Difficult to treat infection in acute on chronic liver failure – Need for novel changes in traditional management

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ABSTRACT

Acute on chronic liver failure (ACLF) patients have inherent immunosuppressed state secondary to persistent endotoxemia and ongoing inflammatory state leading to high risk of developing infections, both de novo and nosocomial. The management of a critically ill patient with advanced liver disease and in severe sepsis has always been a challenge. Current approaches to management of sepsis rely on early antimicrobial use, fluid administration, hemodynamic maintenance and aggressive sepsis focus control. Even with current measures, the mortality from sepsis still remains very high, more so, in liver disease patients. The current report discusses briefly, a prototype of difficult to manage catastrophic infected ACLF patient with central nervous system infection leading to extensive vascular thrombosis of the brain leading to refractory septic shock and multi organ failure. We further discuss briefly on new management scenarios in severe sepsis in cirrhosis patients.

Keywords: ACLF, Cavernous sinus thrombosis, fungal infections, Portal hypertension, severe sepsis

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INTRODUCTION

Bacterial infections are more common in cirrhotics than general population. Cirrhosis associated immune deficiency syndrome is an inefficiency of the innate and adaptive immune system in cirrhotics to prevent or clear infectious

agents. In ACLF, an acute insult and ongoing chronic hepatocellular injury leads to dysregulated host inflammatory response leading to SIRS and propensity for more infectious complications. It has been shown that the risk of infections, severity of complications and mortality in advanced liver disease is related to the expression of monocytic HLA-DR. Sepsis and cirrhosis form a vicious cycle that feeds off each other, leading to multi organ involvement, immunodeficiency and multidrug resistant microbial infections, a state inherently seen in patients of ACLF. Infection related ACLF stands out as a different entity, with a different and far worse prognosis than that is seen with other acute insults. These patients prove a tough cohort to manage with high mortality, substantial financial and resource burden and challenges current treatment guidelines for sepsis. (1, 2) Here we present a patient of ACLF with severe infections leading to rapid deterioration and new onset organ failures that proved refractory to aggressive standard management, questioning a change in current treatment profiles for infectious complications in this special group of patients.

CASE REPORT

A 43 year old male, chronic alcohol abuser with last intake 15 days prior to presentation to the emergency room, complained of progressive painless non cholestatic jaundice since 20 days, associated with progressive abdominal distension and bilateral leg swelling since 10 days. This was followed by slow deterioration in mental status since 5 days and 3 episodes of generalized tonic clonic seizures one day prior to admission.

The family denied illicit drug use and complementary and alternative medication use by the patient. He is not known to have prior epilepsy. He was being managed elsewhere as a case of acute on chronic liver failure with progressive liver failure and hepatic encephalopathy. On examination, the patient was comatose with labored breathing and sluggish pupillary reflexes with anisocoria (left pupil 3mm, right 6mm, fixed). Facial examination revealed periorbital ecchymosis on the right side with relative exophthalmos of the same side (FIGURE. 1).

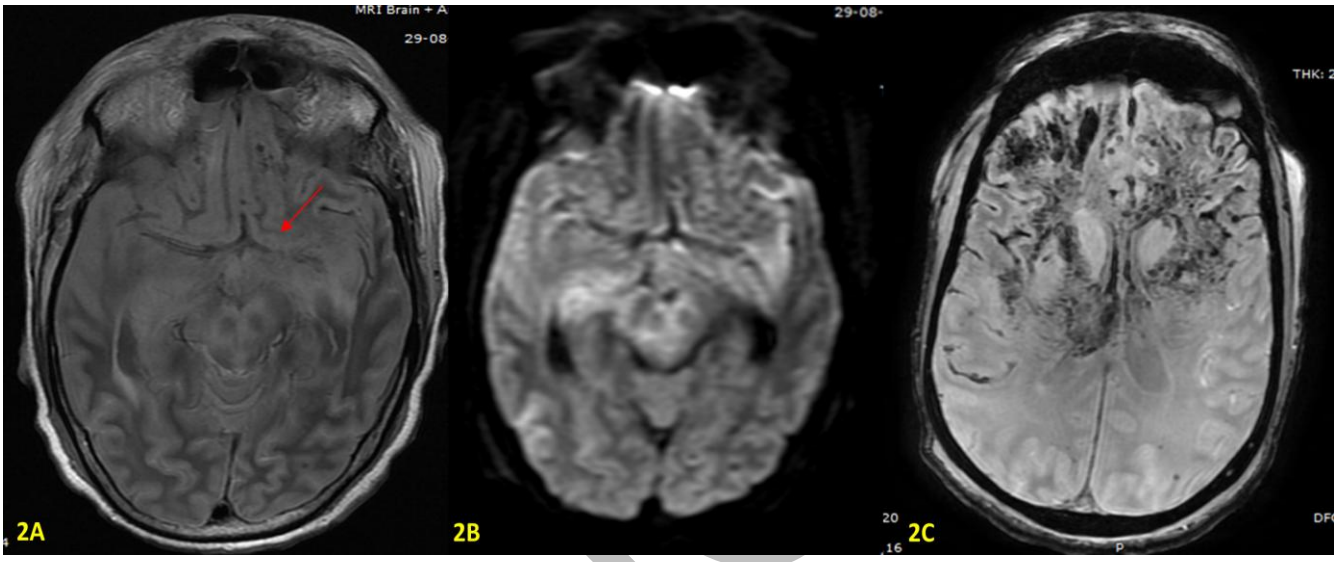
FIGURE 1: Clinical examination revealing unilateral proptosis with periorbital ecchymosis, glazed and cloudy corneal surface on the right side with extensive conjunctival chemosis in the patient.

Right nasal cavity revealed dirty brown foul smelling active discharge. There was no motor activity and bilateral plantars were mute. Pallor was evident along with deep icterus and leuconychia and bilateral pitting pedal edema. Abdominal examination showed firm palpable liver with bilobar enlargement and splenomegaly with grade 3 ascites and multiple small ecchymotic patches over the flanks.

Initial laboratory investigations revealed anemia (hemoglobin 8.2g/dL) with leukemoid reaction (total leucocyte counts 65000 per cumm) with thrombocytopenia (platelets 45000 per cumm) and peripheral smear showing 12% spur cells with megaloblastic changes and neutrophilia with left shift. A computed tomography scan of the head done at the time of admission was normal and subsequently, in view of worsening anisocoria and evidence of Cushing's reflex, magnetic resonance imaging followed by angiography of the brain was undertaken.

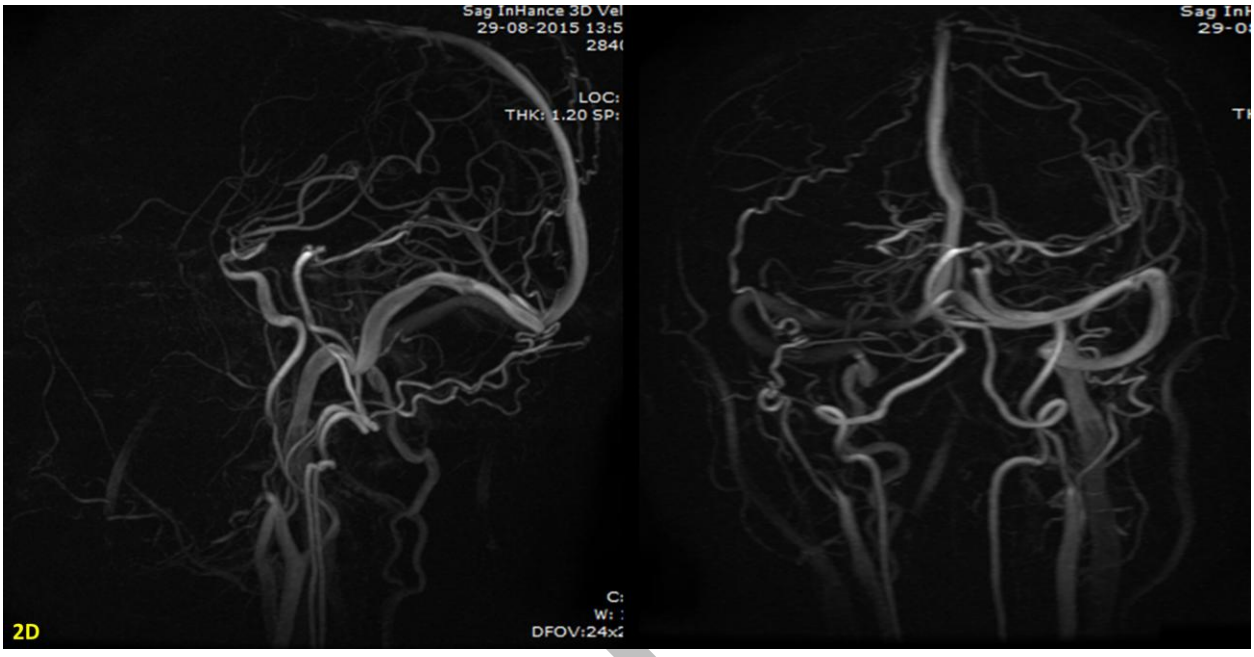
Imaging revealed minimal shift of midline structures to left side (FIGURE 2A), with large area of restricted diffusion involving bilateral fronto-temporo-parietal lobes, right occipital lobe, bilateral basal ganglia, thalami, and further involving ventral mid brain, right pons and right middle cerebellar peduncle consistent with acute infarct (FIGURE 2B, 2C).

FIGURE 2: A – T2 weighted MR imaging revealing mild midline shift (red arrow); B – Diffusion weighted imaging showing large area of restricted diffusion involving bilateral fronto-temporo-parietal lobes, consistent with acute infarct; C - Multiple focal areas of blooming on gradient images are seen within the infarct suggestive of hemorrhagic transformation



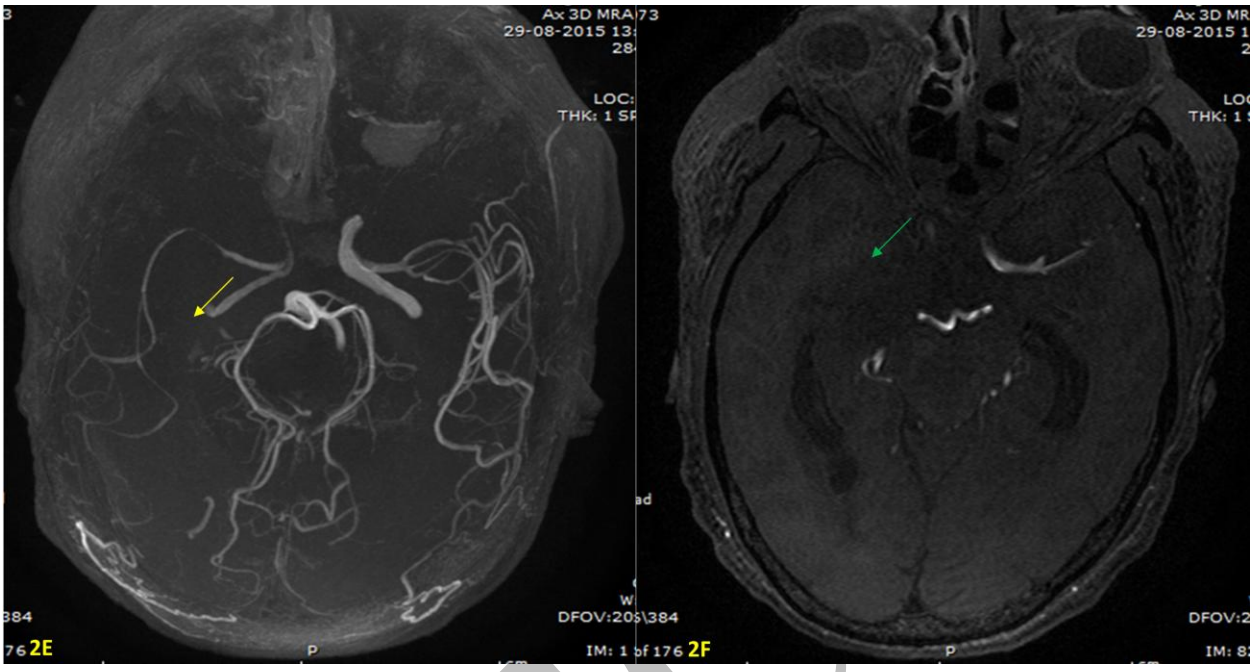
Multiple focal areas of blooming on gradient images were seen within the infarct suggestive of hemorrhagic transformation. There was extension of hemorrhage into bilateral lateral ventricles along with multiple focal microbleeds scattered in bilateral cerebral and cerebellar hemispheres and small subgaleal collection of seen in bilateral parieto-temporal regions. The venography showed thrombosed anterior third of superior saggital sinus and bilateral cortical venous thrombosis. (FIGURE 2D)

FIGURE 2: D – Magnetic resonance venography showing thrombosed anterior third of superior saggital sinus and bilateral cortical venous thrombosis



Arteriography revealed relatively attenuated petrous, cavernous and supraclinoid segments of right internal carotid artery. The right middle cerebral artery and its cortical branches were also attenuated (FIGURE 2E, 2F).

FIGURE 2: E, F – Magnetic resonance angiography revealing relatively attenuated petrous, cavernous and supraclinoid segments of right internal carotid artery (yellow arrow), with attenuation of right middle cerebral artery (green arrow) and its cortical branches. Bilateral anterior cerebral arteries are not visualized consistent with thrombosis; there is partial loss of flow void in left middle cerebral artery.



Bilateral anterior cerebral arteries were not visualized, suggestive of thrombosis. There was also partial loss of flow void in left middle cerebral artery. Posterior third of superior sagital sinus, bilateral transverse and sigmoid sinuses were found to be normal. Nasal swabs revealed growth of Candida glabrata fungus. The patient was aggressively managed with anti edema measures, broad spectrum antibiotics (carbapenam, teichoplanin, colistin and caspofungin). Anti coagulation could not be initiated in view of hemorrhagic infarcts. In spite of aggressive management and organ support, the patient succumbed to the illness 18 hours after admission with worsening multi organ failure and refractory septic shock. Final diagnosis at death was infected ACLF with fungal rhino-sinusitis leading to cavernous sinus and cerebral arterial thrombosis with severe sepsis, septic shock and multi organ failure.

DISCUSSION

Acute on chronic liver failure (ACLF) is a catastrophic syndrome associated with multiple organ failure centered on advanced liver disease associated with immunoparalysis, multiple infections and high rates of mortality. (2) Cirrhosis associated immune dysfunction has recently been in the lime light as one of the major pathogenic mechanism that lead to progressive and new onset multi organ failure and susceptibility towards infections in this sick cohort of patients. It was also

shown that advanced liver disease and ACLF patients, even in the absence of sepsis, behave like patients with severe sepsis and immunoparalysis. Pro-inflammatory and anti inflammatory mechanisms act together in acute on chronic liver failure and tipping of the balance to either side, without adequate control mechanisms lead to deterioration clinically. (3)

Our patient was the prototype of a difficult to manage infected ACLF patient. Initially, what was thought to be progressive liver failure related deterioration in mental status was in fact an evolving catastrophic central nervous system infection. In many patients of advanced liver disease, hepatic encephalopathy is the main cause of worsening or new onset mental status deterioration. In 80% of such patients, a trigger can be identified and management aims at decreasing ammonia burden and correction of triggering event such as infections, electrolyte imbalance or drugs. In the presence of focal or new onset neurodeficits, early brain imaging to rule out organic causes of HE is warranted. (4)

In the current scenario, early brain imaging would have helped in clinching CNS related infection as the cause for dramatic worsening and early broad spectrum antimicrobial therapy and early initiation of anticoagulation could have prevented disease progression. A careful and solid assessment of nervous system at baseline is highly rewarding in patients of advanced liver disease with CNS involvement. Infections leading to ACLF in cirrhotics have been endorsed as an acute event as per the European Association for the Study of Liver (EASL). Moreover, ACLF patients have greater propensity for developing sepsis and multi organ failure in hospital that lead to poor outcomes, depending on the number of organ systems involved.

Acute on chronic liver failure patients with more than 4 organ failures have mortality rates more than 90% in hospital. Management of infected or septic ACLF (iACLF or sACLF) patients are challenging. Patients present to a tertiary liver centre usually late, after going through repeated admissions at peripheral hospitals. They harbor multi site nosocomial infections, develop new onset organ failures and provide very loess time period for aggressive intervention as seen with our patient. Current concepts in severe sepsis shed light on not one, but many ‘golden windows’ of opportunity. (5-8)

Early antimicrobial therapy, early escalation and de-escalation of antimicrobials, choice of antimicrobials at admission (depending on community or hospital acquired complications), severity score based approach to broad spectrum antimicrobial use and utilization of timely immune-modulation (currently a matter of

research) provide the treating physician many opportunities for intervention.

In our patient prior multiple hospital admissions could have lead to fungal sepsis, for which, opportunity for intervention was missed at the onset. In cirrhotics presenting with life threatening infections and immunoparalysis, leading to multi-organ failure, the role of aggressive interventional measures in the form of plasma exchange, continuous hemodiafiltration and liver dialysis during early uncontrolled inflammatory phase could help curb and ameliorate the pro-inflammation related organ failures be reduction of cytokine storm. This has been shown in multiple series, but warrants larger controlled trials in different cohort of patients. (9-12)

Future prospects in management of severe sepsis, especially in advanced liver disease would probably be multi pronged and not just targeting the infectious agent. Supporting role of early broad spectrum antimicrobial initiation based on severity scores, identifying immune dysfunction and immunoparalysis and targeting specific pathways; early and aggressive utilization of organ failure and inflammation ameliorating support systems could improve outcomes in this very sick cohort of patients in the future.

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