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

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 ascites. 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 investigations showed serum albumin 1 g/dL, globulin 3.2 g/dL, B,C 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.
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Figure 1a Loculated pleural fluid over right minor fissure (19 January 2010)

Figure 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
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.\(^5\)\(^-\)\(^10\) 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

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**Figure 3** Bone marrow showing hemophagocytosis (A), many megakaryocytes (B) and early myelofibrosis (C)
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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 methylprednisolone and intravenous immunoglobulin G save life of this patient.

References


รายงานผู้ป่วย

Hemophagocytic Syndrome ร่วมกับหลายอวัยวะเสียหายหน้าที่รุนแรงหลังจากการชิมตับปลา Monkfish ดิบ: ผู้ป่วยรองศีรษิตวิชาจากการให้ยากดภูมิต้านทานและการเปลี่ยนถ่ายพลasma

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บทคัดย่อ: ผู้ป่วยชายไทย อายุ 38 ปี ได้รับการรักษา darm ตับปลา Monkfish (ครอบคลุมเดียวกับปลาคาร์ฟ) และเกิด hemophagocytic syndrome อย่างรุนแรง โดยมีไข้สูง อาร์เม่อทั้งตัว มีน้ำในช่องปอดและช่องท้อง หอบเหนื่อยมาก และไตวาย ผลเลือดตรวจพบภาวะซีดฉับพลัน ร่วมกับเกล็ดเลือดต่ำ ผลไขกระดูกพบ hemophagocytosis, degenerative megakaryocytes จำนวนมาก และ early myelofibrosis ผู้ป่วยได้รับการรักษาด้วย methylprednisolone และ intravenous immunoglobulin G แต่อาการไม่ดีขึ้น ต่อมาจึงมีการเปลี่ยนถ่ายพลาสมา ผู้ป่วยมี bilirubin สูงถึง 13.4 มก/ดล มีภาวะแทรกซ้อนอื่น ๆ ได้รับการเปลี่ยนถ่ายพลasma จำนวน 2-2.5 ปริมาตรพลาสมาของผู้ป่วยต่อวัน เป็นเวลา 7 วัน และทำา hemodialysis ทั้งน้อยเพิ่มเวลา 10 วัน ผู้ป่วยอาการดีขึ้น แต่ยังมีภาวะแทรกซ้อนต่อ นำไปสู่การสิ้นสุดในเวลา 16 วัน ผลเลือดตรวจพบภาวะแทรกซ้อนต่อ อาการกระดูกอาการแทรกซ้อนและภาวะแทรกซ้อนมีการหายลง รวมระยะเวลาที่เกิดอาการไข้และภาวะแทรกซ้อนต่าง ๆ ผู้ป่วยมีภาวะแทรกซ้อนต่าง ๆ ได้รับการรักษาการเปลี่ยนถ่าย 49 วัน รายละเอียดรายละเอียดที่สั้นกว่าพิจารณาต่อเนื่องจากตัวอย่างของปลา Monkfish มีความรุนแรงมากที่เกิด hemophagocytic syndrome และ อวัยวะหลายอวัยวะเสียหายหน้าที่ต่อเนื่องจากภาวะแทรกซ้อนการรักษาด้วย methylprednisolone, intravenous immunoglobulin การเปลี่ยนถ่ายพลasma และการทำา hemodialysis

Key Words : 1 Hemophagocytic syndrome 2 ตับปลา Monkfish 3 การเปลี่ยนถ่ายพลasma 4 ยากดภูมิต้านทาน 5 Disseminated intravascular coagulation