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Case Report

A successful use of therapeutic plasma exchange in a fulminant form of acute fatty liver of pregnancy

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ABSTRACT

Acute fatty liver of pregnancy (AFLP) continues to raise special concerns since its first post-mortem description by Sheehan in 1940. While early diagnosis and expedite delivery are the cornerstone of management, this condition remains fatal for both mother and fetus. Acute fulminant liver failure is the most serious and life-threatening AFLP-related complication and can require liver transplant despite aggressive supportive management. In lieu of transplant, therapeutic plasma exchange (PE) has emerged as a life-saving alternative and has, in few reports, demonstrated efficacy for the reversal of this dangerous condition. Here we present a case report of a patient diagnosed with fulminant liver failure complicating an AFLP and progressed to severe hepatic encephalopathy who was successfully treated with five rounds of plasma exchange.

Introduction

AFLP is an idiopathic disorder that consists of microvesicular fatty infiltration of the liver during pregnancy that can lead to hepatic and renal dysfunctions, coagulopathies, pancreatitis, encephalopathy, fetal acidosis, and multiple organ injuries [1,2]. It occurs late in the third trimester and mostly in the peripartum period, and has a maternal mortality of 7–18% despite maximum medical therapy, although maternal and fetal mortality up to 85% has been reported [1,3,4] Though the etiology of this condition is yet elusive, multiple theories have been put forward, including increased estrogen, fatty acid metabolism derangements, or mitochondrial dysfunction [5,6]. To diagnose AFLP, at least six of Swansea's criteria must be met: nausea, abdominal pain, polydipsia/polyuria, encephalopathy, hypoglycemia, hyperuricemia, leukocytosis, ascites, increased hepatic aminotransferase, increased bilirubin, increased ammonia, renal failure, coagulopathy with increased prothrombin time, microvesicular steatosis on liver biopsy, metabolic acidosis, or pancreatitis [7]. Regardless, AFLP remains a difficult clinical diagnosis, with signs and symptoms reminiscent of other peripartum conditions such as pre-eclampsia, HELLP syndrome or thrombotic microangiopathies.

The primary treatment for AFLP includes rapid termination of the pregnancy followed by symptomatic medical support, which may include transfusions for anemia and coagulation factor deficits, control of hypoglycemia, and electrolyte replacement. Liver transplant has been required for severe or refractory cases [8,9], however the high expense and low availability of liver transplants make this an inconvenience in many parts of the world. Therefore, it is imperative to explore other treatment options for this deadly condition. This case report details the successful treatment of a patient who presented with severe AFLP at term with 5 rounds of plasma exchange.

Case presentation

A previously healthy 31-year-old primipara, primigravida parturient woman presented to the emergency department at 40 weeks and 3 days with a 7-day history of progressive polyuria, polydipsia, headaches, nausea, vomiting, jaundice, and vague abdominal discomfort. She had initially presented to her local caregiver who attempted conservative management, but her symptoms gradually worsened, particularly over the three days prior to admission. Upon examination, she was found to be jaundiced, conscious, tachycardic, normotensive, and oliguric (<0.5 mL/kg/h) with visualization of dark urine. She was afebrile

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Table 1
Laboratory data of the patient before and after treatment with plasma exchange.

Day	1 (pre-treatment)		15 (post-treatment)
WBC (10^3/mm^3)	15.9	Therapeutic plasma exchange (from day 4 to day 8)	14
Hemoglobin (g/dL)	12.5		7.8
Hematocrit (%)	38		23.9
Platelets (10^3/mm^3)	75		256
Prothrombin ratio (%)	20		95
Urea	0.54		0.36
Creatinine (mg/dL)	34		7
Glucose (g/L)	0.45		1.1
AST	325		98
ALT	190		33
Total bilirubin (mg/dL)	206		167.5
Direct bilirubin (mg/dL)	133		107.9
Factor V (%)	28		100
CRP	32.1		12.19

and her oxygen saturation was 97% on room air. No stigmata of cirrhosis were seen. Blood glucose level of 0.48 g/L was measured by a glucometer and urinary protein strip testing was negative.

Neither fetal movements nor cardiac activity were detected, and a bedside ultrasonography demonstrated intrauterine fetal demise without placental abnormalities. Blood work upon admission is shown in Table 1. White blood cell counts were elevated. She was found to have low albumin and glucose and her liver enzymes were 3–4 times greater than the upper limit of normal with Prothrombin ratio (PR) = 20%. She went into spontaneous labor six hours after admission. Vaginal delivery and placental expulsion were atraumatic but managed with close surveillance and transfusion of six units of fresh frozen plasma (FFP).

A liver ultrasound scanning ruled out any obstruction in the biliary tree or hepatic vein thrombosis and demonstrated a normal size and regular capsular contour of the liver, with diffuse bright echotexture.

Based on the characteristic prodromes and clinico-laboratory findings on admission, the exclusion of other differential diagnoses such as viral (hepatitis A, B, C and E serologies were negative) or drug-induced hepatitis as well as an interval less than two weeks between icterus onset and encephalopathy occurrence, she was diagnosed with fulminant hepatic failure secondary to AFLP.

Following her admission, she responded well to fluid resuscitation and her urine output returned to normal. She was rehydrated with 10% glucose solution. The patient was started on continuous infusion of 10% dextrose, prophylactic ceftriaxone 1 g/day as well as oral lactulose, stress ulcer prophylaxis and vitamin K at 10 mg.

Despite conventional supportive medical management, including blood products transfusion, the patient continued to deteriorate both clinically and biologically, with worsening confusion, loss of deep tendon reflexes, abdominal distension, severe pitting lower extremity edema, and worsening thrombocytopenia, but hemodynamic status remained stable. In fact, the patient suffered from a progressive neurological deterioration over the course of her first days of admission attested by an incremental worsening through the West Haven Hepatic Encephalopathy (HE) grades. A diffuse cerebral edema was found on CT scan of the brain, for which she was given mannitol, and she was ultimately diagnosed with a coma (Glascow Coma Scale 8/15) on day six of hospitalization.

Owing to limited treatment options, the decision was made to utilize an intensive PE protocol. The patient underwent 5 daily courses of PE starting on day 4 of hospitalization. During each exchange, two liters of plasma were approximately removed and replaced with 1 liter of FFP and 1 liter of isotonic 4% albumin solution. Throughout treatment, a grade three ascites with pleural effusion was found. The ascetic fluid analysis demonstrated an uncomplicated transudate and the patient responded well to sodium restriction and diuretics. After the fifth PE on day 8 of hospitalization, the patient demonstrated rapid and palpable improvement in the level of consciousness followed by progressive biological normalization that was noted from day 10, and finally all encephalopathic symptoms were totally resolved by discharge. Improved laboratory values prior to discharge are detailed in Table 1. The evolutive patterns of liver biomarkers and platelet count before, during and after PE sessions were summarized in Figs. 1 and 2.

Discussion

AFLP is a serious condition complicating between 1 in 7000 and 1 in 16,000 pregnancies [10]. While prompt delivery remains the mainstay of management, symptoms often last after termination and patients need intensive medical support. Therapeutic PE is the first-line therapy and plays a pivotal role in the remission of a myriad of conditions such as thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome, fulminant Wilson's disease, acute Guillain-Barré syndrome, *etc*. Moreover it is actually considered as one of blood purification (BP) means, so PE, whether used alone or in simultaneous combination with renal replacement therapy (RRT), mainly the High Flow Continuous Veno-Venous Hemofiltation (HFCVVH) or HemoDiafiltration (HFCVVHD) Modalities) have widened the scope of its application in critical care diseases [11,12]. The rationale behind that was undoubtedly the emerging concept of hypercytokinemia-induced critical illness that has surfaced in recent years to enable the understanding of how complex, miscellaneous and even interconnected etiopathogenic processes of those conditions and consequently their management [11]. Indeed it had led so far to made the need for extracorporeal either non-bioartificial supports or biological devices unquestionable and indispensable while facing multiorgan dysfunction, more particularly kidney and/or liver failure [11–16].

Thus PE may be an effective treatment in lieu of a liver transplant for patients with severe and refractory AFLP. In the same vein, and as stated in recently published guidelines of European Association for Study of Liver (EASL) and Japan Society of Blood Purification in Critical Care (JSBPCC), experts encourage and even recommend to apply these extracorporeal BP devices (including PE) in the setting of acute fulminant liver failure, since many studies, despite their questionable design and absence of clear and significant impact on mortality, have reported significant efficacy as a bridge therapy to either spontaneous recovery or liver transplantation [17,18]. In contrast, the American Association for Study of Liver Diseases (AASLD), and before that the American

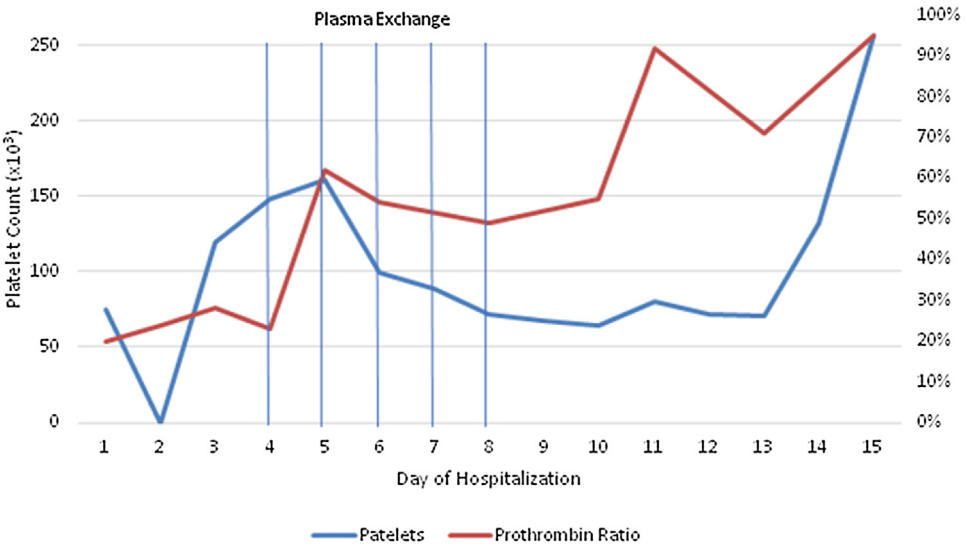

Fig. 1. Evolution of platelet count and prothrombin ratio throughout hospital course.

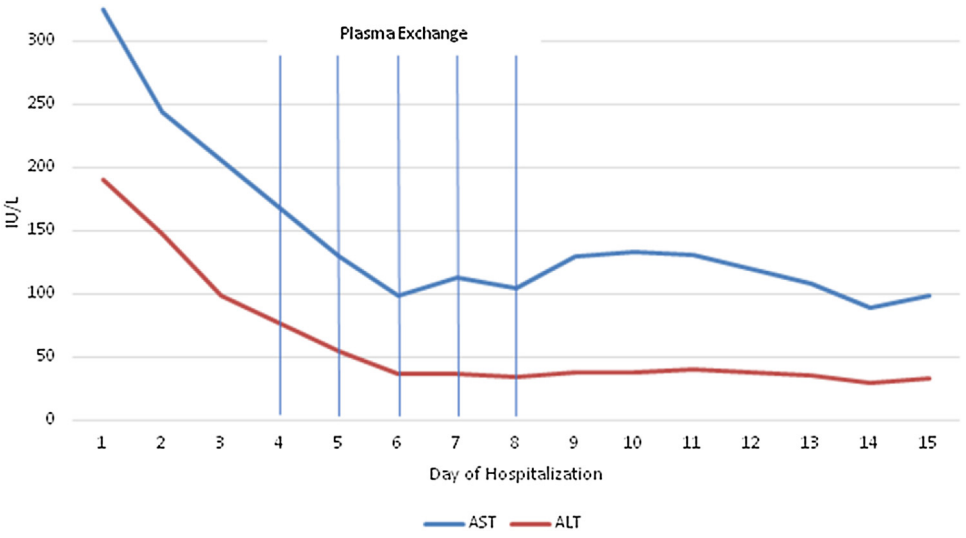

Fig. 2. Evolution of AST and ALT levels throughout the hospital course.

Gastroenterological Association Institute were cautious and have concluded that no solid evidence exists to recommend the implementation of both external artificial (i.e., sorbent-based) or bioartificial liver support systems (i.e., cell-based) in the routine management of acute liver failure (ALF) [19,20].

Even though the latter statement, the emerging cytokines theory has enlarged BP indications (including renal and non renal ones) in critically ill patients. Within this framework, many authors, used commonly PE and they outlined its benefits in patients experiencing fulminant hepatic failure. In fact, it protects liver cells by removing increased hazardous substances of low to high molecular weight from the blood stream such as ammonia, endotoxins, bilirubin, and inflammatory cytokines and can be paired with transfusion of large volumes of FFP and albumin to improve disseminated intravascular coagulation (DIC) and renal function, respectively [8,21]. Additionally, Albumin is a multifunctional protein that displays many interesting features with antioxidant, immunomodulatory, and detoxification functions [22].

However, Japanese teams are prevailing PE as a technique of replacing useful substances rather than clearance of causative humoral mediators. Thus, BP for fulminant forms of ALF is now currently performed with addition of PE, if needed, to the basic method of HFCVVHDF [18]. This approach is endorsed by the JSBPCC and seems useful for preventing massive transfusion of FFP with its well documented side effects. Nevertheless, it should be emphasized that if PE is considered alone, it is advisable to opt for slow mode in order to avoid rapid replacement of large quantities of plasma [17,18].

Over the last decade, the Molecular Absorbent Recirculating System (MARS) was incorporated into the existing BP armamentarium for managing HE. Based on available data and reports concerning the reversal of advanced HE grades were promising but for those regarding overall survival improvement, they were divergent and lukewarm [23–26]. This was likely imputable to lower system efficiency of ammonia clearance and to its adverse events such as coagulopathy worsening [18,26,27]. Also Food and Drug Administration (FDA) has decided to withdraw its approval for its usage for grade 3–4 HE related to decompensation of chronic liver disease [27].

One literature review article found that 50 of 53 patients with severe symptoms treated with PE recovered fully [9], and another large series demonstrated successful treatment in 37 of the 39 patients [8]. A review of the successful treatments by PE reported in the literature can be seen in Table 2. Taken together, these studies report an overall mortality of 5.4%, significantly

Table 2
Literature review.

Study	Year	Location	Number of patients	Time to PE from termination of pregnancy	Number of PE sessions	Outcomes
Current	2018	Morocco	1	4 days	5	Recovered
Hartwell [31]	2014	USA	1	6 days	3	Recovered
Yu [6]	2014	China	5	1–3 days	2–4	4 recovered[a]
Seyyed [9]	2012	Iran	3	0–8 days	3–22	3 recovered
Tang [10]	2012	China	13	6 h	1–3	Reduction in recovery time & hospital stay, no change in mortality compared to those who received cultured liver cells
Jin [8]	2012	China	39	1–5 days	1–4	37 recovered, 2 deaths
Chu [32]	2012	China	11	0–3 days	2–8	10 recovered, 1 death
Martin [1]	2008	USA	6	2 days	2–4	6 recovered

[a] Treated with plasma exchange plus continuous renal replacement therapy.

lower than the 7–18% mortality seen with medical treatment alone. After she underwent a total of 5 sessions with parenteral slow administration of 6 units of FFP and 1liter of isotonic 4% human albumin solution on average per session, our patient also made a full recovery with no complications.

Due to the paucity of data and relative rarity of the disease, it is yet unclear whether it would be best to use PE prophylactically or utilize a "wait and see" approach and delay plasma exchange until all medical therapies have failed. One study reported elevated serum creatinine to be an early indicator of patients who required PE in their series, indicating that it may be a reliable biological marker to differentiate patients who require this step-up therapy from those who will recover with standard symptomatic support [1]. However, given the lack of availability of transplants and the often-delayed presentation of patients in resource-limited settings, we recommend early consideration of PE for patients in these settings, especially at tertiary referral hospitals.

Additionally, it appears that earlier introduction of this treatment paradigm significantly affects efficacy and duration of treatment [8]. However, further studies must be performed to identify which patients are severe enough to indicate immediate PE after pregnancy termination and which may be treated with supportive therapy alone. If PE proves to be insufficient therapy, other blood purification therapies may also be considered in the setting of acute liver failure, including High Flow Continuous Veno-Venous Hemofiltration (HFCVVHF) and, either alone or in combination with PE [17,18,27–30]. However, reports of successes with these options are largely limited to case reports and small series and thus also must be validated in larger, robust and well designed studies to determine efficacy, cost effectiveness, and appropriate timing of these individual or combined options, and to break firmly with previous contrastive outcomes [20].

Conclusion

It is likely that the evolutive pattern of fulminant hepatitis resulting from AFLP could be reversed by therapeutic plasma exchange. It may be used as a bridge to decision-making by providing temporary support while medical therapy is attempted or can be used while awaiting a matched organ donor. However, increasing evidence demonstrates that PE can also be used as a cure for AFLP, especially in severe or refractory forms, by temporarily replacing the liver's functions, giving it time to recover. The current case presents an example of the successful use of a life-saving treatment that should be considered in the management of severe forms of ALFP especially when conservative management appears ineffective. Strong emphasis on the timely use of this tool is of critical importance, and early implementation can play an important role in the reversal of this life-threatening condition.

Disclosure of interest

The authors declared no conflicts of interest.

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