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Case report | Prikaz bolesnika

Acute-On-Chronic Liver Failure Triggered by Dobrava Hantavirus Infection: A Case Report

Akutizacija kroničnog zatajenja jetre uzrokovana infekcijom hantavirusom Dobrava: prikaz slučaja

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Summary

Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome characterised by acute worsening of liver function and extrahepatic organ failure in patients with chronic liver disease. Bacterial infections are the most common trigger; however, viral and zoonotic pathogens remain underrecognized causes. We present a case of ACLF precipitated by presumed Dobrava hantavirus infection, complicated by haemorrhagic shock, acute kidney injury, and fatal outcome.

Sažetak

Akutizacija kroničnog zatajenja jetre (engl. *acute-on-chronic liver failure,* ACLF) predstavlja životno ugrožavajući sindrom karakteriziran akutnim pogoršanjem funkcije jetre i zatajenjem drugih organa u bolesnika s kroničnom bolešću jetre. Bakterijske infekcije su najčešći okidači, iako su virusni i zoonotski patogeni često nedostatno prepoznati. Donosimo prikaz slučaja ACLF-a precipitiranog vjerojatnom infekcijom hantavirusom Dobrava, kompliciranog hemoragijskim šokom, akutnim bubrežnim oštećenjem i smrtnim ishodom.

Introduction

Acute-on-chronic liver failure (ACLF) is a clinical syndrome that develops in patients with underlying chronic liver disease, characterised by acute deterioration of liver function, failure of one or more extrahepatic organs, and high short-term mortality[1]. Bacterial infections are the most common trigger, whereas zoonotic infections are rarely recognized in this context. While supportive management may be effective in some cases, liver transplantation remains the only definitive therapy for highly selected patients not responding to conservative measures[2].

Hantaviruses are recognised as significant human pathogens with reservoirs in animals such as rodents[3]. Depending on the serotype, these viruses are known to cause two clinical syndromes: haemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). HFRS case fatality rate

is 1-15%[4]. Hantaviruses predominantly infect microvascular endothelial cells in various organs, including the lungs, kidneys, heart, liver, and spleen, leading to increased vascular permeability[5]. Vascular permeability leads to leakage, acute kidney injury (AKI), and coagulation abnormalities[6]. In addition to the direct effect the viral infection has on endothelial cells, an immunological response to the infection is suggested to play an important role in the development of HFRS[6]. There is no specific treatment. Although hepatic involvement in hantavirus infection is well documented, it has predominantly been described in the context of transient liver enzyme elevation or, in rare cases, as a trigger of autoimmune liver disease[7,8]. Hantavirus infection precipitating ACLF has, to our knowledge, not been previously described.

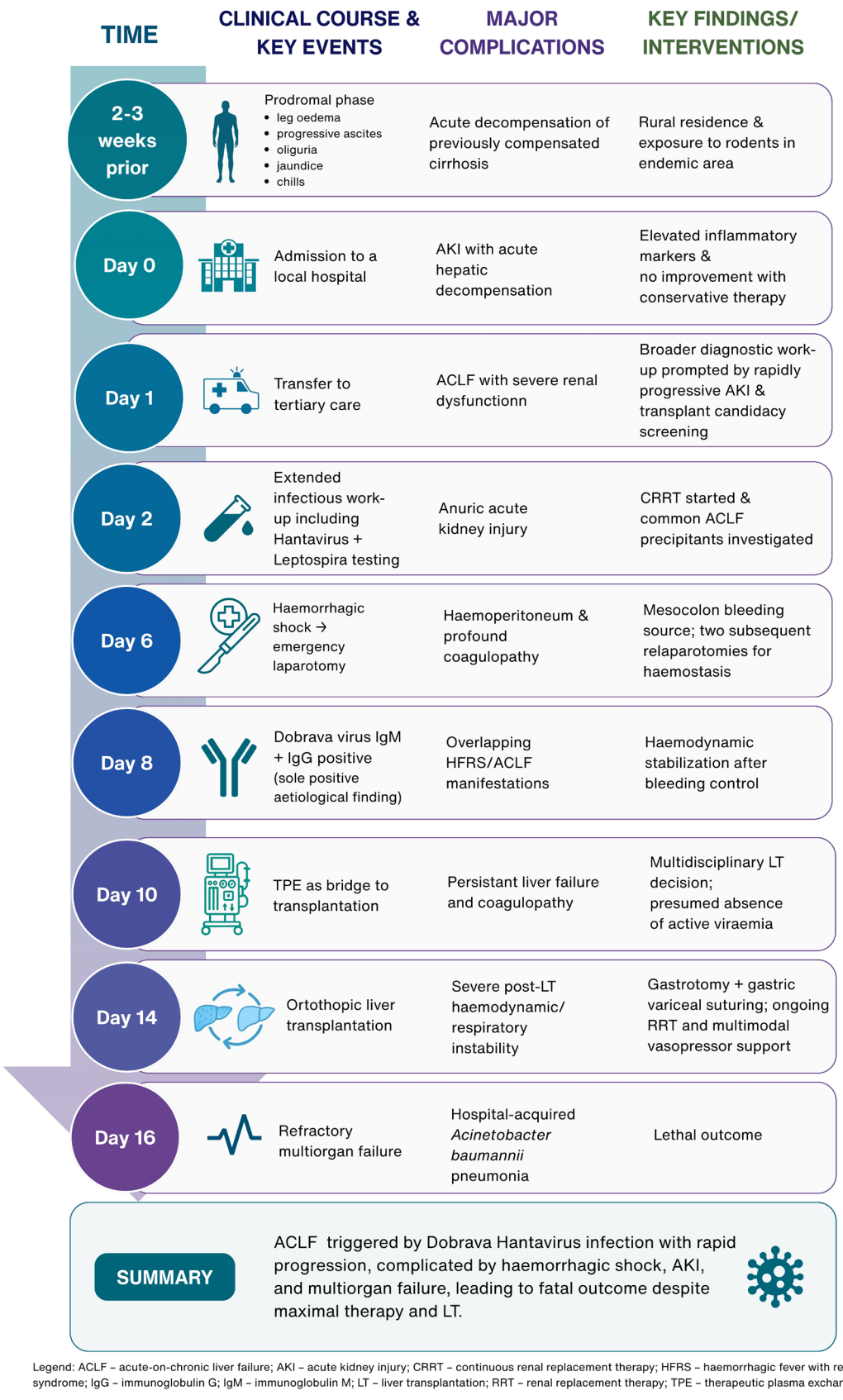
We present a case analysis of a patient with compensated advanced chronic liver disease who developed ACLF precipitated by hantavirus infection. Informed consent and institutional ethics board approval were obtained.

Patient Presentation

A 53-year-old man from a rural area presented initially to a local hospital with signs of acutely decompensated cirrhosis. The patient had prior compensated advanced chronic liver disease due to alcohol consumption, arterial hypertension, gonarthrosis, and moderate mitral regurgitation. His chronic therapy included antihypertensives, diuretics, a statin, a proton pump inhibitor, and vitamin supplements. The patient developed leg oedema, jaundice, progressive ascites, and oliguria two to three weeks before hospitalization. Although he reported chills, he was afebrile on initial assessment. No antibiotic treatment was initiated before hospitalization. Initial work-up verified AKI with elevated inflammatory biomarkers. Due to the lack of improvement with conservative therapy and suspected ACLF with possible hepatorenal syndrome, he was transferred after a 24-hour hospitalization in the local hospital on Day 1 to a tertiary institution where continuous renal replacement therapy (CRRT) was started. Although the clinical picture was compatible with ACLF, the unusually rapid progression of kidney injury and early requirement for CRRT prompted a broader diagnostic evaluation to identify potential precipitating factors and alternative causes of renal dysfunction.

A comprehensive immunologic and microbiologic evaluation was undertaken. Blood, ascites, and urine cultures remained sterile. Serology for hepatitis B, C, A, and E viruses, as well as HIV, was negative. The patient was five months abstinent from alcohol before hospitalization. Immunologic testing, including antinuclear antibodies (ANA), anti-smooth muscle antibodies, antimitochondrial antibodies, liver-kidney microsomal type 1 antibodies, soluble liver antigen/liver-pancreas antibodies, and antineutrophil cytoplasmic antibodies (ANCA), was negative. Cryoglobulins were not detected. Previous investigations had excluded Wilson's disease and haemochromatosis. Given the patient's rural background and the unusually severe and rapidly progressive kidney injury, additional testing for zoonotic infections, including Leptospira (microscopic agglutination test) and hantavirus infection (indirect immunofluorescence assay), was performed on Day 2 after more common precipitants of ACLF had been excluded.

In the following days, clinical signs of haemorrhagic diathesis became evident. On Day 6, the patient developed haemorrhagic shock. Laboratory findings are presented in Table 1 and the timeline of events in Figure 1. Emergency upper endoscopy showed signs of portal gastropathy without major bleeding. A CT scan confirmed haemoperitoneum, requiring emergency laparotomy, which identified the mesocolon of the hepatic flexure as the source of bleeding. Two additional urgent relaparotomies were later required to achieve haemostasis. Positive serology on Day 8 confirmed Dobrava virus infection (IgM and IgG positive). Following surgical control of the bleeding source, the patient achieved haemodynamic stabilization; however, laboratory parameters continued to indicate progressive liver failure (Table 1). At this stage, the clinical course posed a significant management dilemma. While severe coagulopathy and haemorrhagic complications may occur in ACLF, the newly identified Dobrava hantavirus infection likely also contributed to the bleeding tendency and multiorgan dysfunction, making it difficult to determine the relative contribution of each process. Given the ongoing deterioration, the case was discussed by a multidisciplinary liver transplant team to assess the likelihood of reversibility and the potential role of liver transplantation. An infectious disease specialist was consulted regarding the Dobrava hantavirus infection and confirmed that, given the duration of infection, active viraemia was presumed no longer present and viral reactivation was not a concern, and the decision to list the patient was made. Therapeutic plasma exchange was performed on Day 10 to address the severe refractory coagulopathy and bridge the patient to liver transplantation. An orthotopic liver transplant was performed on Day 14, along with a gastrotomy with suturing of gastric varices. Explant histopathology confirmed liver



Legend: ACLF – acute-on-chronic liver failure; AKI – acute kidney injury; CRRT – continuous renal replacement therapy; HFRS – haemorrhagic fever with renal syndrome; IgG – immunoglobulin G; IgM – immunoglobulin M; LT – liver transplantation; RRT – renal replacement therapy; TPE – therapeutic plasma exchange.

Figure 1. Timeline of main clinical events

Slika 1. Vremenski slijed glavnih kliničkih događaja

Table 1. Laboratory findings during hospitalization
Tablica 1. Laboratorijski nalazi tijekom hospitalizacije

	Day 1 (at transfer)	Day 6 (haemorrhagic shock)	Day 10 (before TPE)	Day 11 (after TPE)	Day 14 (day of LT, before LT)	Day 16 (day of death)
Hb (g/L)	112	65	79	93	76	97
L (x10^9/L)	23.7	19.2	27.7	25.5	25.6	11.2
Trc (x10^9/L)	144	26	45	40	13	27
INR	1.89	2.45	1.93	1.42	2.82	1.39
APTT (s)	48.0	131.4	47.6	31.0	54.5	31.4
Fibrinogen (g/L)	1.3	0.5	1.6	1.7	1.1	2.1
Bilirubin (µmol/L)	302	160	240	197	262	184
ALP (U/L)	384	312	216	145	181	122
AST (U/L)	205	268	1445	574	282	391
ALT (U/L)	67	89	369	165	60	258
GGT (U/L)	596	350	72	45	40	20
Urea (mmol/L)	20.4	11	1.6	1.7	2.0	5.5
Creatinine (µmol/L)	683	479	96	93	101	65
CRP (mg/L)	63	46.8	14.8	11.8	13.2	82.7
PCT (µg/L)	6.87	3.2	0.66	0.39	0.28	4.88
Child Pugh class	C	/	/	/	C	/
MELD-Na score	39	/	/	/	41	/
CLIF-C ACLF score	61	/	/	/	81	/

Legend: TPE - therapeutic plasma exchange, LT- liver transplantation, Hb - haemoglobin, L- leukocyte count, Trc - thrombocyte count, ALP - alkaline phosphatase, AST - aspartate aminotransferase, ALT - alanine aminotransferase, GGT - gamma-glutamyl transferase, CRP - C-reactive protein, PCT - procalcitonin, CLIF-C ACLF score - Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure score.

Reference range: Hb (men) = 138 - 175 g/L; Lk = 3.4 - 9.7 x10^9/L; Trc = 158 - 424 x10^9/L; APTT = 20 - 30 s; Fibrinogen = 1.8 - 4.1 g/L; Bilirubin = 3 - 20 µmol/L; ALP = 60 - 142 U/L; AST = 11 - 38 U/L; ALT = 12 - 48 U/L; GGT = 11 - 55 U/L; Urea = 2.8 - 8.3 mmol/L; Creatinine = 60 - 104 µmol/L; CRP < 5 mg/L; PCT < 0.25 µg/L.

cirrhosis and did not identify features of acute alcohol-associated hepatitis or any alternative pathological process that could explain the episode of liver failure. Immunosuppressive therapy consisted of basiliximab, methylprednisolone, tacrolimus, and mycophenolate mofetil. The posttransplant course was complicated by haemodynamic and respiratory instability, requiring significant multimodal vasopressor support. Bilateral chest tubes were placed due to pleural effusions. Renal replacement therapy was maintained throughout the postoperative period. A new hospital-acquired *Acinetobacter baumannii* pneumonia led to further deterioration. Unfortunately, multiorgan failure progressed, and, despite all efforts, the patient died on Day 16 of hospitalization.

Discussion

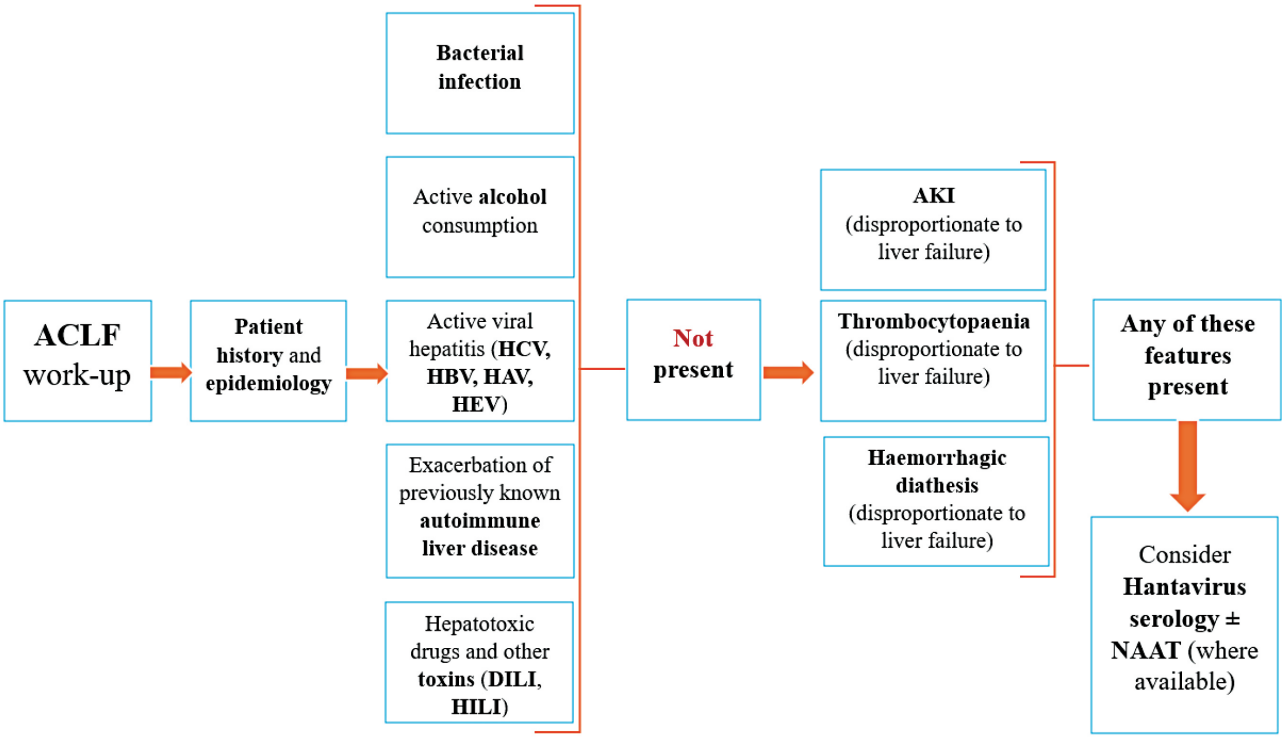
ACLF is a life-threatening syndrome characterised by acute worsening of liver function and extrahepatic organ failure in patients with chronic liver disease. The most common triggers of ACLF are bacterial infections, accounting for 37-46% of cases in Western cohorts[1,9]. Active alcohol consumption is the next most common precipitating factor, responsible for up to 38% of cases in alcohol-predominant cohorts[1]. Viral infections with hepatitis B and E viruses are important triggers in endemic regions (Asia and Africa) [1,10,11]. However, in up to 43% of ACLF cases, no precipitating factor is found[1].

Zoonotic and non-hepatotropic viruses are not part of a routine work-up in patients with ACLF pri-

marily due to the predominance of bacterial triggers. However, when no obvious trigger is identified, or the clinical presentation is atypical, consideration of alternative infectious triggers may be warranted.

In our case, a significant AKI with a rapid need for CRRT, accompanied by an exaggerated haemorrhagic diathesis, disproportionate to the stage of liver decompensation, initiated a broader microbiological and serological AKI work-up. Dobrava, Hantaan, and Seoul hantaviruses more frequently cause a more severe form of HFRS, while patients infected with Puumala virus often have a milder clinical course[5]. Acute liver failure due to hantavirus infection has not been described as a separate entity, but severe liver dysfunction has been noted during severe HFRS with multiorgan failure. A significant elevation in liver enzymes seems to correlate with the severity of HFRS[12]. In patients with HCPS, viral antigens (mostly Sin Nombre virus) were sporadically detected in hepatocytes, sinusoidal endothelial cells, and Kupffer cells[5]. While in patients with HFRS, liver involvement is mostly reported in Seoul virus infections, where it manifests as an acute viral hepatitis picture with lobular necrosis and elevation of liver enzymes[5]. With Hantaan virus infections, focal midzonal necrosis and mild mononuclear infiltrates were found in the liver[5]. Viral antigens were not specifically reported in liver specimens in HFRS patients[5]. Two case reports presented autoimmune liver disease precipitated by hantavirus infection, one that describes the exacerbation of a previously known autoimmune liver disease[8], while the other presents an acute, possibly autoimmune, hepatitis with positive ANA antibodies[7]. Chronic hepatitis due to hantavirus infection has not been identified. Although serologic studies have detected antibodies in some patients with chronic liver disease, a causal relationship has not been determined[7].

To our knowledge, this is the first reported case of ACLF precipitated by highly probable Dobrava hantavirus infection, complicated by haemorrhagic shock, AKI, and the need for liver transplantation. This case highlights Dobrava hantavirus infection as a rare but severe trigger of ACLF, presenting with disproportionate AKI and profound coagulopathy. In patients with ACLF presenting with atypically severe renal dysfunction or bleeding diathesis, particularly when accompanied by a compatible epidemiological history, evaluation for zoonotic infections may be warranted.



Legend: ACLF - acute-on-chronic liver failure, HCV - hepatitis C virus, HBV - hepatitis B virus, HAV - hepatitis A virus, HEV - hepatitis E virus, DILI - drug-induced liver injury, HILI - herb-induced liver injury, AKI - acute kidney injury, NAAT - nucleic acid amplification testing.

Figure 2. Proposed algorithm for hantavirus work-up in ACLF patients

Slika 2. Predloženi algoritam dijagnostičke obrade infekcije hantavirusom u bolesnika s akutizacijom kroničnog zatajenja jetre (ACLF)

In our case, hantavirus infection was determined to be the precipitating factor of ACLF based on positive serology (IgM and IgG) for Dobrava virus and on systematic exclusion of other more common causes such as bacterial infections, alcohol-associated hepatitis, viral hepatitis, and autoimmune liver disease. Also, the indirect immunofluorescence assay used has a reported sensitivity of 98% and specificity of 91% for Dobrava, Hantaan, and Puumala infections[13], and our report yielded negative results for the other hantaviruses tested (Hantaan, Puumala, Saaremaa, and Seoul). Also, the clinical course with rapid deterioration of kidney function and haemorrhagic diathesis, not entirely explained by the degree of hepatic decompensation, further supports Dobrava hantavirus infection as the precipitating event.

To conclude, Dobrava hantavirus infection should be recognised as a potential, albeit rare, precipitating factor of ACLF. Although routine screening is not warranted, clinicians should consider zoonotic infections in patients with atypical presentations, particularly those with disproportionate AKI, haemorrhagic diathesis, and relevant epidemiological exposures. The present case further illustrates the complexity of transplant decision-making when ACLF develops in the setting of a severe systemic infection with overlapping clinical features. (Figure 2).

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