Herpesviridae. A Young Man with Acute Liver Failure and Hemolysis

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D. Pérez-Torres et al. (eds.), *Best 2022 Clinical Cases in Intensive Care Medicine*, Lessons from the ICU,
https://doi.org/10.1007/978-3-031-36398-6_11

Learning Objectives

- Diagnostic approach to an acute liver failure.
- Differential diagnosis of autoimmune hemolytic anemia.
- Treatment of severe autoimmune hemolytic anemia.

11.1 Introduction

We present a rare case of a young man with Epstein Barr virus (EBV) primoinfection, leading to fulminant hepatitis, associated with severe autoimmune hemolytic anemia (AIHA) and multiorgan failure. Although the severity of this disease is uncommon, rapid assessment, focused diagnostics, and the start of proper intensive care and organ support are crucial.

Case Presentation

A 26-year-old man with no relevant medical history visited his general practitioner with one-week-long headaches. In the absence of any other symptoms, only nonsteroid analgesics were prescribed without further examination. A few days later, he developed fevers up to 40 °C and mild pain in the right upper quadrant. The patient presented with these symptoms and mild icterus at the Infectious Disease Clinic. There was no history of traveling, contact with toxins, or hepatotoxic medication. Because of the progression of his condition—decreased level of consciousness and anuric renal failure—he was admitted to our Intensive Care Unit (ICU).

11.2 Investigations

At admission, the clinical investigation showed a patient with drowsiness, hemodynamically stable, with normal capillary refill time, and without any respiratory insufficiency. Fever and mild pain in the right hypochondrium were present. He remained anuric for the first hours, fulfilling acute kidney injury stage 2 according to the Acute Kidney Injury Network (AKIN). Abdominal and head computer tomography showed only hepatosplenomegaly with no other pathologic findings. His lab tests at admission revealed a slight anemia, conjugated hyperbilirubinemia, elevated liver function tests (LFT), urea, creatinine, as well as high procalcitonin and C-reactive protein levels. Hyperferritinemia, unmeasurable high lactate dehydrogenase (LD), and extremely low haptoglobin were found—see Table 11.1. With a working diagnosis of hepatitis and hemolysis, extensive microbiological and autoimmune screening was initiated—results are mentioned in Table 11.2.

Table 11.1 Lab results at ICU admission

Lab results	Value	Lab results	Value
Hemoglobin	67 g/L	Ammoniac	36 µmol/L
Leukocytes	36.2×10^9/L	Creatinine	440 µmol/L
Platelets	187×10^9/L	Urea	26 mmol/L
Bilirubin (conjug.)	305 (205) µkat/L	CRP	47 mg/L
AST	4.6 µkat/L	Procalcitonine	26.1 µg/L
ALT	2.8 µkat/L	Ferritin	24.230 µg/L
GGT	1.9 µkat/L	Ceruloplasmin	0.42 g/L
LD	Unmeasurable high	Haptoglobine	Unmeasurable low

AST aspartateaminotransferase, *ALT* alaninaminotransferase, *GGT* gamaglutamyltransferase, *LD* lactatedehydrogenase, *CRP* C-reactive protein

Table 11.2 Microbiological, virological, and autoimmunity tests, which were performed (positive findings are marked bold)

Micro/virology	Immunology
Leptospira, legionella (antibody)	Antinuclear antibodies
Hepatitis A, B, C, E (PCR/antibody)	Extractable nuclear antibodies
Herpes virus 1,2 (PCR)	Antidouble-strand DNA antibodies
Cytomegalovirus, parvovirus B19 (PCR)	Anti-neutrophil cytoplasmic antibodies
Human immunodeficiency virus (PCR)	Rheumatoid factor
Varicella zoster virus (PCR)	Antismooth muscle antibodies
SARS-CoV-2 (PCR)	Liver kidney microsomes autoantibodies
Parainfluenza, influenza, human herpesvirus 6 (antibody)	Antimitochondrial antibiodies
EBV – Early antibody and viral capsid antigen + PCR	Anti-actin antibodies

11.3 Differential Diagnosis

The most common causes of acute liver failure are infectious (viral), toxic-induced, autoimmune, or metabolic. In addition to the patient's history and course of disease, laboratory tests play a major role in differential diagnosis—polymerase chain reaction (PCR) and antibody testing for hepatotropic viruses and (in Central Europe) uncommon bacterial infections. Toxicologic screening can be done, but the spectrum of toxins is broad and only a few of them can be routinely tested (e.g., acetamino-

phen). Autoimmune screening can reveal the presence of antimicrosomal and smooth-muscle antibodies. Metabolic causes, mainly Wilson's disease, can be excluded with normal ceruloplasmin blood levels and genetic testing (ATP7B gene).

Hemolytic anemia, diagnosed by the decrease of hemoglobin and erythrocyte levels, LD, low haptoglobin, and conjugated hyperbilirubinemia can be primary (inherited, like in sickle cell anemia and thalassemia) or secondary associated with infections, drugs, hematologic malignancy, autoimmune conditions, or as a reaction to a transfusion. The mechanism of erythrocyte lysis involves the production of antibodies against antigens on the erythrocyte wall and the destruction of the erythrocyte intravascularly or in the spleen. According to the type of antibodies, anemias can be divided into AIHA with warm antibodies, cold agglutinin disease (CAD), and paroxysmal night hemoglobinuria (PNH). Direct and indirect Coombs tests, flowcytometry, and focused genetic testing in special cases [1] are the cornerstones of diagnostics.

In our case, the positivity of EBV antigens was found on day 3, confirmed by an extreme load of EBV in plasma—more than 400,000 copies/mL. All other microbiological tests were negative. Hematological tests performed on the first day revealed incomplete warm IgG antibodies. Flowcytometry of the peripheral blood was negative for PNH or malignant lymphocyte clones. Diagnosis of EBV hepatitis and secondary warm AIHA was made.

11.4 Treatment

The patient received standard organ support according to the clinical evolution—one run of continuous renal replacement (indicated on day 2 for lasting anuric renal failure and hyperkalemia), with the use of a polymer absorption filter to control hyperbilirubinemia. A broad-spectrum antibiotic (meropenem) was prescribed until the first negative microbiological test was achieved (discontinued on day 5). There was a need for repeated erythrocyte transfusions on the first days because of rapid hemolysis with hemoglobin falling to 60 g/L. All blood transfusions were given warmed. As there is still no approved antiviral drug for EBV, the off-label use of valaciclovir (1 g three times a day perorally) was discussed and later started due to persistently high EBV loads in plasma. Hemolytic anemia was treated with corticosteroids (prednisone 1 mg/kg) and immunoglobulin (0.5 g/kg a day for 5 days) infusions. Hemolysis was sufficiently controlled on day 5.

11.5 Clinical Evolution, Outcome, and Follow-up

After eight days in the ICU, the patient was transferred in stable conditions to the nephrology ward. His renal function was completely restored after two weeks, and he was discharged from the hospital. LFT fell to normal values in one month. Corticosteroids were tapered without a relapse of hemolysis. The cause of renal failure was diagnosed as a tubulointerstitial lesion of viral etiology. Three months later, the patient returned to work.

11.6 Discussion

Epstein Barr virus is a common herpetic deoxyribonucleic acid (DNA) virus, causing infectious mononucleosis and hairy leukoplakia. Infection is also associated with some hematological malignancies. Primary infection is very common in young people, usually with mild symptoms such as pharyngitis, fever, and lymphadenopathy. More than 90% of the European population has measurable antibodies. In rare cases, severe complications like splenic rupture, meningoencephalitis, hemolytic anemia, or triggered hemophagocytic lymphohistiocytosis are described. In our case, fulminant hemolysis was present. EBV infection with IgG-mediated warm AIHA is uncommon, although well described [2]. Differential diagnosis of AIHA type is critical because of different first-line treatments and exclusion of underlying hematological disease. The etiology of renal failure in our patient was initially unclear, and progression was acute and required renal replacement. Further examination in the nephrology unit was done, but renal biopsy was deferred because of anatomical conditions and restoration of renal functions. The definitive diagnosis of viral-induced tubulointerstitial nephritis was made. The use of polymer absorption is still a controversial therapy but is relatively established in hyperbilirubinemia, caused by hemolysis in this patient. The causal treatment of EBV infection is unavailable at the moment. Nearly all infections are mild and treated symptomatically. Because of persistent high viral loads in plasma PCR controls, an off-label valaciclovir course was initiated, based on case reports and the experience of transplantation nephrologists. This treatment resulted in a rapid decrease in EBV load. No autoimmune disease or underlying hematological conditions were found and the patient was fully immunocompetent.

Take-Home Messages

- Viral hepatitis is one of the most common causes of hepatic failure.
- Autoimmune-mediated hemolysis can be associated with a viral infection.
- Corticosteroid course and immunoglobulin infusion are the first-line treatment for warm AIHA.

Summary

In this case, we present a previously healthy young man with a short history of headaches and fever. He presented with signs of liver and renal failure at admission to the hospital and was transferred to the ICU for the progression of multiorgan failure. From initial exams, a diagnosis of hepatitis and autoimmune hemolytic anemia was made. Broad microbiological and hematological testing was performed. Upon investigation, the cause was determined to be a primary infection with Epstein Barr virus. This infection caused hepatitis and hemolytic anemia. A severe course of hemolysis required repeated transfusions. Continuous renal replacement with polymer absorption was needed because of anuric renal failure and hyperbilirubinemia. After the diagnosis of present warm agglutinins, hemolysis was successfully treated with corticosteroid and immunoglobulin infusions. Upon stabilization, the patient was transferred to a nephrology unit where his renal functions were completely restored. Successful off-label treatment of EBV with valaciclovir was later performed.

Acknowledgments We want to thank our colleagues from the department of hematologic oncology and nephrology (Dr. Lysak and Dr. Kielberger) for frequent consultations and help with diagnostics and treatment.

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