The importance of considering hepatitis E as a differential for acute hepatitis

Caroline A Young
Alyn L Cratchley

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Abstract

We present the case of a patient with acute transaminitis, with positive anti-smooth muscle antibody and hepatitis E antibodies. The remainder of the non-invasive liver screen was unremarkable. A liver core revealed moderately active acute hepatitis with portal and parenchymal inflammation, including apoptotic bodies and focal confluent necrosis. The features were in keeping with an acute hepatitis, with a differential of either drug, viral or autoimmune aetiology. Hepatitis E RNA was subsequently detected by PCR. This case illustrates the importance of considering hepatitis E as a differential for acute hepatitis, in a patient with autoantibodies. Review of the literature revealed several similar reports, studies suggesting increased hepatitis E seroprevalence in patients with autoimmune hepatitis, and studies finding autoantibody positivity in up to 50% of patients with acute hepatitis E. Together, these findings indicate a not-uncommon association, and so emphasize the importance of considering hepatitis E as a differential for acute autoimmune hepatitis.

Keywords AIH; autoimmune hepatitis; HEV

Case report

A 48 year old female presented with jaundice and pruritus. Her past medical history included type one diabetes and pernicious anaemia. Serology indicated an acute hepatitis, with total bilirubin 79 (0-21umol/L), ALT 2189 (0-34iu/L), ALP 250 (30-130iu/L), and albumin 25 (35-30 g/L). Anti-smooth muscle antibodies were detected. ANA, ANCA, anti-mitochondrial antibody, and anti-LKM antibody were negative. IgM was mildly elevated; IgA and IgG were within normal limits. A viral screen showed hepatitis E IgM and IgG positivity, but antibodies to hepatitis A, B, and C were negative. CMV, EBV and adenovirus were not detected by PCR. Serum iron studies were unremarkable, and alpha-1 antitrypsin and ceruloplasmin levels were within normal limits. In light of these results, PCR for hepatitis E was requested and an ultrasound-guided liver biopsy was performed. Clinically the diagnosis was favoured to be autoimmune hepatitis given the medical history and presentation.

Caroline A Young ***BMBCh MA PhD,*** *Academic Clinical Lecturer in Histopathology, University of Leeds, UK. Conflicts of interest: none declared.*

Alyn L Cratchley ***MBChB FRCPath,*** *Consultant Histopathologist, Leeds Teaching Hospitals NHS Trust, Leeds, UK. Conflicts of interest: none declared.*

The liver biopsy showed a preserved architecture, with no evidence of fibrosis. The portal areas were expanded by a moderate inflammatory infiltrate of predominantly lymphocytes, with only occasional plasma cells and eosinophils identified (Figure 1A), and associated with mild interface activity. The hepatic portal veins showed a degree of endothelialitis (Figure 1B). The bile ducts were unremarkable.

The parenchyma showed frequent lymphocyte-predominant inflammatory foci, acidophil bodies, and small foci of confluent necrosis associated with pigmented hepatocytes and haemosiderin laden Kupffer cells (Figure 1C). There was no significant steatosis or cholestasis.

The DPAS special stain highlighted prominent areas of Kupffer cell hyperplasia. Otherwise special stains showed no evidence of iron deposition within hepatocytes, copper associated protein or alpha-1 antitrypsin.

Overall, the findings of a moderately active acute hepatitis with portal and parenchymal inflammation, including frequent apoptotic bodies and focal areas of confluent necrosis, raised the differential of either drug, viral or autoimmune-induced acute hepatitis and clinical–pathological correlation was advised. It was noted that the inflammation contained relatively few plasma cells, so whilst the morphology had a pattern which would fit with autoimmune hepatitis, the lack of significant plasma cells meant that the biopsy was not diagnostic; the hepatitis E IgM and IgG raised the possibility of acute hepatitis E, which would also account for the histological findings.

Clinically, the patient was commenced on prednisolone for a suspected autoimmune hepatitis (in light of the raised anti-smooth muscle antibody and medical history of other autoimmune diseases). Hepatitis E RNA was subsequently detected by PCR (viral load 2.9 million iu/ml), confirming acute hepatitis E infection. The prednisolone was then weaned. The patient was followed-up with monitoring of LFTs, which returned to normal limits within 6 weeks, clotting factors, and a repeat PCR for hepatitis E RNA to confirm viral clearance. The source of the hepatitis E was unknown, but could have been the patient's household pets or dietary contamination.

Discussion

Here we present a case of acute hepatitis secondary to hepatitis E virus that was initially diagnosed and treated as autoimmune hepatitis. This case illustrates the importance of considering hepatitis E as a differential for acute hepatitis, even in countries where hepatitis E is not commonly encountered, and in patients

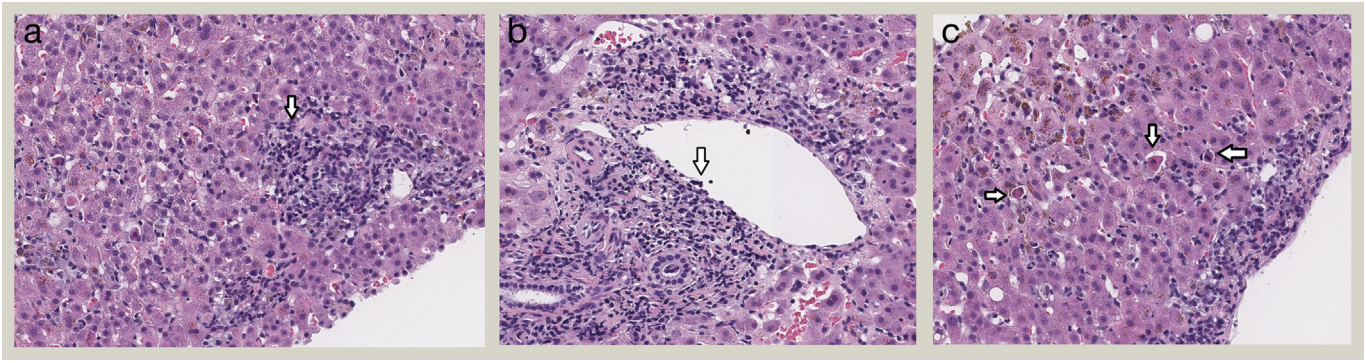

Figure 1 Liver core biopsy histology. (**a**) This shows a portal tract (bottom right), expanded by predominantly lymphocytes (a single plasma cell is indicated). The surrounding parenchyma contains acidophil bodies and focal inflammation. (**b**) This portal tract is expanded by lymphocytic inflammation. The arrow indicated a focus of endothelialitis (lymphocytes undermining the endothelial layer of the vessel). (**c**) The parenchyma contains numerous acidophil bodies (arrows). The edge of a portal tract is visible on the bottom right side of the image.

with autoantibodies raising the possibility of an alternative liver disease.

There were 1202 cases of hepatitis E diagnosed in the UK in 2019, which has increased in prevalence since 2010 due to increased transmission within the UK, but the figure has remained relatively stable over the past 5 years.[1] Hepatitis E is spread via the faecal-oral route.[2] The virus is endemic in many developing countries, but exists as a zoonosis in many developed countries, where it is transmitted through the consumption of undercooked meat, particularly pork.[2] In immunocompetent individuals, hepatitis E is usually asymptomatic or may cause an acute hepatitis which is, as in this case, self-limiting.[2] However, the virus may cause a more aggressive disease in the immunosuppressed (where chronic infection may be established), patients with a pre-existing liver disease and pregnant women.[2] Hepatitis E is a notifiable disease.[1]

Our case illustrates the difficulty in differentiating between autoimmune hepatitis and acute hepatitis E, in a patient with serology suggestive of both diseases. The distinction cannot be reliably made by histology, and confirmation of viraemia is required. The same diagnostic dilemma has been reported in travellers and migrants from countries where hepatitis E is endemic,[3,4] and patients from non-endemic countries.[5] Hepatitis E should be considered and tested for in all cases of an unexplained acute presentation of hepatitis.[1]

A study has shown higher hepatitis E virus IgG antibodies in patients with autoimmune hepatitis compared with healthy controls,[6] although this finding was not replicated in a study from the Netherlands where hepatitis E is endemic.[7] Two studies have shown high autoantibody positivity (up to 50%) in patients with acute hepatitis E.[8,9] The reason for the association between hepatitis E and autoantibodies is not understood, but could include hepatitis E virus serologically mimicking autoimmune hepatitis by inducing a hypergammoglobulinaemia, hepatitis E virus infection triggering an autoimmune hepatitis, or patients with autoimmune hepatitis being at increased risk of hepatitis E.[5,6] Furthermore, hepatitis E infection should also be considered in patients with known autoimmune hepatitis who present with a 'flare'.[10]

In conclusion, this case and the related literature illustrate a not-uncommon finding of raised autoantibodies in a patient with acute hepatitis due to hepatitis E, emphasizing the importance of considering hepatitis E as a differential for acute autoimmune hepatitis. ◆

Practice points

- Hepatitis E should be considered as a differential for all patients presenting with an acute hepatitis, even in patients with raised autoantibodies and even in countries where hepatitis E is not endemic.
- Autoimmune hepatitis and hepatitis E cannot be reliably distinguished by histology; confirmation of viraemia is required.

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Self-assessment questions

1. How can hepatitis due to hepatitis E be distinguished from autoimmune hepatitis?

A. History
B. Detection of autoantibodies
C. Detection of antibodies to hepatitis E
D. Histology
E. Confirmation of viraemia

Answer: E

2. What would commonly be seen on the non-invasive liver screen in autoimmune hepatitis?

A. Raised IgM, AMA positive
B. Raised IgG, Autoantibody positive (smooth muscle antibodies)
C. ANCA positive
D. ANA positive (Anti Scl70 antibody)

Answer: B (A is suggestive of PBC, C of PSC and D of systemic sclerosis and SLE)