Diagnostic dilemma and management pitfalls of acute liver failure in resource limited Sub Saharan Africa: a case report

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ABSTRACT

Background: Despite recent advances in management of acute liver failure (ALF), morbidity and mortality are still significantly high. Management strategies amongst others involve determination of etiology and greater than 50% of cases often require liver transplantation.

Case presentation: A 36-year old Cameroonian male presented to our facility (a tertiary level health institution in Cameroon) with 10 days history of gastrointestinal symptoms (diarrhea, abdominal pain, and vomiting) for which he auto-medicated with herbs and intravenous cefriaxone for 3 days. Two days prior to the presentation he developed yellowish discoloration of the eyes which prompted consultation. His evolution inpatient was marked by development of ALF Lack of necessary diagnostic tools and intensive care unit substandard care led to worsening of ALF. The patient died on day 6 of hospitalization.

Conclusion: The case presented brings to lamp light the difficulties encountered in making an aetiologic diagnosis for ALF and the substandard care provided in patients with ALF in resource-limited settings. A lot still needs to be done to empower facilities in developing nations in care of ALF.

Key words: acute liver failure, diagnosis, management, pitfalls, case report.

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Background

Acute liver failure (ALF) is a rare devastating disease associated with significant mortality and morbidity in the absence of immediate intensive care, specific treatment, and liver transplantation [1]. According to the American association for the study of liver disease (AASLD) and the European Association for the Study of the Liver (EASL), ALF is characterized by a rapid decline liver function marked by evidence of coagulopathy [International Normalized Ratio (INR) > 1.5] and clinically apparent alteration in mental status secondary to hepatic encephalopathy without pre-existing cirrhosis [2,3]. Classification of ALF into subgroups, namely, hyper-acute, acute, and sub-acute according to the interval between the onset of hepatic encephalopathy and first onset of disease symptoms was shown to be unhelpful in predicting outcome for patients [4]. According to the AASLD 2011 release, approximately 2,000 cases of ALF are reported yearly in the United States, while in Europe, the burden still remains unclear due to unavailable data on prevalence and incidence [2,3].

The AASLD recommends the finding of the precise etiology of ALF to guide management decisions [3]. The most frequent causes of acute liver failure worldwide include viral hepatitis [particularly Hepatitis A virus (HAV), Hepatitis B virus (HBV)], medication overdose (in particular paracetamol), idiosyncratic drug reactions, ingestion of toxins, and metabolic disorders [5]. Other rare causes are Wilson's disease, ischemic hepatitis, Budd Chiari syndrome, Reye's syndrome, and malignancy [6]. Outcome of ALF remains sombre, especially in the developing countries with limited availability of intensive care units (ICUs) and liver transplantation. Patients with ALF require critical care and the AASLD recommends such patients to be hospitalized and closely followed up in an ICU [3]. Despite critical care in the pre-transplant era mortality remained high at more than 80% [7]. Liver transplantation has greatly reduced the mortality of ALF in available facilities with survival rates of over 80% in an EASL report [2]. In our review of literature using Google Scholar, PubMed, African Journal Online, and HINARI search engines, we could not retrieve any case of ALF from sub Saharan Africa literature. We herein report the case of an ALF in a patient with diagnostic and management challenges.

Case Presentation

A 36-year old male patient from the Northern region of Cameroon, Sub-Saharan Africa who presented to

our health facility (a tertiary level health institution in Cameroon) with a 10 days history of watery stools, epigastric pains, and vomiting. Ten days prior to presentation, he started having loose stool. The stools were not bloody, not mucoid, and were not associated with abdominal pains or fevers. He reported haven taking regular meals like other house hold member prior to onset symptoms. These prompted him to buy Ceftriaxone from a local drugstore which was served by nearby nurse at home 2 g/24 hourly for 3 days with regression of watery stools. Evolution was marked 4 days later with sudden onset of fever with chills, several episodes of post-prandial vomiting prompting another auto-medication with herbal medicine (unknown) for 2 days without relieve. Worsening of initial symptoms 1 day later associated with non-radiating intense epigastric pains and yellowish discoloration of his eyes prompted consultation to our health facility. He denied recent intake of paracetamol and consumption of alcohol. He did not consume other potential liver toxins such as mushrooms.

His past medical history was significant for chronic passive HBV infection. At his HBV follow-up visit 2 weeks earlier, his HBV viral load was 641 IU/l, liver enzymes were normal and an abdominal ultrasound showed no morphologic evidence of chronic liver disease. His Human immunodeficiency virus (HIV), Hepatitis C virus (HCV), and Hepatitis D virus (HDV) serologic test were all negative. He had no other known medical condition.

On admission he was conscious and oriented, his Glasgow coma scale was 15/15. His Blood pressure was 160/95 mmHGm, heart rate 97 beats per minute and his temperature was 37.6°C. He had marked sclera and conjunctivae icterus. The abdominal examination was normal but for right hypochondria tenderness. There was no stigmata of chronic liver disease or portal hypertension. The rest of the physical examination was without particularity.

A tentative diagnosis of gastrointestinal infection in a patient with chronic HBV was made. He was hospitalized and managed conservatively with fluids; Normal saline 9% 500 ml 8 hourly and Dextrose 5% 500 ml 12 hourly, gastric protectant; Omeprazole 40 mg 24 hourly IV, antispasmodics; phloroglucinol 80 mg 8 hourly IV, and anti-emetics Levusulpiride 25 mg IV 8 hourly.

His laboratory work up showed; normal full blood count (Hemoglobin 15.8 g/dl, white cell count 4,400 cells/ml and Platelets 167,000 cells/ml), elevated liver enzymes: aspartate aminotransferase; 3,332 IU/l, alanine aminotransferase; 5,249 IU/L, total bilirubine; 12 mg/dl, direct bilirubine; 4.5mg/dl: serum electrolytes Na+/k+/cl- 138.92/3.52/85.55 (meq/dl): Blood Urea Nitrogen (BUN)/creatinine; 47 mg/dl /1.36 mg/dl; prothrombine time: 5.7% and INR: 24.0

Based on the massive liver cytolysis associated with an INR > 1.5 without signs of hepatic encephalopathy, a diagnosis of severe acute hepatitis was made. Possible etiologies were: viral (HAV infection or HBV reactivation), Bacterial, fungal parasitic, or toxic [herb or medication (ceftriaxone) induced].

Evolution in the ward was marked on day 1 post admission with onset of agitations, incoherent speech and asterixis suggestive of a type A grade 2 hepatic encephalopathy. The diagnosis of ALF was made. He was then transferred to the intensive care unit and started on Lactulose 1 sachet 8 hourly, Rifaximin 200 mg: 2 tabs 8 hourly mannitol 10% 500 cc daily

On day 4 of hospitalization, the patient had projectile vomiting, macroscopic hematuria, and developed altered sensorium with Glasgow Coma Scale 10/15 (E4 V1 M5). His blood pressure was high at 212/110 mmHg, temperature 40°C, respiratory rate 30 breaths per minute, and pulse 120 beats per minute consistent with systemic response inflammatory syndrome (SIRS). Blood culture and a repeat full blood count were uneventful.

The following were added to his treatment; vitamin K1 10 mg/IM single dose, transfusion of three pints of fresh frozen plasma, ceftriaxone 2 g IV daily, and hypertension was managed with intravenous titrated nicardipine. Patient, however, passed away on day 6 post admission

Discussion

We report a case fatality of ALF in a Cameroonian male with chronic inactive HBV infection. The patient's clinical presentation, laboratory work up and inpatient follow-up features met both the AASLD and EASL diagnostic criteria for ALF. Despite making a clear-cut diagnosis of ALF in this patient, it remains unclear whether this patient's ALF was unifactorial or multifactorial.

Viral hepatitis (especially HAV and HBV) are frequently causes of ALF [8,9]. The patients' gastrointestinal symptoms prior to development of ALF suggest HAV, also a reactivation of his previous HBV, cannot be undermined as a possible cause. Despite under reporting, herb induced hepatotoxicity remains a major problem in sub Saharan Africa [10]. Clinical manifestations of herb induced hepatotoxicity range from asymptomatic to fulminant acute liver failure. Our client's ingestion of traditional portions (herbs) prior to onset of jaundice and other features of ALF also suggest herbs as a potential cause of our patients ALF. Medication induced liver injury are a subset of toxic hepatitis, a known cause of ALF [11,12]. Ceftriaxone a third generation cephalosporin is widely used because of its long half-life, high tissue penetration rate and relatively good safety profile [11]. Ceftriaxone, however, causes elevated liver enzymes and cases have been reported of hepatitis with ceftriaxone being the culprit [13]. This patient's ceftriaxone intake prior to onset of symptoms and worsening hepatitis with progression to ALF with continues use of ceftriaxone may suggest ceftriaxone as a possible cause of ALF in this patient.

The pathogenesis of ALF includes both direct and immune mediated injury. In ALF, innate immune system activation is etiology specific [14]. Pathogen-associated molecular damage is more frequent with hepatotropic viruses, whereas endogenous signals derived from injured cells called damage associated molecular patterns are more frequent with toxins [14]. Yet there were no resources for an autopsy evaluation to determine the pattern of injury in our patient. Most patients with ALF have consistent clinical features, acute loss of hepatocellular function, systemic inflammatory response and multi-organ system failure [4]. Our patient while in the ward presented with altered level of consciousness, signs of raised intracranial pressure with reactional hypertension suggestive of cerebral edema, SIRS and macroscopic hematuria. Cerebral edema and multiple organ failure mediated by SIRS are the two main causes of death in patients with ALF [12]. SIRS is mediated by the release of pro-inflammatory cytokines which contributes to cerebral edema by decreasing cerebral vascular tone thus increasing thus causing cerebral hyper-perfusion [12].This SIRS could explain signs of raised intracranial pressure presented by our patient. Spontaneous bleeding occurs in less than 10% of cases. It is secondary to liver failure and increased consumption of procoagulant factors [15].This could explain macroscopic hematuria.

The main goal of management in ALF is to provide supportive care and treat complications present. The patient received supportive care and complications were equally managed. The AASLD recommends that even in the absence of active infection, antibiotic, and antifungal therapy should be considered for all the patients who show progression to high-grade encephalopathy or those with evidence of significant systemic inflammation [4]. Our patient was in SIRS and was thus rightfully given ceftriaxone. Bleeding diathesis is a common feature of ALF due to decreased production of clotting factors by the damaged liver [16]. Historically management involves transfusion of fresh frozen plasma, platelets, cryoprecipitate, and packed red cells with no evidence of coagulopathy correction [17]. For this patient's bleeding disorder, he was transfused three pints of fresh frozen plasma and received supplemental doses of vitamin K. The EASL recommends liver transplant for ALF adult patients who have marked altered mental status and features of severe liver injury [2]. This patient met these criteria and was therefore a candidate for liver transplant. This was not done.

On a bigger picture, the occurrence of one inciting factor does not exclude the implication of other possible causative agents [9]. The etiology of ALF has been shown in several cases to be multifactorial. Our clients ALF could thus possibly be toxic from different toxins (medication and herbs) or both toxic and viral. However limited resources made it difficult for a true picture of the etiology to be ascertained. The actual cause of this patient's ALF remains unclear due to circumstances of diagnosis and lack of resources. Despite intensive care unit management, the unit is substandard and unable to provide the minimum package required for supportive care and complication management. Also, in our setting, there is no transplant unit which is most reliable form of definitive management of ALF [18].

Conclusion

From this clinical case, we notice that ALF continues to be a life-threatening condition, especially in SSA where diagnostic and management capabilities are still limited. Considering the high infection burden in the region together with increasing abusive consumption of prescribed and non-prescribed drugs, it is time policy makers reflect on management capabilities to cope with potential future increasing ALF cases in the region.

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List of Abbreviations

AASLD	American association for the study of liver disease
ALF	Acute liver failure
EASL	European association for the study of liver disease
HAV	Hepatitis A virus
HBV	Hepatitis B virus
SIRS	Systemic inflammatory response syndrome

Consent for publication

Written informed consent was obtained from the patient's family.

Ethical approval

Ethical approval was obtained from the Yaounde Central Hospital ethical review board.

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Summary of the case

1	**Patient (gender, age)**	36 year old , male
2	**Final Diagnosis**	Acute liver Failure
3	**Symptoms**	Diarrhea, jaundice, altered sensorium, hematuria
4	**Medications**	Ceftriaxone,herbal medicine,lactulose,rifaximin,mannitol
5	**Clinical Procedure**	Diagnosis of ALF, transfer to ICU
6	**Specialty**	Hepatology and Gastroenterology