Case Report

Hemophagocytic Syndrome in Dengue Hemorrhagic Fever with Severe Multiorgan Complications

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A 46 year old woman who presented with severe multiorgans involvement including liver, brain, cardio-pulmonary failure, gastrointestinal bleeding, progressive cytopenia, DIC and hemophagocytic syndrome during the convalescent phase of Dengue type II has been successfully treated primarily with pulse methyl prednisolone and high dose intravenous immunoglobulin G. The authors believe that HPCS are not infrequently seen with high mortality and recommended early diagnosis and treatment with the regimen. This is the first complete report of hemophagocytic syndrome in adult dengue hemorrhagic fever in Thailand. The literature of HPCS in DHF was reviewed and discussed.

Keywords: *Hemophagocytic syndrome, Dengue hemorrhagic fever, Severe multiorgan complications*

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In recent studies on dengue hemorrhagic fever[1-5] various severe complications with high fatality namely encephalopathy, severe hepatic failure, disseminated intravascular coagulation and multiple organs failure have been reported which are unusual in the previous studies. The authors reported here an adult Thai female who survived the severe multiorgan involvement with definite evidence of hemophagocytic syndrome (HPCS) by the treatment with pulse methyl prednisolone and high dose intravenous immunoglobulin G.

Case Report

A 46-year old Thai female patient (HN 337110) was transferred to Vichaiyut Hospital in Bangkok on October 4, 2006 with the history of high fever, nausea and vomiting 4 days previously. She was immediately admitted to another hospital on the first day of disease and intravenous antibiotics were given and the fever seemed to be better yet nausea and abdominal discomfort persisted. She then asked to be transferred to the presented hospital. On admission the temperature was 37.5□C and fever gradually came down to normal. Physical examination revealed no rash, no dyspnea, no edema, clear lungs, no hepatosplenomegaly nor lymphadenopathy. CBC revealed Hct 31.6%, Wbc 5,200/mm^3, 51% PMN with 39% band form, 10% lymphocyte and 87,000/mm^3 platelets, Blood chemistry revealed elevated transaminasemia (SGOT 151 units/Lt, SGPT 95 units/Lt), albumin 3.1 gm%, LDH 2004 units/Lt. The clinical diagnosis of dengue fever was made and Dengue Virus (NS_1Ag) was positive. She asked to be discharged on October 6 because "she felt better".

On the first day after the discharge, she had diarrhea 4 times with black colored stools associated with severe headache and dyspnea on exertion. She, therefore, was readmitted to the hospital on October 7, 2007.

Physical Examination on the 2nd admission revealed temperature of 37.6□C, blood pressure 130/80 mmHg, pulse 50 per minute with extra beats. Edema of both legs, jaundice, dyspnea and petechial spots at

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the back and extremities were noted. Crepitation on both lungs was detected. There was neither hepatosplenomegaly nor lymphadenopathy.

Laboratory Investigations revealed hematocrit 30%, wbc 11650/mm3, 61% PMN, 9% band, 3% myelocytes and promyelocyte, 10% lymphocyte, 17% atypical lymphocyte and platelets of 18,000/mm^3. Coagulogram revealed PTT 62.8 seconds (C = 27.9), PT 13.3 sec (INR 1.4), TT 23 sec (C 8.2), mixing test PTT and PT showed no circulating anticoagulant, D-dimer 561 □g/Lt (< 300). Direct and Indirect Coomb's test were negative. Serum ferritin was 7095 ng/ml and then dropped to 2079 ng/mL on October 10. Antinuclear factor was 1:80 speckle type and anticytoplasmic antibody was negative. Blood chemistries revealed SGOT 474 units/Lt, SGPT 229 units/Lt, albumin 2.8 gm%, total protein 5.7 gm%, alkaline phosphatase 346 units/Lt, LDH 6462 units/Lt, BUN 9 mg%, creatinine 0.5 mg%, CPK 278 units/Lt and normal electrolytes. Urinalysis was negative. Stool was positive for occult blood.

Dengue IgM antibody was positive and Dengue IgG was 1:5120 for type 2 and 1:1280 for type 4. EBV IgG was 1:320. EBV IgM and viral load were negative. Hepatitis B antigen and Hepatitis C antibody were not detected. Blood cultures were negative. Chest X-rays showed bilateral pleural effusion, more on the right with cardiomegaly.

Progress and treatment (Fig. 1)

On first day of the second admission, the patient experienced severe headache with the finding of thrombocytopenia, therefore the possibility of intracranial bleeding was strongly suspected. A single donor platelet of one unit and intravenous dexamethasone 4 mg every 6 hours were started and tapered off quickly. The computerized tomogram of the brain revealed no abnormality. Two units of pack red blood cells were also given to correct anemia probably due to gastrointestinal bleeding.

In the following morning, her condition had improved; less headache and good appetite. Laboratory tests showed rising platelets to 66,000/mm^3 but rather stable hematocrit of 31%. LDH increased from 6462 to 9100 units/Lt and total bilirubin rose from 0.9 to 1.4 mg% These findings indicated progressive hemolysis. SGOT increased from 474 to 1344 units/Lt and SGPT from 229 to 596 units/Lt within 24 hours. At this point hemophagocytic syndrome was suspected

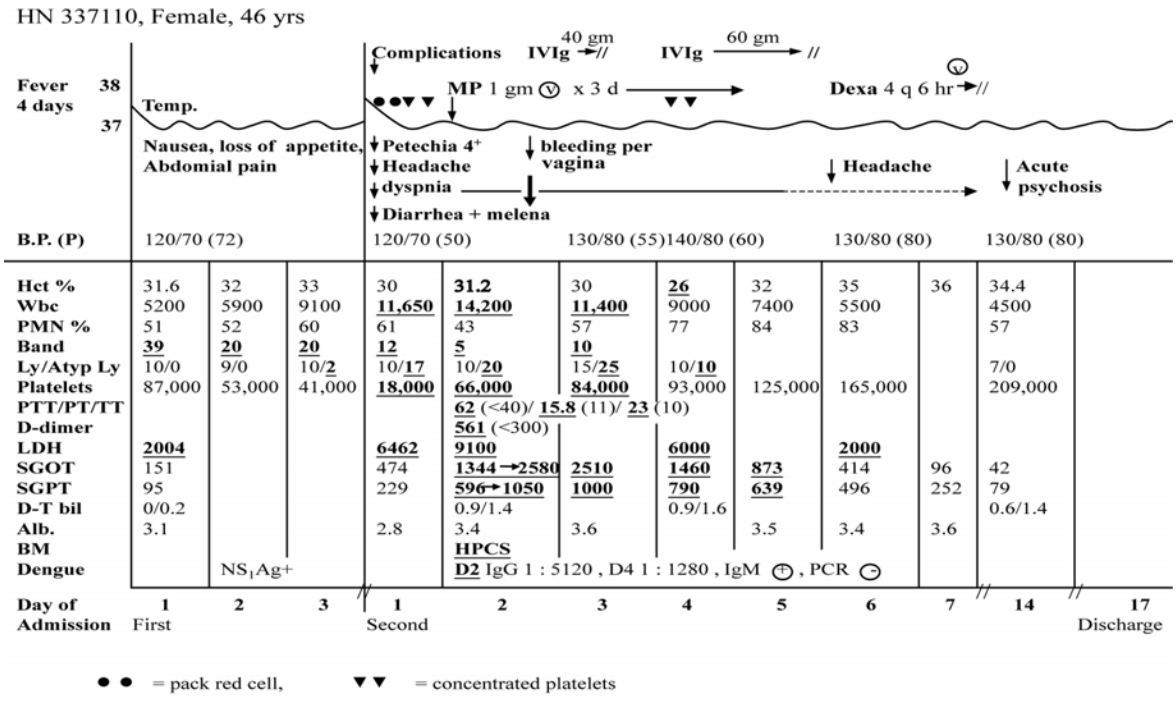

Fig. 1 Unusual manifestations of a non-shock DHF patient with hemophagocytic syndrome presented at convalescent phase

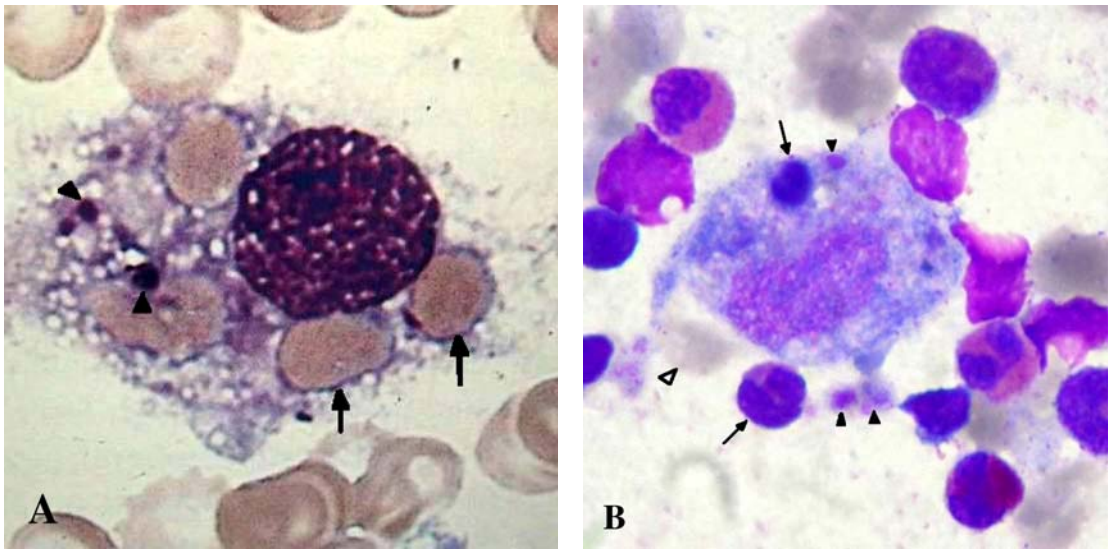

Fig. 2 Hemophagocytosis in the bone marrow by mature histiocytes
A) ingested platelets (▲) and red blood cell (→)
B) ingested leukocytes (→), platelets (▲) and red blood cell (**Δ**)

and bone marrow study revealed 50% cellularity with abundant hemophagocytosis (Fig. 2A-B) adequate megakaryocyte, increased reactive lymphoid cells and shift to the left of granulopoiesis. No malignant cells or microorganism was found. Reactive Hemophagocytic syndrome secondary to DHF with severe complications was then diagnosed. Intravenous pulse methyl prednisolone 1 gm daily was given for 3 days. Twelve hours later the patient developed severe dyspnic and having bleeding per vagina. O_2 saturation was 94.55% under O_2 mask of 5 litre/minute. Intake and output was 1350 and 300 ml respectively. Clinical diagnosis of severe vasculitis leakage syndrome in DHF was then made. Electrocardiogram showed sinus bradycardia at rate of 43/minutes with non-specific ST-T change. Intravenous flurosemide along with fluid restriction was then applied. The significant rising of liver enzymes within 12 hours was observed (Fig. 1). At this point with severe and deteriorated clinical conditions, the authors decided to give intravenous immunoglobulin G at the dosage of 1 gm/kg/day in conjunction with methyl prednisolone which was already started 12 hours previously.

On the 3rd day of the second admission, she was much improved, had less dyspnic with O_2 saturation of 95% and heart rate of 50/minute. Edema of both legs and pulmonary congestion were less. Laboratory changes are shown in Fig. 1. Intravenous immunoglobulin was discontinued after the total amount of 40 gm v but pulse methyl prednisolone was continued.

On the 4th day the patient's condition became worse, she was more dyspnic with increased jugular pulse pressure. Output was more than intake 1500 ml per day. Fluid intake was more restricted. CBC showed progressive anemia, with nucleated red blood cells and polychromasia indicated progressive hemolysis. High dose of intravenous immunoglobulin G at 1 gm/kg/d (for a total dose 60 gm) was restarted for 40 hours.

During the fifth to seven day of hospitalization, the hemogram and liver enzyme were gradually improved. However, only one remaining problem was fluid overload causing severe dyspnea at night. With full supportive measures combined with restriction of fluid intake plus frequent intravenous flurosamide, she was gradually improved. However, on the 6th hospital day, she developed severe headache and was somnolent. These symptoms occurred after discontinuation of methyl prednisolone for 24 hours. Dexamethasone, therefore, was restarted intravenously at the dose of 4 mg every 6 hours and gradually tapered off within 2 days. The patient was dramatically improved. On the 14th day of admission she developed acute psychotic attack. Yet the second computerize tomogram of the brain did not show any significant abnormality. Her

condition gradually improved and she was discharged on the 17th day of hospitalization. At the 4-month follow-up she had fully recovered fully and no hematological abnormalities were longer observed.

Discussion

The patient developed multisystemic complications on the eighth day of Dengue hemorrhagic fever type 2 or on the other hand at the fourth day of the convalescent period. The serious complications presented with four major systems namely; first, the hematologic complications of thrombocytopenia, gastrointestinal bleeding, hemolysis, and mild DIC; secondly, encephalopathy presented by severe headache and psychosis, thirdly, hepatic dysfunction and fourthly cardiopulmonary distress. Hemophagocytic syndrome (HPCS) was found at the same time of these complications.

With regards to the pathogenesis of these severe complications, it is understood to be multifactorial. Prolonged shock, severe acidosis, DIC, bleeding and multiorgan failure are common mechanisms in fatal cases[4,5]. Furthermore, direct injury by the dengue virus to various vital organs such as platelet; skin, lungs, heart muscle bone marrow, lymph nodes[6,7] and hepatic cells[8-9] had been documented. Besides the dengue antigen was also demonstrated in the brain[10-12] and cerebrospinal fluid[13-15]. These overt viral antigens will stimulate the hyperactive of both T-cells and macrophages, and overt active cytokines production will induce the vascular injuries followed by the immense leakage of intravascular fluid into interstitial tissue resulting in cellular edema, cellular damage, necrosis and cell death. HPCS is caused by a hyperimmune interaction by the immune aberrated host macrophages and etiologic diseases either lymphoid malignancy or infection caused by bacteria, fungus and viruses-namely Dengue 2 virus in the presented case, causing more complications and severity of the disease.

Thrombocytopenia and progressive hemolysis is undoubtedly the result of HPCS. Granulocytosis is unusual in DHF yet it had been reported in DHF children[4] yet in the presented case it may reflect the response to hemolysis. The elevation of hepatic transaminases are usual for DHF which may last for about 6 weeks. However, in the presented patient the rapid elevation of transminase enzyme occurred in the convalescent period is an unusual feature. Cardiopulmonary failure is most probably related to hypercytokinemia which occurred during HPCS leading to severe leakage of intravascular fluids rather than the involvement of cardiac muscles. Encephalopathy in the presented case may also be from HPCS. However, the dengue viral involvement of the brain cannot be excluded because of the limited study of the cerebrospinal fluid. Finally, the patient responded dramatically to the treatment of HPCS by pulse methyl prednisolone and intravenous immunoglobulin G therapy, these complications were under controlled. The authors, therefore, believe that HPCS play an important role in the occurrence of these complications.

Hemophagocytic syndrome is uncommon in DHF. From Nelson's study severe hemophagocytosis was found in bone marrow at post-mosem findings of 9 DHF children[16], whereas this phenomena was not observed in the other milder DHF in whom bone marrow study was performed at the same period[17-20]. This finding raised the significant role of severe hemophagocytosis and the severity of DHF. During the last 7 years, there were a few reports of hemophagocytic syndrome in DHF[21-25]. In reviewing the literature only six cases (three adults and three children) were available for clinical analysis[21-24]. Cytopenia was presented in all, where as hypotension in 4 cases and moderate liver impairment in one case. In all cases HPCS was diagnosed during the acute phase of DHF. None of these six cases died and they received only full supportive treatment for DHF. However, there was no encephalopathy or other systemic complication in these six cases which was quite different from the presented patient. In the DHF patient, hapatic encephalopathy posted a very high mortality rate. It was reported to be almost half in one series[1] and 11% in the other.[3] Comparing the clinical features between the previous six and the presented patient, it suggests that HPCS in DHF may present a wide spectrum of the disease severity from mild to moderate and severe.

Recently, at least in Thailand, the authors have seen many more cases of adults DHF who presented with severe multiorgans involvement which may contribute to the deaths of DHF in some hospitals. The authors believe that all these severe complications related to the HPCS, which usually responded dramatically to pulse methyl prednisolone and high-dose intravenous immunoglobulin G in the early phase of HPCS. The authors, therefore strongly recommend that HPCS should be looked at for DHF patients presenting with unusual progressive cytopenia and multiorgan complications. The early use of pulse methyl prednisolone and high doses of intravenous immunoglobulin G should be able to save the life of the DHF patient with HPCS and multiorgan complication, which usually

presented high fatality. In addition, the treatment of fluid overload associated with severe leakage syndrome must be done including fluid restriction, infusion of albumin or hyperosmotic fluid to convert the leakage at the earlier stage.

References

1. Kalayanarooj S. Clinical manifestation of dengue: usual and unusual manifestations of dengue. In: Kalayanarooj S, editor. Studies/collaborative studies on dengue infections/dengue hemorrhagic fever at Queen Sirikit National Institute of Child Health (Children's Hospital). Bangkok, Thailand: Desire; 2003: 98-9.
2. Kalayanarooj S, Osotkrapan S, Nimmannitya S. Abnormal elevation of hepatic transaminase in dengue hemorrhagic fever patients. In: Kalayanarooj S, editor. Studies/collaborative studies on dengue infections/dengue hemorrhagic fever at Queen Sirikit National Institute of Child Health (Children's Hospital). Bangkok, Thailand: Desire; 2003: 237-49.
3. Lum LC, Lam SK, George R, Devi S. Fulminant hepatitis in dengue infection. Southeast Asian J Trop Med Public Health 1993; 24: 467-71.
4. Nimmannitya S, Thisyakorn U, Hemsrichart V. Dengue haemorrhagic fever with unusual manifestations. Southeast Asian J Trop Med Public Health 1987; 18: 398-406.
5. Chan KP, Lau GK, Doraisingham S, Chan YC. Adult dengue deaths in Singapore. Clin Diagn Virol 1995; 4: 213-22.
6. Innis BL. Dengue and dengue hemorrhagic fever. In: Porterfield JS, editor. Exotic viral infections. New York: Chapman and Hall Medical; 1995: 103-46.
7. Laohapand T, Panchatikanond P, Malasit P, Myint KS, Innis B, Suvatte V. Histopathology and localization of dengue virus antigen in tissues of dengue hemorrhagic fever patients [abstract]. Southeast Asian J Trop Med Public Health 1990; 21: 707.
8. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. Trans R Soc Trop Med Hyg 2006; 100: 608-14.
9. Sumarmo, Wulur H, Jahja E, Gubler DJ, Suharyono W, Sorensen K. Clinical observations on virologically confirmed fatal dengue infections in Jakarta, Indonesia. Bull World Health Organ 1983; 61: 693-701.
10. Nogueira RM, Filippis AM, Coelho JM, Sequeira PC, Schatzmayr HG, Paiva FG, et al. Dengue virus infection of the central nervous system (CNS): a case report from Brazil. Southeast Asian J Trop Med Public Health 2002; 33: 68-71.
11. Kankirawatana P, Chokephaibulkit K, Puthavathana P, Yoksan S, Apintanapong S, Pongthapisit V. Dengue infection presenting with central nervous system manifestation. J Child Neurol 2000; 15: 544-7.
12. Garcia-Rivera EJ, Rigau-Perez JG. Encephalitis and dengue. Lancet 2002; 360: 261.
13. Pancharoen C, Thisyakorn U. Neurological manifestations in dengue patients. Southeast Asian J Trop Med Public Health 2001; 32: 341-5.
14. Angibaud G, Luaute J, Laille M, Gaultier C. Brain involvement in Dengue fever. J Clin Neurosci 2001; 8: 63-5.
15. Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LT, Raengsakulrach B, et al. Neurological manifestations of dengue infection. Lancet 2000; 355: 1053-9.
16. Nelson ER, Bierman HR, Chulajata R. Hematologic phagocytosis in postmortem bone marrows of dengue hemorrhagic fever. (Hematologic phagocytosis in Thai hemorrhagic fever). Am J Med Sci 1966; 252: 68-74.
17. Bierman HR, Nelson ER. Hematodepressive virus diseases of Thailand. Ann Intern Med 1965; 62: 867-84.
18. Na-nakorn S, Suingdumrong A, Pootrakul S, Bhamarapravati N. Bone marrow studies in Thai hemorrhagic fever. Bull World Health Organ 1966; 35: 54-5.
19. Nelson ER, Bierman HR, Chulajata R. Hematologic findings in the 1960 hemorrhagic fever epidemic (dengue) in Thailand. Am J Trop Med Hyg 1964; 13: 642-9.
20. Butthep P, Bunyaratvej A, Bhamarapravati N. Dengue virus and endothelial cell: a related phenomenon to thrombocytopenia and granulocytopenia in dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 1993; 24(Suppl 1): 246-9.
21. Wong KF, Chan JK, Chan JC, Lim WW, Wong WK. Dengue virus infection-associated hemophagocytic syndrome. Am J Hematol 1991; 38: 339-40.
22. Rueda E, Mendez A, Gonzalez G. Hemophagocytic syndrome associated with dengue hemorrhagic fever. Biomedica 2002; 22: 160-6.
23. Lu PL, Hsiao HH, Tsai JJ, Chen TC, Feng MC, Chen TP, et al. Dengue virus-associated hemo-

phagocytic syndrome and dyserythropoiesis: a case report. Kaohsiung J Med Sci 2005; 21: 34-9.
24. Ramanathan M, Duraisamy G. Haemophagocytosis in dengue haemorrhagic fever: a case report. Ann Acad Med Singapore 1991; 20: 803-4.
25. Veerakul G, Sanpakit K, Tanphaichitr VS, Mahasandana C, Jirarattanasopa N. Secondary hemophagocytic lymphohistiocytosis in children: an analysis of etiology and outcome. J Med Assoc Thai 2002; 85(Suppl 2): S530-4.

Hemophagocytic syndrome ในผู้ป่วยไข้เลือดออกซึ่งมีภาวะแทรกซ้อนรุนแรง ได้รับการรักษารอดชีวิตด้วย *pulse methyl predinsolone* และอิมมูโนโกลบูลิน *G* เข้าเส้นเลือดดำขนาดสูง

ถนอมศรี ศรีชัยกุล, สมพนธ์ บุณยคุปต์, เติมเกียรติ กาญจนภูมิ, เชาว์ กนกโอวาท, ครรชิต ลิขิตธนสมบัติ, อภิชัย ลีละสิริ

ได้รายงานผู้ป่วย หญิงไทย อายุ 46 ปี เป็นไข้เลือดออก dengue 2, ภาวะความดันโลหิตปกติ มีอาการแทรกซ้อนรุนแรง 4 ระบบ กล่าวคือ ตับ สมอง หัวใจ และปอด ผู้ป่วยมีระดับเม็ดเลือดน้อยตลอด มีภาวะเลือดแห้งกระจายไปทั่ว และ hemophagocytic syndrome ร่วมด้วย ทั้งหมดนี้เกิดขึ้นพร้อมกันในระยะพักฟื้น ผู้ป่วยได้รับการรักษาด้วย pulse methyl prednisolone ขนาด 1 กรัมต่อวัน เป็นเวลาสามวัน แต่อาการไม่ดีขึ้น จึงได้ให้ intravenous immunoglobulin G ขนาดสูง 1 กรัมต่อน้ำหนักตัวหนึ่งกิโลกรัม ต่อวัน x 2 วัน ผู้ป่วยรอดชีวิต และสามารถกลับบ้านได้ในวันที่ 17 หลังรับไว้ ผู้รายงานเชื่อว่า hemophagocytic syndrome เป็นกลไกที่สำคัญซึ่งทำให้เกิดภาวะแทรกซ้อนรุนแรงในผู้ป่วยรายนี้ ซึ่งสามารถรักษาให้รอดได้ด้วยวิธีการดังกล่าวข้างต้น ผู้รายงานได้เน้นว่า ในผู้ป่วย DHF ที่มีภาวะเม็ดเลือดน้อยตลอด และมีอาการแทรกซ้อนหลายระบบซึ่งพบมากขึ้นในปัจจุบันและมีอัตราตายสูง แพทย์ผู้รักษาควรนึกถึงภาวะแทรกซ้อนที่สำคัญคือ hemophagocytic syndrome ซึ่งเป็นกลไกสำคัญทำให้เกิดอาการแทรกซ้อนดังกล่าว แพทย์ควรรีบให้การวินิจฉัยและรักษาอย่างรวดเร็ว เพื่อให้ผู้ป่วยสามารถรอดได้