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Acuta Fulminant B Hepatitis with Encephalopathy: A Case Report

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Abstract: ***A male, 41 years old complaint of weakness, nausea, vomiting and yellowish eyes a week prior to admission .lab result revelaed increased of SGOT and SGPT. Positive HBs Ag detection and hepatomegaly on ultrasonography. The patient was managed as acuta fulminant B hepatitis as a protocol, but unfortunately the patient death due to encephalopathy hepatic and shock septic.***

Keywords: fulminant hepatitis, acuta liver failure, icterus

1. Introduction

Acute liver failure (ALF) is a condition wherein the previously healthy liver rapidly deteriorates, resulting in jaundice, encephalopathy, and coagulopathy. There are approximately 2000 cases per year of ALF in the United States. Viral causes (fulminant viral hepatitis) are the predominant cause of ALF in developing countries. Fulminant hepatitis (FH) is a rare but devastating disease, often affecting young individuals, despite recent therapeutic advances, is associated with significant morbidity and mortality. Fulminant hepatic failure is characterized by the development of severe liver injury with impaired synthetic capacity and encephalopathy in patients with previous normal liver or at least well compensated liver disease. The etiology of fulminant hepatic failure refers to a wide variety of causes, of which toxin induced or viral hepatitis are most common. The two most common causes of death in patients with ALF (Acuta liver Failure) are cerebral oedema and multi organ system failure. These events are precipitated by the systemic inflammatory response syndrome (SIRS), which is medi-ated by release of pro-inflammatory cytokines such as: tumour necrosis factor-α, interleukin (IL)-1β, and IL-6. We report one death case with acuta fulminant B Hepatitis with encephalopathy hepatic.

2. Case Presentation

A male 41 years old, Balinese, complaint of weakness since 1 week prior to admission. Nausea and vomiting also present. The patient said become yellowish on the eyes since three days prior to admission and also the urine colour become brownish as a tea. Patients also complained of discomfort in the upper right abdomen since 3 days before admission. Fever and cough were denied. There were disturbance of sleeping since one week. History of heart disease, liver, lung, kidney, diabetes, hypertension were denied. No family history have the same problem before. No history of takong alcohol and no history of blood transfusion before.

On physical examination, we found the vital sign were normal, icteric on the both sclera of the eyes. No abnormality detected on pulmo and hearth. Tenderness on the abdominal region on the upper right quadran. The liver was palpable 3 cm below arcus costae and 3cm below of processus xiphoideus. Extremities were normal.

Laboratory result revealed the cell blood count: Hemoglobin: 14,3 gr/dL, WBC: 14,8x 10^3/uL, PLT: 77x $10^{3/}$uL, Fasting Blood sugar: 57 mg/ dL, Blood sugar ad random: 182 mg/ dL, renal function test were normal (BUN: 33 mg/ dL, creatinin serum: 0,9 mg/dL), liver function test: albumin: 2,5 g/dL, globulin: 5,0 g/dL, total bilirubin: 29,52 mg/dL, direct bilirubin: 26,6 mg/dL, indirect bilirubin: 2,92 mg/ dL, Alkali Phosfatase: 148 U/L, Gamma GT: 90 U/L, SGOT: 121 U/L, SGPT:1156 U/LViral marker (Anti HCV: negative, HBsAg: Positive). Result of the abdominal ultrasonography was hepatomegaly.

The patient was diagnosed with: acuta fulminant B hepatitis with grade 1encephalopathy hepaticum. The therapy were: IVFD NaCl 0,9%: aminoleban: D5% 1:1:1 20 drop per minute, antiviral lamivudin 1x150 mg, esomeprazol 1x40 mg, ondancetron 4 mg TID, curcuma 1 tab TID, lactulosa TID, hepamerz 4 ampules within 500cc NaCl 0,9% 20drops per minute, and antibiotic ceftriaxon 2x1 gram.Unfortunately the patient getting worst and death due to encephalopathy hepaticum and septic shock.

3. Discussion

Fulminant hepatitis (FH) is a rare but devastating disease, often affecting young individuals, despite recent therapeutic advances, is associated with significant morbidity and mortality. Fulminant hepatic failure is characterized by the development of severe liver injury with impaired synthetic capacity and encephalopathy in patients with previous normal liver or at least well compensated liver disease. The etiology of fulminant hepatic failure refers to a wide variety of causes, of which toxin induced or viral hepatitis are most common.[1]

Hepatitis B is probably the most common viral cause of FHF and the incidence may be underestimated, since precore or pre-S mutant viruses may escape by routine serology. The overall incidence varies widely in different reports, again reflecting the overall incidence of viral hepatitis in different geographic regions. Since there is evidence, that new antiviral treatment strategies against HBV may avoid fatal liver failure, the reduced possibility of complete immune response leading to elimination of HBV, led to an ongoing controversy of the initiation of antiviral.Prior to transplantation, most series suggested a less than 15% survival in patients with FH. Currently, the overall short-

term survival (one year) including those undergoing transplantation is greater than 65%.[2]

The Practice Guideline Committee of the American Association for the Study of Liver Diseases(AASLD)defines acute liver failure as "liver disease characterized by the development of hepatic encephalopathy and coagulation abnormalities, usually an international normalized ratio (INR) of ≥1.5 or more, in patients without pre-existing cirrhosis, and an illness of <26 weeks duration". The most frequent causes of acute liver failure worldwide include viral hepatitis [particularly hepatitis A virus (HAV) and hepatitis B virus (HBV)], medication overdose (in particular paracetamol), idiosyncratic drug reactions, ingestion of toxins, and metabolic disorders. According to the European Liver Transplantation Registry, the most common causes of transplanted FH be- tween 1972 and 2007 were viral causes (HAV: 1%; HBV: 15%), paracetamol overdose (8%), non-paracetamol drug overdose (11%), indeterminate causes (48%), and other causes (17%). (*European Liver Transplant Registry*. In another survey carried out in the United States between 1998 and 2008, the major aetiologies of ALF in 1147 patients were paracetamol overdose (46%) followed by indeterminate causes (14%), drug-related ALF (11%), HBV (7%), other causes (7%), autoimmune hepatitis (AIH; 5%), ischemic hepatitis (4%), HAV (3%), and Wilson's disease (2%). [4,5]

Table 1: The causes of fulminant hepatitis.[6]

Table 2. Causes of fulminant hepatitis.

Viral	**Hepatitis A, B, C, D, E, CMV HSV, EBV**
Toxic dose-dependent	**Acetaminophen (paracetamol)**, Isoniazid, Tetracycline, Methotrexat, Carbon tetrachloride, Amphetamins, **Amanita phalloides-Toxin**
Metabolic	**M. Wilson**, alpha-1-AT-deficiency, Galactosemia, Tyrosinemia, Reye-Syndrome
Vascular	**Budd-Chiari-Syndrome**, veno-occlusive disease, shock, heart failure
Miscellanous	**Autoimmune-hepatitis**
Associated with pregnancy	HELLP Syndrome

Note. The bold font indicate the main causes of fulminant hepatitis. CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; EBV Epstein-Barr Virus.

The two most common causes of death in patients with ALF are cerebral oedema and multiorgan system failure. These events are precipitated by the systemic inflammatory response syndrome (SIRS), which is mediated by release of pro-inflammatory cytokines such as: tumour necrosis factor-α, interleukin (IL)-1β, and IL-6. These SIRS mediators contribute to cerebral oedema by decreasing cerebrovascular tone thus, causing cerebral hyperperfusion. Although a compensatory anti-inflammatory response syndrome mediated by antiinflammatory cytokines (IL-4, IL-10, transforming growth factor-β) exists concomitantly in patients with ALF to dampen the SIRS, this persistent compensatory anti-inflammatory response syndrome may not be beneficial as it can lead to sepsis and late mortality.[7]

In our case, the causa of mortis was encephalopathy hepaticum and septic shock. ALF is therefore the clinical syndrome that results from pro and antiinflammatory cytokines spilling into the systemic circulation from the liver. The accumulation of proinflammatory substances in hepatic failure results in neurological abnormalities, aggravation of injury to the liver/other organs, suppression of the ability of residual hepatocytes to perform organ-specific functions (sick cell syndrome), and inhibition of the hepatic regenerative response.

4. Management

The survival of patients with acute liver failure has improved over time because of early disease recognition and better intensive care management. Despite this, mortality remains high without liver transplantation and exceeds 80% in the most severe cases. Patient outcome is often determined by the severity and number of organ failure. Cerebral oedema represents an important cause of death in patients with ALF. Although its incidence may be declining, up to 25% of patients are still succumbing to the sequelae of intracerebral hypertension. Patients with progressive encephalopathy, grade III or IV, require intubation and sedation as high-grade encephalopathy usually occurs as a consequence of cerebraledema. The pathogenesis of cerebral oedema in patients with ALF appears to be multifactorial. Prolonged time periods of cerebral perfusion pressure (CPP) < 50 mmHg or an intracranial pressure (ICP) of >40 mmHg are associated with a poor neurological outcome. CPP below 40 mmHg for more than 2 hours was considered a contraindication for liver transplantation; however, a case series of four patients with refractory ICP elevation above 35 mmHg and CPP below 50 mmHg who made a full neurological recovery contradicted previous findings. [6,8,9]

The management of patients with FHF requires a thorough infrastructure and understanding to deal with the complications that may be present, including renal failure, circulatory dysfunction, coagulopathy, gastrointestinal bleeding, encephalopathy, cerebral edema and metabolic disturbances like metabolic acidosis and hypoglycemia. In the course of these complexities, patients with FHF should be managed in an intensive care unit and should be transferred as soon as possible to centers with a liver transplant program. Liver transplantation remains the main promising option of treatment of FHF. However, depending on the etiology, specific therapies may be used. For example, N acetylcysteine can significantly improve prognosis of patients with acetaminophen intoxication. Other interventions may be helpful in other specific settings as: forced diuresis, silibilin and activated charcoal in patients with amanita phalloides poisoning. Due to the development of new antiviral medication Hepatitis B virus infection can be treated even in the acute phase. Acyclovir may improve prognosis in patients with herpes virus infection and FHF.

Transjugular intrahepatic portosystemic stent shunt is the treatment of choice in patients presenting with FHF due to acute Budd-Chiari syndrome. Liver support systems that substitute in part the functions including detoxification and homeostasis of metabolism have been developed and tested. In our case, we give the hepamerz to maintenance the hemostasis between aromatic amino acid and branch chain amino acid balances that may improve the encephalopathy hepatic. The efficacy has been demonstrated in only a small number of patients. [2]

Acute and severe acute hepatitis is not an indication for liver transplantation. However, patients may progress to fulminant hepatitis/acute liver failure. Thus, patients must be monitored for signs of recovery versus deterioration. Basically, the prognosis of fulminant hepatitis depends on halting further cell damage and on the ability of the hepatocytes to replicate, thereby resulting in liver regeneration. Regeneration is likely to decrease with age and history of prior damage to liver cells. This explains, why a higher risk of death is observed in older patients with acute hepatitis and in those with a preexisting underlying liver disease. Prognosis deteriorates dramatically once hepatic encephalopathy sets in. Conventional orthotopic liver transplantation is the only proven therapy for patients with severe fulminant hepatitis when they progress to liver failure indicated by hepatic encephalopathy and fulfil King's College Criteria: INR >6.5 or 3 of the following 4 criteria: (1) patient age <11 or >40 years, (2) serum bilirubin >300 µmol/l, (3) time from onset of jaundice to the development of coma of >7 days, and/or (4) INR >3.5.Fulminant liver failure due to HBV is rare, but it has a high mortality rate and poor prognosis for the patient. The mortality rate is even higher when there is co-infection with hepatitis D virus (HDV). A large inoculum is associated with a shorter incubation period than with other fulmi- nant liver failure. In contrast, a quick immune response is more closely related to the development of fulminant liver failure than to increased viral replication [10-13]

Table 2: King's College criteria for selecting recipient of emergency liver transplants.[14]

Table 2 King's College criteria for selecting recipients of emergency liver transplants

Acetaminophen-induced ALF	Non-acetaminophen-induced ALF
Strongly recommended list for OLT if:	List for transplantation if:
Arterial lactate > 3.5 mmol/L after early fluid resuscitation	INR > 6.5 and encephalopathy present irrespective of grade
List for transplantation if:	Or if any 3 of the following features (encephalopathy irrespective of grade) are present:
Arterial pH < 7.3 or arterial lactate > 3.0 mmol/L after adequate fluid resuscitation	Age < 10 yr or > 40 yr[1]
	Interval from jaundice to encephalopathy > 7 d[1]
List for transplantation if all 3 of the following occur within a 24-h period:	INR ≥ 3.5
Grade 3 or 4 hepatic encephalopathy	Serum bilirubin ≥ 300 µmol/L
INR > 6.5	Unfavorable etiology, such as seronegative hepatitis, idiosyncratic drug reaction or Wilson disease
Creatinine > 300 µmol/L	

Circulatory dysfunction and hypotension occur frequently in patients with ALF. There is evidence of a high cardiac output, low systemic resistance state with alterations in hepatic and splanchnic blood flow in these patients. Arterial hypotension that persists despite adequate fluid resuscitation requires the addition of vasopressors. medication to maintain CPP. Norepinephrine is the preferred agent; however, more recently the vasopressin analogue terlipressin has been used in ALF with conflicting results Patients with ALF develop significant coagulopathy due to diminished production of clotting factors by the damaged liver. Correcting the coagulopathy has historically involved the transfusion of fresh frozen plasma, platelets, cryoprecipitate, and packed red blood cells. However, the use of these products often does not correct the coagulopathy. Supplemental doses of vitamin K also does not improve the coagulopathy in acute liver failure he use of FFP should be discouraged unless there is active hemorrhage, or the patient is haemodynamically unstable. If the correction of coagulopathy is necessary and adequate correction cannot be achieved with FFP, particularly in a volume overloaded patients, recombinant human factor VIIa should be considered. Recombinant factor VII (rFVIIa) helps to form as table clot by establishing complexes with exposed tissue factor, and it also enhances platelet activation.[10-14]

Patients with fulminant hepatitis are particularly susceptible to both bacterial and fungal infections. The milieu of inflammation and necrosis in ALF is presumed to predispose patients to infection due to complement de- ficiency, and/or impaired polymorphonuclear or Kupffercellfunction. Bacteraemia has been reported in between 22% - 80% of ALF patients and fungemia noted in 32%. Patients with ALF should therefore be screened aggressively for evidence of infection. The use of prophylactic antibio- tics remains controversial. However, they have been shown to significantly reduce the risk of sepsis, decrease the risk of progression to high-grade encephalopathy and increase the potential for successful transplantation; having said this, survival was not affected. According to the AASLD guidelines, in the absence of active infection, antibiotic and antifungal therapy should be considered for all patients who show progression to high grade encephalopathy or those with evidence of significant systemic inflammation.[10-15]

5. Conclusion

Fulminant hepatitis is a complex clinical "syndrome" which requires early diagnosis and aggressive management. The management of fulminant hepatitis challenges our best skills because of its rapid progression and frequently poor out- comes. Early identification of ALF and the administration of etiology-specific treatment are crucial to improve the outcome. Extrahepatic organ failure should be well managed with advanced intensive care management. Better targeted use of liver transplantation techniques becomes important to save the patients who fail to recover spontaneously. A better understanding of the pathophysiology of fulminant hepatitis will probably lead to further improvement in survival rates.

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