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AN ACUTE INFECTION DUE TO HEPATITIS E IN THE CONTEXT OF A PATIENT WITH RITUXIMAB AND METHOTREXATE THERAPY

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ABSTRACT

Background: This report presents the influence of immunosuppression by new rheumatological therapies on hepatitis E virus infection in a 54-year-old male patient with an anti-synthetase syndrome and treatment with methotrexate and rituximab.

Case description: The patient arrived at the Emergency Department with epigastric pain, vomiting and dark urine. Initial examination revealed signs of inflammation and hepatic dysfunction. Subsequent laboratory tests and imaging confirmed acute hepatitis E infection in the context of recent initiation of rituximab therapy. Despite initial suspicion of pancreatitis, subsequent investigations ruled out pancreatic involvement. Treatment with ribavirin, along with supportive measures, led to significant clinical improvement with resolution of jaundice, ascites, and oedema.

Conclusions: This case underscores the importance of considering hepatitis E in patients with autoimmune conditions, especially when initiating immunosuppressive therapies, a situation that is not well described in scientific literature and is increasingly common, necessitating proper recognition.

KEYWORDS

Antisynthetase syndrome, hepatitis E, methotrexate, rituximab

LEARNING POINTS

- Suspect hepatitis E virus infection in the presence of persistent liver failure of unknown cause.
- Recognise immunosuppression as a cause of increased risk of hepatitis E infection.
- Take into account the repercussions of immunosuppressive therapy such as rituximab regarding hepatitis E infections in immunocompromised patients.

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INTRODUCTION

Hepatitis E virus infection has a transmission and pathogenesis that is still not fully understood, and its incidence is on the rise, especially among immunocompromised patients. Diagnosis is based on the suspicion of liver failure of unknown cause, confirmed through serological tests and detection of viral RNA. There is no approved vaccine, and treatment varies depending on the immune status and the phase of the disease.

CASE DESCRIPTION

A 54-year-old male patient with previous history of hypertension and diabetes mellitus, was under Rheumatology follow-up for antisynthetase syndrome. He had no known allergies or family history of diseases of interest, a pack-a-day smoker and occasional drinker with no recent travel history. The patient continued his usual treatment with methotrexate, folic acid, metformin, prednisone 5 mg, valsartan, omeprazole, rosuvastatin, with rituximab recently added to his routine treatment 15 days prior. The patient came to the Emergency Department with a 24-hour history of epigastric pain radiating in a belt-like manner, associated with vomiting and dark urine. On the initial examination, body temperature was 38.3 ºC, blood pressure 143/78 mmHg, heart rate 108 beats/min with an oxygen saturation of 98%. The abdomen was soft, slightly painful on palpation, with intestinal sounds present normal in intensity and frequency, without signs of ascites or signs of peritoneum irritation. Finally, the patient was admitted to the Gastroenterology department of our hospital.

Laboratory tests reveal leukocytosis of 18,000 × 10^3/mm^3; total bilirubin of 4.4 mg/dl, predominantly direct fraction with 3.69 mg/dl, ALT 735 UI/l, alkaline phosphatase 199 UI/l, lipase 1168 UI/l and PCR 149. Abdominal ultrasound and endoscopic ultrasound showed hepatic steatosis without biliary tract abnormalities.

During hospitalisation, due to suspected pancreatitis based on clinical and laboratory findings, the patient was kept on absolute fasting with scheduled analgesia. An abdominal CT scan was requested, showing only a pattern of hepatic steatosis. Subsequently, the pain improved, and an oral diet was reintroduced, but there was worsening of cholestasis and cytolysis with progressive elevation of bilirubin and liver enzymes. Methotrexate and rituximab were discontinued due to the risk of toxicity, and further investigations included serological studies for liver disease, upper endoscopy to rule out biliary content and hepatic Doppler ultrasound, which showed no thrombosis or vascular abnormalities.

In subsequent days, serologies for hepatitis A, B, C; HIV, Coxsackievirus; IgG, IgM, IgA, complement, ceruloplasmin, alpha-1 antitrypsin; autoimmunity for autoimmune hepatitis (ANA, Anti-LKM, anti-smooth muscle antibodies) and general autoimmunity were all negative. Due to persistent symptoms, additional serologies (hepatitis E, parvovirus, herpes simplex virus) and other bacteria (*Legionella*, *Borrelia*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, *syphilis*, *Chlamydia pneumoniae*, *Brucella*, *Salmonella typhi*) were performed, resulting positive for hepatitis E virus (RT-PCR RNA) genotype 3f.

The findings of acute hepatitis E accompanied the worsening of the patient's clinical and laboratory status with progressive elevation of bilirubin, and the appearance of ascites and oedema of the lower extremities. The decision was made to initiate treatment with ribavirin 600 mg for 3 months, along with spironolactone and furosemide. The patient improved with the disappearance of ascites, oedema, and jaundice, as

Day after admission	Day 1	Day 2	Day 5	Day 7	Day 9	Day 10	Day 12	Day 15	Day 19	Day 22	Day 40	Day 60
Total bilirubin (mg/dl)	4.91	5.19	5.55	7.81	10.97	12.1	15.5	19.15	22.4	19.5	10.27	5.7
Direct bilirubin (mg/dl)	4.34	4.57	5.04	7.24	7.4	10.7	13.9	17.05	20.5	17.4	9.6	5.07
Indirect bilirubin (mg/dl)	0.57	0.62	0.51	0.57	3.57	-	1.54	2.1	-	2.82	0.7	0.69
AST (UI/l)	470	451	700	953	1023	-	936	891	885	690	92	47
ALT (UI/l)	680	650	1115	1494	1449	-	1151	909	883	512	92	44
GGT (UI/l)	849	788	1122	1115	874	-	638	411	173	265	111	201
Alkaline Phosphatase (UI/l)	223	198	259	296	269	-	247	235	192	262	159	163
LDH	304	-	430	-	-	-	323	302	284	-	270	-
CRP (mg/l)	151	86	-	31	36.5	-	45.5	96	56	-	17	18

Table 1. Analytical values per day of the patient during their hospital stay.

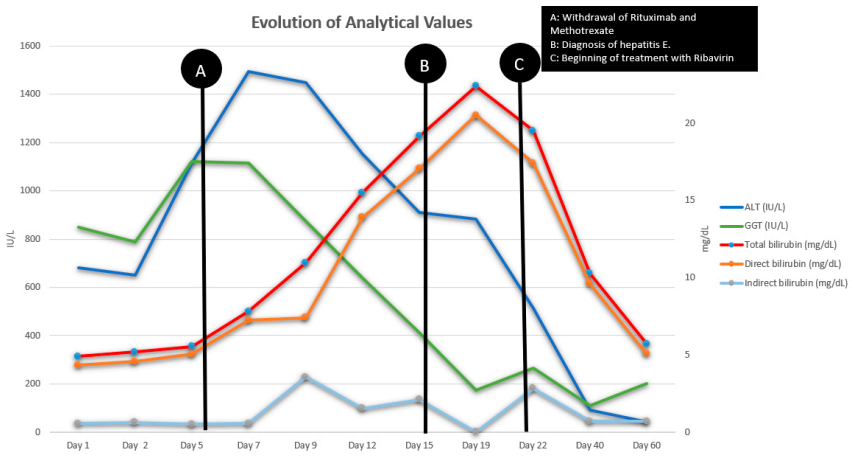

Figure 1. Evolution of analytical values throughout admission determining the different interventions performed. The elevation of transaminase and bilirubin enzymes and their relative decrease is observed after the withdrawal of the immunosuppressive medication, in addition to the normalisation of the values after the ribavirin regimen.

well as normalisation of cholestasis and liver function values. The patient is currently asymptomatic and enjoys a good quality of life.

DISCUSSION

Hepatitis E virus (HEV) infection is caused by a single-stranded RNA virus belonging to the Herpesviridae family. HEV transmission is mainly faecal-oral, and to a lesser extent, bloodborne and vertical in genotypes 3 and 4[1-4]. HEV infection is a common cause of acute hepatitis, affecting an estimated 3.5 million patients and causing around 56,000 deaths annually worldwide. In Spain, according to the Hospital Discharge Records in the CMBD Data System from the Ministry of Health of Spain, between 2016 and 2022, 688 cases of acute hepatitis E infection were recorded with a prevalence of 0.1–0.3/100,000 people and associated mortality ranging from 0.2%–0.4%. However, the prevalence of anti-HEV IgG antibodies, indicating exposure to the virus, is estimated to be 0.6%–7.3% of the general population[5,6].

HEV can manifest as acute or chronic liver failure and extrahepatic manifestations (Guillain-Barré syndrome, haematological, renal manifestations), being associated with acute pancreatitis. It is of great importance in pregnant and immunocompromised patients, such as solid organ transplant recipients[7-9]. Chronic latent infection has also been described in HIV-infected patients and non-Hodgkin lymphoma patients receiving rituximab, suggesting that immunosuppression predisposes to chronic infection[1,3,9].

The diagnosis lacks standardised tests. It is crucial to consider the presence of HEV in groups at risk of rapidly progressing liver disease, such as pregnant women, patients with underlying liver disease, solid organ transplant recipients and those with haematological malignancies[4,9,10]. Detection of anti-HEV IgM antibodies and HEV RNA in serum or faeces is recommended for acute infection, and HEV RNA detection in serum for chronic infection[10].

The treatment of hepatitis E varies according to the immune status and disease phase, considering transplantation in cases of fulminant liver failure if there are no contraindications. In acute hepatitis, standard therapeutic measures are applied, and the role of antiviral therapy (ribavirin) in immunocompromised patients with acute infection is not established. In chronic hepatitis E, the basic treatment involves reducing immunosuppression, starting with tacrolimus in cases of solid organ transplant recipients. Ribavirin therapy is recommended for genotype 3 infection with a regimen of 600–1000 mg for 12 weeks as monotherapy, without demonstrating clear benefits and contraindicated in pregnant women due to its potential teratogenicity[8,9]. Monitoring and evaluation of treatment

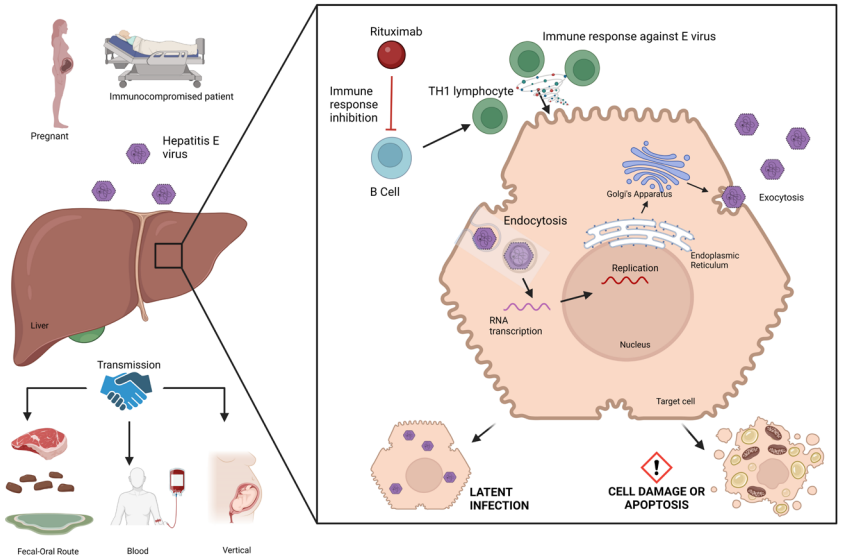

Figure 2. Mechanism of transmission and infection of the hepatitis E virus. It is observed how the hepatitis E virus, through its different transmission routes, is introduced into the hepatocyte to produce a replication of its genetic material, generating new viruses. This leads to the destruction of the host cell or the permanence of the virus within the hepatocyte, generating a latent infection. In case of therapy with rituximab, the immunological response to destroy the virus and the infected cell is depleted.

response for ribavirin toxicity are necessary during and after treatment, quantifying HEV RNA in serum and faeces at week 12. In case of treatment failure, there is no established alternative therapy, although pegylated interferon alpha and sofosbuvir have been considered, but their use is limited due to questionable efficacy and safety. Despite various research efforts, there is still no approved vaccine for hepatitis E[7-10]. Therefore, it suggests that immunocompromised patients with rheumatological diseases treated with anti-CD20 drugs or methotrexate may be at higher risk of acute and chronic hepatitis E infection. In this case, the patient presented clinical features of acute infection that resolved with the withdrawal of immunosuppressive therapy and with ribavirin. However, it is worth asking what the key intervention in the improvement of the patient's condition was, since it is controversial whether it is the withdrawal of treatment or therapy with ribavirin that demonstrates significant benefits. However, it is clearly defined that the attitude to follow that has shown the most benefit is the withdrawal of immunosuppressive treatment and standard measures against liver failure.

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