Case Report

Enterovirus 71-Induced Fulminant Cardiopulmonary Failure: A Case Report

Pornumpa Bunjoungmanee MD*,
Auchara Tangsathapornpong MD*

** Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*

Background: *The spectrum of diseases attributed to enterovirus (EV) 71 includes herpangina and hand-foot-and-mouth disease (HFMD). EV71 can occasionally cause neurological complications, such as meningitis, encephalitis and poliomyelitis-like paralysis. Neurogenic pulmonary edema (NPE) is a fatal complication in children with EV71 encephalitis.*
Case Report: *A previously healthy, fully immunized 4-year-old girl presented with fever, cough, rhinorrhea and emesis. She had no skin or oral mucosal lesions related to HFMD. After admission, she had generalized tonic seizures 3 times and rapidly developed hypotension with cardiac arrest. Chest radiograph showed pulmonary edema without cardiomegaly. Cardiac enzymes were elevated. The cerebrospinal fluid (CSF) glucose level was also elevated with no CSF pleocytosis. Histologically, the brain specimen showed perivascular lymphocytic infiltration with hypoxic ischemic encephalopathy. The real time polymerase chain reactions for pan-EV and EV71 from CSF were positive.*
Conclusion: *Children with EV71 associated NPE have a high case-fatality rate. Early identification and treatment of related cardiopulmonary disorders is of great importance.*

Keywords: *Enterovirus 71, Neurogenic pulmonary edema, Encephalitis*

J Med Assoc Thai 2017; 100 (Suppl. 5): S259-S263
Full text. e-Journal: *http://www.jmatonline.com*

A previously healthy, fully immunized 4-year-old girl was admitted to the Pediatric Department in August 2014 due to a fever of 4-day duration. At that time, there was no report of hand, foot and mouth disease (HFMD) in the nursery where she attended. She had the history of HFMD and herpangina in 2012 and 2013, respectively. On the first day, she developed fever, cough and nasal discharge. She was seen by the medical practitioner who prescribed paracetamol, nasal decongestant and anti-tussis and seemed to be getting better. Three days after the outpatient visit, she was brought to the hospital with high grade fever, vomiting, watery diarrhea and restlessness. On examination, she was fully conscious, temperature was 39.0°C, dry lips and sunken eyeballs. No rash or oral ulcer was seen. A diagnosis of acute gastroenteritis was made and she was hospitalized.

After the treatment with intravenous fluid and anti-emetic drug, she still had persistent vomiting. Twelve hours after admission, the child was irritable and developed abdominal pain. Abdominal examination was unremarkable. Fourteen hours after admission, she had a brief generalized tonic seizures 2 times. Her temperature was 36.7°C, respiratory rate was 42 breaths per minute, heart rate was 150 beats per minute and blood pressure was 96/40 mmHg. Her pulse oximetry reading was 99%. The child was drowsy but responsive to verbal command. She did not show stiff-neck or abnormality in her lungs. Cold clammy skin was noted but neither a rash nor oral ulcer was seen. The blood sugar was elevated (280 mg/dL). Oxygen supplement, diazepam and phenytoin were given.

Fifteen minutes later, she had a third time of generalized tonic seizures for 15 seconds and became unresponsive. The heart rate and the blood pressure could not be measured and external cardiac massage was started immediately after intubation. A large amount of pink frothy fluid was aspirated from the lungs when she was endotracheally intubated. Despite the resuscitation efforts, she was declared dead with respiratory failure and severe pulmonary edema.

Laboratory results showed a peripheral total white blood cell count $10.3x10^9$/L with 63% neutrophils, 23% lymphocyte and 14% monocytes. The cerebrospinal fluid (CSF) glucose level was also elevated with no CSF pleocytosis. The creatine kinase-

Correspondence to:
Bunjoungmanee P, Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathumthani 12120, Thailand.
Phone: +66-2-9269514
E-mail: peer_tu@yahoo.com

MB and troponin-T were elevated (70.8 and 4.5 ng/mL, respectively). Chest radiograph showed pulmonary edema without cardiomegaly (Fig. 1). Histologically, her brain specimen showed perivascular lymphocytic infiltration with hypoxic ischemic encephalopathy (Fig. 2). The CSF real time polymerase chain reactions for pan-EV and EV 71 were positive, although the blood for antibody titers, the stool specimen and the nasopharyngeal swab were negative for EV.

A younger brother of the girl was subsequently admitted to the hospital in the following day, with suspected EV infection. He had fever, vomiting and looked ill. No rash or oral ulcer was seen. Intravenous fluid, paracetamol and anti-emetic were given. The Clinical recovery was complete without complication. Throat swab and stool specimen were negative for EV.

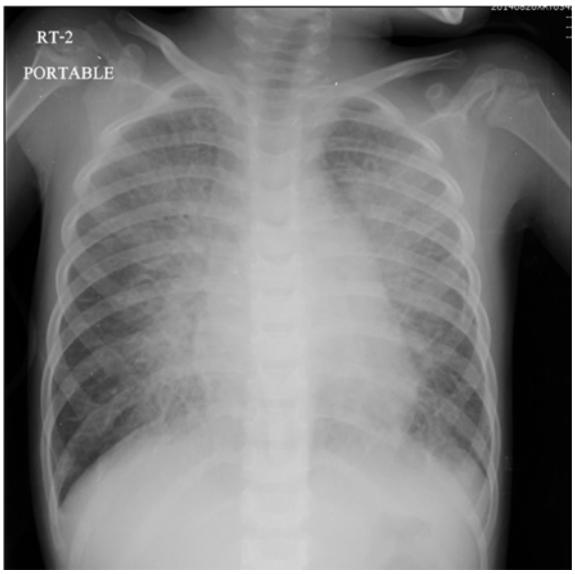

Fig. 1 Chest radiograph showed pulmonary edema without cardiomegaly.

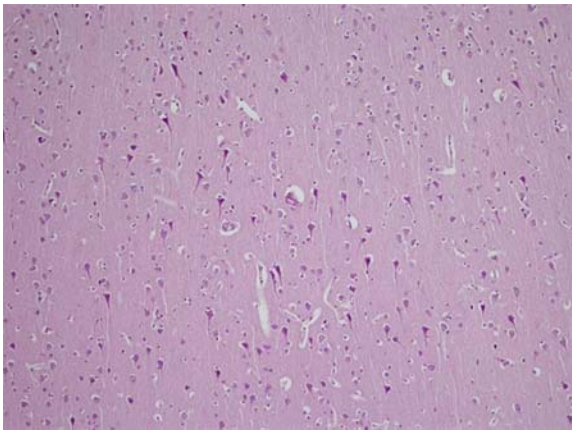

Fig. 2 The brain tissue showed perivascular lymphocytic infiltration with hypoxic ischemic encephalopathy.

Discussion

Thailand is the endemic area of EV71 and fatal infection has been reported. The cases of HFMD were highest during June to October, with 41,392 to 65,606 cases (morbidity rate was 63.56 to 71.73 per 100,000 persons) and 2 to 3 deaths reported (mortality rate was 0.003 to 0.004 per 100,000 persons) annually between 2013 to 2015.

Although most of children with EV71 infection display rash recognized easily, a few cases exhibit atypical symptoms, thereby increasing difficulty for diagnosis and some case can progress to rapid deterioration. In the present case, she had not been diagnosed with EV infection due to no rash or oral ulcer. Nearly 15% of severe EV infection did not have skin rash or vesicular lesion[1]. The absence of oral ulcers associated with more severe disease and children without oral ulcers should be monitored closely[2]. Her clinical features such as high temperature greater than 39°C, duration of fever greater than 3 days, absence of skin lesion, diarrhea, seizure and hyperglycemia, meet the risk factor for severe case[3]. Therefore, the physician should pay attention to children with atypical symptoms and early recognition of cardiopulmonary failure, especially in an area with EV outbreak.

In the patient presented, brainstem encephalitis was the cause of neurogenic pulmonary edema, vasomotor collapse and rapidly deteriorating clinical course. Although no CSF pleocytosis, the isolation of EV71 from the CSF by the real time polymerase chain reactions for pan-EV and EV71 were positive. Unlike other EV, the detection rate of EV71 in the CSF of patients with EV71 is very low (0 to 10%)[4,5]. Few patients with neurological complications revealed no CSF pleocytosis[6]. EV71 infection predominantly involves central nervous system and presents the diverse neurologic manifestations. Brain stem encephalitis is the most frequent manifestation. An etiologic link between brainstem encephalitis and pulmonary edema has been suggested and most of fatal cases results from autonomic nervous system (ANS) dysfunction. Deaths usually occur within 6 to 24 hours after admission[7,8].

Elevation of the cardiac enzymes in this patient represented myocardial injury. Myocardial dysfunction and cardiogenic shock were reported in

patients with EV71 infection[9]. Histological examination of her brain revealed perivascular lymphocytic infiltration with hypoxic ischemic encephalopathy. Fatal neurological complications of EV71 infection consist of histological manifestations of perivascular inflammatory infiltration, neuronal degeneration, necrosis, softening of the white matter, neurophagia and macrophage/microglial nodules[10].

Cytokines in the central nervous system and systemic inflammatory responses play the important roles in the pathogenesis of EV71-associated encephalomyelitis[11-14]. Intravenous immunoglobulin (IVIG) is recommended for treating the severe EV71 disease in many countries. It is significantly decreased mortality by attenuated the pro-inflammatory and anti-inflammatory cytokines production in the early phase of devastating complications of EV71 associated ANS dysregulation. A most favorite survival might have been obtained by earlier IVIG treatment during the ANS dysregulation.

The HFMD guidelines used from Thailand are based on the WHO guidelines. IVIG is recommended for grade 3 (HFMD with ANS stage) and may be considered for grade 4 (HFMD with cardiopulmonary failure stage) if IVIG has not previously been administered[15]. Because IVIG is frequently used to treated in HFMD with severe complication for which evidence of its efficacy is insufficiently documented. Improved evidence-based management and treatment of HFMD is essential preparation. The Study is underway in multicenter intervention trial to assess the efficacy and safety of IVIG as a therapeutic intervention[16]. In the present case, her clinical deteriorated rapidly from ANS dysregulation to pulmonary edema and she was died before IVIG administration.

To date, the effective treatment or prophylaxis for EV is currently unavailable and most EV71 infections are asymptomatic or result in mild disease, which limits the effectiveness of public health interventions. By the analogy of poliomyelitis, the best measure for disease prevention and control is vaccine, which several vaccines for EV71 are currently under development[17,18].

Conclusion

In spite of the fact that children with EV71 associated NPE have a high case-fatality rate, early identification and treatment of related cardiopulmonary disorders is of great importance. A high index of suspicion is essential for prompt management in high-risk case particularly in the event of an outbreak of EV infection with awareness of early sympathetic symptoms (ANS dysregulation) such as persistent tachycardia.

What is already known on this topic?

Typically, EV71 infection causes a self-limiting disease. Severe case with cardiopulmonary and neurological complications has been reported. Although most of children with EV71 infection display rash recognized easily, a few cases exhibit atypical symptoms, thereby increasing difficulty for diagnosis and some case can progress rapidly deterioration.

What this study adds?

Nearly 15% of severe EV infection did not have skin rash or vesicular lesion[1]. The absence of oral ulcers is associated with more severe disease and children without oral ulcers should be monitored closely. Therefore, the physician should pay attention to children with atypical symptoms and early recognition of cardiopulmonary failure, especially in an area with EV outbreak.

Acknowledgements

We are thankful to Dr. Rome Buathong, Bureau of Epidemiology, Ministry of Public Health, Thailand for helping EV 71 identification.

Potential conflicts of interest

None.

References

1. Lee KY, Lee YJ, Kim TH, Cheon DS, Nam SO. Clinico-radiological spectrum in enterovirus 71 infection involving the central nervous system in children. J Clin Neurosci 2014; 21: 416-20.
2. Pan J, Chen M, Zhang X, Chen Y, Liu H, Shen W. High risk factors for severe hand, foot and mouth disease: a multicenter retrospective survey in Anhui Province China, 2008-2009. Indian J Dermatol 2012; 57: 316-21.
3. Owatanapanich S, Wutthanarungsan R, Jaksupa W, Thisyakorn U. Risk factors for severe enteroviral infections in children. J Med Assoc Thai 2016; 99: 322-30.
4. Ooi MH, Wong SC, Podin Y, Akin W, del Sel S, Mohan A, et al. Human enterovirus 71 disease in Sarawak, Malaysia: a prospective clinical, virological, and molecular epidemiological study. Clin Infect Dis 2007; 44: 646-56.
5. Ooi MH, Wong SC, Mohan A, Podin Y, Perera D,

Clear D, et al. Identification and validation of clinical predictors for the risk of neurological involvement in children with hand, foot, and mouth disease in Sarawak. BMC Infect Dis 2009; 9: 3.
6. Perez-Velez CM, Anderson MS, Robinson CC, McFarland EJ, Nix WA, Pallansch MA, et al. Outbreak of neurologic enterovirus type 71 disease: a diagnostic challenge. Clin Infect Dis 2007; 45: 950-7.
7. Wang SM, Liu CC. Enterovirus 71: epidemiology, pathogenesis and management. Expert Rev Anti Infect Ther 2009; 7: 735-42.
8. Ooi MH, Wong SC, Lewthwaite P, Cardosa MJ, Solomon T. Clinical features, diagnosis, and management of enterovirus 71. Lancet Neurol 2010; 9: 1097-105.
9. Fu YC, Chi CS, Chiu YT, Hsu SL, Hwang B, Jan SL, et al. Cardiac complications of enterovirus rhombencephalitis. Arch Dis Child 2004; 89: 368-73.
10. Shekhar K, Lye MS, Norlijah O, Ong F, Looi LM, Khuzaiah R, et al. Deaths in children during an outbreak of hand, foot and mouth disease in Peninsular Malaysia: clinical and pathological characteristics. Med J Malaysia 2005; 60: 297-304.
11. Wang SM, Lei HY, Huang KJ, Wu JM, Wang JR, Yu CK, et al. Pathogenesis of enterovirus 71 brainstem encephalitis in pediatric patients: roles of cytokines and cellular immune activation in patients with pulmonary edema. J Infect Dis 2003; 188: 564-70.
12. Wang SM, Lei HY, Yu CK, Wang JR, Su IJ, Liu CC. Acute chemokine response in the blood and cerebrospinal fluid of children with enterovirus 71-associated brainstem encephalitis. J Infect Dis 2008; 198: 1002-6.
13. Wang SM, Lei HY, Huang MC, Su LY, Lin HC, Yu CK, et al. Modulation of cytokine production by intravenous immunoglobulin in patients with enterovirus 71-associated brainstem encephalitis. J Clin Virol 2006; 37: 47-52.
14. Wang SM, Lei HY, Liu CC. Cytokine immunopathogenesis of enterovirus 71 brain stem encephalitis. Clin Dev Immunol 2012; 2012: 876241.
15. World Health Organization. A guide to clinical management and public health response for hand, foot and mouth disease (HFMD) [Internet]. Geneva: WHO Press, 2011 [cited 2016 Dec 24]. Available from: http://www.wpro.who.int/publications/docs/GuidancefortheclinicalmanagementofHFMD.pdf.
16. Chea S, Cheng YB, Chokephaibulkit K, Chotpitayasunondh T, Rogier vD, Hafy Z, et al. Workshop on use of intravenous immunoglobulin in hand, foot and mouth disease in Southeast Asia. Emerg Infect Dis 2015; 21: e140992.
17. Chang PC, Chen SC, Chen KT. The Current Status of the Disease Caused by Enterovirus 71 Infections: Epidemiology, Pathogenesis, Molecular Epidemiology, and Vaccine Development. Int J Environ Res Public Health 2016; 13: E890.
18. Reed Z, Cardosa MJ. Status of research and development of vaccines for enterovirus 71. Vaccine 2016; 34: 2967-70.

รายงานผู้ป่วย: เชื้อ Enterovirus 71 ชักนำให้เกิดภาวะหัวใจและปอดล้มเหลวชนิดรุนแรง

พรอำภา บรรจงมณี, อัจฉรา ตั้งสถาพรพงษ์

ภูมิหลัง: *การติดเชื้อ Enterovirus (EV) 71 จะมีอาการได้หลายรูปแบบ เช่น โรค herpangina และโรค hand-foot-and-mouth (HFMD) อาจก่อให้เกิดภาวะแทรกซ้อนทางระบบประสาท เช่น meningitis encephalitis และ poliomyelitis-like paralysis โดย neurogenic pulmonary edema (NPE) เป็นภาวะแทรกซ้อนสำคัญที่ทำให้ผู้ป่วย encephalitis จากเชื้อ EV 71 เสียชีวิต*

รายงานผู้ป่วย: *เด็กหญิงอายุ 4 ปี สุขภาพแข็งแรงดี ได้รับวัคซีนครบตามเกณฑ์มาด้วยอาการไข้ ไอ น้ำมูกและอาเจียน ไม่มีผื่นหรือแผลในช่องปากที่สัมพันธ์กับโรค HFMD ภายหลังเข้ารับการรักษาในโรงพยาบาล ผู้ป่วยมีอาการชัก 3 ครั้ง ลักษณะ generalized tonic จากนั้นมีความดันโลหิตต่ำและหัวใจหยุดทำงานอย่างรวดเร็ว ภาพถ่ายรังสีทรวงอก ตรวจพบลักษณะ pulmonary edema โดยไม่มีหัวใจโต ระดับเอ็นไซม์ของหัวใจมีค่าสูง ผลตรวจน้ำไขสันหลัง มีระดับน้ำตาลสูงแต่ไม่พบเม็ดเลือดขาว ผลชิ้นเนื้อสมองมีลักษณะ perivascular lymphocytic infiltration และ hypoxic ischemic encephalopathy ร่วมกับผล real time polymerase chain reaction สำหรับ pan-EV และ EV 71 ให้ผลบวก*

สรุป: *เด็กที่ติดเชื้อ EV 71 และมีภาวะ NPE มีอัตราตายค่อนข้างสูง ดังนั้นการวินิจฉัยโรคอย่างรวดเร็วและให้การรักษาภาวะ cardiopulmonary disorder ได้อย่างถูกต้องเป็นสิ่งที่สำคัญ*