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FATE OF PATIENTS WITH LATE-DETECTED HEPATITIS C INFECTION - CASE REPORTS

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Chronic hepatitis C virus infection represents an insidious disease that is often detected with signs of liver cirrhosis or hepatocellular carcinoma. It is practicaly impossible to achieve a significant therapeutic progress in these patients without performing a liver transplantation. However, due to underdeveloped program of organ donations, this kind of intervention, as the last helpful procedure, is often not realized.

This study presents three patients (out of 121 treated patients) followed during a two-year period. The patients had been initially registered when the stage of their disease became severe: liver failure with signs of decompensation. Antiviral therapy (pegylated interferon and ribavirin) in these patients have no use, hence only a corrective therapy is administered. Pathohistological findings in two patients revealed hepatocellular carcinoma, and in one case lethal outcome was the result of severe hepatic decompensation, hepatopulmonary and hepatorenal syndromes, as well as developed cardiopulmonary failure. Lethal outcome occurred in the period of 2 to 14 months after the first visit to a doctor. One patient was on the list for liver transplantation; however, surgery was not performed and soon after a fatal outcome ensued. *Acta Medica Medianae 2011;50(2):49-52.*

Key words: *chronic hepatitis C, liver cirrhosis, hepatocellular carcinoma, antiviral agents*

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Introduction

Hepatitis C virus infection (HCV) is a progressive disease that has a high rate of morbidity and significant mortality. It is estimated that the number of persons with the infection represents approximately 3% of the world population at present, or 170-200 million cases (1,2). The number of the infected is increasing, each year by 3-4 million new patients (3). In 85% of chronically infected persons there are conditions that can lead to a disease progression into liver cirrhosis and hepatocellular carcinoma (2,4-6). At the same time, most patients with chronic HCV infection are candidates for liver transplantation (2,7,8). Therapeutic response in these patients greatly depends on the virus genotype. Namely, genotypes 1 and 4 cause a lower percentage of therapy response (50-55%) than genotypes 2 and 3 (80%). Unfortunately, the most common virus genotype in Europe is genotype 1, with subtypes 1a and 1b. The number of infected people in Serbia is between 100-150 thousands. As for the genetic background of our country, there is an identical genotype background as on the territory of the Mediterranean, which is dominated by virus genotype 1 (8). It should be noted that disease is not equally widespread in the population. It is particularly frequent among drug users, hemophiliacs and patients on hemodialysis (10,11). Disease evolution significantly depends on the virus genotype, timely recognition of disease and therapeutic approach to patients. The disease course is asymptomatic and very often is registered in advanced stage when the therapeutic approach is very inefficient due to already developed irreversible changes in the liver and other organs.

Hepatitis C is a systemic disease that may appear in a wide spectrum of clinical manifestations. Generalized signs and symptoms of chronic HCV infection include: fatigue, joint pain, itching, sleeping disturbance, changes in appetite, nausea and depression. In patients with liver cirrhosis, the liver function is impaired and can develope portal hypertension, ascites, spontaneous nose and gums bleeds, jaundice and the syndrome of cognitive impairment. Also, there are associated, the „so-called" extrahepatic manifestations of chronic hepatitis C infection (12-14). The presence of co-infection (HBV, HIV, etc.) or some comorbid condition (alcohol abuse, toxicomania) significantly accelerates disease progression, leading to a fatal

outcome (15,16). Contemporary therapeutic approach to chronic HCV infection consists of pegylated interferon application once a week, administrated by subcutaneous injections and daily ribavirin intake (1,3,11). Because of the relative ineffecti-veness of the therapy and presence of non-responders and relapsers, a triple therapy is supported in the world today. This therapy includes the use of HCV protease and polymerase inhibitors, beside the aforementioned medications (17).

Aim of the study, patients and methods

The work presents three patients in whom the diagnosis of hepatitis C infection was set at the time the disease took a fatal course. Out of 121 patients tested and treated during the two years of observations (2009-2010), three cases were selected. They had a fast-evolving disease course, which from the time of establishing the diagnosis rapidly led to death. Diagnosis of the disease was carried out with conventional testing methods: clinical examination, laboratory tests, serologic tests, histopathological examinations and PCR HCV-RNA and genotyping method. The aim of the study was to determine potential comorbid conditions or the presence of co-infections that might influenced such evolutionary end of the disease. At the same time, patients' age and gender characteristics were observed as well as a genotypic background of hepatitis C virus.

Results

Patient M.M., protocol number 2962/08, was born in 1938 and was retired. The patient was first seen at the end of 2008. At the first examination the patients' findings were suspected for advanced stage of liver disease and the diagnosis of liver cirrhosis was set. Organomegaly was observed (the liver was palpable at 1-2 cm below the costal arch, with sharp edge, uneven surface, slightly tender to palpation; spleen was enlarged by approximately 2-3 cm). Additionally to these findings, palmar erythema was registered in the patient, together with the presence of varices during abdominal examination. The patient was well nourished, in good mood and ready for cooperation, willing to receive medical assistance. Heteroanamnestic data excluded alcohol consumption. Among performed laboratory tests, the following abnormal values emphasized: erythrocytes sedimentation rate (51/77), low platelet count (44*109/L), high levels of alpha-fetoprotein (12 times increased, 121.72 ng/mL). Alkaline phosphatase value (ALP) and gamma-glutamyl transpeptidase (gamma-GT) differed from normal values. Total bilirubin was 34.6 mmol/L with simultaneously mild aminotransferase elevation, aspartate aminotransferase (AST) 54 U/L and the values of alanine aminotransferase (ALT) were normal (34 U/L). Albumin level was 32 g/L and prothrombin time 54%. An ultrasound finding of the upper abdomen was in correlation with clinically verified organomegaly, without the presence of ascites. In further examination, the presence of HCV antibodies was verified in the patient, while HBsAg and AtHIV were negative. Analysis by PCR method proved the presence of HCV-RNA, with 11.196.000 viral copies, as well the virus genotype 1. Follow-up of the patient showed a progressive body weight reduction and the appearance of dull pain at the right and left costal arch. A multislice computed tomography (MSCT) of the liver was performed, in which a tissue change was observed, pointing to possible infiltrations or intensive liver repair. A sample of alterated hepatic tissue was taken with targeted liver biopsy. The result of pathological examination of the sampled material indicated a primary liver hepatocellular cancer. Exitus letalis occurred within one year from the initial contact with the patient.

Patient R.Lj., protocol number 958/10, born in 1952, was employed as a clerk. She was hospitalized during her first visit to a physician due to severe malaise, loss of appetite, yellowish staining of eyes and skin, palmar erythema and a large number of spider nevi on the chest, face and hands. Urine discoloration was also reported. Further clinical examination of the patient revealed enlarged liver, 2 cm below the costal arch, and the spleen was palpable on the left costal arch. She was admitted with the diagnosis of liver cirrhosis. After hospital admission, the patient underwent a series of analysis: erythrocyte sedimentation rate 80/90, platelet count (148* 109/L) was relatively within the normal range, AST 142 U/L, ALT 321 U/L, gamma-GT 600 U/L, ALP 520 U/L, alpha-fetoprotein 35.35 ng/ml with positive AtHCV finding. Analyses of HIV antibodies and HBsAg were negative. There was no data of alcohol consumption. During hospitalization, progression of bilirubin values (680 mmol/L) was observed. Paraclinical tests were started, so the patient underwent an echo of the upper abdomen, CT of the liver and liver MSCT. During the tests, infiltrative changes in the right and left liver lobe were determined. A targeted biopsy of determined changes was performed, with three samples taken. Polymerase chain reaction on HCV-RNA was positive but genotyping was not done. Exitus letalis occurred two months after the initial contact with the physician, with the signs of hemorrhagic syndrome. Histopathological findings of the taken samples indicated hepatocellular carcinoma.

Patient M.S., protocol number 3405/8, was born in 1953 and was a sociologist by profession. The patient was hospitalized with the signs of weakness, poor urination, sudden increase in the abdomen girth, churning in the stomach, nosebleed and a weakened breathing on the right side of the chest. The diagnosis on admission was liver cirrhosis. Complete laboratory analysis showed mild aminotransferase increase AST 62 U/L, ALT 58 U/L (inverse serum aminotransferases). Bilirubin

values, alkaline phosphatase and gamma-GT showed no change compared to the normal range. Albumins were decreased (23.1 U/L), as well as the value of total protein (54 g/L) and prothrombotic time (28s), while the alpha-fetoprotein level was slightly above the normal values, or 11.93 U/L. In the course of further examination, pulmonary roentgenography was performed when pleural effusion was detected on the right side. Because of compromised breathing, a pleural puncture was repeatedly performed, with release of large amount of fluid, over one liter. Echo examination of the upper abdomen showed a small liver floating in ascites and enlarged spleen (145 mm). Antibodies to HCV were detected. Performed PCR HCV-RNA was positive for the virus genotype 1. Judging by her attitudes, the patient did not initially seem to take the illness seriously. After the liver compensation, the patient was followed in an outpatient care unit and a liver transplantation was proposed. For that reason the patient was sent for a second opinion in the Clinical Center in Belgrade, Department of Hepatology, where she was put on the waiting list for liver transplantation. The first liver transplantation attempt was not performed because of graft damage. In the meantime, the patient redeveloped the symptoms of hepatopulmonary and hepatorenal syndromes. In addition to these problems, the patient became encephalopatic, the signs of cardiac weakness also appeared, after which she was hospitalized in cardiology unit, where the lethal outcome occurred.

Discussion

Presented patients were hospitalized for the first time with the signs not clearly indicative of chronic hepatitis C infection. Hepatitis C infection is difficult to determine because of its insidious course, so that patients can have it in their organism for many years (11,12). During this time, in certain percentage of patients (65 to 80%), HCV infection progresses causing different degree of liver damage, and in the worst cases even cirrhosis or liver cancer. Frequently, patients visit a physician after the signs of decompensated disease have already occurred (jaundice). Sometimes, patients are monitored under different diagnoses, because of gallbladder ultrasound findings, without further analysis of registered problems (11-13).

Hepatitis C infection alone can have in its progression some supportive factors, in the form of other infectious agents' presence (hepatitis B or HIV) or other hepatotoxic substances (alcohol, corticosteroids use and others) (10). The observed patients had no other factors associated with progression of hepatitis virus infection. The disease is likely to have lasted for a long period of time, from l5 to 20 years, perhaps longer. During this time, patients had no knowledge of the infection presence. Upon hospital admission, chronic HCV infection was verified, but the applied therapy did not have an etiological character, only corrective one due to advanced disease stage. Implemented correction measures were complex. They were directed to the disease compensation (albumins intake, careful diuretics intake), struggle with threatening encephalopathy (diet, L-ornithine, L-aspartate, eubiotics intake, intestinal sterilization with antibiotics, enemas, etc.), and correction of hemorrhagic syndrome (plasma infusions, coagulation factors, platelets). Due to development of hepatopulmonary syndrome and compromised respiration with massive pleural effusion in one patient, pleural punction was repeatedly done.

The situation in these patients is significantly complicated because of poorly organised organ donation program and the lack of liver transplantation services. Liver transplantation, as the only option in these situations, usually comes down to pondering, and patients rarely, for the lack of time, reach this life-saving intervention (7).

Rapid fatal outcome in these patients with chronic HCV infection imposes the need for disease recognition as early as possible, so that therapeutic attempts could be made in order to preclude lethal outcomes. Also, in patients with liver transplantation indication, transplantation should be performed as soon as possible.

Conclusion

The three presented patients had the first contact with an infectologist as the most competent expert in managing HCV infection in terminal stage of the disease. Etiological treatment was not successful in the treatment of these patients (pegylated interferon plus ribavirin). In two patients, exitus letalis resulted from hepatitis C infection complications or the presence of hepatocellular carcinoma. In one patient, the life-threatening complaints, at one moment of the disease evolution, originated from pleural effusion. Liver transplantation was not undertaken in one patient, although pretransplantation preparations were already started. Also, our patients did not show the presence of co-morbid conditions.

These findings impose a need for active HCV infection search in the so-called non-risk groups, as potential patients get the chance to be treated according to contemporary recommendations.

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SUDBINA BOLESNIKA SA KASNO OTKRIVENOM HEPATITIS C INFEKCIJOM - PRIKAZ BOLESNIKA

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Hronični virusni hepatitis C predstavlja podmuklu bolest koja se često otkriva u vreme prisutnih promena, tipa ciroze jetre ili hepatocelularnog karcinoma. Kod ovih bolesnika praktično ne može biti učinjen značajan terapijski pomak, izuzev realizovanja transplantacije jetre. Međutim, zbog nedovoljno razvijenog donatorstva organa, ovakva intvencija, kao poslednji spasonosni zahvat, često se ne realizuje.

U radu su prikazana tri bolesnika (od 121-og lečenog bolesnika) praćena tokom dvogodišnjeg perioda. Bolesnici su prvi put registrovani kada je njihova bolest imala težak stepen: insuficijenciju jetre sa znacima dekompenzacije. Antivirusna terapija (pegilovanim interferonom i ribavirinom) kod ovakvih bolesnika nema primenu, te je samo sprovođena korektivna terapija. Kod dva bolesnika je patohistološkom obradom dokazno prisustvo hepatocelularnog karcinoma, dok je kod jedne bolesnice smrtni ishod nastao usled teške dekompenzacije jetre, pojave hepatopulmonalnog i hepatorenalnog sindroma i razvoja kardiopulmonalne slabosti. Smrtni ishod je kod bolesnika nastupio u periodu od dva do 14 meseci od momenta prvog susreta. Jedna od prikaznih bolesnica bila je na listi za transplantaciju jetre, međutim, operacija nije izvedena i nedugo zatim usledio je smrtni ishod. *Acta Medica Medianae 2011;50(2):49-52.*

***Ključne reči**: hronični hepatitis C, ciroza jetre, hepatocelularni karcinom, antivirusna terapija*