Case report

Hemophagocytic Syndrome with Fulminant Multi-organ Failure after Tasting Raw Monkfish Liver: The Patient Survived by Immunomodulators and Plasma Exchange Therapy

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Abstract : *A Thai male 38 year old had tasted raw liver prepared from Japanese monkfish 16 days prior to development of fever, marked edema, massive pleural effusion and ascites associated with acute oliguric renal failure. Hemophagocytic syndrome was diagnosed by severe progressive anemia, thrombocytopenia, plenty of degenerative megakaryocytes and hemophagocytosis along with severe liver failure, as shown by deep jaundice, as well as acute oliguric renal failure. The patient received methylprednisolone and intravenous immunoglobulin G without a benefit in the first course. The second course was given along with daily plasma exchange 2-2.5x plasma volumes/day for 7 days and daily hemodialysis for 10 days. He gradually improved on day 6th of the extensive treatment. Late disseminated intravascular coagulation detected on the basis of progressive anemia, thrombocytopenia and increased D-Dimer was successfully treated by low dose intravenous heparin therapy. This is the first case of nearly fatal hemophagocytic syndrome following raw monkfish liver ingestion. Since the complications are very severe, the health authority should inform the public about the real danger of ingested unusual food wrongly believed to be of health benefit.*

Key Words : ● *Hemophagocytic syndrome* ● *Raw monkfish liver* ● *Plasma exchange* ● *Immunomodulator* ● *Disseminated intravascular coagulation*

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Hemophagocytic syndrome is characterized by fever, cytopenia, multi-organ failure, disseminated intravascular coagulation with a high fatality rate of over 70 percent. Two major etiologic disorders were reported: first - lymphoid malignancy and second - mostly from infectious diseases including virus, bacteria, fungus and protozoa. In Thailand, this syndrome is common, but only few cases were reported. They are caused by malignant lymphoma, Epstein-Barr virus (EBV)[2,3] and dengue hemorrhagic fever[4]. At present, with early diagnosis and effective management, the majority of patients survived.

The purpose of this report is to present a near fatal hemophagocytic syndrome patient, following tasting of raw monkfish liver, with emphasis on the diagnosis and effective management and, finally, the danger of ingestion of unusual food falsely believed to be of health benefit. This article is approved by the ethic committee of Vichaiyut hospital

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Report of the patient

The patient was a 38-year-old male admitted to Vichaiyut hospital on 19 January 2011. Five weeks

before the admission (14 December 2010), he traveled to Taiwan and tasted raw monkfish liver, but he felt that it was very bitter and did not eat it. Twelve days later he had low grade fever for 5 days followed by high fever for 5 days. Therefore, he was admitted in the first hospital (31 December 2008) with high fever and pleural effusion was found. Laboratory investigations showed hematocrit 40.5%, white blood count 23.13 x 10^9/L with neutrophil 85%, platelet 308 x10^9/L, blood urea nitrogen (BUN) 12 mg/dL (7-20 mg/dL), SGOT 15 u/L (5-35 u/L), albumin 4.7 g/dL (3.5-5.0 g/dL), globulin 2.25 g/dL (2.3-3.5 g/dL).

He was treated as a case of infectious disease without improvement. Therefore, he moved to the second hospital on 7 January 2009. Physical examination revealed high fever, generalized edema, dyspnea, pleural effusion and ascitis. Examination of pleural and ascitic fluid revealed white blood cells of 20 x10^9/L with 96% neutrophil. Culture from the fluids and blood was negative. Many antibiotics were given without improvement. Five days later, BUN was 89 mg/dL, hematocrit 29%, platelets 90 x10^9/L, white blood count 19.0 x10^9/L with 96% neutrophil. A hematologist was consulted. The diagnosis was hemophagocytic syndrome as evidenced by a plenty of megakaryocytes and hemophagocytosis in the bone marrow smear. He received methylprednisolone 1 g intravenous per day for 3 days and intravenous immunoglobulin G (IVIG) 1 g per kg body weight for 2 days but there was no improvement. Laboratory findings showed serum albumin 1 g/dL, globulin 3.2 g/dL, B_1C 75 mg/dL (88-252 mg/dL) and negative anti-Dengue IgM.

The patient still had high fever, anasarca and more dyspnea. Five days later, BUN rose to 149 mg/dL and hemodialysis was performed but no improvement. Two days later, he developed deep jaundice, direct bilirubin 5.7 mg/dL (0-0.2 mg/dL) and total bilirubin 9 mg/dL (0.2-1.2 mg/dL), SGOT 2181 u/L (5-35 u/L), SGPT 766 u/L (0-40 u/L), LDH 1599 u/L (150-450 u/L). Plasmapheresis was performed and the patient was transferred to Vichaiyut hospital on 19 January 2009.

Physical examination showed blood pressure 110/90 mmHg, pulse 120/minutes, temperature 38°C, respiration 30/minute, orthopnea, deep jaundice, anasarca, lethargy, petechial spots both upper and lower extremities. Chest examination showed decreased breath sound right lower lobe. There was massive ascites. Liver and spleen were not palpable due to massive ascites.

Laboratory investigations revealed Hct 26%, white blood count 12.7 x10^9/L, neutrophil 96%, platelet 12 x10^9/L, PTT 39 second (25-35 sec), PT 21.7 seconds (INR 1.8), Direct and indirect Coombs' test: negative, LDH 1017, serum ferritin 4,160 ng/ml (15-450 ng/ml), SGOT 219 u/L, SGPT 185 u/L, GGT 627 u/L (8-78 u/L), Alkaline phosphatase 556 u/L (40-120 u/L), albumin 3.1 g/dL, globulin 1.9 g/dL, direct bilirubin 11.5 mg/dL, total bilirubin 13.4 mg/dL, BUN 104 mg/dL, Cr 2.8 mg/dL (0.5-1.0 mg/dL), 24-hour urine protein 4.4 g.

Chest X ray showed loculated pleural fluid over right minor fissure (Figure 1a). Ultrasonography of whole abdomen disclosed ascites and 14-cm splenomegaly. Echocardiogram was normal.

Polymerase chain reactions (PCR) for Dengue, Chickungunya and Epstein-Barr virus in serum were negative. Dengue antibody titer IgG 1: 40, IgM negative. CMV IgM negative, IgG 1: 1286. IgM antibodies to typhus, mycoplasma, toxoplasmosis and rickettsia were negative. Anti-nuclear antibody (ANA) profile: negative, rheumatoid factor: negative, protein electrophoresis: normal.

The patient progression and treatments are summarized in figure 2. Since the first day of admission, plasma exchange using 15-20 units of fresh frozen plasma (2-2.5 of plasma volume) was performed daily for 7 days, along with hemodialysis in order to take the body fluid out between 500-3000 ml per day for 10 days. Platelet transfusion was given after plasma exchange or hemodialysis. The patient was markedly improved as shown by decreased dyspnea, ascites and jaundice. However, he still had high fever, intravenous methylprednisolone 1 g daily for 3 days and intravenous IVIG G 1 g/kg body weight for 2 days were given on the fourth day of admission.

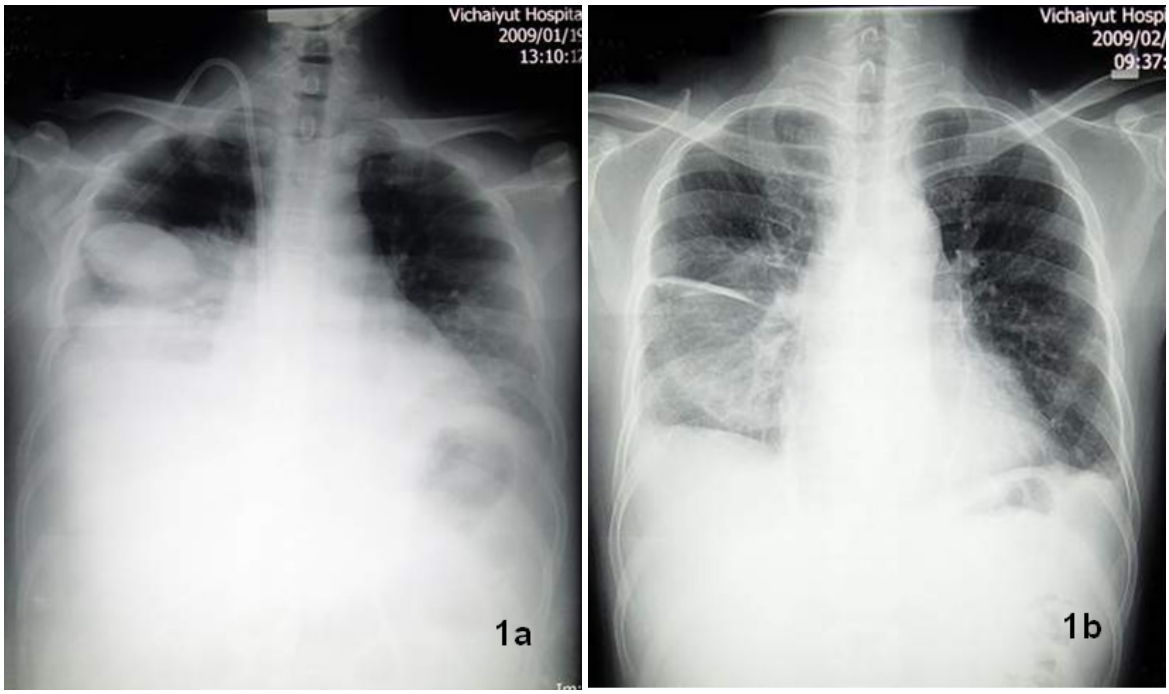

Figure 1a Loculated pleural fluid over right minor fissure (19 January 2010)

1b Small fluid in right minor fissure (16 February 2010)

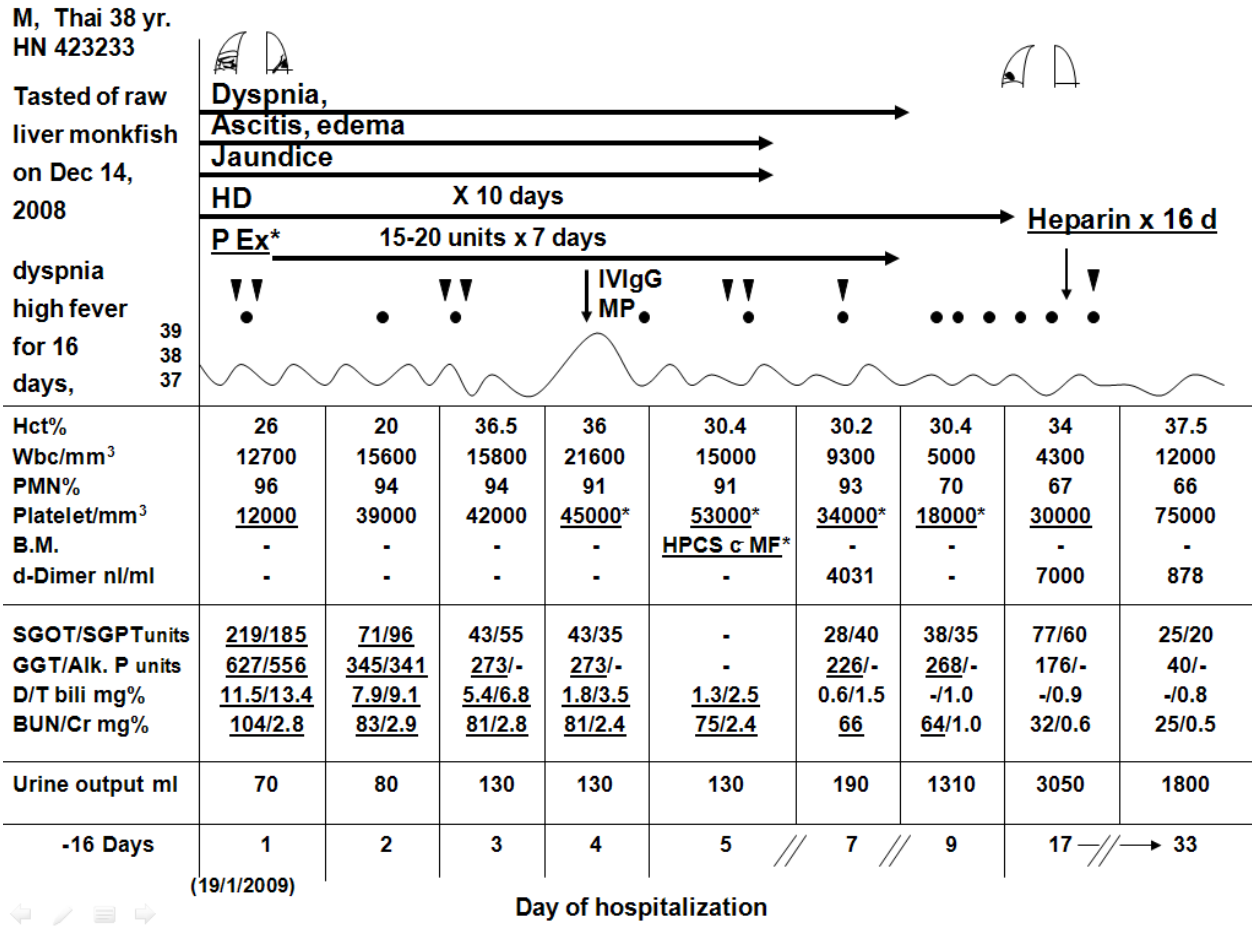

Figure 2 The Course of illness after admission at Vichaiyut hospital

MF = myelofibrosis; HPCS = Hemophagocytic Syndrome; bili = bilirubin, ▼ = red blood cells; ● = single donor platelet; HD = hemodialysis; PEx = plasma exchange

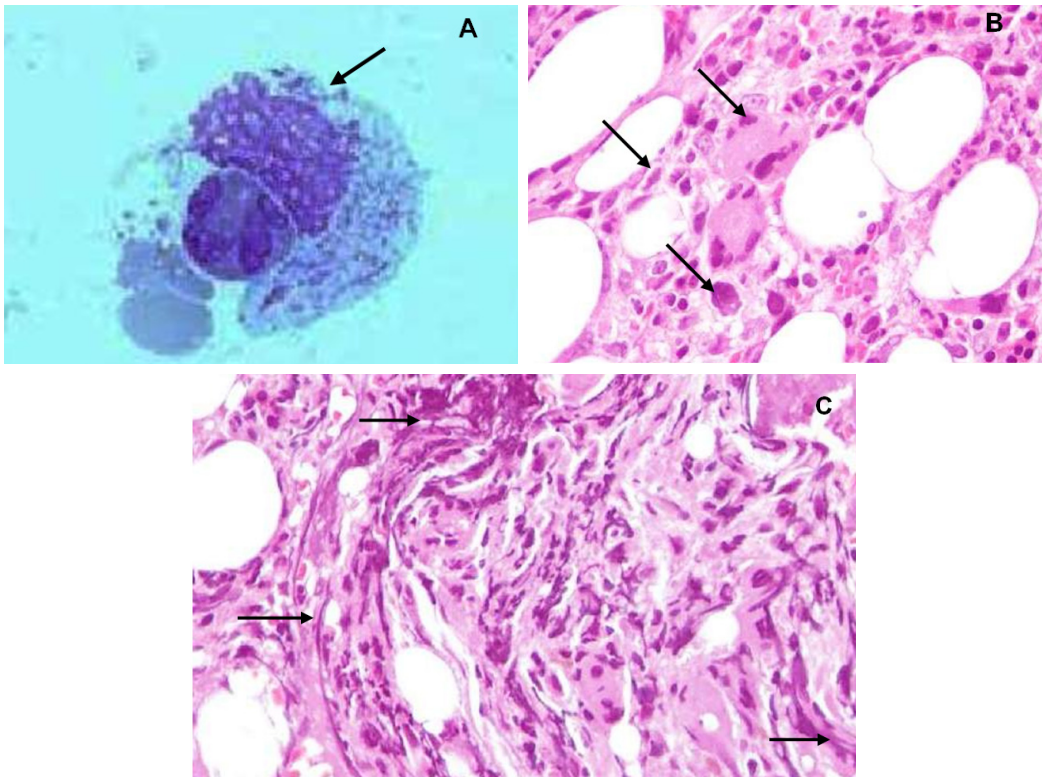

Figure 3 Bone marrow showing hemophagocytosis (**A**), many megakaryocytes (**B**) and early myelofibrosis (**C**)

Fever gradually came down to normal. Repeated bone marrow examination on the fifth day of admission revealed hemophagocytosis and a plenty of hematopoietic cells including megakaryocytes with early myelofibrosis (Figure 3 a-c).

Two days after discontinuation of plasma exchange, severe thrombocytopenia was detected followed by anemia, D-Dimer was increased from 4,031 ng/mL to 7,000 ng/mL (< 500 ng/mL). Platelet antibody (anti-human leukocyte antigen-HLA) was negative. Chronic disseminated intravascular coagulation (DIC) was diagnosed, intravenous unfractionated, heparin was given 9 u/kg body weight/hour for 16 days. CBC one day before discontinuation of heparin showed hematocrit 37.5%, WBC 12.0 $x10^9$/L, neutrophil 66% lymphocytes 34%, platelet 75 $x10^9$/L and D-Dimer 278 ng/mL.

The patient improved markedly. He became afebrile, good appetite and no dyspnea. Urine output was over 3,000 mL per day. The SGOT, SGPT, GGT and creatinine results were normal. The remaining problems were mild anemia, thrombocytopenia and proteinuria, which must be followed up.

Discussion

At present, there are many reports emphasizing on side effects from the ingestion of raw viscera, particularly liver and gall bladder, of calf fish. These reports were from Taiwan, Hong Kong, Korea, Japan, U.S.A, India, Vietnam and Thailand.[5-15] The typical symptoms after ingestion of the raw fish liver are nausea, vomiting, diarrhea within few hours following by hyperkalemic oliguria and edema within few days, as well as acute hepatic failure. However, there has been no report of hemophagocytic syndrome following the intake of these materials.

This patient presented with the syndrome, which can go along with the severe illness after the ingestion of raw liver of monkfish that is in the same family of calf fish. The first differential diagnosis at the beginning was dengue hemorrhagic fever. However, this is excluded by negative dengue studies and the prolonged clinical course. The important features consisted of hemophagocytic syndrome. The bone marrow showed hemophagocytosis, numerous degenerative dysplastic megakaryocytes, myelofibrosis, severe leakage of fluid into

pleural space, ascites and acute liver failure as shown by hyperbilirubinemia as high as 13.4 g/dL, which indicated very poor prognosis. All of these findings are derived from severe ineffective hyperimmune reaction leading to stimulation of macrophage and T lymphocyte resulting in cytopenia and massive release of many cytokines.

It should be noted that the patient did not respond to the first course methylprednisolone and immunoglobin G because of severe massive hypercytokinemia. Plasma exchange to remove the cytokines and toxin along with hemodialysis combined with second course of methylprednisoline and intravenous immunoglobulin G save life of this patient.

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รายงานผู้ป่วย

Hemophagocytic Syndrome ร่วมกับหลายอวัยวะเสียหน้าที่รุนแรงหลังจากการชิมตับปลา Monkfish ดิบ : ผู้ป่วยรอดชีวิตจากการให้ยากดภูมิต้านทานและการเปลี่ยนถ่ายพลาสมา

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บทคัดย่อ : *ผู้ป่วยชายไทย อายุ 38 ปี ได้ชิมตับดิบของปลา Monkfish (ตระกูลเดียวกับปลาคาร์ฟ) และเกิด hemophagocytic syndrome อย่างรุนแรง โดยมี ไข้สูง อาการบวมทั้งตัว มีน้ำในช่องปอดและช่องท้อง หอบเหนื่อยมาก และไตวาย ผลเลือดตรวจพบภาวะซีดฉับพลัน ร่วมกับเกล็ดเลือดต่ำ ผลไขกระดูกพบ hemophagocytosis, degenerative megakaryocytes จำนวนมาก และ early myelofibosis ผู้ป่วยได้รับการรักษาด้วย methylprednisolone และ intravenous immunglobulin G แต่อาการไม่ดีขึ้น ต่อมามีตับวายเฉียบพลัน มีดีซ่าน bilirubin สูงมากถึง 13.4 มก/ดล มีไตวายเฉียบพลันร่วมกับปัสสาวะออกน้อยจึงได้รับการเปลี่ยนถ่ายพลาสมาปริมาณ 2-2.5 ปริมาตรพลาสมาของผู้ป่วยต่อวัน เป็นเวลา 7 วัน และทำ hemodialysis ดึงน้ำออก เป็นเวลา 10 วัน ผู้ป่วยอาการดีขึ้น ไม่หอบ บวมและเหลืองน้อยลง แต่ยังมีไข้สูงจึงได้รับ methylprednisolone และ intravenous immunoglobulin อีกหนึ่งครั้ง พบว่าไข้ลงและอาการดีขึ้นเป็นลำดับ ต่อมาผู้ป่วยซีดลง เกร็ดเลือดต่ำ และ D-Dimer ขึ้นสูงถึง 7000 นก/ดล ได้รับการวินิจฉัยว่าเป็น disseminated intravascular coagulation จึงได้รับการรักษาด้วยเฮปารินขนาดต่ำทางหลอดเลือดดำเป็นเวลา 16 วัน ผลเลือดปรากฏว่าอาการซีดและระดับเกร็ดเลือดดีขึ้น อาการทางไตและทางตับดีขึ้นเป็นลำดับ รวมระยะเวลาที่เกิดอาการไข้และภาวะแทรกซ้อนต่างๆ และได้รับการรักษาจนดีขึ้น 49 วัน รายงานนี้ได้แสดงให้เห็นว่าพิษจากตับดิบของปลา Monkfish มีความรุนแรงมากทำให้เกิด hemophagocytic syndrome และ อวัยวะหลายอันเสียหน้าที่ผู้ป่วยรอดชีวิตจากการรักษาด้วย methylprednisolone, intravenous immunoglobulin การเปลี่ยนถ่ายพลาสมาจำนวนมาก และการทำ hemodialysis*

Key Words : ● *Hemophagocytic syndrome* ● *ตับปลา Monkfish ดิบ* ● *การเปลี่ยนถ่ายพลาสมา* ● *ยากดภูมิต้านทาน* ● *Disseminated intravascular coagulation*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2554;21:261-6.