CASE REPORT

Treating chronic hepatitis E: when is enough enough?

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SUMMARY

We present a 38-year-old white British man who was taking long-term immunosuppressive medication following kidney transplantation. On routine review, he was noted to have an isolated and asymptomatic rise in alanine aminotransferase. After thorough investigation, he was found to have positive IgM and IgG serology to hepatitis E virus—and given the duration of his transaminitis, he was determined to have chronic hepatitis E infection. Treatment options were complicated by the presence of his kidney transplant, by chronic anaemia and by his wish for concomitant fertility treatment. Ribavirin therapy was instituted with a dramatic and immediate drop in serum viral load, although stool viraemia persisted. No clear protocols guide duration of treatment in chronic hepatitis E infection, but protracted faecal virus shedding predicts viral recrudescence, and treatment should continue at least until the stool is clear of virus.

BACKGROUND

There is a current hepatitis E virus epidemic in Europe, which, although largely asymptomatic, is increasingly seen to be associated with extra-hepatic manifestations, such as bilateral brachial plexopathy, and to be a cause of rapidly progressive chronic hepatitis in transplant recipients. There are four genotypes, which are associated with different clinical presentations and epidemiology. Early beliefs that hepatitis E only causes a hepatitis A-like acute illness have been disproven as chronic infections are seen in patients who are immunosuppressed, particularly evident in the solid organ transplant population. Chronic infection may be asymptomatic in the early stages, but can rapidly lead to cirrhosis. Treatment aimed at viral eradication is therefore warranted. Given that increasing numbers of patients are living with immunosuppression, we anticipate that chronic hepatitis E infection will become an increasingly important clinical problem. There are no clear and definitive guidelines for treating chronic hepatitis E infection, and our experience will contribute to the evidence base for establishing best practice in this field.

CASE PRESENTATION

A 38-year-old Caucasian man developed idiopathic focal segmental glomerulosclerosis in 1996, resulting in end-stage kidney failure by 2000. He received a deceased donor kidney transplant in 2006, but required retransplantation from a living donor in 2011 due to aggressive disease recurrence. He was therefore immunosuppressed for many

years, his allograft function being maintained on a regimen of oral tacrolimus, prednisolone and weekly plasma exchange.

Surveillance blood tests in September 2013 revealed a markedly elevated alanine aminotransferase (ALT) level of 271 IU/L (normal range: 4–59) (figure 1A). This was an isolated abnormality, with other measured liver function tests being normal. He was entirely asymptomatic.

INVESTIGATIONS

A panel of tests were performed to determine the cause of the biochemical abnormality. IgM and IgG antibodies directed against hepatitis E virus were eventually detected in the serum, and viral RNA was detectable in serum and stool. Transaminitis persisted for 9 months (figure 1A) until treatment was commenced with ribavirin, indicating chronic infection. Subsequent genotyping of the hepatitis E virus, performed at the Virus Reference Department, Public Health England, showed this to be the zoonotic genotype 3. The source of the infection is unknown; acquisition from food is most likely although blood components have also been shown to be a possible source.

DIFFERENTIAL DIAGNOSIS

Serological testing showed no evidence of prior exposure to hepatitis A, B or C, cytomegalovirus or HIV. Screening tests for coeliac disease were negative. Common autoantibodies (smooth muscle, gastric parietal cell, mitochondrial, liver/kidney microsomal and Hep2 antinuclear antibodies) were also absent. An ultrasound of the liver was unremarkable, excluding structural abnormalities as a cause for the transaminitis.

TREATMENT

The patient's coexisting medical conditions as well as social factors complicated treatment in this case. Reducing immunosuppression alone has been successful in some cases (especially immunosuppressive regimens that target T cell function), but has obvious drawbacks in the case of transplanted organs. Interferon has been used to treat hepatitis E infection but is also associated with rejection of transplanted organs.

In this case, initial attempts were made to clear the virus by reducing the prednisolone dose from 10 mg per day to 7.5 mg per day, but this was unsuccessful as after 2 months, the serum viral load was unaltered. Further reductions in immunosuppression were deemed to be too risky as the patient had previously lost a transplanted kidney due to disease recurrence.

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Figure 1 (A) ALT and haemoglobin levels before, during and after treatment. Abnormally high ALT levels returned to normal following ribavirin treatment. A drop in haemoglobin levels in February 2015 was due to intensification of ribavirin therapy. (B) Serum viral load dropped rapidly following initiation of ribavirin. Stool viral load was lower in absolute terms, but was slower to fall. Two 'blips' in serum viral load are unexplained, but may be due to poor compliance. ALT, alanine aminotransferase.

Ribavirin may be effective in patients who do not respond to immunosuppressive dose reduction, so our patient commenced treatment with 400 mg twice per day in August 2014, resulting in near-immediate normalisation of ALT levels (figure 1A). Virus RNA in the blood dropped from a maximum 2.6 million copies/ml to undetectable by 9 weeks (figure 1B). Surprisingly, viraemia was again detected several weeks later.

Virus was slow to clear from the stool, becoming undetectable 13 weeks after the virus disappeared from the bloodstream (figure 1B). This, together with the late recurrence of viraemia described above, led to concerns about inadequate dosing or patient non-adherence. Viral loads responded to adherence counselling and an increased dose of ribavirin (total daily dose increased to 1000 mg in November 2014 and then reduced to 400 mg twice per day in February 2015 in response to an unacceptable fall in haemoglobin).

OUTCOME AND FOLLOW-UP

Absence of viraemia 6 months after completing treatment is a good indication of a sustained virological response. From treatment completion (March 2015) until the time of writing, our patient's liver function tests have remained normal, and he remains RNA negative. He has been asymptomatic with respect to his infection throughout treatment.

DISCUSSION

Several hepatitis E genotypes are known.¹ Although the four genotypes have distinct clinical and epidemiological characteristics, they belong to a single serotype.

In developing countries, genotypes 1 and 2 dominate. Like hepatitis A, they are endemic and spread by the faecal-oral

route. While fulminant liver failure and death are rarely seen with genotypes 1 or 2 infection, they are a significant cause of mortality in pregnant women in high prevalence countries.

In the UK, genotypes 3 and 4 are more common. These are swine viruses, and infection is zoonotic. Consumption of undercooked pork products is the likely mode of acquisition. These latter genotypes have been associated with a variety of extra-hepatic complications, including neurological manifestations such as brachial neuropathies and Guillain-Barré syndrome.² Although mostly asymptomatic, symptomatic infection usually follows an acute and self-limiting course. Chronic infection is rarely seen, but a European epidemic has appeared in immunosuppressed individuals, particularly in the context of organ transplantation, and may be associated with rapid progression to cirrhosis. There is also growing concern about the potential spread of hepatitis E via transfusion of blood components.³

Our patient's clinical history did not reveal any obvious mode of acquisition, although his immunosuppression was a risk factor for developing chronic infection. The lack of clear risk factors is consistent with other reports.¹ Thus, a high index of suspicion is required to identify this virus as the cause of hepatitis or asymptomatic deranged liver function tests. Historically, hepatitis E was considered a travel-associated infection, and the disease is likely to have been underdiagnosed. In the light of this case report, we advise that anyone with unexplained hepatitis, regardless of travel history, should be tested for hepatitis E.

Ribavirin, the drug ultimately successful in this case, is more commonly used to treat hepatitis C infection. It is a guanosine analogue that inhibits viral replication, and treatment is associated with a drop in haemoglobin levels due to haemolytic anaemia. A reduction of approximately 2 g/dL is usually

associated with good therapeutic response—in hepatitis C treatment, at least. This sometimes necessitates treatment interruption or blood transfusion. Our patient was already chronically anaemic due to chronic kidney disease and was dependent on regular erythropoietin injections. Regular blood transfusions are undesirable due to the potential for human leukocyte antigen-antibody development, which could impact on the foreign kidney. As an added complication, our patient was planning to undergo fertility treatment. Semen could not be stored for 7 months after the cessation of ribavirin treatment, due to its teratogenicity.

Those who have persistent viral shedding in stool have increased risk of relapse once treatment is stopped.⁴ It has been postulated that this is due to replication of virus outside the liver, possibly within the colon itself. Consistent with this, we found it necessary to continue treatment until stool viral load was undetectable.

One case series suggested that 3 months of ribavirin is usually adequate, and that a high lymphocyte count on commencing treatment predicts treatment success.⁵ That case series reported 95% clearance using ribavirin monotherapy with a relapse rate of 10%.⁵

Learning points

- ▶ Hepatitis E is an under-recognised cause of both acute and chronic hepatitis.
- ▶ Patients who are immunosuppressed are at risk of chronic infection.
- ▶ Treatment options are limited and must be tailored to individual patient factors, including comorbidities and family planning.
- ▶ Ribavirin treatment should continue until stool viral load is negative.

Treatment algorithms have been proposed,⁶ and the topic of hepatitis E infection in patients with solid organ transplants has been reviewed.⁷ The British Transplant Society recently published a specific guideline for the diagnosis and management of hepatitis E, based on the latest understanding of the disease.⁸ Further experience will facilitate development of more robust evidence-based treatment protocols for this increasingly recognised infection.

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