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LETTER TO THE EDITOR

Chronic hepatitis E in an immunocompetent patient

Dear editor,

We recently read with great interest the paper by Philippe Colson et al., [1] reporting a case of chronic hepatitis E in absence of severe immunodeficiency. Since chronic hepatitis E is generally described in immunocompromised patients, the observation in this study emphasizes that immunosuppression is not the sole factor for prolonged HEV infection and warning for chronic HEV in ''healthy'' individuals is important in case of persistent HEV infection and liver injury.

Chronic HEV infection is commonly reported in Europe. Herein, we reported a case of chronic hepatitis E in an immunocompetent individual who acquired HEV infection by consuming shellfish in China. Chronic HEV infection was proven by detection of HEV viral protein in liver tissue in December 2015 and fecal HEV RNA in May 2017, and by persistent positive anti-HEV IgM and IgG. Immunocompetent status of this patient was validated by normal T lymphocyte counts. Initial liver biopsy revealed acute hepatitis lesion with marked inflammatory activity. Our finding corroborated the observation by Philippe Colson et al. and implied that physical immunosuppressive situation is not the only factor responsible for HEV chronicity.

This patient (had given informed consent) is a 55-year-old Chinese man who presented in our center at the end of 2015 for shellfish poisoning with extremely high level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) (ALT: 311 U/L, AST: 48 U/L, GGT: 227 U/L). The results of serologic test for hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus and cytomegalovirus were negative. Acute hepatitis E was primarily diagnosed based on positive anti-HEV IgM and clinical presentation (Fig. 1A). Liver biopsy revealing scattered expression of HEV viral protein in both cytoplasm and nucleus by immunohistochemistry with antibody against HEV open reading frame 2 (ORF2) further confirmed HEV infection (Fig. 1B). The serum ALT, AST, GGT and ALP declined to normal level in one week (Fig. 1C). Histological analysis revealed hepatocyte swelling, ballooning and Kupffer cell aggregation in this patient (Fig. 1D and E). Mild hepatocellular cholestasis with a few acidophilic bodies and spotty necrosis was observed. Portal tracts were infiltratued with abundant mixture inflammatory cell, including lymphocyte, macrophages and eosinophils, consistent with acute hepatitis (Fig. 1F). Masson and Reticular fiber staining showed no obvious fibrosis (Fig. 1G). No anti-viral therapy was applied to this patient except usage of liver-protective and transaminase-descend medicines. Review of medical record showed that the patient did not report any transmission other than consumption of seafood. In fact, HEV have ever been detected in contaminated shellfish in China with a rate of 17.5% per kilogram of shellfish [2]. It is reasonable to speculate that this patient got HEV infection by consuming shellfish.

Immunocompetent status is defined in this patient who is immunodeficiency virus (HIV)-negative, has no hematological malignancies and no immunosuppressive treatment. Immunological analysis further conceivably confirmed the immunocompetent status with normal level of total T lymphocyte count (2058/μL), CD4-T cell counts (1121/μL) and CD8-T cell counts (868/μL) (Fig. 1H). He drank socially and diagnosed with a weakly alcoholic fatty liver but his immunoglobulin levels were normal.

The patient presented persistent positive anti-HEV IgM and IgG during one and half year follow-up (Fig. 1A). In May 2017, HEV RNA was detected by a reverse transcription polymerase chain reaction (RT-PCR) assay and following nest-PCR in stool and urine specimen (Fig. 1I). Serum level of ALT, AST, GGT and ALP were kept normal during one and half year follow-up (Fig. 1C). There was no elevation of serum total bilirubin in the acute stage and follow-up (Fig. 1J).

Up to present, documents of chronic HEV infection have been exclusively associated with immunocompromised patients that include HIV patients, cancer patients receiving chemotherapy and organ transplantation recipients. Chronic hepatitis E was also described in a few cases with undefined disease conditions, but those patients are conceivable of immunocompromise [3]. Although Grewal et al. reported a case of chronic genotype-3 HEV infection in an immunocompetent patient [4], it remains a debate whether this patient with a history of an autoimmune dis-

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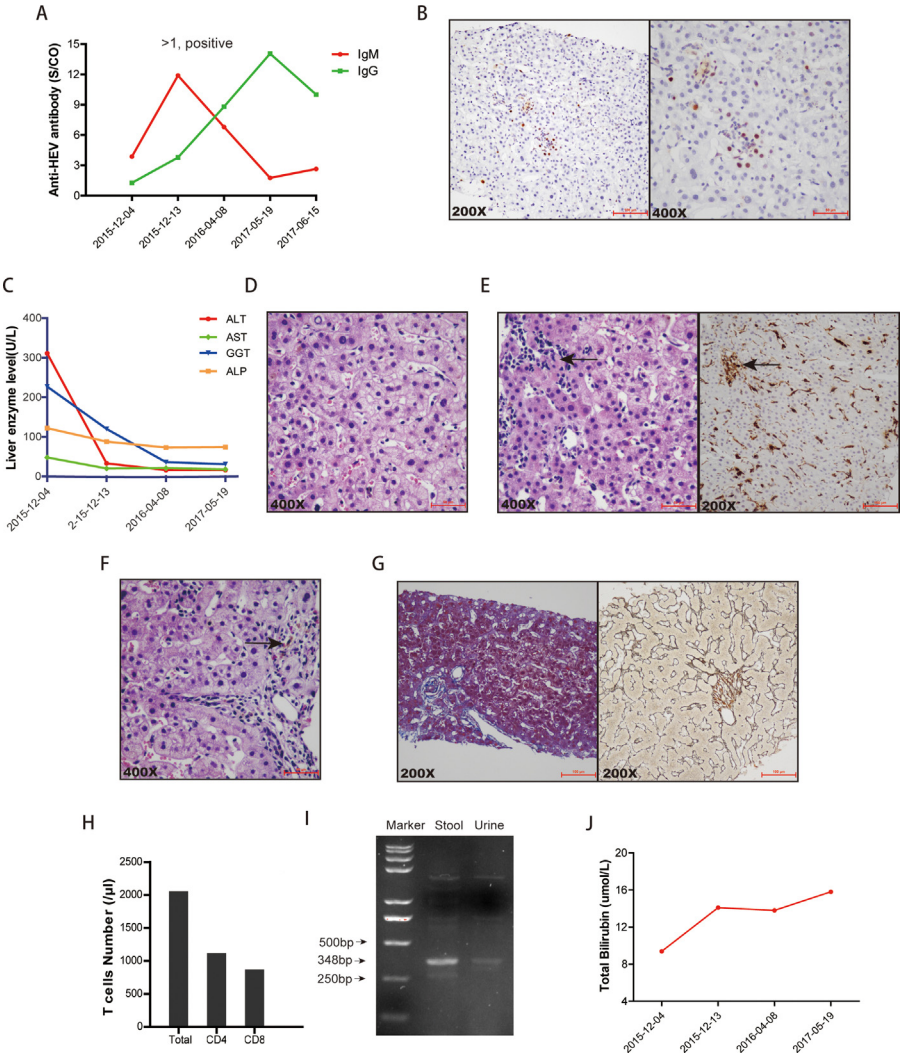

Figure 1 HEV detection, pathological presentation, and serological examination in this patient. A. Serum level of anti-HEV IgM and IgG from initiation to present. B. HEV viral protein in liver biopsy visualized by immunohistochemistry with anti-HEV ORF2 antibody. C. Liver enzymes ALT, AST, GGT and ALP measured in the patient serum (ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase). D. Liver biopsy revealed hepatocyte swelling, ballooning (H and E). E. Kupffer cells aggregation revealed by H and E (left) and CD68K immunohistochemistry (right) staining. F. Abundant mixture inflammatory cells infiltration in portal tracts (H and E). G. Masson and Reticular fiber staining showed no obvious fibrosis. H. Total T cells and CD4-T and CD8-T cells measured in patient serum. I. Detection of HEV genome by nested RT-PCR in stool and urine samples. J. Total bilirubin levels measured in the patient serum.

ease and received several courses of immunosuppressive therapy can be considered as ''truly'' immunocompetent without immunological data available [5—7]. Our report is a certain case of chronic hepatitis E developed in immunocompetent status, since the basal level of T lymphocyte count, immunoglobulin level, and normal liver enzyme in our patient proved a truly immunocompetent status. Complying with the case reported by Philippe Colson et al., Our study therefore corroborated the existence of HEV chronicity in absence of physical immunosuppressive situation, emphasizing the need to understand the novel mechanisms of HEV persistence.

In summary, our case report provides extensive information on the clinical course of HEV infection in immunocompetent individual. This unique observation served as warning for chronic HEV in ''healthy'' individual that bears the foremost importance of other factors contributing to chronic hepatitis E in addition to deficient immunity. Further follow-up is required to supervise the viral persistence, liver fibrotic progression, liver function of this patient. The underlying mechanisms of chronic hepatitis E in immunocompetent population are warranted based on further accumulated clinical observations and comparation of clinical features with that in immunosuppressive patients.

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Contributions of authors

Y. W. contributed to study concept and design; acquisition of data; analysis and interpretation of data; literature search; writing of the manuscript. S. L. contributed to acquisition of data. Q. P. contributed to study concept and critical revision of the manuscript. J. Z. contributed to study concept, study supervision and critical revision of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at: https://doi.org/10.1016/j.clinre.2019.08.002.

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