, U/L	17	78 (29–3350)
Alkaline phosphatase, U/L	11	165 (107–274)
Total bilirubin, mg/dL[d]	13	0.4 (0.2–5.1)
Albumin, g/dL[e]	14	4.1 (2.9–4.7)
CSF		
WBC/cm^3	12	41.5 (5–259)
Lymphocytes, %	12	98.5 (55–100)
Protein, mg/dL[e]	11	35 (8–55)
Glucose, mg/dL[b]	13	86 (20–201)

[a] Conversion factor to SI units: ×0.25.
[b] Conversion factor to SI units: ×0.0555.
[c] Conversion factor to SI units: ×0.165.
[d] Conversion factor to SI units: ×17.1.
[e] Conversion factor to SI units: ×10.

extremity rashes, vomiting, and cough (table 1). Eighty-three percent of the case patients had either extremity rashes or oral ulcers. The extremity rashes were often subtle and scant and could have been easily missed if not specifically looked for. Neurological manifestations were noted in 13 case patients (45%); of these, 8 had seizures and 5 had flaccid weakness of ⩾1 limb. None of the case patients reported an acute or chronic underlying illness at admission. All patients had received age-appropriate immunizations.

All case patients reported a history of fever before hospitalization, and 20 (69%) were documented to have a temperature ⩾37°C at the time of admission to the hospital (table 2). Two case patients (7%) had a temperature of ⩾40°C. The other common findings at presentation were cyanosis, poor peripheral perfusion, pulmonary crepitations, tachycardia, and tachypnea. No case patient had conjunctival hemorrhage, significant lymphadenopathy, or peripheral edema.

The chest radiographs showed perihilar opacification consistent with pulmonary edema in 17 (71%) of 24 case patients with available data. The heart was of normal size in all but 1 case patient, who had borderline cardiomegaly. Echocardiograms showed a poorly contractile globular left ventricle in all 24 case patients who were tested.

Laboratory findings included an elevated WBC with increased neutrophils, an elevated platelet count, and abnormal coagulation profiles with elevated prothrombin and partial thromboplastin times (table 3). Eleven case patients had a platelet count >500,000 cells/mL. Blood cultures were sterile in all 9 case patients who were tested. No consistent abnormalities in electrolyte levels or indicators of renal or hepatic dysfunction were noted in case patients. Creatinine kinase levels were not significantly raised in the majority of patients tested; elevated levels were noted in some case patients after cardiopulmonary resuscitation or seizures. CSF samples were obtained from 12 case patients; of these samples, 11 showed pleocytosis (>5 cells/mL) with a lymphocytic predominance, whereas 1 was normal. There were no gross abnormalities in the CSF glucose and protein levels. Bacterial cultures of CSF were negative in the 7 patients who were tested.

Clinical course. Sixteen of 29 case patients had sinus tachycardia on admission; 11 other patients had sinus tachycardia develop during hospitalization. Twenty-eight patients (97%) required assisted ventilation because of severe respiratory distress;

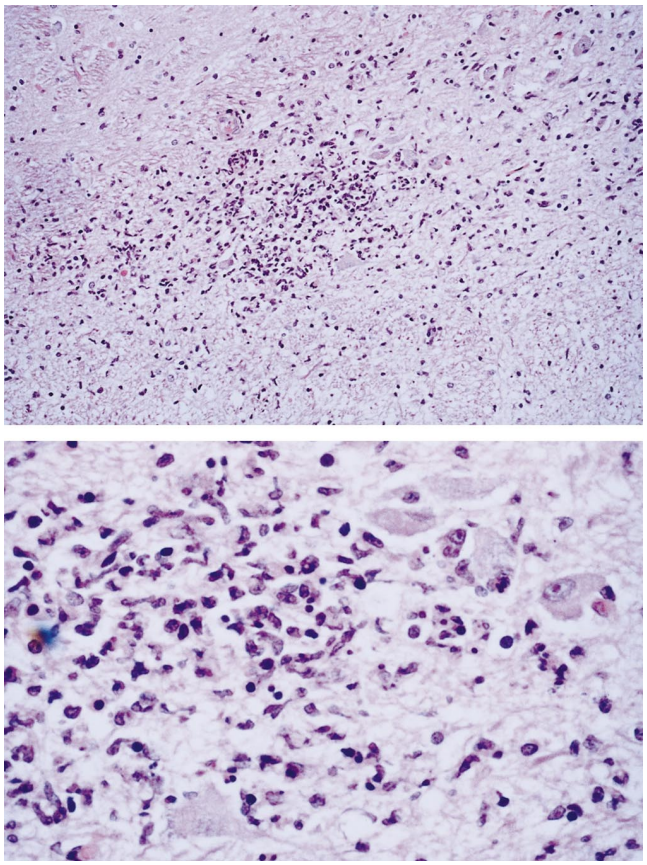

Figure 1. *Top,* Low-power photomicrograph showing a focus of intense parenchymal inflammatory infiltrates and neuronal degeneration and necrosis. *Bottom,* Higher-power magnification showing mixed inflammatory infiltrate and neuronophagia. Hematoxylin and eosin. Original magnification, ×50 *(top)* and ×158 *(bottom)*.

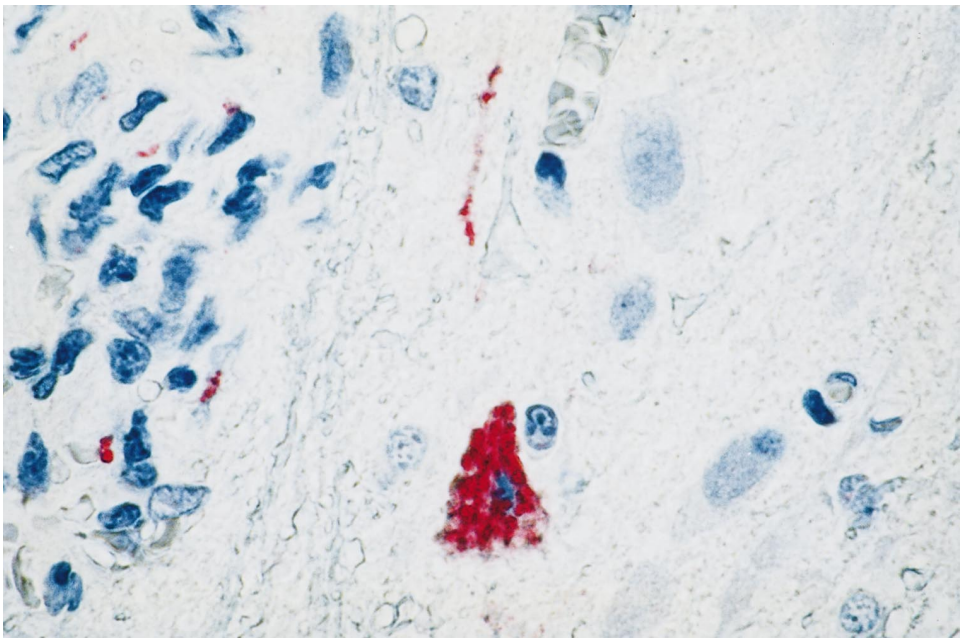

Figure 2. Enterovirus 71 viral antigens, as seen in a single neuron. Note immunostaining of a neuronal process, either dendrite or axon, as well as immunostaining within an area of inflammatory cells. Naphthol/fast-red substrate with light hematoxylin counterstain. Original magnification, ×250.

pink, frothy secretions from the endotracheal tube were noted at intubation in 16 patients (57%). All patients received mechanical ventilation without difficulty. The median peak respiratory pressure was 25 mm Hg (range, 20–40 mm Hg), the median respiratory rate was 52 breaths/min (range, 30–60 breaths/min), and the median fraction of inspired oxygen was 75% (range, 25%–100%). Fourteen patients (48%) had small volumes of fresh blood or coffee-ground materials noted in vomitus or nasogastric aspirates; no other features consistent with a bleeding diathesis were documented. Eight patients reported seizures before hospitalization, whereas 8 others developed seizures for the first time after admission. Despite supportive therapy, cardiac arrest occurred within a median of 9.0 h (range, 0.6–319.5 h) after hospitalization, usually after a period of refractory bradycardia and hypotension.

Pathological studies. Cultural constraints precluded extensive autopsy studies; consent for postmortem examination was therefore obtained for only 4 case patients. CNS tissue from the 4 autopsied patients showed congestion, edema, and perivascular and meningeal lymphocytic infiltration. Brain-stem tissue, which was available for 2 patients, showed extensive neuronal degeneration and necrosis associated with an inflammatory reaction resembling microabscesses (figure 1*A,* 1*B*). Immunohistochemical staining with an anti-EV71 monoclonal antibody showed focal staining of neurons and mononuclear inflammatory cells in 4 of 5 case patients from whom CNS tissue was obtained (figure 2). Immunohistochemical assays for other pathogens in CNS tissue were negative. No viral antigen (EV71 or other viruses) was seen in all the other tissues that were examined. The lungs showed congestion and edema, with diffuse alveolar damage and mild-to-moderate inflammatory infiltrates. Examination of all 10 cardiac tissue specimens showed normal myocardium with no evidence of inflammation or myocyte necrosis or degeneration. Other viscera, including the liver, kidneys, and adrenals, were normal.

Microbiological studies. EV71 was isolated in specimens from a total of 6 case patients. Two patients had EV71 isolated from a rectal swab only; 1, from a throat swab only; 1, from serum and throat and rectal swabs; 1, from pancreatic and lung tissue; and 1, from spinal cord. The latter 2 patients, who had tissue isolates of EV71, and 2 additional patients were positive, by immunohistochemical assays, for EV71 in CNS specimens. Another case patient had echovirus 25 isolated from a serum specimen, and, as described elsewhere [20], several case patients had an adenovirus detected from various specimens. These viruses were also detected from patients with nonfatal HFMD [21]. The virologic data were insufficient to make definitive conclusions regarding the cause of illness in the case patients who died.

Discussion

The rapid onset and progression of cardiac and pulmonary failure in previously healthy children stand out as a unique and puzzling feature of this disease. A large cluster of deaths resulting from a similar illness has been described in only one

other instance, during an extensive outbreak of HFMD caused by EV71 in Taiwan in 1998 [13–18]. The manifestations of tachycardia, shock refractory to fluid and inotropic therapy, pulmonary edema, and echocardiographic evidence of ventricular dilatation and hypocontractility clearly demonstrate substantial cardiac dysfunction, which, in young children, usually suggests a myocarditis [22]. The absence of inflammation in cardiac tissue from 10 case patients, however, led us to look for other pathogenic mechanisms for the cardiac and pulmonary manifestations.

The histopathological findings of severe brain-stem encephalitis led us to consider CNS pathology as a possible key to the disease process. Although most patients had some evidence of CNS disease (e.g., cells in CSF, seizures, lethargy, and paralysis), these findings were not sufficiently severe enough to suggest that CNS involvement caused the rapid progression of cardiopulmonary disease resulting in death. Additional neurological findings may have been masked by, or attributed to, the refractory shock and pulmonary edema. At least some of the cardiopulmonary findings can be attributed to the encephalitis. Damage to some areas of the brain stem can cause neurogenic pulmonary edema. Several mechanisms, including an increase in pulmonary vascular pressure (caused by sympathetic stimulation and elevated catecholamine levels) and an increase in pulmonary endothelial permeability, have been proposed to explain the pathogenesis of neurogenic pulmonary edema [23–33]. It is thought that some of these physiological changes could account, in part, for the cardiovascular manifestations. Fulminant neurogenic pulmonary edema was believed to contribute to disease in patients from Peninsular Malaysia and Taiwan who had a similar clinical presentation of HFMD and died [15–18, 34–36]. In addition, pulmonary edema has been described in cases of poliomyelitis with extensive damage to the dorsal nucleus of the vagus and the vasomotor centers of the brain stem [37–40]. Furthermore, a cluster of 44 rapid deaths of children with a brain-stem pathology nearly identical to that seen among the case patients in Sarawak was reported in Bulgaria in 1975 [41, 42]. The presentation and clinical course of this unique fatal disease could be explained by the rapid onset and progression of brain-stem encephalitis. Features such as the abnormal blood coagulation profiles and gastrointestinal bleeding observed in some case patients, however, suggest that other factors (e.g., viral sepsis) might have contributed to the disease process.

The etiology of this unique clinical presentation is still under investigation. For most patients, the prodromal illness was indistinguishable from that seen in uncomplicated cases of HFMD that were primarily associated with EV71. In fact, no clinical feature was identified that could reliably predict which patients were likely to develop severe disease resulting in death. The strongest links to EV71 were isolation of the virus from several case patients who died and detection of its antigens in neurons in the brain stem from 4 of 5 case patients from whom CNS tissue was obtained. However, further evidence is required to define the link between EV71 infection and the fatal disease. The fact that only 2 outbreaks of deaths (i.e., this outbreak and the one in Taiwan) with this clinical picture have been reported, despite the occurrence of numerous HFMD and EV71 outbreaks worldwide, raises the possibility that other factors (e.g., toxins, medicines, or environmental exposures) or other infectious agents might contribute to the disease process. For example, a fastidious adenovirus has also been isolated from several case patients who died [20]. Adenoviruses have been reported to cause a cardiomyopathy that is not associated with inflammatory changes in cardiac muscle [43]. Studies are presently being conducted to assess the etiologic role, if any, of these agents and other factors in the pathogenesis of this unique illness. These studies should provide clues to the prevention and treatment of this devastating illness.

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