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## Editorial

## Hepatitis E virus as an agent of hepatocellular carcinoma



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Autochthonous infections with hepatitis E virus (HEV) have increasingly been described in developed countries during the last 12 years (Kupferschmidt, 2016). This emergence has revealed unforeseen features (Kamar et al., 2017). HEV genotypes 3 and 4 have been shown to have a porcine reservoir, and farm pig-derived products, particularly liver sausages, have been described as a major documented source of HEV transmission to humans (Colson and Raoult, 2017). Concurrently, the clinical spectrum of HEV infection has unexpectedly broadened. HEV genotype 3 infections have been reported since 2008 to become chronic and cause chronic hepatitis in severely immunocompromised individuals, mostly transplant recipients and HIV-infected patients with low CD4 cell counts (Kamar et al., 2017). In addition, cirrhosis was described in approximately 5% of these chronic cases, as early as 2 years post-infection. Furthermore, it has gradually become apparent that HEV infections can be associated with neurological disorders, which may occur in about 5% of acute infections, and also with kidney injury and hematological disorders (Kamar et al., 2017). Nonetheless, one should not lose sight of the potential for HEV to cause both chronic hepatitis and subsequent cirrhosis, which raises the question regarding whether it might not also cause hepatocellular carcinoma (HCC), as is the case for the other causative agents of chronic hepatitis and cirrhosis, i.e. hepatitis B virus (HBV) and hepatitis C virus (HCV).

Two recent articles published in this journal reported an association between HEV and HCC. Amougou Atsama et al. described a significantly greater anti-HEV IgG (but not IgM) prevalence in 67 HCC patients in Cameroon infected with HBV or HCV (42%) compared with 67 HBV- or HCV-infected patients with chronic liver disease but no HCC (13%) and 67 HBV- and HCV-negative patients (10%) (Amougou et al., 2017). These authors hypothesized that past HEV infection may increase the severity of HBV or HCV infection and accelerate progression to HCC in such a setting. In China, Bai et al. found a three-fold greater HEV seroprevalence among 103 patients with liver cancer than in 950 control volunteers (31% vs. 13%) (Bai et al., 2018). In that study, HBV and HCV co-infections were not documented in the HCC patients,

and HEV seroprevalence was also significantly increased in association with other cancers. In addition, it was pointed out that the cancer patients may have been at greater risk of HEV exposure as they likely received a higher number of blood transfusions than the controls, and also that their immunosuppression could have favored chronic HEV infection. Also, among 32 Ghanaian HCC patients with jaundice, HEV was detected in two cases alone (6%) and in nine cases in co-infection with HBV (28%) (Owusu et al., 2018). Hence, the majority of HEV cases co-occurred with HBV infection. Finally, the present authors recently described HCC associated with chronic hepatitis E in a 65-year-old cirrhotic patient with a history of follicular lymphoma (Borentain et al., 2018). He exhibited chronic liver cytolysis for 8 years in the absence of any documented etiology of chronic hepatitis other than HEV of genotype 3.

HCC is the sixth most frequent cancer and the third most frequent cause of cancer death worldwide (Forner et al., 2012). Although it was found to be greater in developing countries, the incidence of HCC almost doubled in developed countries during the 21st century, mainly as a consequence of liver cirrhosis (Njei et al., 2015). It makes sense that HEV can cause HCC, as can all other viral agents of chronic hepatitis (Forner et al., 2012). As is the case for HCV, the HEV genome is a single-stranded positive sense RNA that has not been shown not to integrate totally or partially into human DNA. Furthermore, as is suspected for HCV, HEV may promote HCC through chronic inflammation and possibly disturbances of the cellular pathways due to interactions between viral proteins and host factors (Kanda et al., 2013).

The reason why the association between HEV and HCC has so rarely been reported could be that chronic hepatitis E appears restricted to severely immunocompromised individuals in developed countries, thus its overall incidence is low (Kamar et al., 2017). In addition, although liver cirrhosis has been shown to develop shortly after HEV infection (Gerolami et al., 2008; Kamar et al., 2017), HCC may take much more time to occur than cirrhosis. In the case report presented by Borentain et al., the patient presented chronic liver cytolysis for  $\geq 8$  years (Borentain et al.,

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2018). In addition, HEV may only be a co-factor in HCC occurrence, in association with other causative agents such as HBV, HCV, and/or alcohol. Moreover, chronic HEV infection, when diagnosed, can be cured by reducing the dosage of immunosuppressive drugs, or by ribavirin therapy in approximately 80% of patients with a 3-month duration therapy, and with an additional 6-month course in almost all cases of virological non-response or relapse (Kamar et al., 2017). Finally, it is very likely that HEV infection may be overlooked in HCC patients, as it still is in many settings, including acute and chronic hepatitis (Colson and Raoult, 2017).

Taken together, previous data warrant testing more systematically in further studies on the link between HEV and HCC. For this purpose, cohorts of patients with HCC of known or unknown etiology should be tested for the presence of anti-HEV antibodies and HEV RNA. This will allow determining whether any association between HEV infection and HCC exists and HEV can promote the occurrence of HCC. In addition, severely immunocompromised cirrhotic patients diagnosed with chronic hepatitis E should be screened for HCC before and after viral clearance is attained.

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### Conflict of interest

The authors have no conflicts of interest to declare. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or in the preparation, review, and approval of the manuscript.

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