BMC Infectious Diseases

CASE REPORT

Open Access

Chemotherapy-induced febrile neutropenia followed by acute hepatitis E virus infection in rectal cancer patient with synchronous liver and lung metastasis: a case report

Dongdong Zhang[1,3†], Zhihong Chen[2†], Jixiang Wu[3], Ning Ning[3], Lin Chen[3] and Xiaodong Tian[4*]

Abstract

Background Hepatitis E virus (HEV) typically induces self-limiting infection but can establish persistent infection, particularly in patients with compromised immune systems. However, the literature on HEV infection in patients undergoing chemotherapy is limited.

Case presentation A 46-year-old Chinese male patient with rectal cancer underwent ten cycles of chemotherapy and targeted therapy. Routine blood tests revealed grade 4 bone marrow suppression necessitating emergency admission. On the second day following admission, the patient presented with high fever that was determined to be chemotherapy-induced febrile neutropenia (FN). However, despite the recovery of white blood cell counts, the fever persisted, and the levels of aminotransferases and bilirubin continued to rise. Two weeks after admission, next generation sequencing of blood samples revealed evidence of HEV. The patient underwent symptomatic and supportive treatment and was discharged after a 30-day hospitalization. One month after discharge, the transaminase and bilirubin levels were within the normal range.

Discussion The fatality rate of FN is alarmingly high. To prevent progression to sepsis syndrome and potential mortality, it is imperative to initiate empirical treatment with broad-spectrum antibiotics. As the differential diagnosis of elevated liver enzymes in immunocompromised patients encompasses a wide range of possibilities, the exclusion of HEV infection is crucial when diagnosing drug-induced liver injury (DILI).

Conclusion This case highlights the importance of healthcare providers being vigilant in identifying HEV infection in patients with solid tumors who experience FN and DILI. Early implementation of comprehensive supportive treatment is crucial for reducing the duration of disease and enhancing patient prognosis.

Keywords Chemotherapy, Febrile neutropenia, Hepatitis E virus, Liver injury, Case report

†Dongdong Zhang and Zhihong Chen contributed equally to this work.

*Correspondence:
Xiaodong Tian
bddyyytxd@163.com
Full list of author information is available at the end of the article

Introduction

Febrile neutropenia (FN) is a serious complication of chemotherapy treatment and may present as the only clinical sign of infection. If FN is not addressed in a timely manner, it may increase the risks of sepsis, septic shock, prolonged hospitalization, delayed chemotherapy, and potentially progression to multisystem organ failure with fatality [1, 2]. During chemotherapy, neutrophil proliferation is adversely affected as the bone marrow is destroyed because of the inability of chemotherapy drugs to differentiate between rapidly growing malignant cells and rapidly growing normal cells. Therefore, the reduction in peripheral neutrophil count caused by hematopoietic dysfunction is termed neutropenia. In a patient with neutropenia, fever may be the only indication of an infection because of the patient's inability to produce an inflammatory response [3]. The continuation of empirical broad-spectrum antibiotics until neutrophil recovery has been the standard approach, especially for high-risk patients with neutropenia persisting for more than seven days [4, 5].

Hepatitis E virus (HEV) is considered a shy small member of the Hepeviridae family and is found only in some endemic nations, with pigs as the primary host. Over the past three decades, this virus has rapidly emerged as an equally concerning issue as other hepatitis viruses have [6]. Strains of HEV infecting humans belong to the *Orthohepevirus* genus, which is divided into four species (A–D). Human cases of hepatitis E are caused by strains within species A, which comprises eight genotypes [7]. Insufficient knowledge of clinicopathological features, limited resources for diagnosis, a lack of systematic surveillance, and poor sanitation appear to be major reasons for the poor suspicion index, late diagnosis, and inadequate estimation of disease burden due to HEV.

The current literature has placed greater emphasis on the prevalence of HEV in pregnant women, chronic liver disease, HIV infection, and solid organ transplantation [8–11]. Few reports exist regarding such cases in individuals with solid tumors who are receiving chemotherapy [12]. We report a case of rectal cancer with synchronous hepatic and pulmonary metastases, who developed concurrent chemotherapy-induced FN and acute HEV infection during treatment. This case report has been reported in line with the CARE criteria (including citation) [13].

Case report

A 46-year-old Chinese male patient with height of 172 cm and weight of 87 kg was diagnosed in February 2024 with low rectal cancer accompanied by synchronous liver and lung metastasis. Pathological examination revealed adenocarcinoma, with clinical American Joint Committee on Cancer (AJCC) TNM staging for rectal cancer (8th ed., 2017) classified as $cT_4N_{2b}M_{1b}$. The patient tested positive for a circumferential resection margin (CRF) and extramural vascular invasion (EMVI) via enhanced pelvic magnetic resonance imaging (MRI). There was no previous history of smoking or alcohol consumption. Additionally, there was no abnormal health information regarding first-degree relatives. On February 18, 2024, the patient underwent venous infusion port implantation. Genetic testing indicated that the combined positive score (CPS) was 2 points, the tumor proportion score (TPS) was less than 1%, and mutations in KRAS exons 4 and the nonmutated BRAF gene were characterized as having a microsatellite stable (MSS) status. Tumor mutational burden (TMB) measure was 8.6 mut/Mb.

Ten cycles of chemotherapy and targeted therapy, FOLFOXIRI (irinotecan, oxaliplatin, leucovorin, 5-FU) and bevacizumab, were administered until July 5, 2024. Two evaluations conducted during this period indicated a partial response (PR), with a significant reduction in the size of the primary tumor. One week prior to hospitalization, the patient experienced skin rash, oral ulcers, diarrhea, limb numbness, and worsening rectal bleeding. On July 18, routine blood tests revealed grade 4 bone marrow suppression necessitating emergency admission, accompanied by grade 3 liver function injury. Recombinant human granulocyte-colony stimulating factor (rhG-CSF) and recombinant human thrombopoietin (rhTPO) were administered subcutaneously. Enteral and parenteral nutrition support therapy (26 kcal/kg/d) and human serum albumin were also administered. On July 20, the patient developed fever, with a peak temperature of 39.5 °C. No symptoms of abdominal pain, coughing, or urethral irritation were observed. Considering the absolute neutrophil count, a diagnosis of chemotherapy-induced febrile neutropenia was made.

According to the results of bacterial culture and consultations by the infectious diseases department, sequential anti-infective treatment regimens of ertapenem, imipenem and cilastatin, imipenem and cilastatin plus moxifloxacin, moxifloxacin plus cefoperazone and sulbactam, and cefoperazone and sulbactam plus linezolid were conducted. Throughout this period, sputum culture consistently revealed a high presence of *Acinetobacter baumannii* (+ ++), indicating the presence of carbapenem-resistant *Acinetobacter baumannii* (CRAB). Cultures obtained from peripheral and central venous blood were negative. A chest computed tomography (CT) scan conducted on July 29 revealed the presence of small bilateral pleural effusions. An abdominal CT scan revealed the presence of gallbladder stones with cholecystitis and a small amount of effusion in the abdominal cavity without any expansion in bile ducts within or outside the liver. On July 30, fever recurred, with the temperature

rising to 39.5 °C; however, these symptoms did not align with the manifestations of lung disease. Magnetic resonance cholangiopancreatography (MRCP) imaging also confirmed the absence of dilatation in both the intrahepatic and extrahepatic bile ducts, which contradicted the persistent elevation observed in transaminase levels and bilirubin concentrations, as direct bilirubin is commonly associated with obstructive jaundice. Consequently, next-generation sequencing (NGS) analysis was performed to identify the source of infection, which suggested HEV infection. Thus, the diagnosis of HEV infection was finally confirmed with positive results for IgM antibodies in the blood. The clinical diagnosis was severe hepatitis, and bilirubin levels indicated liver failure. Subsequently, his body temperature returned to normal on August 1, and a gradual reduction in aminotransferase levels occurred (Figs. 1, 2, 3, 4 and 5). Bilirubin levels reached their highest point on August 5 and gradually returned to the normal range (Fig. 6). The patient was discharged after a 30-day hospitalization with a stable condition. The treatment timeline for the patient is outlined in Table 1. One month after discharge, the levels of transaminase, bilirubin, and other liver function markers returned to the normal range.

Discussion

FN places a significant burden on patients in terms of hospitalization and mortality. The reported in-hospital mortality rates for neutropenia/FN range from 2.6% to 7.0% for adults with solid tumors [14]. While there is no

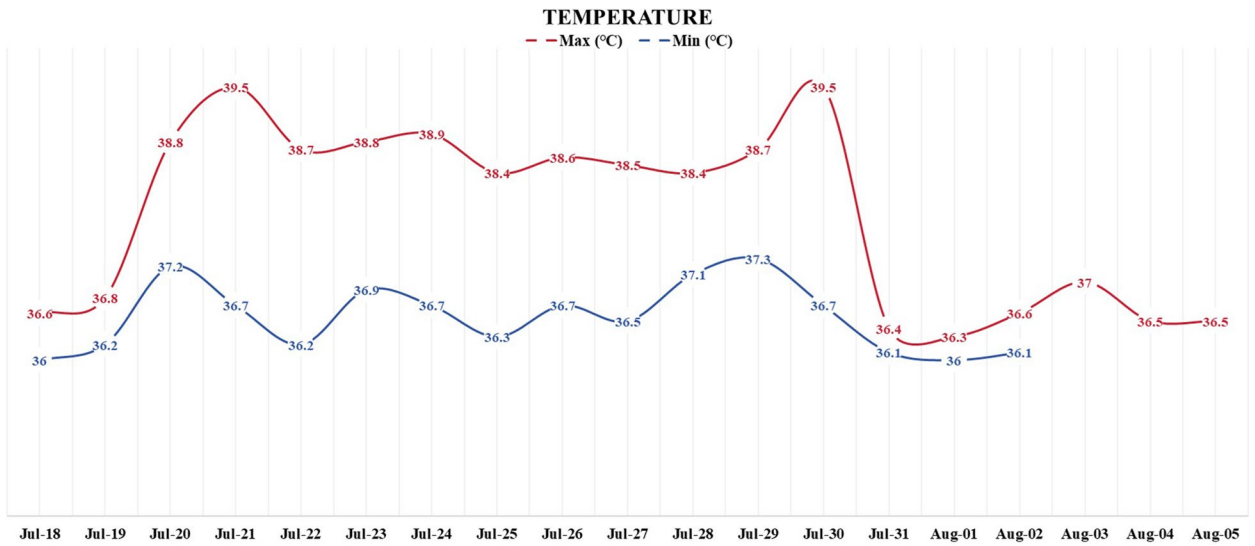

Fig. 1 Fluctuations in body temperature

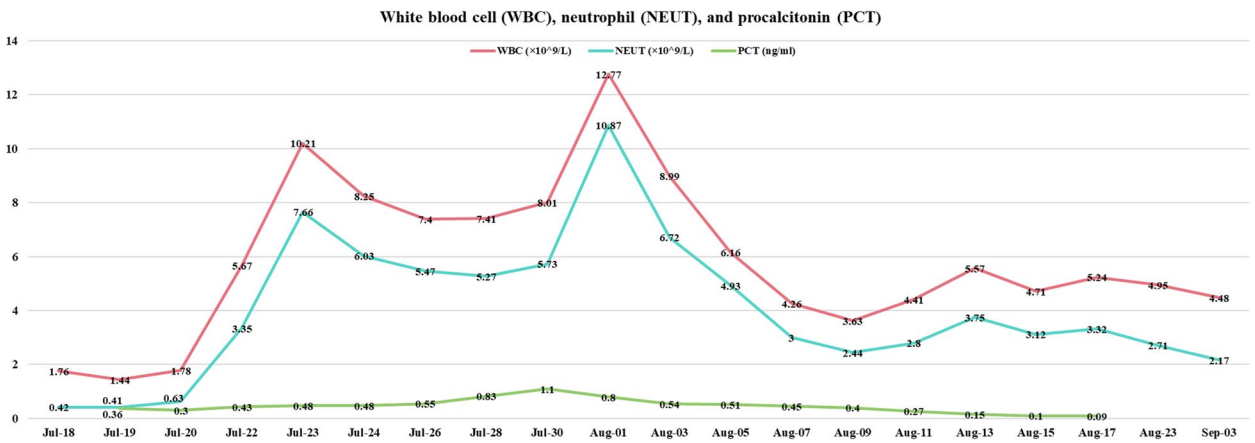

Fig. 2 Evolving pattern of blood routine examination

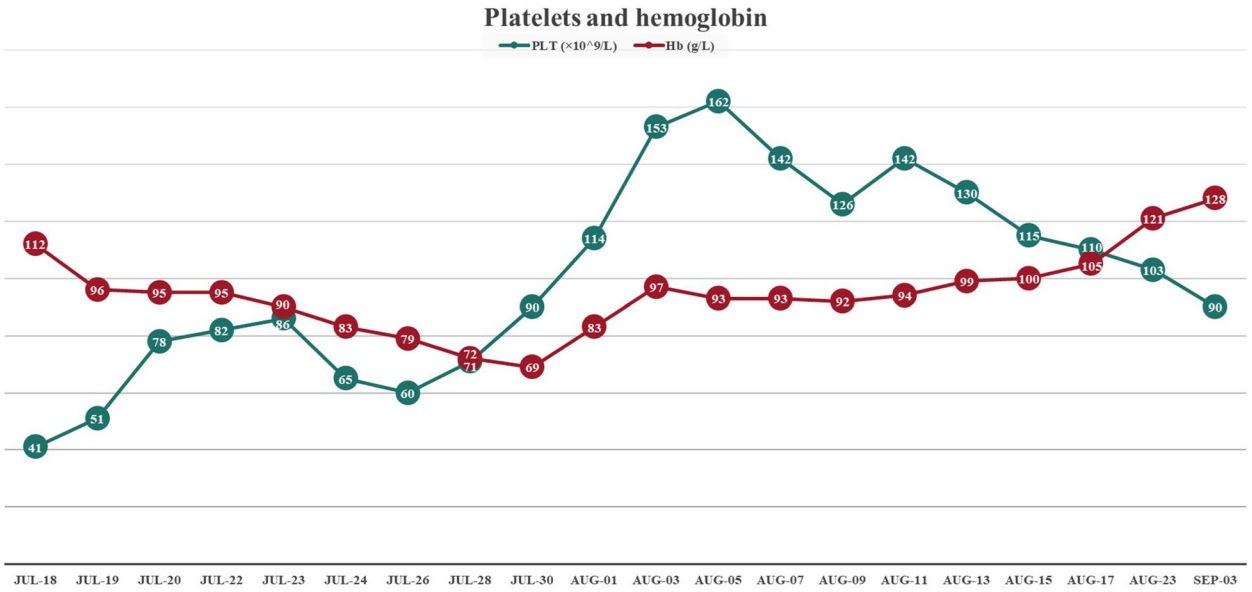

Fig. 3 Trend of platelet and hemoglobin levels

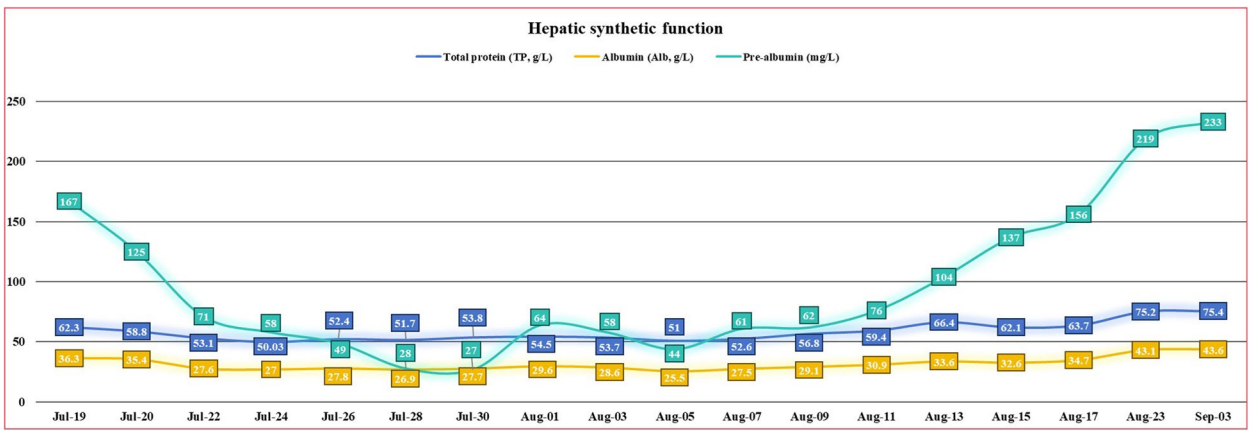

Fig. 4 Alterations in hepatic synthetic function

standard classification for neutropenia, a patient is generally considered neutropenic when their absolute neutrophil count (ANC) falls below 1.5×10^9/L ($1500/mm^3$). FN, considered an oncologic emergency, is defined by the Infectious Diseases Society of America, American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) as an oral temperature $\geq$38.3 °C (101.0 °F), a sustained temperature $\geq$38.0 °C (100.4 °F) for 1 h, and an ANC $<0.5 \times 10^9$/L or an ANC that is expected to decrease to $<0.5 \times 10^9$/L within 48 h [15–17].

This patient presented with a pre-admission ANC of 0.41×10^9/L. On the second day post-admission, he developed pyrexia, with temperature peaking at 39.5 °C. Consequently, a diagnosis of FN was established, leading to the administration of ertapenem as an empiric broad-spectrum antibiotic for anti-infective therapy. Data from a study at the University of Texas MD Anderson Cancer Center found that an infectious source can be identified in 50% of patients with FN. An additional 3% to 5% of cases have noninfectious etiologies. The remaining 45% of patients do not have a clear cause of fever. However, respiratory tract infections are the most common type of infection in patients with FN, and gram-positive organisms are more common in these infections [18]. Clinical specimens are routinely submitted to the hospital's clinical laboratory for analysis. Clinicians should monitor bacterial

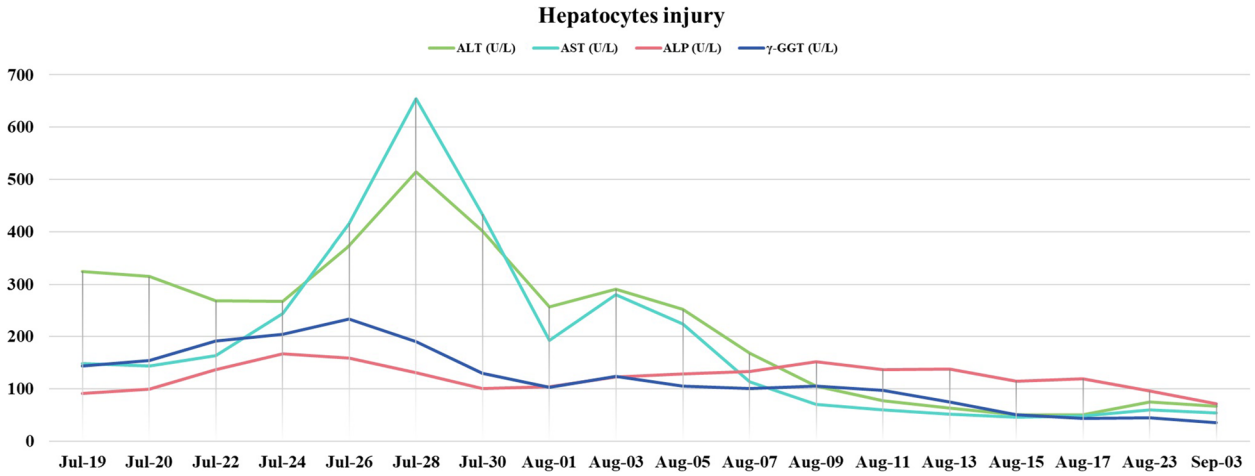

Fig. 5 Extent of hepatocyte damage

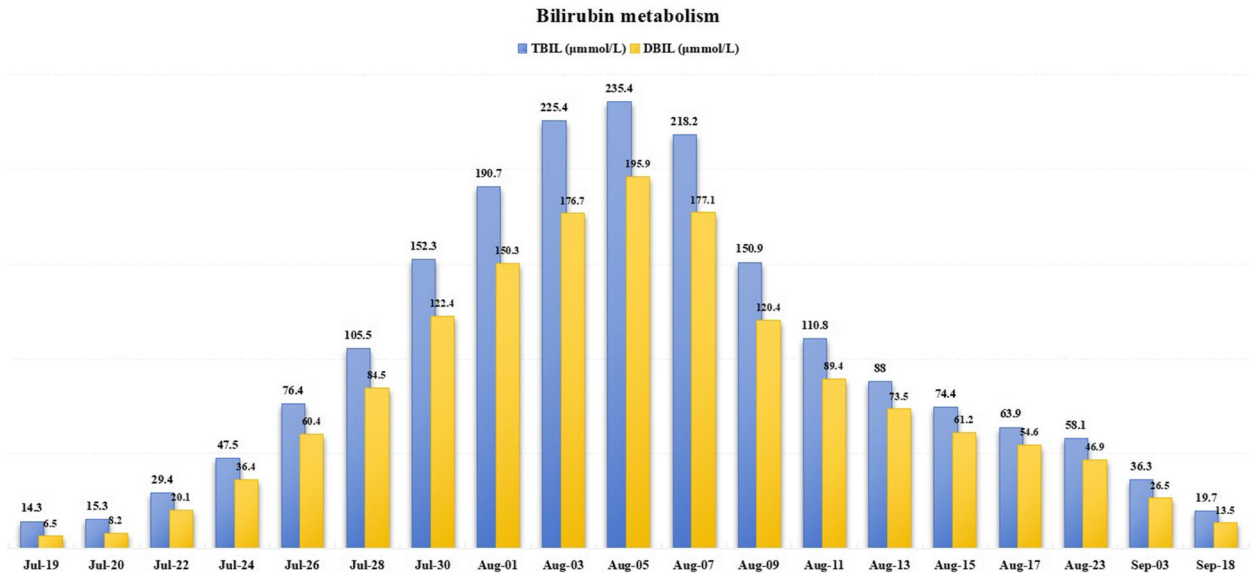

Fig. 6 Variations in bilirubin levels

Table 1 Timeline for patient's treatment

Date	July 18	July 20—July 30	August 1	August 5	August 18
Events	Admission	Fever, anti-infective treatment, enteral and paraenteral nutrition	Blood NGS analysis identified HEV	Bilirubin levels reached their highest point	Discharge

culture and antimicrobial susceptibility testing results daily to guide antimicrobial therapy. If no microbiological documentation is found, initial empirical treatment should be reviewed at 72–96 h regardless of whether an escalation or de-escalation approach is employed [4]. The identification of *Acinetobacter baumannii* in the sputum culture prompted adjustment of subsequent anti-infective treatment based on basis of the drug susceptibility testing for this patient.

As the differential diagnosis of elevated liver enzymes in immunocompromised patients is broad, an important differential diagnosis of acute hepatitis E is drug-induced liver injury (DILI). Given the high prevalence of polypharmacy and DILI in elderly populations, coupled with

their increased susceptibility to HEV infection, those patients are particularly vulnerable to clinical diagnostic challenges [19]. Importantly, when a diagnosis of DILI is made, particularly in patients with predominant aminotransferase elevation, it is key to first exclude HEV infection [20]. This patient presented with aminotransferase levels on admission that exceeded normal values by more than 5 times, leading to the consideration of DILI caused by chemotherapy. Fever persisted with a progressive increase in bilirubin levels, while the white blood cell count returned to normal. Following the exclusion of obstructive jaundice as a diagnosis, further investigations into the cause of infection are urgently needed.

The clinical manifestation of hepatitis E are highly variable and dependent on the patient's immune status [21], including elevated liver enzymes, jaundice and nonspecific symptoms such as fatigue, itching and nausea. Patients with confirmed acute hepatitis E should be monitored for aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), bilirubin and the international normalized ratio (INR). Liver damage in immunocompromised patients has been reported to be generally less acute and less extensive than that in immunocompetent individuals, with often a subclinical/anicteric course and only a slight undulating elevation of transaminases over time [22]. This also explains why HEV infection in this patient group is easily overlooked for weeks or even months. The first appearance of HEV RNA occurs shortly before the onset of symptoms. Around the time of clinical onset, biochemical markers become elevated and antibodies start to appear, with IgM antibodies appearing first, followed soon after by IgG antibodies. IgM antibodies are relatively short-lived (usually no longer than three to four months but may persist for up to a year); however, the IgG response is long lasting with increasing antibody avidity over time.

Acute HEV infection does not usually require antiviral therapy. In almost all cases HEV infection is spontaneously cleared. Ribavirin treatment may be considered in cases of severe acute hepatitis E or acute-on-chronic liver failure. Immunocompromised individuals and those with chronic liver diseases should avoid the consumption of undercooked meat (pork, wild boar and venison) and shellfish. The European Association for the Study of the Liver (EASL) suggested that immunocompromised patients consume meat only if it has been thoroughly cooked to temperatures of at least 70 °C [23]. Chronic HEV infection refers to the persistent presence of HEV RNA for a duration exceeding 3 months [7]. Immunocompromised individuals typically exhibit an inability to promptly clear HEV from their system through autoimmunity following initial infection, thereby increasing their susceptibility to developing chronic hepatitis E. The patient is currently in a phase of close monitoring. NGS testing is scheduled to be repeated 3 months after diagnosis to rule out chronic HEV infection, followed by the initiation of subsequent chemotherapy and targeted therapy.

The patient's liver function was fully restored, followed by two sessions of chemotherapy using the FOLFOXIRI regimen. Currently, the primary rectal lesion and the majority of lung metastases have been resected, while oligometastatic lesions in the liver have largely regressed. The patient has now undergone treatment for over 14 months and remains in a state of near no evidence of disease. Maintenance therapy is being administered regularly using the capecitabine plus bevacizumab regimen.

Conclusion

The FOLFOXIRI regimen poses a high risk of FN in patients with colorectal cancer. To prevent progression to sepsis syndrome and potential mortality, initiating empirical treatment with broad-spectrum antibiotics is imperative in all patients presenting with fever and neutropenia. Exclusion of HEV infection is crucial when diagnosing DILI, especially in patients with predominant aminotransferase elevation. The detection of HEV RNA through nucleic acid amplification is a reliable diagnostic method for detecting HEV infection in immunocompromised individuals. The clinical management of immunodeficient patients infected with HEV requires meticulous attention, emphasizing the urgency of comprehensive treatment to impede disease progression.

Abbreviations

FN	Febrile neutropenia
HEV	Hepatitis E virus
AJCC	American Joint Committee on Cancer
CRF	Circumferential resection margin
EMVI	Extramural vascular invasion
MRI	Magnetic resonance imaging
CPS	Combined positive score
TPS	Tumor proportion score
TMB	Tumor mutational burden
FOLFOXIRI	Irinotecan, oxaliplatin, leucovorin, 5-FU
PR	Partial response
rhG-CSF	Recombinant human granulocyte-colony stimulating factor
rhTPO	Recombinant human thrombopoietin
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CT	Computed tomography
MRCP	Magnetic resonance cholangiopancreatography
NGS	Next-generation sequencing
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
NCCN	National Comprehensive Cancer Network
DILI	Drug-induced liver injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
INR	International normalized ratio
EASL	European Association for the Study of the Liver

Acknowledgements
Not applicable.

Declaration of Generative AI and AI-assisted technologies in the writing process
Not applicable.

Authors' contributions
DZ, ZC: Conceptualization, Data curation, Visualization, Writing- Original draft preparation. JW, LC: Investigation, Writing- Original draft preparation. NN: Investigation. XT: Supervision, Validation, Writing- Reviewing and Editing.

Funding
No funding.

Data availability
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
This study is exempt from ethical approval in our institution, due to the number of cases being less than three.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

Author details
[1]Peking University First School of Clinical Medicine, Peking University First Hospital, Beijing, People's Republic of China. [2]Golden Gate University, San Francisco, USA. [3]Department of Gastrointestinal Surgery, Peking University International Hospital, Beijing, People's Republic of China. [4]Department of Hepatobiliary and Pancreatic Surgery, Peking University First Hospital, No.8 Xishiku Street, Xicheng District, Beijing 100034, People's Republic of China.

Received: 21 October 2024 Accepted: 8 May 2025
Published online: 13 May 2025

References

1. Foley AM, Hoffman M. CE: Febrile Neutropenia in the Chemotherapy Patient. Am J Nurs. 2023;123(5):36–42. https://doi.org/10.1097/01.NAJ.0000931888.96896.a1.
2. Cossey J, Cote MCB. Evaluation and management of febrile neutropenia in patients with cancer. Jaapa. 2024;37(8):16–20. https://doi.org/10.1097/01.JAA.0000000000000054.
3. Barré S, McElwee J, Calhoun C, Weant KA, Maldonado A, Bell CM. Review of Hematological and Oncological Emergencies. Adv Emerg Nurs J. 2022;44(2):84–102. https://doi.org/10.1097/TME.0000000000000399.
4. Averbuch, D., et al., European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica, 2013. 98(12): p. 1826–1835. https://doi.org/10.3324/haematol.2013.091025
5. de Naurois J, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2010;21(Suppl 5):v252–6. https://doi.org/10.1093/annonc/mdq196.
6. Nagoba, B.S. and A.S. Rayate, Hepatitis E virus infections. World Journal of Virology, 2024. 13(2). https://doi.org/10.5501/wjv.v13.i2.90951
7. Orosz, L., et al., Pathogenesis and clinical features of severe hepatitis E virus infection. World Journal of Virology, 2024. 13(2). https://doi.org/10.5501/wjv.v13.i2.91580
8. Mirzaev UK, et al. Systematic review and meta-analysis of hepatitis E seroprevalence in Southeast Asia: a comprehensive assessment of epidemiological patterns. BMC Infect Dis. 2024;24(1):525. https://doi.org/10.1186/s12879-024-09349-2.
9. Al-Shimari FH, et al. Systematic review of global hepatitis E outbreaks to inform response and coordination initiatives. BMC Public Health. 2023;23(1):1120. https://doi.org/10.1186/s12889-023-15792-8.
10. Gupta T, Dhiman S, Sharma A. Menace of hepatitis E in pregnancy: unleashing the threat of fulminant liver failure. BMJ Case Rep. 2024;17(3):e257234. https://doi.org/10.1136/bcr-2023-257234.
11. Mohamed I, Sanders K, Hillebrand DJ. Chronic Hepatitis E Virus Manifesting as Elevated Transaminases in a Heart Transplant Patient. ACG Case Rep J. 2024;11(3): e01308. https://doi.org/10.14309/crj.0000000000001308.
12. Okumura H, Miyamoto A, Suzuki F, Takaya H. Acute Hepatitis E Infection during Chemotherapy for Lung Cancer: A Case Report. Chemotherapy. 2023;68(3):155–9. https://doi.org/10.1159/000530802.
13. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017;89:218–35. https://doi.org/10.1016/j.jclinepi.2017.04.026.
14. Boccia R, et al. Chemotherapy-Induced Neutropenia and Febrile Neutropenia in the US: A Beast of Burden That Needs to Be Tamed? Oncologist. 2022;27(8):625–36. https://doi.org/10.1093/oncolo/oyac074.
15. Griffiths, E.A., et al., NCCN Guidelines(R) Insights: Hematopoietic Growth Factors, Version 1.2022. J Natl Compr Canc Netw, 2022. 20(5): p. 436–442. https://doi.org/10.6004/jnccn.2022.0026
16. Freifeld AG, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52(4):e56-93. https://doi.org/10.1093/cid/cir073.
17. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2013;31(6):794–810. https://doi.org/10.1200/JCO.2012.45.8661.
18. Molina KC. Best Practices in the Management of Infectious Complications for Patients With Cancer: Management of Febrile Neutropenia. J Adv Pract Oncol. 2023;14(3):201–6. https://doi.org/10.6004/jadpro.2023.14.3.4.
19. Davern, T.J., et al., Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. Gastroenterology, 2011. 141(5): p. 1665–72 e1–9. https://doi.org/10.1053/j.gastro.2011.07.051
20. Fontana RJ, et al. Incidence of Hepatitis E Infection in American Patients With Suspected Drug-Induced Liver Injury Is Low and Declining: The DILIN Prospective Study. Am J Gastroenterol. 2022;117(9):1462–70. https://doi.org/10.14309/ajg.0000000000001869.
21. Lenggenhager D, Weber A. An Update on the Clinicopathologic Features and Pathologic Diagnosis of Hepatitis E in Liver Specimens. Adv Anat Pathol. 2018;25(4):273–81. https://doi.org/10.1097/PAP.0000000000000195.
22. Kamar N, et al. Influence of immunosuppressive therapy on the natural history of genotype 3 hepatitis-E virus infection after organ transplantation. Transplantation. 2010;89(3):353–60. https://doi.org/10.1097/TP.0b013e3181c4096c.
23. Dalton HR, et al. EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol. 2018;68(6):1256–71. https://doi.org/10.1016/j.jhep.2018.03.005.

Publisher's Note