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Hepatic decompensation in the absence of obvious precipitants: the potential role of cytomegalovirus infection/reactivation

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ABSTRACT

Details of two patients with alcohol-related and mixed aetiology cirrhosis who developed acute-on-chronic liver failure/hepatic decompensation with no obvious precipitants are reported. Cytomegalovirus (CMV) infection or reactivation was diagnosed in both, and required treatment with ganciclovir in one. Both returned to baseline hepatic function and remain well. Physicians should be alert to the possibility that CMV might cause or contribute to hepatic decompensation in patients with cirrhosis, even if they are not severely immunocompromised, and especially if they are alcohol misusers.

INTRODUCTION

Acute liver decompensation is the main cause of hospitalisation in patients with cirrhosis, and it has been defined as the rapid development of at least one clinical complication between ascites, hepatic encephalopathy, gastrointestinal haemorrhage and bacterial infection.[1] One of the keys to adequate management of hepatic decompensation is the prompt identification of its precipitating event, if any. This can be a direct liver injury (ie, a binge causing alcoholic hepatitis, drug-induced liver toxicity, superimposed viral hepatitis, portal vein thrombosis, ischaemia) or the consequence of systemic insults such as surgery, variceal bleeding or infection.[2] In a significant proportion of patients (up to 43% of more severe cases[1]), the precipitant factor remains undetected.

Recent data from the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium show that 3-month mortality of patients hospitalised for acute liver decompensation is 22%, while 9% undergo liver transplantation. In the subgroup of patients with more severe illness, that is those patients who present with or develop acute-on-chronic liver failure (ACLF), 3-month mortality reaches 51%.[1] Unfortunately, there is no universally accepted definition of ACLF, thus precluding the acquisition of clear-cut epidemiological data. Recently, Jalan *et al*[3] proposed the following working definition of ACLF: a syndrome occurring in patients with chronic liver disease, characterised by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the international normalised ratio (INR)) and failure of one or more extra-hepatic organs.

The pathophysiology of ACLF remains largely unknown. An important mechanism in the development of this syndrome seems to be altered host response to injury, with deregulated inflammation, and further predisposition to infection.[2] In particular, systemic inflammatory response syndrome (SIRS), once established, is associated with increased inflammatory cytokine response, ACLF development and perpetuation, with establishment of a vicious cycle of inflammation-decompensation.[4] For these reasons, prompt identification and adequate management of any precipitating events impinge on prognosis.

We report the case of two brothers, one with alcohol-related and one with mixed aetiology cirrhosis, who developed a first episode of acute liver decompensation and ACLF in the absence of obvious precipitants.

CASES

In December 2013, a 44-year-old man presented to our department with a history of fever, vomiting, diarrhoea (up to 8 watery stools per day) and abdominal pain over a period of 10 days. He also reported cough,

dysuria and rapid weight gain. His history was significant for smoking, previous hepatitis C virus (HCV) infection with spontaneous resolution and alcohol misuse, but he reported abstinence over the previous 15 days.

Physical examination revealed fever (38°C), jaundice, rhonchi and wheezes over the middle right lung field, an enlarged liver, abdominal discomfort, mild ascites and flapping tremor. Blood pressure was 120/80 mm Hg and heart rate 130 bpm. Routine laboratory examination showed high white cell count with a relative increase in monocytes (1800 el/µL on a total of 13 040 el/µL leucocytes), elevated C reactive protein (54.7 mg/L) and abnormal liver function tests (aspartate aminotransferase (AST) 185 U/L, alanine aminotransferase (ALT) 54 U/L, bilirubin 162.1 µmol/L, γ-glutamyl transferase (GGT) 365 U/L, INR 1.53, ammonia 58 µmol/L). The chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score was 7. Abdominal ultrasound confirmed cirrhosis (Model for End-Stage Liver Disease (MELD) score 20) and ascites, but explorative paracentesis was not feasible because of the small volume of fluid.

A diagnosis of ACLF and SIRS was made, and acute alcoholic hepatitis suspected; however, steroids were not started. Chest X-ray documented parahilar opacity in the right upper lobe, and urine dipstick was compatible with urinary tract infection. The patient was started on broad-spectrum antibiotics, with rapid remission of the abdominal pain. On day 11 after admission, diarrhoea and fever (up to 38.2°C) continued (figure 1, top panel). Faecal culture and assessment for *Clostridium difficile* toxins were negative.

Contrast-enhanced thoracic and abdominal computerised tomography was performed and showed a 2.5 cm nodule in the right upper lobe of the lung, 1 cm enlarged lymph nodes on mediastinal, axillary, abdominal and pelvic sites, and irregular liver margins. Echocardiography showed no evidence of endocarditis, and tuberculosis screening was negative.

Extensive microbiological screening, to include HAV, HBV, HCV, HEV, *Borrelia burgdorferi*, *Bartonella*, *Leptospira*, *Rubella*, *Chlamydia*, *Treponema pallidum*, *Mycoplasma*, *Plasmodium*, HIV and cytomegalovirus (CMV), was performed. Of note, HAV-IgM was negative, HBV serology showed no signs of previous infection and HCV antibodies were positive with negative HCV-RNA. CMV-IgM was positive, and CMV-DNA viral load was 1473 copies/mL. Ganciclovir was started on day 20 at a dose of 5 mg/kg/die. Fever slowly lowered and disappeared on day 28.

The patient was discharged with a MELD score of 14, no ascites and no symptoms. A positron emission tomography scan confirmed pulmonary malignancy, which was removed by thoracoscopic lobectomy; histology was compatible with adenocarcinoma and no radio/chemotherapy was needed. On 8-month follow-up, the patient remains well and substantially compensated from a liver standpoint (no ascites, MELD 15).

In April 2014, this patient's 49-year-old brother, suffering from HCV and alcohol-related cirrhosis, was referred to our outpatient clinic for rapid development of tense ascites and ankle swelling. The patient reported progressive weight gain over the previous week (from 65 to 79 kg), accompanied by abdominal discomfort, diarrhoea and low-grade fever (up to 37.3°C). He was a smoker and had a history of chronic alcohol misuse, but he had been abstinent for 2 months, which was confirmed by relatives. He had precarious living and social conditions. He had been diagnosed with cirrhosis (MELD score 18) 1 month earlier, and abdominal computerised tomography had also shown considerable fatty infiltration and a minor amount of peri-hepatic ascites. Upper gastrointestinal endoscopy revealed duodenitis with duodenal erosions; no oesophageal varices were documented.

Physical examination showed jaundice, moderate ascites and marked ankle swelling. Blood pressure was 125/70 mm Hg and heart rate 85 bpm. Laboratory examination showed high white cell count (15 090 el/µL, 43% lymphocytes), mild thrombocytopaenia (132.000/mL) and worsening of liver function (AST 110 U/L, ALT 65 U/L, INR 2.02 after vitamin K supplementation, bilirubin 147 µmol/L; MELD score 22). Renal function was normal. HCV load was 67 UI/mL. HAV, HBV and HEV serology was negative, with no signs of previous infection. The patient was admitted with a diagnosis of acute liver decompensation; an exploratory paracentesis showed no evidence of bacterial peritonitis, urine dipstick and blood cultures were negative. Abdominal ultrasound showed no signs of portal thrombosis; an echocardiogram showed normal cardiac function with minor increase in pulmonary pressure.

The patient was treated with empiric antibiotic therapy (piperacillin and tazobactam) and parenteral diuretics (up to 700 mg/day of potassium canrenoate and 40 mg/day of furosemide, based on electrolytes). Nevertheless, his weight continued to increase and a 6 L paracentesis was performed on day 7 (figure 1, bottom panel).

Considering his recent family history, viral screening was performed soon after his hospital admission: CMV-DNA quantification was negative but CMV-IgM was positive, suggesting recent viral infection. Antiviral treatment was not started because of rapid viral clearance and unfavourable risk–benefit ratio, considering the tendency towards spontaneous resolution of symptoms: fever had resolved on day 5 and diarrhoea had progressively improved with no treatment. The patient was discharged on day 25 with no fever, no abdominal symptoms, a MELD score of 19 and a weight of 63 kg. He remains well on 90-day follow-up, with an MELD score of 18.

DISCUSSION

CMV is a ubiquitous double-stranded DNA virus belonging to the Herpesviridae family. CMV infection can

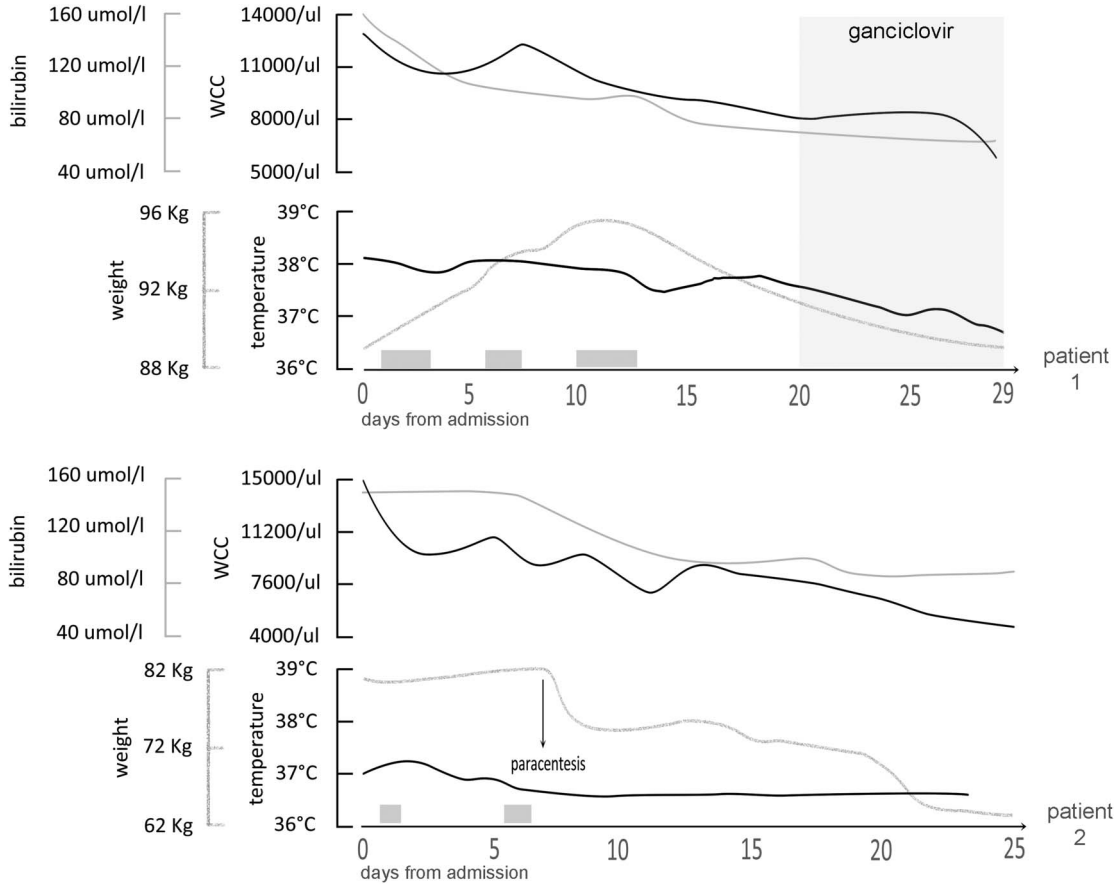

Figure 1 Time course of relevant laboratory and clinical variables in patient 1 (top panel) and patient 2 (bottom panel) during their hospital stay. Thick grey bars indicate episodes of diarrhoea, and the grey-shaded area indicates the period of treatment with ganciclovir in patient 1 (WCC, white cell count).

occur via blood or tissue exposure, or through close contact. Infection is diagnosed as the presence of at least one of the following: detection of CMV-DNA via culture or molecular techniques, seroconversion with the appearance of anti-CMV IgM antibodies or a four-fold increase in anti-CMV IgG titres. Active infection can be either the first infection in a naïve patient, a reactivation of an endogenous latent virus, or a reinfection by a different strain in an already infected patient.[5]

CMV disease is defined as a combination of infection, and clinical symptoms and signs. The spectrum of illness is strictly dependent on the host immune system: in the immunocompetent adult, primary CMV infection is most commonly subclinical and can sometimes result in a heterophile-negative mononucleosis syndrome, but it is, rarely, able to lead to severe organ-specific complications. Treatment is usually not warranted in immunocompetent patients with self-limiting illness. In the immunocompromised host, reactivation is more frequent and, as well as primary CMV infection and re-infection, is associated with significant morbidity and mortality. The spectrum of illness in this population can more easily vary from organ-specific impairment such as colitis, hepatitis and pneumonia, to a multisystem disorder. Treatment of these patients is usually initiated with intravenous ganciclovir until resolution of symptoms, often followed by a course of oral valganciclovir. Over the past few years, a grey zone has been defined between patients considered to be more at risk of infection, notably transplant recipients and HIV-infected patients, and the immunocompetent population: critically ill patients, such as those admitted to intensive care units, have shown a prevalence of active infection of up to 36%, with a negative influence on their prognosis.[6] The extent of this grey zone has not been clearly defined. It has been shown that molecular signs of recent CMV reactivation are also relatively common in cirrhotic patients[7 8] before transplantation, but infection has been suggested to be mild or asymptomatic.

When considering the clinical cases presented here, the first doubt is whether CMV acted as a simple opportunistic 'spectator' or as an active pathogen with a direct influence on prognosis. In other words, whether our patients had CMV infection or CMV disease. Of note, biopsies were not performed, thus the diagnosis rested on clinical and laboratory findings. Both our patients showed symptoms (diarrhoea, fever and abdominal pain) that are typical of CMV colitis, along with decompensation of a previously stable cirrhosis. We can think of two different roles for the virus in our patients: (1) a

primary precipitating illness; (2) a key component of the well-described vicious cycle in which an inflammatory response leads to immune deregulation and to a consequent infection, worsening inflammation.[4] As for the first point, it is known that in a significant proportion of patients presenting with liver decompensation or ACLF, clinicians are unable to define a precipitating factor.[1] Routine investigations in such patients are not usually as comprehensive as those performed in major immunocompromised states, such as the post-transplant setting. Our patients were not severely immunocompromised, but liver disease and alcohol misuse may have acted synergistically on reactivation and loss of control of the replicating virus. Cirrhosis is a condition in which depression and overstimulation of the immune system coexist,[9] and alcohol misuse contributes to a further impairment in the immune response. This is interesting when considering the potential for CMV infection or reactivation, for two main reasons: first, latent CMV control is strictly dependent on CD4+ and CD8+ T-cell function, which is deranged in cirrhosis as a result of high antigen load due to bacterial translocation,[10] and natural killer cell function, which is impaired in relation to chronic alcohol consumption.[11] Second, CMV reactivation is stimulated by three main pathways: (1) release of tumour necrosis factor α (TNFα), which binds to TNFα receptor on latently infected cells, with the activation of nuclear factor κB and initiation of viral replication; (2) release of inflammatory prostaglandins, with cyclic AMP (cAMP) activation and (3) catecholamine-mediated production of cAMP.[5] TNFα production is enhanced both in liver failure and in chronic alcohol consumption, because of enhanced gut permeability and consequent lipopolysaccharide-mediated Kupffer cell activation, resulting in increased serum levels of TNFα and other pro-inflammatory cytochines.[12] This latter mechanism is amplified in the setting of our second hypothesis, that is, viral reactivation as a result of immune deregulation caused by SIRS, which, in turn, leads to further worsening of the inflammatory state. This mechanism might have been in action in the first patient, in whom bacterial infection could have increased the predisposition to CMV reactivation, until viral infection became prevalent.

The two patients differed in clinical severity (acute decompensation vs ACLF), concomitant precipitant events (none vs bacterial infection), and the type of management required for the CMV infection. The second patient was not treated with antivirals, as he had shown greater control of infection with rapid clearance of CMV-DNA and progressive amelioration of symptoms. The first patient was treated with antivirals, as he showed much poorer response to the infection and worse general status. This somehow parallels the intermediate position of our patients between severely immunocompromised patients, and the immunocompetent population. As far as treatment is concerned, it is also worth noting that in our first patient, clinical history could also suggest alcoholic hepatitis, potentially leading to deleterious initiation of steroids if the viral aetiology had not been considered.

In conclusion, we have presented the cases of two brothers in whom CMV infection/reactivation may have played a crucial role in precipitating acute hepatic decompensation and ACLF, respectively. As identification and early treatment of precipitants impinge on the prognosis of both such conditions, it is our impression that screening for CMV may be worthy, especially when additional predisposing factors such as alcohol consumption are present.

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