Clinical Case Report

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Hepatitis E infection in a patient with rheumatoid arthritis treated with leflunomide

A case report with emphasis on geoepidemiology

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Abstract

Rationale: Hepatitis E is an infectious disease due to inflammation of the liver caused by hepatitis E virus (HEV) and represents one of the most common causes of acute hepatitis and jaundice in the world. Although data of hepatitis E infection in patients with rheumatoid arthritis (RA) are accumulating, little is known on the course of HEV infection. We reported, for the 1st time, a case of patient with RA with hepatitis E that developed during leflunomide therapy in combination with low-dose steroids.

Patient concerns: We present a 39-year-old woman, affected by RA and treated with leflunomide, reported diffuse itching and persistent fatigue laboratory data revealed elevated liver enzyme levels.

Diagnosis: Positivity for anti-HEV IgM and IgG was observed. HEV-RNA of the genotype 3 was detected, indicating acute E hepatitis.

Interventions and outcomes: Leflunomide was stopped and restarted 5 months after the initial diagnosis at the same dosage, with a close clinical and laboratory follow-up. The virus was eradicated from the serum without chronic transformation. The patient is alive and well 7 months after the initial diagnosis.

Lessons: To our knowledge, this report is the 1st case of acute E hepatitis in a patient with RA developed during leflunomide therapy in combination with low-dose steroids. Moreover, geoepidemiology of infection is important, due to the fact that Abruzzo, a central region of Italy, has the highest HEV seroprevalence in general population, related to the zoonotic transmission of the infection from domestic and wild animals. Our case highlighted that immunosuppressive therapy, and in particular leflunomide, could be safely reintroduced after the resolution of the infection and the clearance of the virus. Further studies are needed to evaluate potential advantages in serologic testing for HEV infection as a part of the routine workup done to patients with rheumatic diseases and selected for immunosuppressive therapy.

Abbreviations: ACPA = anticitrullinated protein antibody, CRP = C-reactive protein, DAS = disease activity score, DMARDs = disease-modifying antirheumatic drugs, GT = genotype, HBV = hepatitis B virus, HCV = hepatitis C virus, HEV = hepatitis E virus, RA = rheumatoid arthritis.

Keywords: hepatitis E infection, hepatitis E virus, leflunomide, rheumatoid arthritis

1. Introduction

Hepatitis E virus (HEV) is a nonenveloped single-stranded positive RNA virus belonging to Hepeviridae family.[1] There are at least 4 human pathogenic HEV-genotypes (GT1–4), which display a specific geographical distribution.[1,2] In particular, GT1 and GT2 infect only humans, are spread by the fecal-oral route, and are prevalent in regions with low sanitation standards. GT3 and GT4 are the most prevalent strains in industrialized countries, and the infection with such strains is considered a zoonosis, being pigs, wild boars, and deers the major source of infection. Although rare, interhuman infection seems possible, in particular through blood products.[3]

Hepatitis E is an infectious disease due to inflammation of the liver caused by HEV and represents one of the most common causes of acute hepatitis and jaundice in the world.[2] The course of HEV infection is variable, from a clinically asymptomatic and self-limiting condition in the vast majority of cases, to a mild self-limiting hepatitis, with fatigue, nausea, itching, and jaundice, the latter occurring only in a small percentage of patients, mainly old males.[4] Acute liver failure is a rare complication, mainly occurring in patients with chronic liver disease, and being fatal in 0.5% to 3% of young adults. However, it can account for up to 30% of mortality in pregnant women in the 3rd trimester.[2] Chronic infection, described with GT3 and GT4 genotypes, is defined as the persistence of detectable HEV-RNA in serum for 6

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months in immunocompetent and 3 months in immunocompromised patients.[4] In particular, solid organ transplant receivers may develop a chronic infection in >50% of cases,[5,6] and data concerning its incidence in individuals infected with the human immunodeficiency virus, or patients with hematologic or rheumatic disorders receiving immunosuppressive therapy, are accumulating in the literature.[7–9] In these patients, chronic infection can rapidly lead to liver cirrhosis and failure.

In addition, several extra-hepatic manifestations, in particular neurologic, renal, hematologic, and rheumatic, have been reported in association with HEV infection.[10–12]

Hepatic involvement is one of the most common complications of immunosuppressive treatment in patients with rheumatoid arthritis (RA). Reactivation of viruses such as hepatitis B (HBV) and hepatitis C (HCV) viruses, or de novo hepatic infection can occur as side effect of conventional synthetic (cs) or biologic (b) disease-modifying antirheumatic drug (DMARD) therapy.[13–15]

We report a case of acute hepatitis E in a patient with RA during immunosuppressive treatment with leflunomide and a stable dose of prednisone and receiving hepatitis B prophylaxis with entecavir.

2. Case presentation

In January 2018, a 39-year-old woman with severe arthritis of wrists and metacarpophalangeal joints was admitted to our Rheumatology Unit. The affected joints were warm, erythematous, swollen, and painful, but fever was not detected, and the general physical examination found no abnormalities, except a systolic murmur on the left 4° intercostal space. She was born in Albania, has been living in L'Aquila, a city of the Abruzzo region of central Italy, for 8 years, and did not travel abroad over the previous months. Her medical history was remarkable for a chronic autoimmune thyroiditis, a congenital subaortic defect of the interventricular septum, and a previously resolved, HBV infection. She had a 13-year history of rheumatoid factor-positive and anticitrullinated protein antibody-positive RA with joint erosions. In the past, she had been treated with subcutaneous injections of methotrexate 15 mg/wk, with good response, until May 2017, when she was admitted to Pneumology Unit of our hospital due to the occurrence of fever, worsening dyspnea, and nonproductive cough. High resolution computed tomography of the lungs revealed limited areas of ground glass opacity in the upper right and left lobes. Cultures of bronchoalveolar lavage fluid were negative for most common bacteria, including mycobacteria. Methotrexate was stopped, and a prolonged course of corticosteroids and broad-spectrum antibiotics were started.

On current hospital admission, treatment for RA included prednisone 5 mg/d; other chronic medications were L-thyroxine 50 μg/d, esomeprazole 40 mg/d, inhaled fluticasone furoate/vilanterole 92/22 μg/d, cholecalciferol 25,000 IU/mo. Figure 1 displays a summary of the clinical and laboratory course of the patient. The activity (DAS28-C-reactive protein [CRP] 5.22) and severity (namely seropositivity and erosive disease) of RA required the reintroduction of DMARD treatment. However, in consideration of the medium–high risk of these drugs on reactivation of HBV (anti-Hbc and anti-Hbs positive patient with negative HBV-DNA), she started prophylactic therapy with entecavir 0.5 mg/d. One month after, leflunomide 20 mg/d was added.

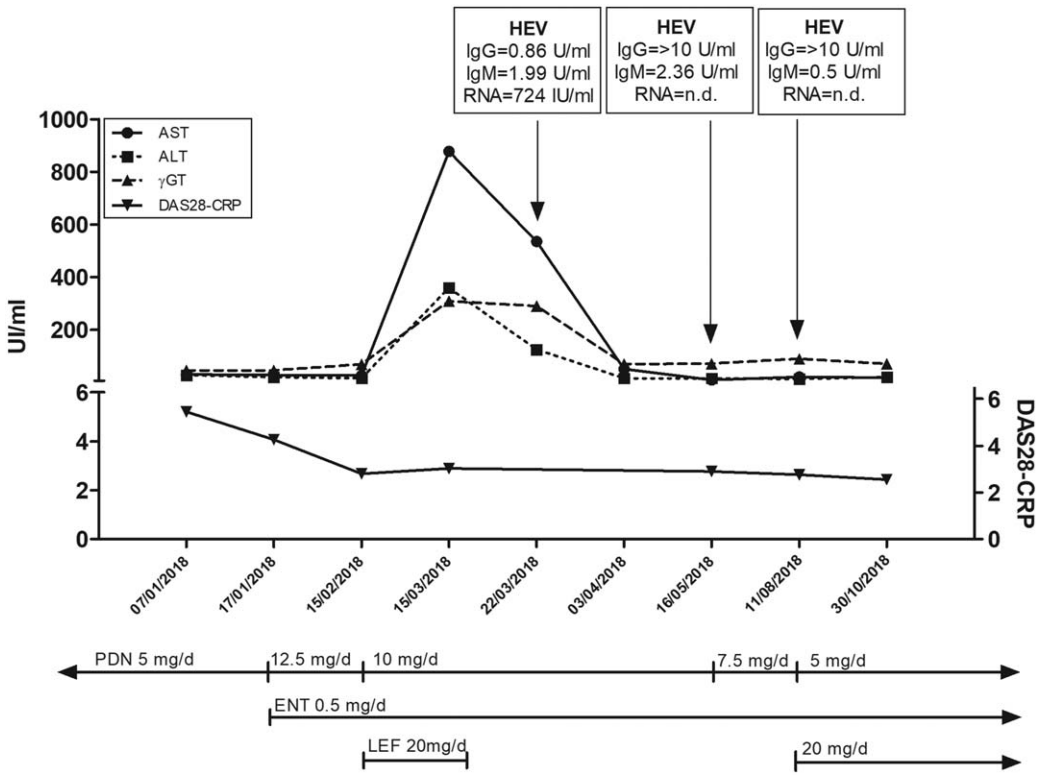

Figure 1. Course of liver enzymes and disease activity, considering HEV infection and immunosuppressive treatment for rheumatoid arthritis. ALT = alanine aminotransferase, AST = aspartate aminotransferase, DAS28-CRP = disease activity score 28-C-reactive protein, ENT = entecavir, HEV = hepatits E virus, LEF = leflunomide, PDN = prednisone, γ-GT = gamma-glutamyl-transferase.

In March 2018, 1 month after starting treatment with leflunomide and 2 months after starting treatment with entecavir, she complained diffuse itching and persistent fatigue. Laboratory data revealed elevated liver enzyme levels, and she was admitted to Infectious Diseases Unit of our hospital. Two hypotheses were proposed: firstly, a drug-induced liver injury hence with possible hepatotoxic drugs including leflunomide was stopped; secondly, a reactivation of occult hepatitis B despite therapy with entecavir, so HBV-DNA was tested. Blood counts, total protein, albumin, total bilirubin, electrolytes, renal tests, CRP, and coagulation test results were within normal ranges. Antinuclear antibodies and other autoimmune hepatitis serologic markers were also negative. An ultrasound scan of the abdomen showed no abnormalities of the liver or gallbladder, no dilation of the intrahepatic or extrahepatic bile ducts and no evidence of thrombosis of the suprahepatic veins or portal venous system. A broad spectrum of other hepatotropic viruses, including hepatitis A and hepatitis C viruses, herpes simplex virus, cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, and parvovirus B19, was also tested but recent infections could be ruled out. HBV-DNA was also negative. Interestingly, positivity for anti-HEV IgM (1.99 IU/mL) and IgG (0.86 IU/mL) was observed. HEV-RNA of the GT3 genotype was 724 IU/mL indicating acute E hepatitis. The patient reported a consumption of undercooked pig sausages some weeks before the onset of symptoms. During the follow-up, her clinical conditions gradually improved, the transaminase levels diminished within 3 weeks, no specific antiviral therapy was started and she was discharged.

After the resolution of the infection and the clearance of the virus, because of persistent articular complaints, leflunomide was restarted at the same dosage, with a close clinical and laboratory follow-up to rapidly reveal any sign of liver injury. Seven months later, liver enzyme levels were normal. Anti-HEV IgG persisted, and anti-HEV IgM decreased to the threshold value. HEV-RNA was negative in the serum.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

3. Discussion

There are several causes of increased liver function tests in patients with rheumatic diseases, including drug toxicity, liver involvement by the rheumatic disease itself, concomitant autoimmune hepatic disease, or infections, and an accurate differential diagnosis is important to choose the best treatment for the patient.[13–15] In the case we described here, the occurrence of acute liver injury could be associated with the introduction of leflunomide and entecavir, giving suspect for a drug toxicity. However, we detected ongoing acute E hepatitis and such finding underscores that in immunocompromised patients with liver cytolysis, investigations for HEV infection must be performed routinely, especially in high endemic areas, as is the case for Abruzzo region.

The HEV is an ubiquitous virus and outbreaks occur against an endemic background in areas with inadequate drinking water safety and sanitation.[1,2] Although the difference in test sensitivity and the frequently asymptomatic course of the disease, HEV seroprevalence in Europe could be estimated ranging from 7.5% to 31.9%, with an average rate of 19.16%.[16] A recent critical review estimated that HEV seroprevalence varied from 0.12% to 49% in Italy, with the highest rates being reported from the central region of Italy.[17] In particular, Abruzzo region seems to have the highest seroprevalence in general population.[17,18] In Italy, GT3 genotype occurs in the majority of the locally acquired acute HEV infection, related to the zoonotic transmission of the infection from domestic and wild animals. The majority of autochthonous cases of HEV infection were clearly related to the ingestion of raw or undercooked local pork meat.[19] In our patient, we were not able to identify a certain the source of infection; in particular, she did not have recent travel history or exposure to blood products, and no other family members complained symptoms or clinical signs related to hepatitis. However, patient referred to regularly eat pork sausages and, in particular, she reported a consumption of undercooked pig sausages some weeks before the onset of symptoms.

Interestingly, although several observations show that acute polyarthritis should be added to the systemic manifestations of HEV infection,[20] in our patient, we did not observe a worsening of RA, in terms of patient-related symptoms or disease activity measured by DAS28-CRP.

Twenty-six cases of hepatitis E developed during the treatment of RA with DMARDs were reported in a recent literature review.[21] In particular, 20 patients were treated with targeted synthetic (ts) or bDMARDs with or without csDMARDs and 6 patients with csDMARDs, namely methotrexate, bucillamine, mizoribine, actarit, and tacrolimus; low-dose steroids were used in 16 cases. Interestingly, our case showed for the 1st time a HEV infection related to the treatment with leflunomide with low-dose steroids.

Unfortunately, we did not have stored serum samples from earlier times to confirm whether our patient developed hepatitis as a result of primary acute or chronic infection of HEV. However, the clinical course of our patient was self-limiting, the virus was eradicated from the serum without chronic transformation, and we did not observe recurrence of hepatitis nor persistent infection of HEV infection during the following 7 months, even after the reintroduction of leflunomide.

In general, the outcome of HEV infection seems favorable in patients with inflammatory arthritides treated with immunosuppressants, with no evolution to chronic hepatitis or fulminant liver failure.[22] In case of hepatitis E occurrence, discontinuation of DMARDs is recommended, and administration of ribavirin may be necessary in high-risk patients.[4] Our case highlighted that csDMARDs, and in particular leflunomide, could be safely reintroduced after the resolution of the infection and the clearance of the virus, with a close monitoring of hepatic function tests and HEV-RNA.

4. Conclusion

Although case reports of hepatitis E infection in patients with RA are accumulating,[9,21–23] little is known on the course of HEV infection in patients with inflammatory rheumatic disorders. We reported a case of patients with RA with hepatitis E that developed during leflunomide therapy in combination with low-dose steroids. In immunocompromised patients with unexplained liver cytolysis, investigations for HEV infection must be performed routinely, including not only tests for IgG and IgM antibodies, but also RT-PCR assays for HEV-RNA in blood and stool specimens, due to the fact that these patients may have no detectable antibodies even when the virus is present.[24] Likewise, the reintroduction of immunosuppressive drugs can be considered once the polymerase chain reaction tests for HEV-RNA revert to negative in blood and/or stool specimens. Further

studies are needed to evaluate potential advantages in serologic testing for HEV infection as a part of the routine workup done to patients with rheumatic diseases and selected for DMARD therapy.

Author contributions

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