**Scholars Journal of Medical Case Reports (SJMCR)** **ISSN 2347-6559 (Online)**
***Abbreviated Key Title: Sch. J. Med. Case Rep.*** **ISSN 2347-9507 (Print)**

A United of Scholars Academic and Scientific Society, India

# Pulmonary Embolism Following Hemophagocytic Lymphohistiocytosis

**Hiromichi Ohsaka MD.PhD., Hiroki Nagasawa MD., Atsuhiko Shindo MD., Ikuto Takuchi MD., Kei Jitsuiki MD., Shunsuke Madokoro MD., Kento Sonoda MD., Kouhei Ishikawa MD.PhD., Kazuhiko Omori MD.PhD.,Youichi Yanagawa MD.PhD***
Department of Acute Critical Care Medicine, Shizuoka Hospital, Juntendo University, Izunokuni city, Shizuoka, Japan

***Corresponding author**
*Youichi Yanagawa*

**Article History**
*Received: 02.12.2018*
*Accepted: 13.12.2018*
*Published:30.12.2018*

**DOI:**
10.36347/sjmcr.2018.v06i12.014

**Abstract:** A 33-year-old man was struck by a car. Whole body computed tomography (CT) showed multiple injuries. After admission, he developed a high fever of unknown origin. He complicated with Enterobacter cloacae infection, following pulmonary and deep venous thrombosis in his right leg. Later, he was diagnosed with hemophagocytic lymphohistiocytosis (HLH). Finally, his general condition improved and he was transferred to a rehabilitation facility. This is the first report of a patient who developed pulmonary embolism followed by HLH as a complication of trauma. Overlapping enhanced inflammatory reactions caused by trauma, sepsis and PE may have induced HLH in the present case.
**Keywords**: Pulmonary embolism; sepsis; hemophagocytic lymphohistiocytosis.

## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) comprises a heterogeneous group of diseases that are characterized by a hyper-inflammatory state due to uncontrolled T cell, macrophage, and histiocyte activation, accompanied by excessive cytokine production [1]. HLH is associated with a high mortality rate, and the treatment itself is associated with significant morbidity and a risk of mortality [1, 2]. A high degree of suspicion for HLH is important, as early treatment and aggressive supportive care are critical for its management [2]. Pulmonary embolism (PE) can be also life threatening and difficult to diagnose as the signs and symptoms are not specific [3]. The complication of combined HLH and PE is extremely rare [4, 5]. We herein report a case of combined HLH and PE as complications after severe trauma.

## CASE REPORT

A 33-year-old man was struck by a car while walking in a drunken state. As he was unconscious, he was transported to our hospital by an ambulance. His past history included Sjögren's syndrome. A physical examination on arrival, revealed the following: Glasgow Coma Scale, 6; blood pressure, 150/90 mmHg; heart rate, 150 beats per minute (BPM); respiratory rate, 22 breaths per minute; oxygen saturation under 15 liters of oxygen by mask, 96%; and axillary temperature, 38.6 °C. He had bruising on his head, right ankle, hip, inguinal region and leg. The main results of a blood biochemical analysis are shown in Table-1. Whole body computed tomography (CT) showed traumatic subarachnoid hemorrhage, liver injury, mesenteric injury, right tibial fracture, pelvic fracture, left multiple rib fracture, left pulmonary contusion and left scapula fracture. He underwent tracheal intubation and mechanical ventilation under sedation, and was admitted to the intensive care unit. After admission, he developed a high fever of unknown origin; however, his consciousness and respiratory function improved and he was extubated on the 5th hospital day. Magnetic resonance imaging revealed left upper monoparesis. He was therefore diagnosed with left avulsion of the brachial plexus. His D-dimer level increased day by day; thus, a continuous infusion of heparin was started from the 7th hospital day (when transfusion was unnecessary) to prevent deep venous thrombosis. On the 10th hospital day, his temperature was >40°C and he was shivering. A blood culture revealed Enterobacter cloacae; he also had disseminated intravascular coagulation. He was therefore treated with antibiotics and antithrombin III product. His high fever was not controlled by these treatments. Cardiac echo, which was performed to evaluate the cardiac valves suggested pulmonary hypertension and enhanced CT revealed pulmonary and deep venous thrombosis in his right leg (Figure-1). He was negative for heparin-induced thrombocytopenia antibodies. Accordingly, heparin infusion was continued. On the 20th hospital day, a blood analysis revealed pancytopenia, a high level of ferritin and hemophagocytosis on smear preparation. He was therefore diagnosed with HLH (Figure-2). Steroids were not administered due to the presence of pulmonary embolism; however, the antibiotic was adjusted based on the drug sensitivity of the bacteria. After these managements, his inflammatory response, including his

body temperature and blood findings, gradually improved. Internal fixation was performed to treat his leg fracture and he developed a high fever again, which persisted for one week. This condition was also gradually improved by antibiotics. Finally, his general condition improved and he was transferred to a rehabilitation facility.

Enhanced CT revealed pulmonary and deep venous thrombosis (arrow) in the patient's right leg.

The smear preparation shows hemophagocytosis.

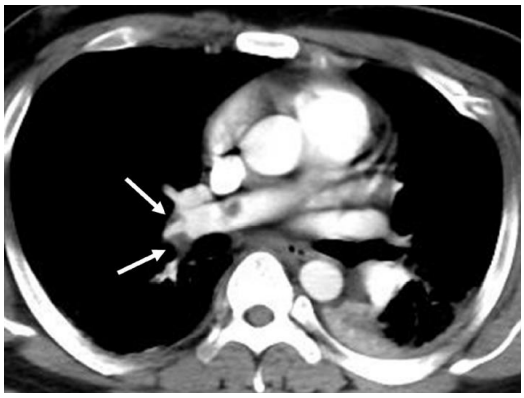

**Fig-1: Enhanced truncal computed tomography (CT)**

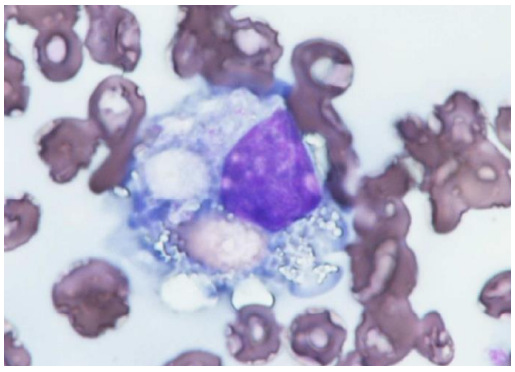

**Fig-2: Smear preparation**

**Table-1: Results of the blood and culture analyses**

| **Blood gas analysis: ($FiO_2$ 1.0)** | | |
|---|---|---|
| pH 7.207 | $PCO_2$ 37.2 mmHg | $PO_2$ 68.5 mmHg |
| $HCO_3^-$ 14.2 mmol/l | base excess -1.7 mmol/l | lactate 12.1 mmol/l |

**Cell blood count and biochemical analysis**

| | |
|---|---|
| White blood cells | 20,100/µl |
| Platelets | 24.6 x $10^4$/µl |
| Total bililbin | 0.5 mg/dl |
| Aspartate aminotransferase | 518 IU/l |
| Creatine phosphokinase | 2424 IU/l |
| Blood urea nitrogen | 18.3 mg/dl |
| Glucose | 197 mg/dl |
| Potassium | 4.5 meq/l |
| C-reactive protein | 0.21 mg/dl |
| Activated partial thromboplastin time | 29.3 (25.2) sec |
| Prothrombin time-international normalized ratio | 1.07 |
| Fibrinogen | 264 mg/dl |
| Hemoglobin | 16.3 g/dl |
| Total protein | 7.2 g/dl |
| Alanine aminotransferase | 190 IU/l |
| Amylase | 46 IU/l |
| Creatinine | 0.97 mg/dl |
| Sodium | 135 meq/L |
| Chloride | 98 meq/l |
| D-dimer | 41.7µg/ml |

**DISCUSSION**

This is the first report of a patient who developed PE followed by HLH. In the two previous reports on PE and HLH, the patients developed HLH first followed PE as a complication of steroid treatment for HLH [4, 5]. The cause of PE in the present case was bed rest, leg fracture and the delayed commencement of heparin infusion due to multiple injuries, in addition to direct or indirect endothelial injury of the leg [6]. Furthermore, the patient may have had a strong inflammatory response to the traumatic injury, which was probably based on immune system abnormalities because of his history of autoimmune disease and the presentation of a high fever soon after trauma. After

severe tissue injury, patients are known to be exposed to various danger- and microbe-associated molecular patterns, which provoke the strong activation of the neutrophil defense system [7-9]. Neutrophils trigger and modulate the initial posttraumatic inflammatory response and critically contribute to the subsequent repair processes [7]. However, severe trauma can affect the central neutrophil functions, including circulation half-life, chemokinesis, phagocytosis, cytokine release, and respiratory burst. Alterations in the neutrophil biology may contribute to trauma-associated complications, including immune suppression, sepsis, multi-organ dysfunction, and disturbed tissue regeneration [7]. Accumulating evidence suggests that the inflammatory response may be a cause, as well as consequence, of venous thromboembolism (VTE), including deep vein thrombosis (DVT), and pulmonary embolism [10]. Elevation of the C-reactive protein, IL-6, IL-8, and TNF-alpha levels during a response to systemic inflammation is reported to be associated with an increased risk of VTE [11]. Accordingly, a strong inflammatory response to trauma, after sepsis may accelerate VTE after PE, as was seen in the present case.

With regard to PE followed by HLH, PE can induce an inflammatory response. In addition, the present case showed a strong inflammatory response after trauma and was complicated by infection. Infection activates a cascade leading to the auto-amplification of cytokine production: the cytokine storm [12, 13]. These overlapping enhanced inflammatory reactions may have induced HLH in the present case. The treatment of HLH is designed to halt any underlying trigger and control the overactive immune system [14]. Additional immunosuppressive therapy should be initiated immediately in severe cases and in cases in which there is no response to disease-specific therapy after 2 to 3 days. As the inflammatory response and pancytopenia of the present case gradually improved with the adjustment of antibiotics, additional immunosuppressive therapy was not required.

## CONCLUSION

This is the first report of a patient who developed PE followed by HLH as a complication of trauma. Overlapping enhanced inflammatory reactions caused by trauma, sepsis and PE may have induced HLH in the present case.

## ACKNOWLEDGEMENTS

This work received funds from the Ministry of Education, Culture, Sports, Science and Technology (MEXT)-Supported Program for the Strategic Research Foundation at Private Universities, 2015-2019. The title is [The constitution of total researching system for comprehensive disaster, medical management, corresponding to wide-scale disaster].

## Conflict of Interest

The authors declare no conflicts of interest in association with the present study.

## REFERENCES

1. Tothova Z, Berliner N. Hemophagocytic syndrome and critical illness: new insights into diagnosis and management. Journal of intensive care medicine. 2015 Oct;30(7):401-12.
2. Mehta RS, Smith RE. Hemophagocytic lymphohistiocytosis (HLH): a review of literature. Medical Oncology. 2013 Dec 1;30(4):740.
3. Meyer G. Effective diagnosis and treatment of pulmonary embolism: Improving patient outcomes. Archives of cardiovascular diseases. 2014 Jun 1;107(6-7):406-14.
4. Hannebicque-Montaigne K, Le AR, Launay D, Coulon C, Deruelle P, Langlois S. Haemophagocytic syndrome in pregnancy: a case report. InAnnales francaises d'anesthesie et de reanimation 2012 Mar (Vol. 31, No. 3, pp. 239-242).
5. Hisano M, Sugawara K, Tatsuzawa O, Kitagawa M, Murashima A, Yamaguchi K. Bacteria-associated haemophagocytic syndrome and septic pulmonary embolism caused by Burkholderia cepacia complex in a woman with chronic granulomatous disease. Journal of medical microbiology. 2007 May 1;56(5):702-5.
6. Leone M, Boutière B, Camoin-Jau L, Albanèse J, Horschowsky N, Mège JL, Martin C, Dignat-George F. Systemic endothelial activation is greater in septic than in traumatic-hemorrhagic shock but does not correlate with endothelial activation in skin biopsies. Critical care medicine. 2002 Apr 1;30(4):808-14.
7. Kovtun A, Messerer DA, Scharffetter-Kochanek K, Huber-Lang M, Ignatius A. Neutrophils in Tissue Trauma of the Skin, Bone, and Lung: Two Sides of the Same Coin. Journal of immunology research. 2018;2018.
8. Vourc H, Mickael A, Roquilly A, Asehnoune K. Trauma-induced DAMP-mediated remote organ injury and immunosuppression in the acutely ill patient. Frontiers in Immunology. 2018;9:1330.
9. Hauser CJ, Otterbein LE. Danger signals from mitochondrial DAMPS in trauma and post-injury sepsis. European Journal of Trauma and Emergency Surgery. 2018:1-8.
10. Branchford BR, Carpenter SL. The Role of Inflammation in Venous Thromboembolism. Frontiers in pediatrics. 2018;6.
11. Watts JA, Gellar MA, Stuart LK, Obraztsova M, Kline JA. Proinflammatory events in right ventricular damage during pulmonary embolism: effects of treatment with ketorolac in rats. Journal of cardiovascular pharmacology. 2009 Sep 1;54(3):246-52.
12. Giamarellos-Bourboulis EJ. Failure of treatments based on the cytokine storm theory of sepsis: time for a novel approach. Immunotherapy. 2013 Mar;5(3):207-9.

13. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. InSeminars in immunopathology 2017 Jul 1 (Vol. 39, No. 5, pp. 517-528). Springer Berlin Heidelberg.
14. Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood. 2015 Jan 1:blood-2015.