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A man in his 60s with immunodeficiency and hepatitis

EDUCATIONAL CASE REPORT

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Background

Major causes of elevated liver enzymes are toxic, infectious, neoplastic and autoimmune disease. In immunocompromised patients, the spectrum of infectious pathogens causing hepatitis is broader and the immune response is blunted, making diagnosis more challenging.

Case presentation

A man in his sixties had received CAR-T therapy for multiple myeloma.

Six months later, he presented with hepatitis. Initial diagnostic work up with biopsy, CT scan, autoantibody testing and serology for the infectious agents hepatitis A, B, C, E, EBV and CMV did not reveal the cause of his hepatitis. Chronic hepatitis E was ultimately confirmed in PCR testing for hepatitis E virus (HEV) ribonucleic acid (RNA) in blood. The patient was treated with ribavirin for a total of seven months, after which the virus was cleared.

Interpretation

The increasing number of immunocompromised patients means that more patients are at risk of developing chronic hepatitis E. Serologic tests may be unreliable for this patient population, and nucleic acid testing for HEV RNA should be the primary diagnostic approach. HEV can be contracted in Norway, and hepatitis E is an underdiagnosed infection.

A man in his sixties with immunodeficiency was admitted to hospital with hepatitis. Investigation revealed a common condition that is likely underdiagnosed in Norway.

An overweight man in his sixties with hypogammaglobulinaemia and bone marrow failure was admitted to hospital for investigation of hepatitis. He had recently been hospitalised with an uncomplicated respiratory infection. At that time, elevated liver enzymes were noted: alanine aminotransferase (ALT) 160 U/L (reference range 10–70), alkaline phosphatase (ALP) 220 U/L (35–105) and gamma-glutamyl transferase (γ-GT) 330 U/L (15–115). Ultrasound of the liver and biliary tract showed no abnormal findings, although visualisation was suboptimal. Following discharge, liver enzymes were monitored by the patient's general practitioner and remained stably elevated at levels similar to those during hospitalisation. Six weeks later, a rapid rise in ALT to 954 U/L and γ-GT to 449 U/L occurred, prompting acute re-admission for further evaluation.

On admission, the patient reported some fatigue but was otherwise in good general condition, with no organ-specific symptoms. He did not appear jaundiced, although he had recently noticed darker urine. On examination, he was afebrile; the liver was not enlarged on abdominal palpation, and there were no clinical signs of advanced liver disease. The patient reported a modest alcohol intake of 1–2 units per month. Three weeks prior to admission, treatment with semaglutide for obesity had been initiated, but he had not started any other new medications in recent months. His medical history included prostate cancer surgery, diet-controlled type 2 diabetes, and established coronary artery disease (previously treated with percutaneous coronary intervention), for which he was taking acetylsalicylic acid, atorvastatin, diltiazem and isosorbide mononitrate. He also used pregabalin and methadone for neuropathic pain, mirtazapine for depression, pantoprazole for gastroesophageal reflux, valaciclovir for prophylaxis against reactivation of herpes simplex and varicella zoster virus, and trimethoprim-sulfamethoxazole prophylactically for Pneumocystis jirovecii. Additionally, he received intravenous immunoglobulin every four weeks for hypogammaglobulinaemia and once weekly granulocyte colony-stimulating factor (G-CSF) for long-term bone marrow failure.

Blood tests on admission showed C-reactive protein (CRP) 5 mg/L (< 5), leukocytes 1.7 × 10^9/L (3.5–11.0 × 10^9/L), platelets 57 × 10^9/L (145–390 × 10^9/L), ALT 940 U/L, aspartate aminotransferase (AST) 611 U/L (15–45), γ-GT 440 U/L, ALP 221 U/L, ferritin 4 850 µg/L (30–400), bilirubin 28 µmol/L (< 26), international normalised ratio (INR) 1.2 (0.8–1.2), albumin 37 g/L (34–45), IgA < 0.1 g/L (0.7–4.3), IgG 5.3 g/L (6.1–14.9), IgM < 0.1 g/L (0.4–2.1).

Our patient had elevated liver enzymes with a pattern indicating hepatocellular injury. There was no suspicion of impaired hepatic synthetic function, as albumin and INR were within the normal range and bilirubin was only mildly elevated. Differential diagnoses included drug-induced hepatitis, viral hepatitis, autoimmune hepatitis, malignancy, alcohol-related liver disease and metabolic dysfunction-associated steatotic liver disease. The patient reported only modest alcohol intake, and ALT was far higher than would be expected in alcohol-

related liver disease, making this cause unlikely. No phosphatidylethanol test was performed, as the patient was well known to the department, with frequent contact, and there was no suspicion of excessive alcohol use.

Although the patient was overweight and had type 2 diabetes, the elevated liver enzymes were not consistent with metabolic dysfunction-associated steatotic liver disease. Drug-induced hepatitis was an obvious possibility, as several of his regular medications can affect the liver. However, he had been taking these for several months to many years without previous abnormalities in liver tests. Semaglutide was the only new medication, but this is not known to affect the liver (1).

Ten years earlier, the patient had been diagnosed with IgG-kappa multiple myeloma, which relapsed after high-dose chemotherapy with autologous stem cell support. Subsequent lines of therapy had limited effect, and he developed bone marrow failure. Blood tests eight months prior to admission showed neutropenia (neutrophils 0.85 × 10^9/L [1.6–8.3 × 10^9/L]), lymphopenia (lymphocytes 0.39 × 10^9/L [0.8–3.7 × 10^9/L]) and thrombocytopenia (platelets 71 × 10^9/L [145–390 × 10^9/L]). In addition, he had hypogammaglobulinaemia, with IgA and IgM both < 0.1 g/L and IgG 46.5 g/L (6.1–14.9). The M-protein was estimated at 43 g/L. Having exhausted all treatment options available in Norway at that time, he was enrolled in a clinical trial in Southern Europe six months prior to admission. In this trial, he received chimeric antigen receptor T-cell (CAR-T) therapy targeting B-cell maturation antigen (BCMA), resulting in a subsequent fall in M-protein from 43 g/L to 1.5 g/L.
The possibility that the liver injury was a side effect of CAR-T therapy was considered. CAR-T therapy increases the risk of infections and can cause cytokine release syndrome, an acute inflammatory syndrome characterised by fever and multi-organ involvement, including the liver. This typically occurs shortly after treatment, usually within 1–14 days (2). This cause therefore appeared unlikely six months after CAR-T therapy, and there were no other indications of systemic inflammation.

Serological tests for viral hepatitis were performed, which provided no evidence of active infection with hepatitis A, B or C viruses. Both IgM and IgG for hepatitis E virus (HEV) were also negative. For cytomegalovirus and Epstein-Barr virus, IgG was positive and IgM negative, consistent with past infection. No viral DNA was detected in the blood for these two viruses or hepatitis B virus. Combined antibody/antigen testing for HIV was negative.
Based on these results, viral hepatitis was ruled out at that time. The assessment did not take into account that the patient's immunodeficiency could impair antibody responses. It also did not consider that serological testing in patients receiving immunoglobulin therapy cannot distinguish between exogenous and endogenous antibodies. In retrospect, diagnostics for other infectious agents that can cause hepatitis in immunocompromised patients could also have been considered, including herpes simplex virus, varicella zoster virus, adenovirus, enterovirus or syphilis.

CT imaging of the liver in the arterial, portal venous and venous phases demonstrated patent vessels, no evidence of cholestasis or focal lesions, but mild inflammatory changes with periportal oedema and contrast enhancement of the bile ducts. Blood tests for autoimmune hepatitis, including anti-F-actin antibodies (anti-smooth muscle antibodies), were negative.
Following the CT scan, hepatic tumour, portal vein thrombosis and biliary obstruction were ruled out as causes of the elevated liver enzymes. The inflammatory changes were interpreted as part of the patient's hepatitis.

As imaging, autoantibodies and microbiological tests did not reveal the cause of the patient's hepatitis, an ultrasound-guided liver biopsy was performed. Liver enzymes were now improving spontaneously, and the patient was discharged while awaiting the biopsy result, which came one week later. Histology demonstrated chronic active portal and lobular inflammation, scattered single-cell necroses and mild iron deposition in hepatocytes. Inflammation was graded as 3 (0–4) with fibrosis stage 0 (0–4). The absence of plasma cells and interface activity was inconsistent with autoimmune hepatitis, and the histological picture was most consistent with drug-induced or viral hepatitis.
The diagnosis of autoimmune hepatitis is based on assessment of IgG levels, autoantibodies, histological findings and the absence of viral hepatitis. IgG levels could not be evaluated in our patient due to hypogammaglobulinaemia and ongoing intravenous immunoglobulin replacement therapy. Antinuclear antibodies and an extended autoantibody panel (immunoblot for autoimmune liver disease) should have been performed. Histological features of autoimmune hepatitis are non-specific, and a similar picture may be observed in viral hepatitis or drug-induced hepatitis. Findings such as interface activity and plasma cell infiltrates may indicate autoimmune hepatitis.

The findings were discussed with a hepatologist at a university hospital, and it was considered that the overall picture could be consistent with autoimmune hepatitis, even though no anti-F-actin antibodies were detected. Prednisolone 40 mg daily was therefore initiated. Given the diagnostic uncertainty, the patient was to be closely monitored for treatment response. Two weeks after discharge, the patient attended a planned follow-up for multiple myeloma at the study centre in Southern Europe. Much of the hepatitis work-up was repeated there, with the same findings as in Norway, but additional analysis of HEV ribonucleic acid (RNA) in the blood was performed, resulting in 183 million IU/mL. Prednisolone was therefore discontinued, and oral ribavirin 800 mg daily was initiated.
Following admission and the comprehensive work-up, the patient was diagnosed with chronic HEV infection as the cause of his hepatitis. Both the level of transaminases and the degree of histological activity indicated significant hepatic inflammation, which required prompt treatment to prevent rapid fibrosis development. The first-line approach for chronic HEV infection is to reduce any immunosuppressive therapy; this was not feasible in our patient, except for discontinuing prednisolone, which had been given for presumed autoimmune hepatitis. Ribavirin therapy was therefore initiated.

While receiving ribavirin therapy, viral load and liver enzymes gradually declined. A treatment interruption due to medicine supply issues led to a rapid flare-up of hepatitis and a rise in viral load to several million IU/mL. Due to adverse effects, including nausea and psychiatric symptoms (low mood, racing thoughts and sleep disturbance), ribavirin was reintroduced at a reduced dose of 600 mg daily, which was better tolerated.
After three months of continuous ribavirin therapy, liver enzymes had normalised, while HEV RNA remained at 30,000 IU/mL. Treatment was therefore extended for an additional three months. Liver stiffness measurement showed a median stiffness of 7.8 kPa, consistent with the absence of significant fibrosis. After a total of six months of continuous ribavirin therapy, HEV RNA was 9,000 IU/mL.
Our patient did not achieve viral clearance after six months of ribavirin therapy. European guidelines indicate that, in the absence of a response to ribavirin monotherapy, the addition of pegylated interferon-alpha may be considered (3). This option was discussed with haematologists at a university hospital, but interferon therapy was not recommended as the effects of pegylated interferon-alpha in recipients of CAR-T therapy are unknown. This assessment was supported in consultation with European hepatologists with more experience in managing chronic HEV infection. Zinc supplements as an adjunct to ribavirin could be considered, based on pilot studies in which viral clearance was achieved in patients who had not responded to ribavirin (4). Ribavirin 200 mg daily as indefinite suppressive therapy is also a potential option.

At follow-up ten months after discharge, HEV RNA was no longer detectable in blood samples. This was confirmed six weeks later in blood and stool samples. Ribavirin was therefore discontinued. At a subsequent follow-up three months later, viral RNA remained undetectable.

Discussion

Hepatitis E virus (HEV) is believed to be the most common cause of acute viral hepatitis worldwide. The World Health Organization estimates 20 million cases annually (5). Seroprevalence studies in Norway suggest that 10–14 % of the population have been infected with the virus (6,7).

HEV is a ribonucleic acid (RNA) virus, and different genotypes exhibit distinct epidemiology and clinical courses (3). Human disease is primarily caused by genotypes 1–4. Genotypes 1 and 2 only infect humans and occur in Asia, Africa and Central America. Transmission is faeco-oral in areas with poor sanitation and typically results in self-limiting acute hepatitis. Chronic infection has not been observed with genotypes 1 and 2.

Genotypes 3 and 4 are zoonotic viruses that infect a range of animals, with pigs appearing to be the main reservoir. The virus occurs globally, including in Europe, but with considerable regional variation. Human infection in high and middle-income countries most commonly occurs through consumption of undercooked meat or ingestion of water or food contaminated with faeces from

infected animals. Only a small proportion of people infected develop acute symptomatic hepatitis. In immunocompetent patients, the illness is usually self-limiting over 3–6 weeks, whereas immunocompromised patients can develop chronic infection, most commonly with genotype 3. The greatest risk of chronic infection is seen in organ transplant recipients, but other immunocompromised patients, including those with HIV infection, haematological disease, or receiving immunosuppressive therapy for autoimmune disorders, can also be affected. Most patients with chronic infection are asymptomatic, with elevated liver enzymes. Rapid progression to fibrosis and cirrhosis has been reported in transplant recipients (8–9). Extrahepatic manifestations can occur in both acute and chronic disease, including neurological, renal or haematological involvement.

HEV infection is diagnosed either by detection of antibodies or by identification of HEV RNA in blood or stool using PCR methodology. In immunocompetent patients, anti-HEV IgM is usually detectable around symptom onset, while anti-HEV IgG appears shortly thereafter. In immunosuppressed patients, antibodies are often undetectable, and HEV RNA detection is therefore recommended as the primary diagnostic method and for monitoring confirmed cases (10). Chronic infection is defined as the presence of HEV RNA in two samples taken at least three months apart.

In our patient, HEV infection was initially considered as a differential diagnosis, but insufficient attention was paid to the fact that antibody responses may be absent in immunocompromised patients. This led to delayed diagnosis and treatment. Differential diagnostic considerations with respect to autoimmune hepatitis or drug-induced hepatitis can be challenging.

The first-line treatment for chronic HEV infection is reduction of immunosuppression, but this was not feasible in our patient. Second-line therapy is ribavirin, although the optimal dose and treatment duration have not been fully established. The most common dosing reported in studies is 400–800 mg daily, and European guidelines recommend a three-month course before evaluating treatment response. If HEV RNA remains detectable in blood or stool after three months, the recommendation is for treatment to be extended to six months (3). Ribavirin is no longer marketed in Norway, and importation may therefore take time. Known adverse effects of ribavirin include haemolytic anaemia, skin reactions, cough and gastrointestinal symptoms; however, most data on ribavirin stems from studies where ribavirin was given in combination with interferon for the treatment of hepatitis C virus (11).

In cases of ribavirin treatment failure, the addition of pegylated interferon-alpha can be considered. Interferon, however, has numerous adverse effects and contraindications, and it cannot be used in, for example, organ transplant recipients, except in cases of liver transplantation. Early-phase studies have suggested that zinc may have a beneficial effect (4). Sofosbuvir, used for hepatitis C virus infection, has shown activity against HEV in vitro, but clinical studies have not demonstrated satisfactory efficacy (12).

Our case illustrates the diagnostic considerations involved in evaluating elevated liver enzymes in immunocompromised patients. It serves as a reminder that HEV can cause chronic hepatitis in this population and that serological testing as a primary diagnostic tool has poor sensitivity in these patients. The transmission and prevalence of HEV in Norway are likely underdiagnosed, and with the increasing use of immunosuppressive therapy across a growing range of patient groups, heightened vigilance is required. This case also highlights that ribavirin, a deregistered antiviral, is still an important treatment option.

The patient has consented to publication of the article.

The article has been peer-reviewed.

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