Clinical studies on hepatitis B, C, and E virus infection
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CHAPTER 8

Hepatitis E Virus Infection and Hepatic Graft versus Host Disease in Allogeneic Hematopoietic Stem Cell Transplantation Recipients

* contributed equally

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ABSTRACT

Hepatitis E virus (HEV) genotype 3 infection has become important for immunocompromised patients, because of their propensity to develop chronic HEV-infection and liver cirrhosis. We retrospectively investigated the incidence of HEV-infection in patients with elevated ALT levels, in a cohort of 130 allogeneic hematopoietic stem cell (alloHSCT) recipients. Of a total of 130 patients, 123 had one or more episodes of elevated ALT-levels. Five out of these 123 patients had HEV-infection (4%). Interestingly, 3 of these patients had signs of concomitant graft versus host disease (GvHD) of the liver. These data demonstrate that HEV-infection is prevalent among alloHSCT recipients and may be related to the presence of GvHD. HEV-infection should be considered in all alloHSCT recipients with elevated ALT-levels, particularly in patients with GvHD of the liver.
INTRODUCTION

Hepatitis E virus (HEV) is a non-enveloped, single stranded RNA virus, which can be subdivided into at least four genotypes. Genotypes 1 and 2 are human viruses causing acute hepatitis, mainly in young adults in tropical countries. Genotypes 3 and 4 are zoonotic, with pigs as the main reservoir in Europe and parts of Asia. The most prevalent HEV genotype in Europe is genotype 3, which is normally asymptomatic and self-limiting. It does, however, pose a threat to immunocompromised patients who may develop chronic HEV-infection (58-93%) and liver cirrhosis. In a Dutch cohort of 328 allogeneic hematopoietic stem cell transplantation (alloHSCT) recipients, 8 cases of HEV-infection (2.4%) were found of which 5 developed chronic HEV-infection. This suggests that there is a considerable risk of post-transplant HEV-infection for alloHSCT recipients. Most patients with HEV-infection have increased ALT-levels and most alloHSCT patients experience one or more episodes of elevated transaminase levels post-transplantation. The differential diagnosis of elevated liver enzymes including transaminases following alloHSCT is however extensive and includes medication toxicity, pre-existing liver conditions such as fatty liver disease and graft versus host disease (GvHD) of the liver. Moreover, as infections may incite GvHD it can be hypothesized that HEV can provoke GvHD of the liver. Our aim was to identify the prevalence of HEV-infection among alloHSCT patients with elevated ALT-levels.

METHODS

We performed a retrospective analysis of ALT-levels in all 130 patients who received an allogeneic HSCT between January 1st 2005 and April 1st 2015 at our institution. Elevated ALT-levels were defined as: ALT > 50 U/L for at least four consecutive weeks, recurrent elevated ALT-levels > 50 U/L for a shorter period of time with normal ALT-levels in between, or an episode of peaking ALT of > 100 U/L during a period of less than 4 weeks. HEV-RNA was measured at times of ALT-elevation in stored PCR-grade plasma samples using a real-time quantitative PCR amplifying the open reading frame (ORF) 3 region of HEV. For patients with HEV-infection, additional serial plasma samples were retrieved and tested to follow HEV-infection over time.

RESULTS

Patient characteristics are summarized in Table 1. Of 130 alloHSCT recipients (70 men and 60 women), 123 showed one or more episodes of elevated ALT-levels (total: 147 episodes). Hepatic GvHD was diagnosed or strongly suspected (based on elevated cholestatic liver enzymes in combination with biopsy-proven GvHD of skin or intestine, that responded to steroid-therapy) in 19 patients (16% of the 130 alloHSCT patients). For 141/147 episodes of ALT-elevation a plasma sample was available for HEV-RNA testing. Five samples belonging to 5 different patients were HEV-RNA positive, resulting
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Allogeneic HSCT patients (n=130)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>51 (19-72)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male/ Female</td>
<td>70 / 60</td>
</tr>
<tr>
<td>Diagnosis – no. (%)</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>60 (46)</td>
</tr>
<tr>
<td>ALL</td>
<td>23 (18)</td>
</tr>
<tr>
<td>CML</td>
<td>5 (4)</td>
</tr>
<tr>
<td>CLL</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Non Hodgkin Lymphoma</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (15)</td>
</tr>
</tbody>
</table>

Type of allogeneic HSCT – no. (%)

| RIST-sib | 35 (27) |
| RIST-MUD | 64 (49) |
| MA-sib | 12 (9) |
| MA-MUD | 12 (9) |
| CB | 7 (5) |


Table 2. Characteristics of HEV-infected patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age§ (yr)</th>
<th>Underlying disease</th>
<th>Transplantation type (yr)</th>
<th>Hepatic GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 60</td>
<td>CLL</td>
<td>MUD-RIST (2006)</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>M, 37</td>
<td>ALL</td>
<td>MA-MUD (2010)</td>
<td>Yes*</td>
</tr>
<tr>
<td>3</td>
<td>F, 70</td>
<td>CLL</td>
<td>MUD-RIST (2011)</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M, 41</td>
<td>CML</td>
<td>MA-MUD (2012)</td>
<td>Yes*</td>
</tr>
<tr>
<td>5</td>
<td>F, 54</td>
<td>Hodgkin Lymphoma</td>
<td>MUD-RIST (2014)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

§Age at time of HEV diagnosis; *Elevated transaminases and cholestatic liver enzymes have been attributed to hepatic GvHD because they occurred at the time of biopsy-proven chronic GvHD of the gastro-intestinal tract and/or skin. A liver biopsy was not taken.

Abbreviations: CLL: chronic lymphoid leukemia; ALL: acute lymphatic leukemia; CML: chronic myeloid leukemia; MUD: matched-unrelated donor; RIST: reduced intensity stem cell transplantation; MA: myeloablative.
in an HEV-infection prevalence of 4% among alloHSCT recipients with ALT-elevations. All these 5 patients had persistent or recurrent ALT-elevations. Of the five patients with HEV-infection, three had suspicion of concomitant hepatic GvHD; two patients (patient 2 and 4) had biopsy-proven GvHD of the skin and intestine, and suspected GvHD of the liver at the time of HEV infection, in one patient (patient 5) hepatic GvHD was confirmed by a liver biopsy. We describe the case histories of the five HEV-infected patients below (Table 2. and Figure 1).

Patient 1 underwent a reduced intensity alloHSCT (RIST) of a matched unrelated donor (MUD) because of chronic lymphatic leukemia (CLL) in 2006. He developed acute and chronic GvHD of the skin, for which he received prednisolone that could be tapered and finally stopped in 2009. In 2014 a relapse of the CLL occurred which was treated with fludarabine/cyclophosphamide/rituximab (FCR) chemotherapy. This was complicated by chronic varicella zoster infection and herpes simplex infection, for which he received maintenance treatment with valaciclovir and ganciclovir. He was diagnosed with HEV-infection 9 years after alloHSCT, a few months after the last cycle of FCR. Treatment of HEV-infection with ribavirin was initially successful, but after stopping therapy a relapse occurred. Also a second course of therapy did not result in clearance of the virus.

Patient 2 received a myeloablative (MA) MUD alloHSCT because of acute lymphatic leukemia (ALL) in 2010. Three months after alloHST he developed cytomegalovirus (CMV) reactivation, which was treated with valganciclovir, and acute, biopsy-proven GvHD of the skin and intestine which was treated with prednisolone. During this time, ALT-levels were elevated, but they normalized upon treatment for CMV-reactivation and GvHD. Three years later, during an exacerbation of chronic GvHD of the skin and intestine

![Figure 1. Graphic representation of the three patients with HEV-infection and suspected or diagnosed hepatic GvHD (patient 2, 4 and 5). See for detailed description of patient histories the main text.](image-url)
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Patient 1 received a MUD-RIST because of CLL in 2011. The transplantation was complicated by acute and chronic steroid-refractory GvHD of the skin and oropharynx, which was treated with prednisolone, cyclosporin, imatinib and eventually, in 2014, rituximab. She also had disseminated varicella zoster and herpes simplex virus infections for which she received valaciclovir. HEV-infection occurred after rituximab therapy, and was successfully treated with ribavirin. The patient eventually died from recurrent opportunistic respiratory tract infections with Haemophilus influenzae.

Patient 2 received a MUD-RIST because of relapsing chronic myeloid leukemia (CML-BC) in 2012. The transplantation was complicated by acute and chronic steroid-refractory biopsy-proven GvHD of the intestine, which was treated with mesenchymal stem cell transplantation resulting in partial remission. He had peaking ALT-elevations during this period which was attributed to GvHD, iron deposition and medication toxicity. A liver biopsy was not performed. Retrospective analysis of stored plasma samples revealed that he acquired HEV-infection before alloHSCT. HEV-infection and GvHD remained active until he succumbed to systemic yeast infection 16 months after alloHSCT (Figure 1b). In this patient, HEV-infection was diagnosed after his death, and therefore it was left untreated.

Patient 4 received a MA-MUD HSCT because of blast crisis chronic myeloid leukemia (CML-BC) in 2012. The transplantation was complicated by acute and chronic steroid-refractory biopsy-proven GvHD of the intestine, which was treated with mesenchymal stem cell transplantation resulting in partial remission. He had peaking ALT-elevations during this period which was attributed to GvHD, iron deposition and medication toxicity. A liver biopsy was not performed. Retrospective analysis of stored plasma samples revealed that he acquired HEV-infection before alloHSCT. HEV-infection and GvHD remained active until he succumbed to systemic yeast infection 16 months after alloHSCT (Figure 1b). In this patient, HEV-infection was diagnosed after his death, and therefore it was left untreated.

Patient 5 received a MUD-RIST because of relapsing Hodgkin’s lymphoma in 2011, which was complicated by GvHD of the skin and liver. At the time of diagnosis of GvHD, the patient was also diagnosed with HEV-infection (Figure 1c). A liver biopsy taken at

**Figure 1.** Liver biopsy of patient 5: combination of GvHD and HEV-infection.

a. Enlarged 40×, PAS-D-staining. The arrow shows a damaged bile duct as a sign of GvHD.

b. Enlarged 20×, H&E-staining. Lobular inflammatory infiltrate (arrowhead) and Councilman bodies (apoptosis, arrow).

c. Enlarged 20×, H&E-staining. Portal tract with portal vein (+), hepatic artery and bile duct (circle), surrounded by mixed periportal inflammatory infiltrate with some eosinophils (arrow), as can be seen in HEV-infection.

d. Enlarged 40×, H&E staining, detail of 1b. apoptotic bodies (arrow).
that time showed an irregular morphology of the bile duct epithelium, consistent with GvHD. Moreover periportal infiltrates were seen together with some lobular inflammation and Councilman bodies (apoptotic bodies), the latter fitting with both hepatic GvHD and HEV-infection (Figure 2). Analysis of stored plasma samples revealed that HEV-infection preceded GvHD of the liver, suggesting that HEV-infection may have provoked this allo-immune response. The patient responded well to treatment with ribavirin but eventually succumbed to relapsed Hodgkin's lymphoma.
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REFERENCES