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Case Report / Приказ случаја

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Subacute liver failure of unknown origin

Субакутна инсуфицијенција јетре непознате етиологије

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SUMMARY

Introduction Acute liver failure is rare and very complex clinical syndrome, the consequences of the sudden and severe liver dysfunction. There are several causes of this condition (viruses, medications, toxins, metabolic, autoimmune and malignant diseases), but etiological agent often remains undiscovered.

Case Outline A 40-year-old male patient got ill suddenly with signs and symptoms relevant for acute hepatitis, which was confirmed with biochemical analysis. The cause of acute liver failure was not determined. Despite all therapeutic measures, clinical course of the disease was bad: severe icterus, decreased synthetic function of the liver and hepatic encephalopathy developed. In the later, subacute course of the disease, developed ascites, episodes of hepatic encephalopathy and biochemical findings of chronic hepatocellular failure. After three months treatment, in hepatic coma, there was lethal outcome. Histopathological findings confirmed the diagnosis of decompensated liver cirrhosis of unknown origin.

Conclusion The cause of acute liver failure often remains unclear; potential causes should be looked for in infections with unknown viruses or in toxins exposure. The disease is most commonly presented as subacute failure with the development of liver cirrhosis. Survival rate is low.

Keywords: subacute liver failure; acute hepatitis non A-E; liver cirrhosis; hepatic encephalopathy

САЖЕТАК

Увод Акутна инсуфицијенција јетре је редак и веома сложен клинички синдром, настао као последица изненадне и тешке дисфункције јетре. Узроци су бројни (вируси, лекови, токсини, метаболичке, аутоимунске и малигне болести) и врло често се не открију.

Приказ болесника Мушкарац узраста 40 година разболео се нагло са тегобама и знацима акутног хепатитиса, што је биохемијским анализама и потврђено. Узрочник акутног оштећења јетре није доказан. И поред предузетих терапијских мера, клинички ток болести је неповољан: изражен иктерус, пад синтетске функције јетре, развој хепатичке енцефалопатије. У даљем, субакутном току болести долази до појаве асцитеса, епизода хепатичке енцефалопатије и биохемијских показатаља хроничне хепатоцелуларне инсуфицијенције. После три месеца лечења, у хепатичкој коми, долази до смртног исхода. Хистопатолошким прегледом ткива јетре потврђена је дијагноза декомпензоване цирозе јетре непознате етиологије.

Закључак Узрок акутне инсуфицијенције јетре често остаје нејасан; потенцијалне узрочнике треба тражити у инфекцијама са непознатим вирусима или у изложености токсинима. Болест се најчешће презентује као субакутна инсуфицијенција са развојем цирозе јетре. Степен преживљавања је низак.

Кључне речи: субакутна инсуфицијенција јетре; акутни хепатитис не-А-Е; цироза јетре; хепатичка енцафалопатија

INTRODUCTION

Acute liver failure (ALF) is complex clinical syndrome which developes as a consequence of massive or submassive hepatic cell necrosis, with development of hepatic encephalopathy (HE) and severe disturbance in liver functions. It is usually fatal (in 60-90%), most often within the first week of the disease [1]. Since there are several etiological factors, with different clinical course and outcome of the disease and lots of complications, different authors give diverse classifications of ALF [2, 3]. The researches of King's College Hospital, based on a personal experience with 558 patients with ALF and 47 patient with lately developed liver failure, gave new classification of ALF. Their suggestion is that ALF should be used as a frame term, which should be predetermined with prefixes hyper or sub, which would be two extremes of this clinical syndrome. The term hyperacute liver failure relates to the patients who develop encephalopathy up to the seven days after appearance of jaundice. This group of patients has a significant survival rate (around 40%) with the use of usual medications. For patients who develop encephalopathy from 8 to 28 days after appearance of jaundice, the term acute liver failure is being used. These patients have extremely low survival rate

(7%). For patients in who encephalopathy develops after four weeks (from 29 to 84 days after appearance of jaundice) the term subacute liver failure should be used. Survival rate for the last group is low, about 14%. The most common etiological factor was acute hepatitis non- A, non- B, making 83% of all cases [4]. Adopting this terminology allowed standardized approach and interpretation of controlled clinical studies, and also application of new therapeutical methods, including bioartificial liver support and a liver transplantation.

Beside the time relapsing between appearance of jaundice and encephalopathy other prognostic factors of outcome of ALF were discovered, such as level of serum bilirubin, ammonemia, international normalized ratio (INR), thyroid status, etc. Combining these factors different prognostic models were made in order to predict mortality, and to timely indicate the need for liver transplantation, remaining the only therapeutic option [5]. This is especially important for ALF of unknown origin since there is no specific therapy.

CASE REPORT

A 40-year-old male patient, salesman from Belgrade, married, two children, was admitted to the Clinic for Infectious and Tropical Disease in Belgrade, Clinical Centre of Serbia, due to nausea, loss of appetite, aversion to food, dark urine and yellowing of the eyes. The disease started 10 days before admission to the hospital. Epidemiological data excluded possibility of liver infection by primary and potentially hepatotropic viruses, and acute toxic liver failure (caused by alcohol, medications, herbs, different supplements, etc). At admission patient had no fever, he had jaundice, liver was palpable two centimeters below right rib cage, and there were no signs of hepatic encephalopathy. Biochemical analysis suggested to acute hepatitis without hepatocellular insufficiency: aspartate aminotransferase (AST) 1249 U/L, alanine aminotransferase (ALT) 2907 U/L, total-value bilirubin (TBil) 393 μmol/L, direct bilirubin (DBil) 169 μmol/L, gamma-glutamyl transferase (GGT) 194 U/L, alkaline phosphatase (ALP) 115 U/L, prothrombin time (PT) 62.3%, INR 1.3. Hematological analysis were normal. Virological tests excluded hepatitis B virus (HBV) infection (HBsAg, anti-HBc IgM and HBV DNA were negative), hepatitis C virus (HCV) infection (anti-HCV and HCV RNA were negative), hepatitis A virus (HAV) infection (anti-HAV IgM was negative), hepatitis E virus (HEV) infection (anti-HEV IgM negative), as well as Epstein-Barr virus (EBV), cytomegalovirus (CMV), adenovirus, herpes simplex virus (HSV) and West Nile virus (WNV) infection (IgM-class antibodies were negative measured by ELISA). Autoimmune liver disease, Wilson disease and hemochromatosis were excluded too. Multiply increased value of alpha-fetoprotein (AFP) - 659 ng/L was pointing to regenerative potential of the liver. Ultrasound examination of abdomen excluded obstruction of bile ducts, even though gallstone of 1cm was seen in a gallbladder. Thrombosis of hepatic veins was excluded, too. Hematologist excluded hematology disease with possible liver infiltration.

In the further course of the disease fatigue and the loss of appetite continuied, with increase in serum transaminases (AST 3113 U/L, ALT 4957 U/L), jaundice (TBil 655 μmol/L, DBil 256 μmol/L)

and gradual fall of the liver synthetic function (albumin level 31 g/L, PT 46%, INR 1.61, AFP 129 ng/L). Since there was progressive liver failure with threatening hepatocellular insufficiency, prednisone and 20% human albumins were included in the therapy. In the further course there was no positive therapeutic response, hence on the 30th day of treatment patient fulfilled criteria for ALF - PT 40%, INR 1.81. Three days later flapping tremor (asterixis) appeared as a sign of the second phase of hepatic encephalopathy. Lactulosis, L-ornithine-L-aspartate (LOLA) and fresh frozen human plasma were added to the preceding therapy. In further course of the disease patient had episodes of hepatic encephalopathy with severe jaundice (TBil around 500 μmol/L), low AFP (17.5 ng/L) and hepatocellular insufficiency (PT 36%, INR 2.01). At the and of two months treatment, for the first time abdominal ultrasound verified inhomogeneous liver parenchyma, splenomegaly (12.5 cm) and some ascites in the abdomen. Our conclusion was that our patient had subacute liver failure with cirrhotic transformation. The patient was put on the transplant waiting list.

Further course of the disease fit in with to decompensated liver cirrhosis with hepatic encephalopathy. Biochemical analysis showed inversion of tranaminases activity (AST 302 U/L, ALT 281 U/L), hyperbilirubinemia (TBil up to 639 μmol/L), hepatocellular insufficiency (albumin level 30 g/l, PT 27%, INR 2.28) and hyperammonemia (177 nmol/L). Magnetic resonance imaging (MRI) scan of abdomen and magnetic resonance cholangiopancreatography (MRCP) was performed - cirrhotic liver and multiple nodular lesions with atypical MRI characteristics were described. Free fluid in the abdomen, portal hypertension and gallstone were also observed.

After three months treatment patient deepened disorder of consciousness, up to level of coma with hyperpirexia. Lethal outcomes happened 102 days after beginning of the disease, in deep coma. Necropsy of the liver was performed and the cylindrical sample of 3.5 cm was obtained. Architecture of the liver was damaged in cirrhotic manner. Cholestasis was severe and there were great zones of ischemic necrosis of hepatocytes. Coloring on iron was negative, as well on protein associated with copper. There was no tumor tissue of hepatocellular carcinoma (Figure 1).

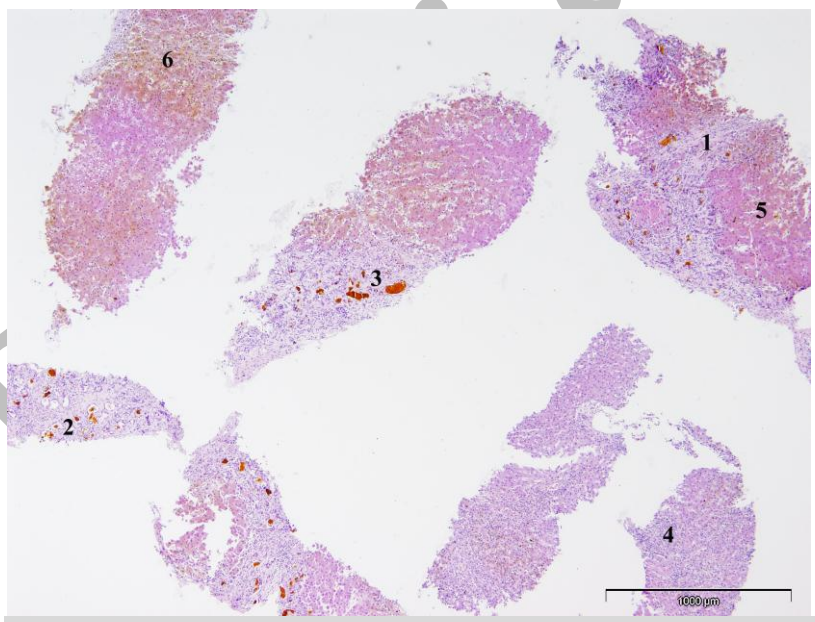

Figure 1. Postnecrotic cirrhosis with signs of liver insufficiency. Fibrosis septa are seen around parenchymal nodules (1). There is proliferation of biliary ductules (2). Bile stasis is seen in some of the dilated ducts (3). Inflammatory infiltrates are scant (4). The parenchyma shows a nodular appearance (5). There are cellular and canalicular cholestasis (6). Some hepatocytes show ischemic change.

DISCUSSION

ALF with following multiple organ dysfunction, hence insufficiency, can be caused by many agents and pathological conditions: viruses, medications, toxins, alcohol, congenital metabolism disorders, autoimmune liver disease, cardiovascular disease, leukemia, reticulosis, etc [6]. Globally, HAV and HEV infection are the most common cause of ALF in developing countries, with mortality rate over 50% [7]. From known primary hepatotropic viruses, HBV is the most common (67.8%) cause of ALF in our country [1]. In the last couple of years in Western Europe and the United States of America raises significance of herbal products caused hepatotoxicity; cases with ALF with lethal outcome have also been reported [8]. Around 50% of ALF in the United States of America is caused by medications, especially acetaminophen [9].

ALF of unknown origin (undetermined cause) is registered with diverse frequency worldwide and it is not depending on epidemiological characteristics of the area - from 11% in Sweden [10] to 38% in Sudan [11]. In our previous research undetermined cause of ALF was second frequent (12.6%), right behind HBV infection. These patients had the worst prognosis, and mortality rate was 100%. Clinical course of the disease was either acute or subacute liver failure [12]. Our patient had subacute course of liver failure (signs of HE appeared 33 days after jaundice) with undetermined cause - infection with known primary and potentially hepatotropic viruses were excluded, as well as occult HBV and HCV infection, autoimmune liver disease, Wilson disease and hemochromatosis. Based on a detailed anamnesis, biochemical analysis and histopathological findings, as well as regarding previous researches [13], this could be the case of infection with unknown hepatotropic virus.

The way the hapatocytes die, to be more precise, the amount of simultaneously died hepatocytes and intra-acinus localization of necrosis are in the centre of today's histological classifications of acute viral hepatitis (AVH). Therefore, there are four basic histological forms of AVH: with focal necrosis, with confluent bridging necrosis, with panacinus necrosis and with periportal necrosis [14]. The outcome of AVH with confluent bridging necrosis varies. It can come to complete or almost complete healing, by recovering of the parenchyma with rare remaining fibrosis. In some patients lethal outcome is possible in the first ten days of the disease with signs of ALF or in two or three months with the signs of subacute liver failure with fibrosis. In rare cases real cirrhosis and nodular regeneration hyperplasia of the parenchyma can be found [15].

In our patient, subacute course of the disease and histopathologically proved liver cirrhosis could relate, by course and outcome, to acute viral hepatitis with confluent bridging necrosis. Liver transplantation is the last treatment option in patients with ALF, when conservative treatment options fail and lethal outcome is imminent [16]. Our patients was put on the transplant waiting list.

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REFERENCES

1. Delić D. Akutna insuficijencija jetre. Beograd: Zavod za udžbenike i nastavna sredstva; 1999.
2. Lucke B, Mallory T. Fulminant form of epidemic hepatitis. Am J Pathol. 1946; 22(5): 867–945.
3. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Sem Liv Dis. 1986; 6(2): 97–106.
4. O'Grady J, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993; 342(8866): 273–5.
5. Kumar R, Shalimar, Sharma H, Goyal R, Kumar A, Khanal S, et al. Prospective derivation and validation of early dynamic model for predicting outcome in patients with acute liver failure. Gut. 2012; 61(7): 1068–75.
6. Mas A, Eodes J. Fulminant hepatic failure. Lancet. 1997; 349(9058): 1081–5.
7. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013; 369(26): 2525–34.
8. Stournaris E, Tziomalos K. Herbal medicine-related hepatotoxicity. World J Hepatol. 2015; 7(19): 2189–93.
9. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010; 52(6): 2065–76.
10. Wei G, Bergquist A, Broome U, Lindgren S, Wallerstedt S, Almer S, et al. Acute liver failure in Sweden: etology and outcome. J Intern Med. 2007; 262(3): 393–401.
11. Mudawi HMY, Yousif BA. Fulminant hepatic failure in an Africa setting: etology, clinical course, and predictors of mortality. Dig Dis Sci. 2007; 52(11): 3266–9.
12. Urošević A. Etiologija, kliničke karekteristike, faktori prognoze i histopatološki nalaz kod bolesnika sa akutnom insuficijencijom jetre. Magistarska teza. Beograd: Medicinski fakultet; 2012.
13. Delić D, Mitrović N, Radovanović Spurnić A, Stojković Švirtlih N, Simonović Babić J. Epidemiological characteristics and clinical manifestations of acute non-A-E hepatitis. Vojnosanit Pregl. 2010; 67 (11): 903–9.
14. Scheuer PJ. Viral Hepatitis. In: MC Sween RNM, Anthony PP, Scheuer PJ, editors. Pathology of the Liver. Edinburg: Churchill Livingstone; 1987. p. 202–23.
15. Begić Janeva A. Patologija jetre i žučne bešike i žučnih puteva. Gornji Milanovac: Dečije novine; 1991.
16. Altinbas A, Bechmann LP, Akkiz H, Gerken G, Canbay A. Acute liver failure. In: Mauss S, Rockstroh J, Wedemeyer H, Berg T, Sarrazin C, editors. Hepatology. A clinical textbook. Hamburg: Medizin Fokus Verlag; 2017. p. 715–29.

