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CASE REPORT

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A case of thrombotic thrombocytopenic purpura induced by acute hepatitis E and successfully controlled by lymphoplasmapheresis plus rituximab

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Abstract

Background Thrombocytopenia is a common extrahepatic manifestation of hepatitis E virus (HEV) infection and is usually transient and self-limited. Thrombotic thrombocytopenic purpura (TTP) is a rare and lethal blood disorder characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and organ involvement. The link between HEV infection and TTP is still unclear.

Case presentation A 74-year-old female was referred to our hospital with complaints of fever, fatigue, nausea and jaundice for 10 days. Liver dysfunction, positive IgM and IgG of HEV, and HEV-RNA viremia prompted the diagnosis of acute hepatitis E, which was followed by a dramatic decline in the platelet count. The presence of schistocytes in the peripheral blood smear, along with decreased ADAMTS13 activity, strongly suggested a diagnosis of TTP. Combination therapy, including 2 courses of lymphoplasmapheresis (LPE), 4 courses of therapeutic plasma exchange, glucocorticoids and rituximab, was applied and contributed to the recovery of platelet. No recurrence of TTP was observed during the follow-up period. To date, this is first patient who developed the initial episode of TTP during the course of HEV viremia. In the meanwhile, LPE was used for the first time in the treatment of HEV-associated TTP.

Conclusions This case highlights the necessity of ruling out TTP in hepatitis E patients with newly developed and severe thrombocytopenia and the values of LPE plus rituximab in treating such patients.

Keywords Hepatitis E, Thrombocytopenia, TTP

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Bacground

Hepatitis E virus (HEV) infection is a common cause of viral hepatitis and represents a significant global public health issue. It is often transmitted via contaminated drinking water or food, occasionally via vertical routes, blood transfusion, and sexual contact [1]. Emerging evidence suggests that HEV infection also has different extrahepatic manifestations, including kidney involvement and neurological and blood diseases [2]. Among the hematological manifestations, thrombocytopenia occurs in approximately 11% of patients with hepatitis E and is mostly mild and self-limited, according to a retrospective study from the UK [3]. Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening blood disorder characterized by fever, hemolytic anemia, thrombocytopenia, and kidney and neurologic dysfunction. The deficiency of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motif 13), which leads to extensive microvascular thrombosis and multiple organ damage, underlies the pathogenesis of TTP. Over 95% of cases are idiopathic TTP, which is frequently mediated by autoantibodies against ADAMTS13 and is sometimes triggered by events such as infection, cancers, drugs and pregnancy [4]. HEV-associated TTP has been documented only by anecdotal case reports [5, 6]. Here, we report the case of an elderly female who simultaneously presented with acute hepatitis E and TTP. To the best of our knowledge, this case is the second patient who developed the first episode of TTP after acute HEV infection and the first one during HEV viremia, providing further evidence to support the role of HEV infection in the development of TTP.

Case presentation

In July 2023, a 74-year-old female was referred to our hospital because of intermittent fever, fatigue, nausea and ongoing jaundice that had lasted for 10 days. The patient was a farmer and reported no use of alcohol, herbal medicine or tobacco. Her medical history included hypertension, type 2 diabetes, and two surgeries to remove her throat polyps and colonic polyps. Before symptom onset, she had eaten pickled food for 10 consecutive days. On examination, the body temperature was 38.9 °C, the pulse was 103 beats/min, the blood pressure was 127/77 mmHg, the respiratory rate was 18 breaths/min, and the oxygen saturation was 96% under oxygen therapy via a nasal cannula at 3 L/min. Icteric skin and sclera and mild edema in both lower limbs were present. The results of routine blood tests before admission revealed liver dysfunction, as indicated by elevated levels of alanine aminotransferase, aspartate aminotransferase, and total and direct bilirubin, as shown in Table 1. The prothrombin time and international normalized ratio were within the normal range. Human immunodeficiency virus infection was excluded. The results of immunological tests were negative for hepatitis A, B and C. Both HEV IgM and IgG were positive according to the results of two qualitative ELISA assays (Cat. WE-7196, WE-7296) from Wantai BioPharm. Epstein–Barr virus and cytomegalovirus were undetected in the blood. Antinuclear antibodies and specific antibodies for autoimmune liver disease were all negative. An enhanced CT scan of the abdomen displayed no gallstones or obstructions of the biliary tract. Taken together, these findings suggested that the patient was likely to have acute hepatitis E and was subsequently transferred to the Department of Liver and Infectious Diseases for further treatment. She was prescribed

Table 1 Laboratory data during the course of disease

Variable	Reference range	Before admission	Day 2	Day 30 (discharge)	Day 225 (last follow-up)
WBC (10^9/L)	3.5–9.5	5.5	5	3.5	9.7
Hemoglobin (g/L)	130–175	129	85	93	144
Platelet count (10^9/L)	125–350	98	6	50	131
Albumin (g/L)		24.2	30.5	31.9	37.7
ALT (U/L)	9–50	1312	166	42	47
AST (U/L)	15–40	1139	113	27	28
AKP (U/L)	45–125	150	103	85	134
GGT (U/L)	10–60	220	122	200	328
Total bilirubin (μmol/L)	0–26	223.6	933.1	36.3	20.9
Direct bilirubin (μmol/L)	0–4	135.2	647.2	16.5	6.5
LDH (U/L)	120–250	464	1823	295	368
Creatinine (μmol/L)	57–111	58	78	48	54
C-reactive protein (mg/L)	0–6	70.8	23.3	2	39.3
PT (s)	11.5–14.5	13.6	14.9	14.8	11.2
D-dimer (μg/mL)	0-0.5	11.12	9.05	1.32	1.93

ALT, alanine transaminase; AKP, alkaline phosphatase; GGT, glutamyl transpeptidase; LDH, lactate dehydrogenase; PT, prothrombin time

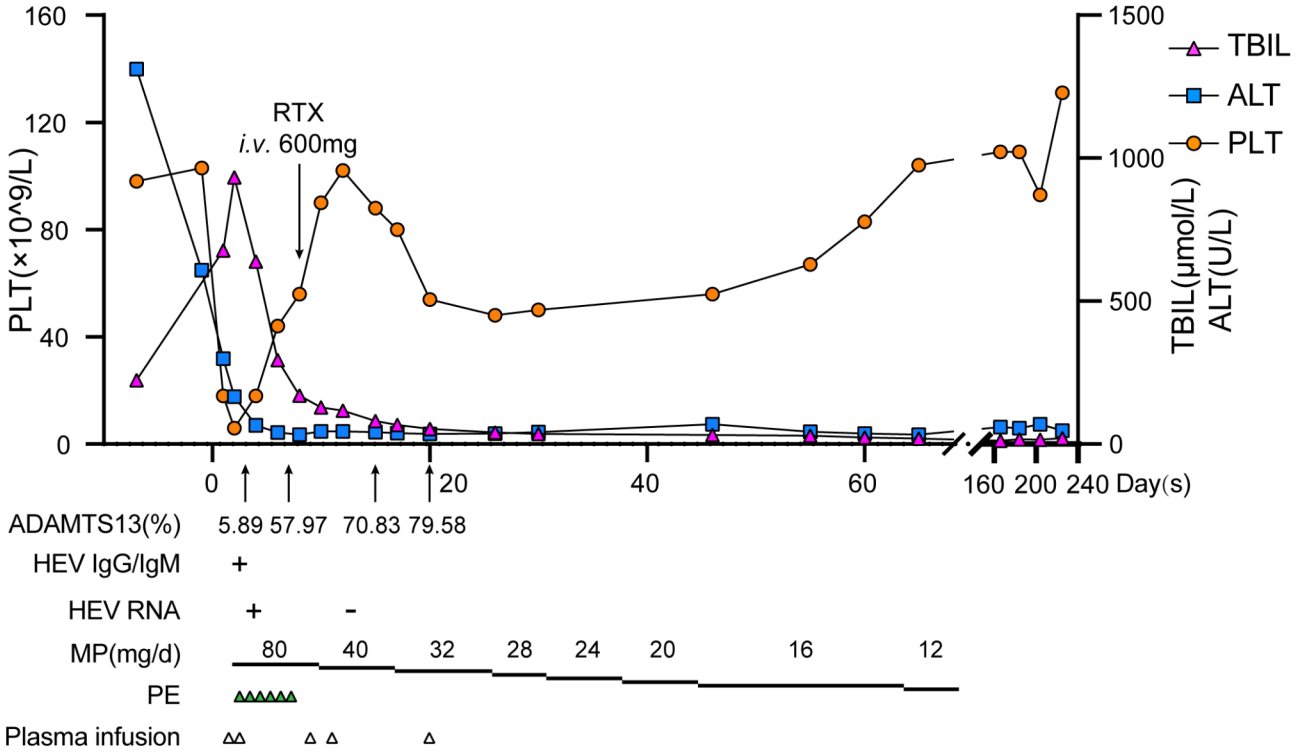

Fig. 1 Therapeutic schedule and alterations in clinical indicators during hospitalization and posthospital follow-up. ALT, alanine transaminase; MP, methylprednisolone; PE, plasma exchange; PLT, platelet; RTX, rituximab; TBIL, total bilirubin

intravenous magnesium isoglycyrrhizinate 200 mg per day, ademetionine 1000 mg per day for liver protection, and meropenem 0.5 g every 8 h for empirical antimicrobial therapy. Metagenomic next-generation sequencing (mNGS) was applied to screen for underlying pathogens in the blood, whereas it provided no clues for infection by any bacteria or DNA viruses. However, we detected HEV-RNA by real time PCR in the patient's blood, which confirmed the diagnosis of acute hepatitis E.

The patient's condition was stable until the second day after admission, when she experienced sudden dyspnea and chest pain. The immediate arterial blood gas analysis revealed a partial pressure of oxygen of 87.3 mmHg and a P/F ratio of 165. The levels of both the myocardial enzyme spectrum and troponin I were increased, whereas no significant ECG changes were observed. In addition, urinalysis showed 2 + protein and 30 to 60 red cells per high-power field in the urinary sediment. Notably, a quick blood test displayed a marked decrease in the platelet count to 6×10^9/L, as well as possible hemolytic anemia, as suggested by increased levels of LDH and reticulocytes (2.5% of erythrocytes). Disseminated intravascular coagulation was ruled out by normal fibrinogen levels and prothrombin times and negative results from the prosthetic paracoagulation test. CT pulmonary angiography showed no evidence of pulmonary embolism. A peripheral blood smear revealed 0.9% schistocytes, providing strong evidence for the diagnosis of thrombotic microangiopathy (TMA), which includes TTP. The PLASMIC score is a frequently used model for quick assessment of the probability of severe ADAMTS13 deficiency in suspected TTP patients [7], and it reached 7 in this patient, indicating a high risk of severe ADAMTS13 deficiency. On the basis of these findings, the patient was highly suspected of having TTP and was immediately administered therapeutic plasma exchange (TPE), accompanied by intermittent plasma transfusion and intravenous glucocorticoids, which were gradually tapered (Fig. 1). Bone marrow aspirate revealed normocellular marrow with scattered schistocytes and immature megakaryocytes and without hemophagocytes or tumor cells. As expected, the activity of ADAMTS13 was 5.89% (normal range, 42.16-126.37%), which confirmed the diagnosis of TTP, though the inhibitory antibodies against ADAMTS13 were not detected. Lymphoplasmapheresis (LPE) is an innovative therapy based on plasma exchange which can also remove pathogenic lymphocytes and mononuclear cells. Compared with traditional TPE, LPE could reduce the number of treatment sessions and plasma volume required for the treatment of TTP [8]. Here, 2 cycles of LPE were attempted after the first cycle of TPE. After a total of 6 courses of plasma exchange, her condition was markedly improved, and her platelet count rose steadily to 61×10^9/L. An intravenous infusion of

rituximab, a monoclonal anti-CD20 antibody, at a dose of 375 mg per square meter of body surface area was used as an additional regimen. The platelet count continued to increase to 102×10^9/L during the following 4 days but subsequently decreased by 47% in the next week. Here, we repeated 2 tests on ADAMTS13 activity, and the levels were both within the normal range, which excluded the possibility of the recurrence of TTP. After that, the platelet level rose gradually and returned to normal at 4 months. HEV-RNA became undetected after 12 days of hospitalization. At the last follow-up, both the liver function and the platelet count remained almost normal, and no relapse of TTP was observed.

Discussion and conclusions

Hepatitis E remains a significant challenge due to its high morbidity worldwide, as well as increased mortality in certain groups including pregnant women, elderly individuals and those with chronic liver disease [9]. The decrease of platelet count is frequently observed in patients with HEV-associated acute liver failure and represents a risk factor for short-term mortality [10]. Severe thrombocytopenia in the setting of HEV infection has been reported previously [11–13] and is generally mediated via an immune mechanism, as evidenced by the existence of anti-platelet antibodies [11]. Here, we present a case of acute hepatitis E complicated by a rapid decline in platelets, as well as kidney involvement. The appearance of schistocytes and hemolytic anemia, along with severe thrombocytopenia, strongly suggested the diagnosis of TMA, a group of microvascular thrombotic diseases involving TTP, Shiga toxin–mediated hemolytic uremic syndrome, and complement-mediated TMA. Testing on ADAMTS13 activity before TPE was impeded by severe hemolysis, thus, we recollected the sample after the first TPE and repeated the test. The obtained ADAMTS13 activity was still less than 10% of normal, i.e., a positive result to prompt the diagnosis of TTP, whereas the inhibitory anti-ADAMTS13 antibodies were undetected, presumably interfered by TPE therapy.

Infection with certain viruses, such as human immunodeficiency virus, cytomegalovirus and COVID-19, has been associated with the development of TTP [4, 14, 15]. Several lines of evidence suggest that HEV infection was the most likely trigger for the outbreak of TTP in this patient. First, the viremia of HEV was presented exactly at the time when TTP occurred, and other potential pathogens for infection were precluded by mNGS testing. Second, bone marrow aspiration revealed no evidence of hematological malignancy or sighs of hemophagocytosis. Additionally, autoimmune disorders such as systemic lupus erythematosus was not considered since the spectrum of antinuclear antibodies was negative. Furthermore, suspected medications such as interferon, clopidogrel and vaccines [16] were not found.

To date, only two cases involving concurrent hepatitis E and TTP have been documented. In 2018, Barciela et al.. reported a 48-year-old male with a medical history of Crohn's disease, choroidal melanoma and recurrent TTP who experienced the sixth relapse of TTP after the occurrence of acute hepatitis E transmitted via cryosupernatant plasma [6]. Both the TTP and the viremia of HEV were successfully controlled by treatment with ribavirin. Recently, Lv and colleagues described a 53-year-old male with symptoms of fever, fatigue, nausea, jaundice and sudden unconsciousness [5]. Hepatitis E was verified by positive anti-HEV IgM and IgG, though HEV-RNA was undetected, and TTP was verified by 0% ADAMTS13 activity and positive ADAMTS13 inhibitor. The patient recovered after receiving combination therapy, including TPE, glucocorticoids, intravenous immunoglobin and 4 doses of rituximab. Compared with the latter one, our patient was managed with a lower plasma exchange volume (25 ml/kg/day versus 35 ml/kg/day) and frequency (6 times versus 12 times) and fewer doses of rituximab (1 versus 4), and without the use of immunoglobin, partly explained by a lack of neurologic involvement, as well as the use of LPE and avoidance of platelet infusion in our patient. In addition, all three patients had evident jaundice and normal clotting function, with no signs of acute liver failure.

In conclusion, severe thrombocytopenia is rare in acute hepatitis E patients but, once developed, warrants prompt investigation to rule out potential TTP. A quick blood smear and testing for ADAMT13 activity are essential for the diagnosis of TTP. Moreover, plasma exchange should be urgently initiated once TTP is highly suspected and LPE may be a good choice due to its advantage in reducing the consumption of plasma. Our case offered further evidence to support HEV infection as a trigger of TTP, even at the time of viremia. However, the incidence of TTP after HEV infection is fairly low, and the underlying mechanism remains elusive and merits further study.

Abbreviations

ADAMTS13	A disintegrin and metalloproteinase with thrombospondin motif 13
HEV	Hepatitis E virus
LPE	Lymphoplasmapheresis
mNGS	Metagenomic next-generation sequencing
TMA	Thrombotic microangiopathy
TPE	Therapeutic plasma exchange
TTP	Thrombotic thrombocytopenic purpura

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Author contributions
B.Y. and Y.Z. treated and followed up the patient. B.Y. and Z.J. collected the data and drafted the manuscript. F.H. and F.L supervised the study and revised the manuscript. All authors reviewed the manuscript.

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Data availability
All the data used in this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Review Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Ethics No. 20241121). Informed consent to participate was obtained from the participant in this study.

Consent for publication
Written informed consent for publication was obtained from the patient.

Competing interests
The authors declare no competing interests.

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