Author’s response to reviews

Title: Chronic hepatitis E virus infection in a leukemia patient presenting with elevated transaminases: a case report

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Author’s response to reviews: see over
Editorial office

1. The title has been formatted according to the Journal title structure.
2. Ethnicity of the patient has been included in the abstract, see Abstract.
3. Ethnicity of the patient has been included in the Case presentation section, see line 77, “A 46-year-old Caucasian male mechanic was transferred…..”
4. All dates have been removed from the revised manuscript.
5. The consent statement has been revised according to the Editorial office, see section Consent.

Reviewer #1

1. We fully agree with the reviewer and have corrected the inaccurate sentences. Patients with HIV infection or hematological malignancy have been added, see Introduction, lines 54 – 58: “Chronic hepatitis associated with viral persistence has been reported among transplant recipients who became infected shortly after transplantation [1, 2], as well as in HIV patients and patients with haematological malignancies [3-5].” References 3 – 5 have been added as well.
2. The discussion has been improved according to the reviewer’s suggestion, see Discussion, lines 163 - 165: “In addition to acute and chronic HEV infections in patients with hematological malignancies [3, 5], HIV patients have been reported with chronic hepatitis E [4].”
3. A chronic infection is now defined in the revised manuscript, see Discussion, lines 140 – 141: “A chronic hepatitis E infection is defined as HEV PCR positive for more than 6 months, thus our patient had a chronic hepatitis E infection.”
4. The development of a chronic infection and the role of rituximab therapy have been added to the manuscript, see Discussion, lines 156 – 160: “It is tempting to speculate, that the chronic course of his HEV infection was in fact fueled by his therapeutically induced immunosuppression. The first step in treating patients with chronic infections is to reduce or stop immunosuppressive agents [15]. In our case rituximab therapy was stopped due to severe fatigue and susceptibility to infections and withdrawal of rituximab might have led to clearance of the virus.” See also Discussion, last paragraph: “In our patient, therapy of the HEV infection would have been discussed if the infection had not spontaneously resolved shortly after its diagnosis, as prolonged viremia might be associated with the development of liver cirrhosis and hepatic failure [16]. Beyond reduction of immunosuppressive therapy, treatment with ribavirin for at least three months seems to be the first treatment option for patients with chronic hepatitis E, even though data are limited [16].”
5. The reviewer is right to show serial ALT, HEV viral load and rituximab therapy over time in a figure, see new Fig. 1.
6. The inaccurate sentence “Henceforth…” is corrected, see Case presentation, lines 93 – 95: “Henceforth, there was a modest, fluctuating transaminitis (month 2: AST 61 U/L, ALT 139 U/L; month 4: AST 108 U/L, ALT 220 U/L; month 6: AST 142 U/L, ALT 337 U/L, month 7: AST 161 U/L, ALT 408 U/L).” See also Discussion, lines 134 – 135: “The diagnosis was based on a modest, fluctuating transaminitis with the ALT ranging from 61 – 408 U/L, a typical pattern seen in chronic HEV infection [15].”

Reviewer #2
1. The spontaneous clearance of the HEV infection is explained in the Discussion, lines 159 – 160: “In our case rituximab therapy was stopped due to severe fatigue and susceptibility to infections and withdrawal of rituximab might have led to clearance of the virus.” The lymphocyte count is now presented in the new Fig. 1.

2. We fully agree with the reviewer regarding the dates, the duration of HEV infection has been clarified in the revised manuscript, see Case presentation, lines 99 – 101: “Retrospectively, the presence of HEV RNA in serum was confirmed in three samples (month 1, 2.0 x 10^7 copies/ml; month 6, 1.0 x 10^7 copies/ml; month 8, 3.0 x 10^5 copies/ml).”

3. References have been updated, recent references (3, 4, 5, 15) have been added.

4. Previous case reports of chronic HEV infection in haematological patients are now discussed in the revised manuscript, as well as possible anti-viral therapies. See Discussion, lines 160 – 165, “Notably, severe complications have also been observed in patients with HEV infection after liver transplantation. In a recently published case, undetected occult HEV infection in a liver transplant donor actually led to chronic hepatitis E and cirrhosis in the recipient [16]. In addition to acute and chronic HEV infections in patients with hematological malignancies [3, 5], HIV patients have been reported with chronic hepatitis E [4].” See also Discussion, lines 157 – 159: “The first step in treating patients with chronic infections is to reduce or stop immunosuppressive agents [15].”