Unusual presentation of more common disease/injury

Clopidogrel, Turkey and a red herring?

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Summary

The authors present the case of acute hepatitis E in a 61-year-old Edinburgh man who had returned from a holiday in Turkey 6 weeks previously. Diagnosis was ambiguous with his presentation initially attributed to a drug-induced liver injury.

BACKGROUND

Hepatitis E infection has been recognised as an important cause of hepatitis in the developing world since the early 1980s. Yet, only recently it has been highlighted as a significant public health concern in developed countries. Unusually, morbidity is higher in patients from developed countries, with a larger cohort developing hepatic complications. Patients from developed countries also suffer greater mortalities at around 10% versus 1% in developing countries. Outcomes are especially poor in pregnant women and in individuals with underlying chronic liver disease; in such patients mortality approaches 70%.¹

Recent reports highlight an unexpectedly high anti-hepatitis E virus (HEV) IgG sero-prevalence in developed countries in comparison to the assumed rarity of the infection, ranging from 3% in Tokyo, Japan,² to 16% in Southwest England³ and 21.3% in US blood donors.⁴ Subclinical infection and misdiagnosis is thought to account for such a discrepancy.¹ In the past few years there has been a large increase in the number of reported cases of clinically diagnosed hepatitis E. Indeed, recent data suggests hepatitis E infection is more common than hepatitis A infection in the UK,⁵ France⁷ and Japan.¹ This increase in reported cases is most likely because of more frequent and technically improved testing together with superior clinical recognition, rather than an actual increase in cases.¹ In Edinburgh, virology recommends screening for anti-HEV IgG, which peaks shortly after infection and persists for years, together with anti-HEV IgM, which is usually detectable at the onset of symptoms with strongly positive results rare after 3 months. The central laboratory for processing hepatitis E virology is in Glasgow. Edinburgh virology does not routinely request PCR or genotyping because of the very brief period of viraemia.

The risk of hepatitis E infection transmission to the international traveller is underestimated. Hepatitis E is responsible for up to 50% of cases of acute hepatitis in endemic regions of the developing world including the Indian sub-continent, Nepal, South-East Asia, China, much of the Middle-East, Africa, Mexico and some regions of South America.¹ Moreover, recent literature underlines the previously undescribed threat of sporadic autochthonous infection in developed countries.¹ The maximum hepatitis E

sero-prevalence occurs at 30 years in the developing world and at around 60 years in the developed world. It shows a strong sex-bias with infection rates up to three times greater in men.¹

Hepatitis E usually presents as an acute self-limiting icteric hepatitis, similar to that described in hepatitis A. The viral incubation period is around 2–9 weeks, with a peak viraemia during incubation and early acute phase. Peak transaminitis occurs at 5–6 weeks post exposure and falls to normal by week 10. At presentation, the mean bilirubin level is ~100 µM and the mean alanine transaminase (ALT) is ~1400 IU/l. Hepatitis E can develop into a fulminant hepatitis and chronic infection is recognised in the immunocompromised.¹

The virus is transmitted via the faecal-oral route. In endemic regions, infection normally follows heavy rainfall and is usually transmitted enterically by water contaminated with sewage or via raw and undercooked shellfish. In autochthonous infection, a zoonotic element is suspected with pigs being the most likely reservoir.¹

CASE PRESENTATION

History of presenting complaint

On 15 July 2010, a 61-year-old white Scottish male presented to acute receiving with pruritic jaundice and headache. He gave a 4-week history of moderate epigastric discomfort and a stone of weight loss. He described poor appetite, disturbed sleep, restlessness and dark urine for 1 week. The patient last passed stool 3 days ago; this was 'somewhat pale'. That day he developed a raised temperature. The day before presenting he described vomiting with bile but no blood.

Medical history

He had a transient ischaemic attack (TIA) 1 month prior to admission and a left lacunar stroke a year ago. Carotid stenosis was below threshold for intervention. A diagnosis of Hodgkin's lymphoma was confirmed in 1973, with relapse in 1981 and subsequent radiotherapy and chemotherapy, but was now in remission confirmed by normal CT in 2008. During the course of his treatment for lymphoma he had a splenectomy.

Medications

His current drug treatment on admission consisted of penicillin V, omeprazole, simvastatin and clopidogrel. Following his recent TIA, the patient was changed from a combination of dipyridamole and aspirin to clopidogrel alone. His current illness began the day after clopidogrel was started. He described no drug allergies except to iodine.

Clinical examination

He was afebrile with a pulse of 100 bpm. He had marked jaundice, dry skin and pale extremities. Livedo reticularis was noted on his hands. Capillary refill was less than 2 s. There was no lymphadenopathy, clubbing or cyanosis. On examination of his gastrointestinal system, there was a midline scar consistent with a previous splenectomy and gynaecomastia. He was tender to palpation in the epigastric region. On examination of his central nervous system, he displayed some symmetrical reduced co-ordination in the upper and lower limbs and a laborious gait consistent with a previous cerebrovascular accident. Examination was otherwise normal.

Social, travel and family history

He was not working as a result of his recent TIA. He had never smoked and consumes approximately six units of alcohol per week. He had returned from a holiday in Turkey 6 weeks previously. He had a family history of peripheral vascular disease.

INVESTIGATIONS

Initial investigations revealed markedly deranged liver function with a bilirubin level of 57 μ M, an alanine aminotransferase of 3626 U/l, an alkaline phosphatase of 364 U/l and a γ -glutamyl transpeptidase of 357 U/l. Albumin levels were initially normal and coagulation was conserved throughout this illness. Liver function tests were in the normal range during his admission for TIA 1 month ago with a bilirubin of 11 μ M, an alanine aminotransferase of 36 U/l and an alkaline phosphatase of 84 U/l.

At presentation, haematology was within normal range except for an isolated monocytosis at 1.44×10^9 /l. An isolated monocytosis is considered most consistent with a viral cause for hepatitis. Renal function was preserved with an estimate glomerular filtration rate above 60 ml/min/1.73 m². Random blood glucose was 5.0 mM. C reactive protein was at the upper end of normal at 9 mg/l.

Chest radiography and abdominal ultrasonography were unremarkable.

Initial liver screen on 15 July 2010 revealed a normal autoimmune profile with negative antinuclear, mitochondrial and smooth muscle antibodies, normal antithyroid peroxidase but strongly positive for gastric parietal cell antibodies. Urine culture and microscopy were unremarkable. Epstein-Barr virus, cytomegalovirus, HIV, *Toxoplasma gondii* and hepatitis A, B and C screening were negative. Paracetamol levels were negative. Amylase levels were in the normal range. Hepatitis E virology was also collected on the day of admission but results took time to be processed because of the off-site location of the processing laboratory.

All drug treatment was withheld with a high suspicion of a drug-induced liver injury. Clopidogrel was thought to

be the most likely causative agent; the patient described that the start of his current illness coincided with his starting clopidogrel.

By 19 July 2010 his liver function had begun to normalise, his ALT has fallen to 1521 U/l, and the patient was advised he could return home but to return to the ward regularly, every 1–2 days, for repeat liver function testing. However, by 25 July 2010, his liver function had once again deteriorated, with an ALT of 2846 U/l. On questioning, he denied taking any medications while outside of hospital. As a precautionary measure, he was once again admitted to the gastroenterology ward for inpatient observation until it was certain his liver function was normalising.

The unusual biphasic pattern of his liver enzymes, with the second peak in ALT occurring while he was at home, strongly suggested an environmental causative agent for his hepatitis. Clopidogrel induced liver injury was the most likely diagnosis. Hepatitis E infection remained to be excluded on return of the virology results.

On 28 July 2010, a needle liver biopsy was performed to help establish a definitive diagnosis. It described a lymphoplasmacytic portal, interface and lobular hepatitis, with mild portal and interface but moderate lobular activity, the overall activity grade being classed as moderate. There was no significant fibrosis. The appearance suggested recent hepatitic flare. There was no evidence of recurrent Hodgkin's disease and/or chronic fibrotic liver disease. Pathology agreed that serology results must be awaited for definitive diagnosis.

The patient was discharged for a second time on 29 July 2010 as his liver function had once again begun to normalise with an ALT of 1409 U/l. He was asked to return to the ward daily to monitor his liver function tests.

DIFFERENTIAL DIAGNOSIS

Initial presentation, examination and liver function tests are suggestive of an episode of acute hepatitis. His preliminary liver screen was negative. He had a normal abdominal ultrasound and a non-specific liver biopsy. Therefore, given that the onset of his symptoms coincided with starting clopidogrel therapy, a clopidogrel-induced liver injury was determined to be the most likely diagnosis. This was supported by an unusual second deterioration in his liver function while discharged home.

However, the patient's recent history of travel to Turkey, a Middle-Eastern country associated with endemic hepatitis E, meant that a diagnosis of hepatitis E had to be excluded by virology. Moreover, while cases exist and it is noted in the British National Formulary, non-infectious hepatitis is considered a very rare adverse effect of clopidogrel with no reported incidences in either the clopidogrel versus aspirin in Patients at Risk of Ischaemic Events and clopidogrel in Unstable Angina to prevent Recurrent Events controlled clinical trials.¹¹ Moreover, the authors could find no reported cases of a clopidogrel induced liver injury associated with an ALT >1000.

TREATMENT

The patient was managed supportively in hospital. There was a high suspicion of drug-induced liver injury. So, his regular medications were immediately discontinued with the exception of his prophylactic penicillin V.

Currently, no specific UK clinical guidelines exist for the management of hepatitis E infection. The British Association of Sexual Health and HIV have issued a United Kingdom National Guideline on Management of Viral Hepatitis A, B and C. Following the guidance for management of hepatitis A, which has a similar presentation and course as hepatitis E, it was recommended that a patient such as ours, who presents as a severe attack with vomiting, be admitted to hospital.¹²

OUTCOME AND FOLLOW-UP

On 12 August 2010, results for anti-HEV IgM and IgG were returned positive and a diagnosis of acute hepatitis E was confirmed. However, because of the diagnostic ambiguity, it was advised that clopidogrel continue to be withheld until his liver function had completely normalised.

On 20 August 2010, the general practitioner (GP) was informed that the patient's liver function tests had completely normalised – on 16 August 2010 his bilirubin was 15 µM, ALT was 35 U/l, alkaline phosphatase was 95 U/l. The GP was advised that the patient may now restart clopidogrel, provided that his liver function was monitored on a weekly basis.

Unfortunately, before he was able to restart his antiplatelet medication, on 27 August 2010 the patient suffered a further stroke and was left with persisting weakness of his right arm.

DISCUSSION

Review of the literature highlights a number of recent cases with important parallels to that of our patient's. Current haematological malignancy and its ongoing chemotherapeutic treatment stand out as important risk factors for a more severe hepatitis E disease course. Moreover, in cases reported in Tokyo, Japan¹³ and Nice, France,¹⁴ the patients, both suffering from lymphoma, developed a chronic infection with the authors suggesting their immunocompromised status meant that they were unable to mount an adequate humoral response to limit the acute infection. Another report documents a case of a lymphoblastic leukaemia patient who suffered an acute hepatitis E infection, which completely resolved to normal liver function and undetectable viral RNA levels. However, the infection then reappeared later that year, 14 weeks following a stem cell transplant. There was a reappearance of viral RNA and a second deterioration of liver function.¹⁵ In all three patients, by far the most likely route of transmission was via contaminated transfusion products.^{13–15}

Taken together these cases highlight the importance of remaining vigilant in a patient such as ours, with a history of recurrent haematological malignancy and treatment, for reactivation of hepatitis E infection and of the possibility of chronicity. Therefore, follow-up is indicated and, in the event of a further relapse of Hodgkin's, careful monitoring of his liver function despite his typical hepatitis E infection course.^{13–15} In all three cases the identification of hepatitis E as the underlying cause for hepatitis required reverse transcription – PCR identification of viral RNA; the infection having resulted from an inadequate humoral response.^{13–15} Another case underlines the sometimes unhelpful role of HEV serology in diagnosis. A male from Würzburg, Germany, developed hepatitis of unknown origin after

travel in 2009 and investigation found positive serology for both HEV and Epstein–Barr virus. RT-PCR for viral RNA was not carried out. Based on the clinical picture and the pattern of the serology it was determined that his hepatitis was caused by Epstein–Barr virus alone. In support of their conclusion, the authors cited literature describing the occurrence of positive values for hepatitis E IgG in hepatitis A, B and C infection and positive values for hepatitis E IgM in acute Epstein–Barr virus and cytomegalovirus infection, in the absence of concomitant hepatitis E infection. Therefore, for definitive diagnosis the authors suggest RT-PCR must be undertaken.¹⁶ This can prove difficult in a delayed presentation such as ours because the period of hepatitis E viraemia is brief – by a few days to weeks after the onset of clinical symptoms, hepatitis E viral RNA is cleared from the blood; however, it is shed in the stool for a further 2 weeks.¹

Universal application of RT-PCR would allow the genotype of HEV to be identified. While genotype 1–2 is responsible for infection in endemic areas, genotype 3 and to a lesser extent 4 is most frequently isolated in cases in the developed world. Genotype 3 is known to cause a more fulminant and sometimes fatal hepatitis. It occurs more often in older males and those with underlying chronic disease.^{1 9 10} Therefore, establishing the genotype would identify patients likely to have a poorer prognosis and consequently in need of more careful monitoring and management. This would presumably improve outcomes in genotype 3 infection. It would have been of interest to know which genotype HEV infection our patient suffered from. Although he had history of recent travel to an endemic region, his age and sex, history of chronic disease and immunocompromisation having had a splenectomy, and more severe clinical picture perhaps better fits a genotype 3 infection.^{1 9 10}

It is very unfortunate that, while our patient had his clopidogrel withdrawn, he suffered a further stroke. It is difficult to see how this could have been avoided given the diagnostic ambiguity – notably the history of illness coinciding with starting clopidogrel and there was unusual biphasic recovery in liver function. As such, everything was done with patient safety at the highest priority.

While misdiagnosis did not occur in our case, instead an unfortunate but currently unavoidable delay in processing HEV virology, hepatitis E is frequently misdiagnosed as a drug-induced liver injury in developed countries. This is a problem which occurs with increasing frequency among older people. This is because current diagnosis of drug-induced liver injury rests only on the fulfilment of three standard criteria (or two together with worsening liver function on reintroducing the suspected agent). That is, a temporal association between the initiation of drug therapy and biochemical evidence of liver injury, a temporal association between the cessation of drug therapy and improvement in liver biochemistry and the exclusion of alternative diagnosis. Indeed, a recent retrospective analysis showed that in 21% of 28 patients from developed countries who had met the standard criteria for drug-induced liver injury did not have the condition, but instead had a hepatitis E infection.¹

Clearly, there is a need for specific guidelines for the diagnosis and management of suspected hepatitis E infection. In lieu of such guidelines, this case outlines the continued

need for an early consideration of hepatitis E infection in all cases of hepatitis of unknown origin in the foreign traveller. In addition, routine screening for potential environmental risk factors for hepatitis E, like consumption of undercooked pork or shellfish, may help clarify diagnosis.¹ Perhaps also a quicker turn-around on hepatitis E virology in Edinburgh may help avert similar problems in the future. This could be achieved by the ability to process hepatitis E virology locally. Literature describing the upward trend in hepatitis E diagnosis in developed countries lends credence to such a suggestion.¹

Learning points

- ▶ Early consideration of a hepatitis E infection is essential in the foreign traveller who presents with a hepatitis of unknown origin.
- ▶ There is a need for specific guidelines in the diagnosis and management of suspected hepatitis E infection.
- ▶ Drug-induced liver injury is considered as a diagnosis of exclusion in hepatitis of unknown origin, following definitive serological investigation.
- ▶ Given its increasing prevalence, hepatitis E virology results turn-around should be accelerated to come in line with that of hepatitis A–C services. It is debatable, however, whether this would have changed our patient's management.
- ▶ The use of RT-PCR in the diagnosis could result in greater diagnostic specificity and genotype specific management.

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