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Deranged liver function tests in a patient with Hodgkin's lymphoma

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1. Case history

A 39-year old man presented in autumn 2012 with a dry cough, night sweats and weight loss and following investigation was found to have Hodgkin's lymphoma. He was treated on the RATHL (Response Adjusted Therapy for Hodgkin's Lymphoma) study protocol, receiving two courses of AVBD (doxorubicin, vincristine, bleomycin, dacarbazine), and having a negative PET scan was randomised to receive AVD. His disease progressed, however, and he required salvage therapy with two cycles of IVE (ifosfamide, epirubicin and etoposide), to be consolidated with an autologous stem cell transplant (SCT). On admission on 10 September 2013 for BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning and transplant, his liver enzymes (LFTs) were noted to be raised (AST 143 U/L; ALT 444 U/L).

Question 1: What are the differential diagnoses for acutely deranged LFTs in this patient and what investigations should be done?

Question 2: What is the significance of HEV in this patient?

Question 3: How should immunosuppressed patients with HEV be managed?

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Evidence-based opinion

What are the differential diagnoses for acutely deranged LFTs in this patient and what investigations should be done?

A full autoimmune and viral hepatitis screen is indicated in this patient. His autoimmune hepatitis screen (ANCA, ANA, anti-mitochondrial antibodies, anti-smooth muscle antibodies, LKM antibodies, liver cytosol 1 antibodies) was negative. A viral hepatitis screen comprising HBsAg, anti-HBcore antibody, HCV antibody, HCV antigen and HAV IgM, HEV IgM, HEV IgG and HEV PCR as well as PCR testing for CMV, EBV and adenovirus were performed. The only positive tests were HEV IgG and HEV IgM (Mikrogen 2.6, c/o 0.314 and >3, c/o 0.651, respectively) and HEV RNA was detected using RT-PCR (ct 22.08). Drug-induced liver injury and disease progression of his lymphoma were ruled out. Computed tomography of the abdomen was performed to assess whether there was hepatic infiltration. This showed only diffuse fatty infiltration of the liver. He received his SCT the same day his HEV results became available. (Fig. 1).

2. Background

Hepatitis E is a non-enveloped single-stranded positive sense RNA virus belonging to the *Hepeviridae* family. Four different HEV genotypes are known to infect humans. HEV1 and HEV2 infect humans only, and are endemic in developing countries, Asia and Africa/Mexico, respectively, causing travel-related HEV in Europe and North America. HEV3 (endemic in North America and Europe) and HEV4 (endemic in Asia) are found in pigs, rodents, deer, wild boar, farmed rabbits and shellfish, and are therefore zoonoses in humans [1,2]. The past 10 years has seen a sharp rise in the number of autochthonous HEV infections, with indigenous HEV cases superseding that of travel-acquired HEV since 2010 in the UK [3]. Transmission of HEV1and HEV2 is mainly faecal-oral, and person-to-person spread is rare, unlike hepatitis A [4]. HEV3 and HEV4 on the other hand are mainly foodborne (ingestion of undercooked pork) with cases of transmission via blood transfusions or organ-transplants also described [5–7].

The incubation period of HEV ranges from 2 to 8 weeks, and less than 5% of infected immunocompetent patients become symptomatic [8]. Symptoms manifest as jaundice, myalgia, malaise, or flu-like-illness, and only rarely cause morbidity or mortality in healthy individuals. A notable exception is pregnant women, up to 20% of whom can develop fulminant hepatitis with acute HEV [9]. Acute HEV infection in patients with a background of chronic hepatitis can also be severe [10]. The past decade has seen recognition of an increasing clinical spectrum of HEV infection. For example, chronic hepatitis E in immunocompromised patients (e.g. solid-organ transplant recipients, haematological patients or HIV patients with AIDS), as defined as a persistent increase in liver-enzyme levels with the presence of HEV RNA in the serum for at least 6 months after the acute phase [11], has been described with increasing frequency. In addition, numerous extra-hepatic manifestations of HEV3 infection have been reported. Neurological complications include Guillain–Barré syndrome, encephalitis, ataxia, brachial neuritis, inflammatory polyradiculopathy and proximal myopathy, occur in up to 5.5% of patients, after both acute and chronic HEV [12]. Renal manifestations include membranoproliferative glomerulonephritis and IgA nephropathy [13]; while thrombocytopenia, and pure red cell aplasia have also been described [14,15].

Diagnosis of HEV relies on the detection of HEV IgM and IgG, both of which appear with the acute elevation of transaminases. However, there is substantial variation in the sensitivity and specificity of commercially available kits [16]. A recent study assessing the most commonly used commercial anti-HEV IgM and IgG using a panel of known positive HEV1 and HEV3 samples found the specificity of tests ranged from 84% (MP Biomedicals, Singapore, former Genelabs) to 99% (Wantai, PE2-assay; Beijing, China), and sensitivity ranged from 54% (Mikrogen recomWell old assay, Neuried, Germany) to 75% (Wantai) [17]. Of note, the Mikrogen *recom*Well HEV IgM and IgG tests are used in our laboratory, and use recombinant antigen from HEV1 and HEV3 only, although manufacturers state HEV2 and HEV4 are detected by cross-reactivity [18]. Additionally, the production of antibodies in the immunosuppressed population is unreliable and the majority of these patients are asymptomatic, with LFTs raised in the 100s rather than 1000s. It is recommended that in this group of patients, HEV RNA detection by PCR is used to diagnose as well as monitor HEV infection. The lack of a sensitive and specific screening test coupled with the lack of awareness of HEV infections has led to cases of HEV misdiagnosed as "drug-induced liver injury" in the past.

In developing countries, improvement in sanitation is key to preventing HEV infection; HEV RNA being found in environmental sewage and seawater samples [4]. However in industrialised countries, where zoonotic HEV infections predominate, emphasis should be placed on the proper cooking of pork products and game; cooking at 71 °C for at least 20 min inactivates HEV [19]. Alternative preventative measures including vaccine development against HEV have been successful in control of HEV epidemics. Vaccine HEV 239 (Hecolin; Xiamen Innovax Biotech, Xiamen, China), has now been licensed in China for use in healthy adults aged 16–65 (including pregnant women). This recombinant HEV vaccine encompasses the ORF 2 capsid protein from HEV1, and has demonstrated safety and efficacy against HEV1 and HEV4 in phase II trials [8,20]. However, its efficacy in the immunosuppressed population has not been assessed [8].

What is the significance of HEV in this patient?

As mentioned above, chronic HEV has been described in various patient groups including solid-organ transplant (SOT) recipients, haematological patients and HIV patients with advanced disease. Once infected with HEV, chronicity is thought to occur in approximately 60% of at risk patients and is defined as a persistent increase in liver-enzyme levels with the presence of HEV RNA in the serum for at least 6 months after the acute phase [11]. Chronicity is mainly linked to an impaired T-cell response (especially the subsets CD2, CD3 and CD4) and to the severity and type of immunosuppression [11,21]. Immunosuppressed patients with chronic hepatitis E can have a rapid progression to liver fibrosis (within 1 year) and about 14% of these patients develop cirrhosis, liver failure and ultimately require transplantation [12,20]. To date HEV chronicity has only been documented with HEV3 and a single case with HEV4 [22], mainly in immunosuppressed patients. The predominance of HEV3 is likely due to reporting bias, as most studies have been from areas where HEV3 is endemic. The mode of transmission of HEV in immunosuppressed patients is as for the general population. Thus all transplant patients should be advised to cook pork products and game at 71 °C for at least 20 min to inactivate HEV [18], or avoid these altogether. Additionally, in SOT and SCT patients, transmissions via the allograft or blood transfusion have been reported [5,6,23]. As blood products are not screened for HEV, this is a possible although rare route of transmission. Seroprevalance studies in healthy blood donors have detected antibodies against HEV (22–27%), and in some cases viraemia (0–0.07%) [24,25].

How should immunosuppressed patients with HEV be managed?

Management of chronic HEV in immunosuppressed patients involves a step-wise approach; reduction of immunosuppression is first-line, with approximately a third of patients achieving sustained virological response (SVR). If immunosuppression

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