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Case report

ACUTE LIVER FAILURE ASSOCIATED WITH HEPATITIS E INFECTION IN A YOUNG MAN WITH IMMUNE THROMBOCYTOPENIA

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SUMMARY

Autochthonous hepatitis E virus (HEV) infection is an increasingly recognized zoonosis in western countries. It is often asymptomatic but may cause severe illness, particularly in immunocompromised patients or those with underlying chronic liver diseases. Even less frequently, cases of acute failure have been reported. In this article, we describe a case of an immunocompetent patient who presented with symptomatic acute HEV hepatitis and progressed to acute liver failure. The patient was transferred to another hospital for further management and transplant consideration. Unfortunately, he developed multi-organ failure thereafter and died before the transplantation became feasible. Subsequently, HEV was confirmed in archived serum by detection of HEV RNA using commercial RT-PCR. The results of this study have confirmed that HEV testing should be included in the initial evaluation of every acute liver failure regardless of travel history, risk factors or underlying chronic liver diseases. This approach might support clinical decisions and enable to use of potential antiviral therapy.

Keywords: Hepatitis E virus, acute liver failure, ribavirin,

INTRODUCTION

Over the past 15 years, hepatitis E virus (HEV) infection has become a global public health issue. First identified during outbreaks in developing countries, HEV genotypes 1 and 2 (HEV-1 and HEV-2) spread via a fecal-oral route and cause self-limiting hepatitis. However, there is an adverse outcome in pregnant women with high mortality [1, 2]. Conversely, HEV genotypes 3 (HEV-3) and 4 (HEV-4) (confined to China and Japan) are responsible for increasing sporadic autochthonous (locally acquired) infections in many countries in the western world [3]. The mode of transmission is mainly zoonotic, with pigs acting as the primary reservoir [4]. The majority of locally acquired HEV infections are asymptomatic with spontaneous clearance of HEV. The impact of HEV infection in Europe is determined by the severe course with fatal outcome or progression to chronicity and cirrhosis in some vulnerable patients [3, 5]. Even less frequently, cases of acute failure have been reported [6, 7]. Acute liver failure (ALF) is a rare but life-threatening clinical syndrome. It is defined as encephalopathy, increased aminotransferases and impaired liver synthetic function (international normalized ratio [INR] ≥1,5) in patients without pre-existing liver disease and with a duration of symptoms of less than 28 days [8]. For patients meeting this definition, hospital admission, ideally to a transplant center, is mandatory.

We report a case of acute liver failure associated with HEV infection in à young male with an underlying immune disease.

MATERIALS AND METHODS

A 42-year-old man was admitted to the St George University Hospital, Plovdiv, in early June 2019. He had a 2-week history of progressive fatigue, abdominal discomfort and dark urine. The patient's medical history included immune thrombocytopenia from childhood and spondyloarthritis. His medications included Celebrex 200 mg/day, Piroxicam 20 mg /day and Sulfasalazine 1000 mg /day within the last 2 months. The patient denied risky sexual behavior, blood transfusion in the past 6 months, recent travel abroad and the consumption of undercooked meat or seafood. He drank alcohol socially. At admission, he was alert and oriented, jaundiced and his vital signs were normal. On physical examination, the abdomen was soft but tender in the right upper quadrant with hepato-

and splenomegaly. There were no signs of chronic liver diseases. The remainder of his examinations was unremarkable. Initial investigations revealed significantly elevated aminotransferases and increased total bilirubin. There was impaired synthetic function with an INR 1,7 (Table 1).

Table 1. Laboratory findings in the patient during his stay in the hospital (attached).

Variable	On Admission	2nd day	5th day	7th day	Upon transfer 8th day	Reference range
Haemoglobin, g/l	144	114	102	112	120	140-160
Lc x10^9/l	5,57	3,18	7,57	2,17	2,7	3,5-10,5
Tc x10^9/l	65	56	40	45	40	150-350
INR	1,7	1,7	3,68	4,12	2,2	<1,2
Bilirubin, μmol/l	280	350	926	989	1018,6	5-21
ALT, U/l	5482	4855	787	560	236	10-50
AST, U/l	7407	6820	361	410	412	10-60
Protein, g/l	55	60	39	35	39	60-82
Albumin, g/l	28	43	33	38	26	33-52
SHE, U/l	5550	-	4300	3100	3600	3500-11500

Serological markers of hepatitis A, B and C, Cytomegalovirus and Epstein-Barr virus were negative or indicated past infection. Serum anti-nuclear, anti-smooth muscle and anti-mitochondrial antibodies were negative. The patient serum was negative for anti-HEV IgG but positive for anti-HEV IgM by ELISA (Euroimmune, Germany). A serological diagnosis of acute HEV hepatitis was made. An abdominal computed tomography scan revealed mid liver enlargement with steatosis, splenomegaly, nobiliary tree dilatation and preserved hepatic vasculature. Peri-pancreatic, peri-hepatic, pelvic and peri-splenic, as well as pleural fluid, were present.

The patent was transitioned to supportive management.

Over a 7-day of admission, the patient's acute hepatitis evolved into acute liver failure with encephalopathy, decreased aminotransferases, increased bilirubin and impaired liver synthetic function. He was initiated on methylprednisolone at a daily dose of 300 mg without improvement.

The next day, the patient was transferred to another hospital for further management and transplant consideration. Unfortunately, he developed multi-organ failure thereafter and died before the transplantation became feasible.

Subsequently, hepatitis E was confirmed in archived serum on admission by detection of HEV RNA (5 057 500 IU/ml) using commercial RT-PCR (Altona, Germany).

DISCUSSION

In this article, we describe a case of a young patient with a chronic immune disease who presented with symptomatic acute HEV hepatitis and progressed to ALF. In the last ten years, several studies have been conducted in Bulgaria, revealing various aspects of HEV infection in the country: seroprevalence surveys in humans [9,10,11], serological data on the presence of HEV antibodies in the animal population [12,13], Deep Bayesian phylogenetic analysis for viral spread control in the country [14] and others. To our knowledge, this is the first report of fatal fulminant hepatitis associated with HEV in Bulgaria.

Hepatitis E infection is an emerging global public health problem. From exotic travel-related hepatitis E, virus infection, mainly HEV-3, has recently become a locally acquired zoonosis in Europe. Laboratory confirmed cases have increased in many countries. Moreover, in some of these countries, HEV -3 is the most common cause of acute viral hepatitis. Due to a recent estimate, there are at least 2 million locally acquired HEV-3 infections in Europe annually, but the incidence varies considerably between countries [15].

Pigs are considered the primary reservoir. Raw pork and pork sausage consumption appear to be a risk factor. However, human infections with HEV have also originated from other sources, including wild boar, deer, rabbits, camels (HEV- 7), rats, and blood products [16]. We didn't find any of the aforementioned risk factors in our patient. However, the origin of such infection is not necessary due to consumption of undercooked meat, as HEV-3 has also been found in shellfish, fresh fruit and salads irrigated with infected water [17,18].

Approximately 70% of HEV-3 infections are asymptomatic [19]. Laboratory confirmed cases represent only a fraction of the remaining infections as many go unrecognized or misdiagnosed. Only a minority infected individuals develop a clinically detectable infection with jaundice, elevated aminotransferases and nonspecific symptoms. Older men are more likely to develop overt acute HEV infection, for a reason still not known. It is believed that underlying liver disease such as steatosis/ fibrosis favors such a course. Most of the patients had concomitant diabetes mellitus or are heavy alcohol consumers, both risk factors for liver steatosis [20]. The steatosis, which was revealed by an imaging study in the presented young patient, remained inexplicable.

In developed countries, HEV (HEV- 3, HEV-4) infections do not pose a risk to pregnant women. However, few

vulnerable patient groups bear the brunt of the infection. Patients with pre-existing chronic liver disease are considered at-risk of acute-on-chronic liver failure or liver decompensation. This risk is further increased in older patients. Another potential at-risk group is immunocompromised patients, in particular solid organ transplant recipients and patients with hematological malignancies. They both are prone to chronicity with rapid progression to liver cirrhosis [3, 5]. In addition, HEV infection might be misdiagnosed as drug-induced liver injury or autoimmune hepatitis, which poses a diagnostic dilemma.

Approximately 20-40% of ALF are caused by HEV (HEV- 1, HEV-2) in developing courtiers [3]. In contrast, only a small number of retrospective case studies of HEV-associated ALF are reported in European countries. For instance, 4% of ALF patients in a multicenter study in Germany had acute HEV-3 infection, and 5% of Scottish ALF patients had evidence of acute HEV from store sera [21, 22]. Whether the HEV infection was causative or simply associated with the liver injury remains unclear.

Many well-known negative prognostic factors were not present in the patient described (old age, chronic liver disease, paracetamol misuse). We assume that non-steroidal anti-inflammatory drugs, autoimmune background (immune thrombocytopenia) coupled with steatosis might contribute to his fatal outcome.

A couple of case reports have shown improved liver function tests after corticosteroid administration in patients with ALF from HEV infection [23]. In addition, there is some evidence to suggest that steroids improved prognosis in patients with ALF [24]. Our patient was trialed on corticosteroid therapy but without effect. A few case studies are also available on ribavirin treatment for acute HEV infection resulting in ALF [6, 25]. This medication was associated with rapid normalization of liver function tests and undetectable HEV RNA. Early ribavirin therapy should be considered in patients with chronic HEV, neurologic inquiries and hematological malignancies [26]**.** Thus, ribavirin is the only currently established therapeutic option for HEV-induced severe acute infection in patients with underlying chronic liver diseases and chronic hepatitis. However, there remains no consensus regarding the role of ribavirin treatment in ALF associated with HEV.

The timely diagnosis of HEV infection could be crucial in the management of severe cases, given the availability of ribavirin. Recent European Guidelines recommended testing all patients with hepatitis for HEV, irrespective of travel history [27]. It is notable that most serological testing for HEV is not reliable on its own but may indicate a contribution to ALF by HEV infection. Moreover, the potential for false-positive and false-negative results must be considered after excluding more common causes of liver injury. Additional RNA-based testing has to be performed if ALF is suspected [23]. As molecular HEV testing was not timely available in the hospital, our delayed molecular confirmation could not have contributed to better management of the patent.

The genotype in this patient was not determined. During the study period, HEV RNA testing with sequencing and genotyping was not routinely performed. This limitation in our knowledge of HEV genotype is partially addressed by data that the predominant circulating genotype in Bulgaria was HEV-3 [14]. In this regard, we may speculate that the fulminant hepatitis could be associated with the particular strain harbored in our patient.

CONCLUSION

The result of this study has confirmed that HEV testing should be included in the initial evaluation of every acute liver failure regardless of travel history or risk factors. Moreover, RNA-bases testing has to be performed in case of fulminant hepatitis to support clinical decisions and enable to use of potential antiviral therapy.

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REFERENCES:

1. Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. *J Hepatol.* 2008 Mar;48(3):494-503. [PubMed]

2. Shalimar, Kedia S, Gunjan D, Sonika U, Mahapatra SJ, Nayak B, et al. Acute liver failure due to hepatitis E virus infection is associated with better survival than other etiologies in endian patients. *Dig Dis Sci.* 2017 Apr; 62(4):1058-66. [PubMed]

3. Kamar N, Dalton HR, Abravanel F, Izopet J. Hepatitis E virus infection. *Clin Microbiol Rev.* 2014 Jan;27(1): 116-38. [PubMed]

4. Debing Y, Moradpour D, Neyts J, Gouttenoire J. Update on hepatitis E virology: Implications for clinical practice. *J Hepatol.* 2016 Jul;65(1): 200-12. [PubMed]

5. Behrendt P, Steinmann E, Manns MP, Wedemeyer H. The impact of hepatitis E in the liver transplant setting. *J Hepatol.* 2014 Dec;61(6):1418-29. [PubMed]

6. Wenter C, Borena W, Oberhuber G, Graziadei I. Acute liver failure in immunocompetent patients infected with hepatitis E. *Wien Klin Wochenschr.* 2019 Sep;131(17-18): 442-5. [PubMed]

7. Festa S, Garbuglia AR, Baccini F, Panzuto F, Capobianchi MR, et al. Acute fulminant hepatitis E virus genotype 3e infection: description of the first case in Europe. *Scand J Infect Dis.* 2014 Oct;46(10):727-31. [PubMed]

8. EASL Guidelines on the management of acute (fulminant) liver failure. *J Hepatol.* 2017 May;66(5):1047-1081. [PubMed]

9. Teoharov P, Kevorkyan A, Raycheva R, Golkocheva-Markova E, Trandeva-Bankova D, Andonov A. Data on the prevalence of hepatitis E virus in Bulgaria. *Proceeding of the Bulgarian Academy of Sciences.* 2014; 67(10):1427-1432. [Internet]

10. Baymakova M, Terzieva K, Popov R, Grancharova E, Kundurzhiev T, Pepovich R, et al. Seroprevalence of

Hepatitis E Virus Infection among Blood Donors in Bulgaria. *Viruses*. 2021 Mar 16;13(3):492. [PubMed]

11. Gancheva G. Viral Hepatitis E in Pleven Region – Clinical, Laboratory and Epidemiological Characteristics. *J of IMAB*. 2021 Apr-Jun;27(1): 3804-3811. [Crossref]

12. Takova K, Koynarski T, Minkov I, Ivanova Z, Toneva V, Zahmanova G. Increasing Hepatitis E Virus Seroprevalence in Domestic Pigs and Wild Boar in Bulgaria. *Animals (Basel)*. 2020 Aug 28;10(9):1521. [PubMed]

13. Tsachev I, Baymakova M, Ciccozzi M, Pepovich R, Kundurzhiev T, Marutsov P, et al. Seroprevalence of Hepatitis E Virus Infection in Pigs from Southern Bulgaria. *Vector Borne Zoonotic Dis*. 2019 Oct;19(10):767-772. [PubMed]

14. Cella E, Golkocheva-Markova E, Sagnelli C, Scolamacchia V, Bruni R, Villano U, et al. Human hepatitis E virus circulation in Bulgaria: Deep Bayesian phylogenetic analysis for viral spread control in the country. *J Med Virol*. 2019 Jan;91(1):132-138. [PubMed]

15. Adlhoch C, Avellon A, Baylis SA, Ciccaglione AR, Couturier E, de Sousa R, et al. Hepatitis E virus: Assessment of the epidemiological situation in humans in Europe, 2014/15. *J Clin Virol*. 2016 Sep;82:9-16. [PubMed]

16. Tarantino G, Ortolani A, Marinelli K, Benedetti A, Marconi G, Calzolari M, et al. Locally acquired hepatitis E virus in Marche Italy: Clinical/laboratory features and outcome. *Dig Liver Dis*. 2020 Apr;52(4): 434-439. [PubMed]

17. La Rosa G, Proroga YTR, De Medici D, Capuano F, Iaconelli M, Della Libera S, et al. First detection of hepatitis e virus in shellfish and in seawater from production areas in Southern Italy. *Food Environ Virol*. 2018 Mar;10(1):127-131. [PubMed]

18. Terio V, Bottaro M, Pavoni E, Losio MN, Serraino A, Giacometti F, et al Occurrence of hepatitis A and E and norovirus GI and GII in ready-to-eat vegetables in Italy. *Int J Food Microbiol*. 2017 May 16;249:61-65. [PubMed]

19. Guillois Y, Abravanel F, Miura T, Pavio N, Vaillant V, Lhomme S, et al. High proportion of asymptomatic infections in an outbreak of hepatitis e associated with a spit-roasted piglet, France, 2013. *Clin Infect Dis*. 2016 Feb 1;62(3):351-7. [PubMed]

20. Dalton HR, Bendall RP, Rashid M, Ellis V, Ali R, Ramnarace R et al. Host risk factors and autochthonous hepatitis E infection. *Eur J Gastroenterol Hepatol*. 2011 Nov; 23(12): 1200-5. [PubMed]

21. Hadem J, Tacke F, Bruns T, Langgartner J, Strnad P, Denk GU, et al. Acute liver failure study group Germany. Etiologies and outcomes of acute liver failure in Germany. *Clin Gastroenterol Hepatol*. 2012 Jun; 10(6):664-9.e2. [PubMed]

22. Crossan CL, Simpson KJ, Craig DG, Bellamy C, Davidson J, Dalton HR, et al. Hepatitis E virus in patients with acute severe liver injury. *World J Hepatol*. 2014 Jun 27;6(6):426-34. [PubMed]

23. Manka P, Bechmann LP, Coombes JD, Thodou V, Schlattjan M, Kahraman A, et al. Hepatitis E virus infection as a possible cause of acute liver failure in Europe. *Clin Gastroenterol Hepatol*. 2015 Oct; 13(10):1836-1842.e2; quiz e157-8. [PubMed]

24. Zhao B, Zhang HY, Xie GJ Liu HM, Chen Q, Li RG, et al. Evaluation of the efficacy of steroid therapy on acute liver failure. *Exp Ther Med*. 2016;12(5):3121-3129. [PubMed]

25. Peron JM, Dalton H, Izopet J, Kamar N. Acute autochthonous hepatitis E in western patients with underlying chronic liver disease: a role for ribavirin? *J Hepatol*. 2011 Jun;54(6): 1323-4; [PubMed]

26. von Felden J, Alric L, Pischke S, Aitken C, Schlabe S, Spengler U, et al. The burden of hepatitis E among patients with haematological malignancies: A retrospective European cohort study. *J Hepatol*. 2019 Sep;71(3): 465-72. [PubMed]

27. EASL Clinical Practice Guidelines on hepatitis E virus infection. *J Hepatol*. 2018 Jun;68(6):1256-1271. [PubMed]

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