CASE STUDY

LIVER CIRRHOSIS WITH CRYPTOGENIC GENESES. CLINICAL CASE

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ABSTRACT

The article presents clinical observation of a patient with cryptogenic cirrhosis of the liver, a chronic diffuse progressive liver disease, which is manifested by structural rearrangement of its parenchyma. Cryptogenic cirrhosis is cirrhosis of uncertain etiology that lacks definitive clinical and histological criteria for a specific disease. Cryptogenic cirrhosis accounts for nearly 5% to 30% of cases of cirrhosis and nearly 10% of liver transplants. The problem of cirrhosis of the liver is extremely relevant, because this pathology is observed mainly in young and able-bodied people. In addition, it takes the first place among the causes of mortality from diseases of the digestive system.

To clarify the diagnosis, laboratory and instrumental diagnostic methods of investigation were performed. Due to severe thrombocytopenia and minor leukopenia, myelodysplastic syndrome was suspected. Metabolic disorders that can be considered as probable in the occurrence of the above-mentioned changes in the liver parenchyma had been ruled out.

KEY WORDS: Cryptogenic liver cirrhosis, varicose veins of the esophagus, patient

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INTRODUCTION

Cirrhosis of the liver (CL) is a chronic, diffuse, progressive disease of the liver, which is manifested by restructuring of its parenchyma in the form of nodular transformation and fibrosis due to necrosis of hepatocytes, the appearance of shunts between the portal and central veins bypassing hepatocytes with the development of portal hypertension and increasing liver failure.

Cirrhosis of the liver takes the first place among the causes of mortality from diseases of the digestive system. In economically developed countries, CL is among the six main causes of death in patients aged 35 to 60 years. According to the World Health Organization (WHO), over the past 20 years, there has been a continuous increase in mortality rates from this disease [1]. Over the last decade, the prevalence of liver diseases in Ukraine has increased significantly, especially among young people: chronic hepatitis – by 2,2 times, and cirrhosis of the liver – by 60%.

Therefore, the problem of CL is extremely relevant, because this pathology is observed mainly in people of young and working age [2]. Despite the absence of clear clinical manifestations, CL is dangerous due to the tendency to progress. The main causes of the development of CL are as follows: alcoholic liver disease (33%), viral hepatitis and non-alcoholic steatohepatitis, others occur less often due to the rarity of the pathology itself – hemochromatosis, Wilson's disease and Budd-Chiari disease, medicinal and cryptogenic hepatitis, etc. The proportion of patients with chronic HCV infection who develop CL within 20 years after infection varies from 2-4% in children to 20-30% in middle-aged patients, with an average of 10-15%.

The leading pathogenetic factor in CL is the development of bridge-like necrosis in the parenchyma, which leads to the death of hepatocytes. The development of connective tissue causes formation of false lobules with subsequent shunting of blood flow to bypass hepatocytes, hypoxia occurs on the background of a chronic inflammatory process. Regenerative cirrhotic nodes compress the terminal branches of the hepatic veins and branches of the portal vein in the portal tracts, which is the main reason for the development of portal hypertension. There are arteriovenous anastomoses between the branches of the hepatic artery and the portal vein in the fibrous septa, and in the late stages of the disease, portal blood outflow is blocked, blood circulation slows down, and in some cases, reverse blood circulation in the portal vein occurs. Immunological disorders and an increase in the level of pro-inflammatory cytokines are observed [3,4].

Clinical manifestations of cirrhosis are quite diverse. In about 20% of patients, the initial stages of the disease are asymptomatic [5]. Depending on the stage of the disease, the following symptoms may be observed: liver enlargement in the early stages, which is replaced by significant decrease in sizes; spleen enlargement; pain of a distending nature, localized in the right hypochondrium; asthenic syndrome; increase in body temperature; dyspeptic manifestations; decrease in body weight; signs of cholestasis; portal hypertension, varicose veins of the esophagus, rectum and stomach; edema; ascites; telangiectasias; hemorrhagic syndrome, manifested by bleeding of the mucous membranes, development of petechiae, hematomas; «hepatic» smell from the mouth; palmar erythema; hepatic encephalopathy; gynecomastia; xanthomas and xanthelasmas [6];

Classification of CL is carried out according to various parameters [7].

1. Morphology classification: morphologically, cirrhosis may be micronodular, macronodular, or mixed. This classification is not as clinically useful as etiologic classification.

Micronodular cirrhosis (uniform nodules less than 3 mm in diameter) is mostlu due to due to alcohol, hemochromatosis, hepatic venous outflow obstruction, chronic biliary obstruction, jejunoileal bypass, and Indian childhood cirrhosis.

Macronodular cirrhosis (irregular nodules with a variation greater than 3 mm in diameter) is the result of hepatitis B and C, alpha-1 antitrypsin deficiency, and primary biliary cholangitis.

Mixed cirrhosis (when features of both micronodular and macronodular cirrhosis are present) usually progresses into macronodular cirrhosis over time.

2. Etiology Classification. Based on the cause of cirrhosis it is sub-classified as follows:

Viral – hepatitis B, C, and D; Toxins – alcohol, drugs; Autoimmune – autoimmune hepatitis; Cholestatic – primary biliary cholangitis, primary sclerosing cholangitis; Vascular – Budd-Chiari syndrome, sinusoidal obstruction syndrome, cardiac cirrhosis; Metabolic – hemochromatosis, NASH, Wilson disease, alpha-1 antitrypsin deficiency, cryptogenic cirrhosis.

Also, the Child-Pugh classification of this disease is now used all over the world, which makes it possible to determine the degree of severity of cirrhosis (initial, moderately expressed and terminal) [8,9]. According to this classification, 5 signs are distinguished, each of which can be evaluated from 1 to 3 points. Then these points are added up, and depending on the number obtained, a class is determined: A, B or C, each of which corresponds to a certain degree of severity of cirrhosis.

- Cirrhosis stage according to Child – Pugh A – 5-8 points;
- Cirrhosis stage according to Child – Pugh B – 7-9 points;
- Cirrhosis stage according to Child – Pugh C – 10-15 points.

In the compensation phase of liver cirrhosis, differential diagnosis with other chronic diseases should be carried out [10]. With decompensation, differentiation is required by certain symptoms of the disease, depending on the clinical manifestation, including jaundice, portal hypertension, and hepatic encephalopathy.

The Model For End-Stage Liver Disease (MELD) score is a calculation aimed to determine the severity of end-stage liver disease and the need for transplantation. The components of the MELD score include creatinine, bilirubin, INR, and sodium [11].

Complications of liver cirrhosis are: hepatic coma (or precoma); bleeding from varicose veins of the esophagus and stomach, hemorrhoidal veins; portal vein thrombosis; bacterial peritonitis; cirrhosis – cancer [12,13].

Mortality is influenced mainly by age at diagnosis and Child's class [14].

CASE REPORT

The patient Mykola S. (25 y.o.): clinical-anamnestic examination, laboratory and instrumental methods of investigation, molecular-genetic study), born in 1997, sought medical help with complaints of general weakness, fatigue, pain in the right hypochondrium, discomfort in the epigastric area, nausea. Considers himself sick for a long time, when icterus of the sclera and skin first appeared. The patient was consulted by a gastroenterologist.

From the anamnesis, it is known that since the age of 17, he periodically noted stool disorders, flatulence. No significant childhood or adult illness in the history, no medication or alcohol use preceding the current complaints.

Objective status: the general condition is of moderate severity, consciousness and cognitive levels are normal, the patient is well-fed, afebrile, the skin and visible mucous membranes are pale pink. Peripheral lymph nodes are not enlarged. The constitution is normosthenic. The abdomen is soft, painful on palpation in the upper parts, the liver +3 cm below the right costal arch, dense.

To clarify the diagnosis, the following laboratory and instrumental diagnostic methods of investigation were performed:

General blood analysis (19.09.2017): ESR – 6 mm/h, hemoglobin – 152 g/l, hematocrit – 44,4, erythrocytes – 4,97×1012/l, leukocytes – 4,02×10^9/l (normal range 3,9-10×10^9/l), segmented granulocytes – 67,5%, eosinophils – 1,4%, basophils – 0,3%, lymphocytes – 22,9%, monocytes – 6,5%), platelets – 57 g/l (normal range 166-389 g/l).

Coagulogram (19.09.2017): international normalized ratio was (INR) 1,11; prothrombin according to Kwik – 76,8%; prothrombin time – 11,2 sec; activated partial thromboplastin time (APTT) – 28,9sec; fibrinogen – 264 mg/dL.

Biochemical blood analysis (19.09.2017) revealed slightly elevated total bilirubin – 22,1 μmol/l (normal range 5,0 – 21 μmol/l), elevated alanine aminotransferase – 69 U/l normal (4-41 U/l) and aspartate aminotransferase – 50 U/l (normal range (4-37 U/l), creatinine 74 – μmol/l, urea – 7,5 μmol/l, total protein – 80 g/l, cholesterol – 325 mmol/l.

Copper (Cu) content in urine by atomic absorption spectrometry with electrothermal atomization on the KAS-120.1 device: 84,7 μg/100 ml.

Copper (Cu) content in blood serum: 9,54 μmol/l (normal range 11,0 – 24,0 μmol/l).

Transferrin level – 251 mg/dL (normal range 200-300 mg/dL); ferritin – 50,8 ng/ml (normal range 28 – 365 ng/ml), ceruloplasmin – 55.6 mg/dL (normal range 22 – 61 mg/dL).

PCR (20.11.2017) was performed to detect cytomegalovirus (CMV DNA): not detected;

Epstein-Barr virus PCR (qualitative determination): detected.

IgM antibodies to HAV(20.11.2017): <0,02 (negative), antibodies to HCV (anti HCV IgG): <0,11 (negative), HBsAg (Australian antigen): 0,75 (negative).

We presented in Echographic changes of the liver and spleen of patient by date of Abdominal ultrasound investigation (06.10.2017) on figure 1. (fig. 1).

The images showed normal sized liver with heterogenous parenchyma of medium echogenicity contours are not even, parenchyma is unevenly compacted, the vascular pattern of the portal veins (left and right lobes) is intensified, enlarged; intrahepatic bile ducts are not dilated. V. portae expanded to 1,6 cm; The gallbladder is deformed, measuring 7,0*3,0 cm; the wall is not thickened, the content is homogeneous; choledoch 0,6 cm; Pancreas without echostructural changes. The spleen is enlarged, measuring 18,5*6,0 cm, homogeneous, with normal structure; v. lienalis expanded to 1,7 cm. Kidneys and bladder without pathological features. Conclusion: Echographic diffuse liver changes? Signs of biliary hypertension, splenomegaly

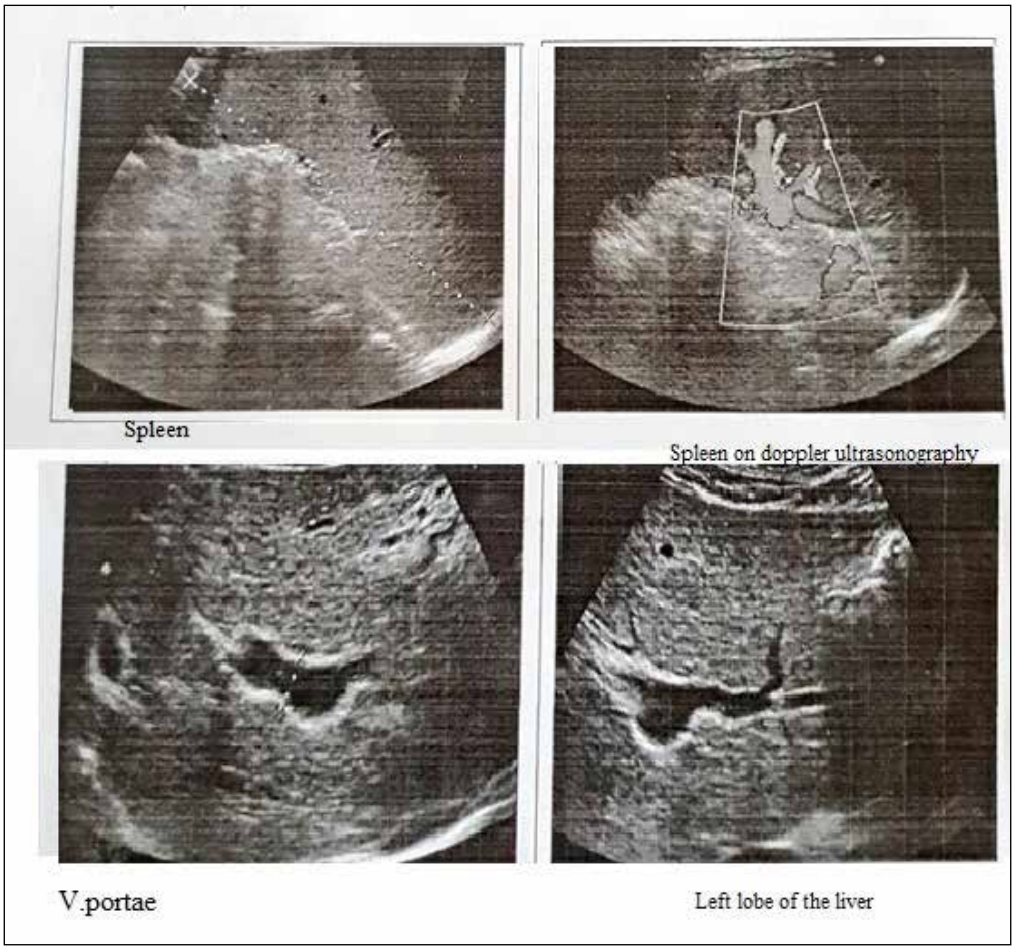

Fig. 1. Echographic changes of the liver and spleen

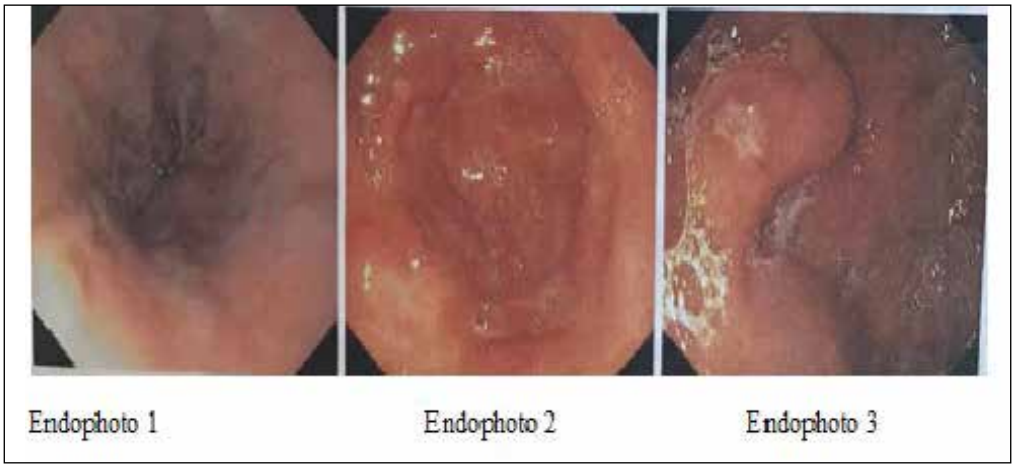

Fig. 2. Esophagogastrointestinal endoscopy

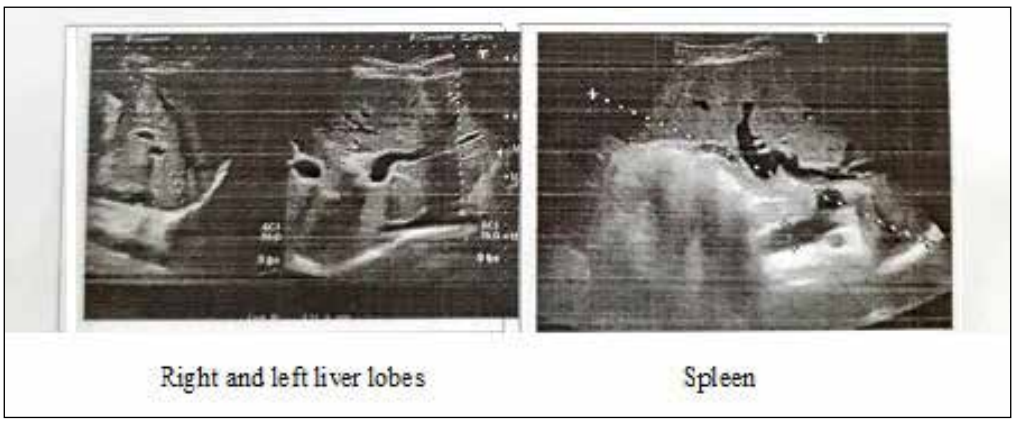

Fig. 3. Echographic dynamics of of the liver and spleen changes

Esophagogastrointestinal endoscopy data (12.10.2017) are presented on figure 2.

The esophagus is freely passable. The mucous membrane is pale pink, hyperemic in the lower third, at a distance of 30 cm from the incisors and to the hiatus, there are 4 varicose veins of the esophagus, which slightly protrude into the lumen by 3 mm. Endophoto 1. The hiatus is at the level of 42 cm from the incisors, it closes partially, it is freely passable, there is no CLE, palisade vessels are not expressed, there are no erosions in the area of the esophageal-gastric junction. With inversion – cardiac fold of 2nd degree.

The stomach is well expanded with air, freely permeable, on an empty stomach contains an increased amount of secretory fluid, bile. The folds of the mucous membrane are tortuous. The mucous membrane is focally hyperemic. In the lower third antral part of the stomach up to 20 small erosions of 2-3 mm in size are detected. Endophoto 2.

The pyorus closes completely, freely accessible for the endoscope. On the wall of the pylorus, on the hypertrophic fold, a rounded shape, 4*6 mm sized ulcer is determined. Endophoto 3.

The ampulla of the duodenum keeps its shape, freely accessible for the endoscope. The mucous membrane is focally hyperemic. The lumen of the postbulbar department is easily filled with air, there is a small amount of bile in the cavity. Peristalsis is preserved, circular folds are well expressed, villi are conical. Duodenal papillae were not visualized.

Conclusion of esophagogastrointestinal endoscopy: 1st stage varicose veins of the esophagus. Chronic esophagitis. Erythematous gastroduodenopathy. Duodeno-gastric bile reflux. Multiple small erosions of the stomach. Ulcer of the pylorus.

Magnetic resonance imaging (12.12.2017): MRI signs of diffuse changes in the liver according to the type of its cirrhotic deformation, appearance of signs of secondary hemochromatosis. Portal hypertension syndrome, splenomegaly. Vascular venous collaterals in the cardioesophageal region and in the region of the portae spleni.

Due to severe thrombocytopenia and minor leukopenia, myelodysplastic syndrome was suspected and the following examinations were performed:

Bone marrow puncture (27.09.2017): atypical mononuclear cells of various degrees of maturity are found in the preparation.

Cytomorphological method (16.10.2017): reduced cellularity in the bone marrow. Cells of the granulocytic series at various stages of maturation, cells of the erythroblastic series (mainly normoblasts), reduced number of megakaryocytes, lymphocytes – 23,0% are represented.

Cytochemical method (16.10.2017): chemical reactions for myeloperoxidase, acid phosphatase, acid non-specific esterase were carried out. Absence of histiocytes/macrophages with an intense reaction to acid phosphatase and acid nonspecific esterase, which is characteristic for myelodysplastic syndrome of refractory anemia (MDS RA).

Immunophenotyping (16.10.2017): 18,1% lymphocytes, 1,4% blasts were identified in the bone marrow. The ratio of T- and B-lymphocytes is within normal limits. Cytomorphological and cytochemical research: suspicion of chronic tautoimmune thrombocytopenia.

Trepan-biopsy of the iliac bone (06.11.2017): bone marrow is normal with signs of reticulin fibrosis, morphological changes are most consistent with myelodysplastic syndrome.

Data of immunohistochemical and morphological examination of bone marrow (15.11.2017) correspond to changes in myelodysplastic syndrome. Immunohistochemical examination: hypocellular bone marrow with markedly reduced megakaryopoiesis, activated erythropoiesis, reduced granulopoiesis and lymphocytosis without signs of atypia/cellular atypia. Histological criteria of dysplastic syndrome are not fulfilled. No signs of Gaucher's disease in the material.

The patient was consulted at the Center for Orphan Diseases «Okhmatdit» (11.12.2017) to rule out lysosomal storage diseases. Data in favor of a hereditary disorder of the metabolism of amino acids, acylcarnitines were not found, Gaucher disease and sphingomyelinase deficiency (Niemann-Pick disease) were excluded:

1. Tandem mass spectrometry of blood plasma: according to the results of the analysis, no violation of the concentration of amino acids and acylcarnitines in the blood was found.
2. Lactate: 1,54 mmol/l
3. Ammonium: 8,3 μmol/l
4. α-1 antitrypsin – 1,44
5. Research on the activity of lysosomal enzymes: B-glucosidase – 8,2 nmol/h/ml of plasma (normal 5,1 – 9,5 nmol/h/ml); chitotriosidase – 17 nmol/h/ml of plasma (norm 0 – 159 nmol/h/ml), acid sphingomyelinase – within reference values.

Molecular genetic study (16.10.2018) to detect the H1069Q mutation by PCR (BI-PASA): no mutation, which causes Wilson's disease, was detected in the ATP7B gene. Genotype, respectively, HGVS p.[=];[=]. However, it is known that Wilson's disease can be caused by more than 300 different mutations in the ATP7B gene, the most common of which is H1069Q.

Based on the results of a comprehensive examination, the diagnosis was established: Cirrhosis of the liver of cryptogenic etiology. Hepatocellular failure, class A according to Child-Pugh. Intrahepatic form of portal hypertension. Varicose veins of the esophagus 0-1 st. Portal gastropathy. Splenomegaly. Hypersplenism. PSE 0-1 st.

On control examination of the patient laboratory results (14.10.2020) showed normal ESR – 6 mm/h, hemoglobin – 151 g/l, hematocrit – 42,8, erythrocytes – 4,47×1012/l, leukocytes – 3,54×109/l (normal range 3,9-10 ,2), segmented granulocytes – 64,4%, eosinophils – 1,3%, basophils – 0,5%, lymphocytes – 25,8%, monocytes – 5,7%), platelets – 57 g/l (normal range 166-389), average hemoglobin content in one erythrocyte – 33,7 pg (normal range 27,0-33,5).

Abdominal ultrasound (16.10.2020) revealed liver enlargement due to the left lobe (left lobe – 10,0 cm, right slightly reduced – 13,0 cm), with uneven contours, unevenly compacted parenchyma of medium echogenicity, emphasized and enriched vascular pattern; intrahepatic bile ducts are not dilated. V. portae expanded to 1,6 cm; The gallbladder is deformed, slightly enlarged, measuring 7,2*3,4 cm; the wall is compacted, the contents in the cavity are heterogeneous; choledoch 0,6

cm; Pancreas without echostructural changes. The spleen is enlarged, measuring 20,0*6,8 cm, homogeneous, with slightly increased echogenicity; v. lienalis expanded to 1,6 cm, tortuous at the gate; parenchymatous veins are dilated. Kidneys and bladder without features. Conclusion: Echographic diffuse liver changes. Pronounced splenomegaly (figure.3).

Esophagogastroduonenoscopy (23.03.2021) showed passable esophagus with moderately hyperemic mucosa, 3 collaterals of varicose veins in the lower third part. The hiatus closes completely. Small amount of liquid in the stomach, moderately hyperemic mucous membrane. Multiple erosions in the prepyloric part of the stomach. The pylorus is rounded. The bulb of the duodenum is easily passable for the endoscope, and the mucous membrane is hyperemic. Postbulbar section without features. The result of the study: Varicose veins of the esophagus of I-II st. Multiple erosions of the stomach.

As it can be seen, there is a slow progression in the clinical course of the disease.

CONCLUSIONS

In this case, with the help of additional methods of examination, metabolic disorders that can be considered as probable in the occurrence of the above-mentioned changes in the liver parenchyma – Wilson-Konovalov disease, Gaucher disease, Niemann-Pick disease – have been ruled out. Cytopenia (thrombocytopenia, leukopenia) was presumably associated with the syndrome of hypersplenism.

Based on the results of a comprehensive examination, the diagnosis of cirrhosis of the liver of cryptogenic etiology was established with a slow progression of the clinical course.

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