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Liver cirrhosis in a patient with alcohol dependence and autoimmune hepatitis

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Abstract. – BACKGROUND: Liver cirrhosis is the end-stage entity for a wide variety of chronic liver pathologies. These include viral hepatitis B and C, alcoholic liver disease, non-alcoholic fatty liver disease, hemochromatosis, Wilson disease, autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis. In the majority of cases, liver cirrhosis remains completely asymptomatic until acute decompensation occurs. Patients may present complications of portal hypertension such as gastroesophageal varices and upper digestive hemorrhage, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome. Establishing the right etiology of cirrhosis is of paramount importance as it helps the treating physician plan the best suitable treatment options and also improves overall outcomes.

CASE REPORT: We present a case of a chronic alcohol consumer, which, over time, resulted in alcoholic cirrhosis. Initial diagnosis comprised of alcoholic liver disease. However, a further look into the medical history of the patients indicated the presence of underlying autoimmune liver disease, such as autoimmune hepatitis, which might have also contributed to the chronic liver injury.

CONCLUSIONS: Multiple factors can lead to liver cirrhosis. Although the most commonly found entity is alcoholism, it cannot be taken as a thumb rule for the only possible etiology. In-depth analysis and proper differential diagnosis should be carefully conducted in order not to miss out on other possible causes. As seen in our case, where an underlying autoimmune hepatitis was found to be the culprit, but due to a long history of alcohol consumption, it was masked at first instance.

Key Words:
Cirrhosis, Steatohepatitis, Sclerosing cholangitis, Autoimmune liver disease, Primary biliary cirrhosis.

Introduction

Alcoholic liver disease encapsulates a large spectrum of disorders ranging from asymptomatic hepatic steatosis to alcoholic steatohepatitis and, finally, cirrhosis[1]. Diagnosing alcoholic liver disease requires a history of chronic alcohol consumption and also an exclusion of other liver pathologies. It also requires correctly staging the grade of liver fibrosis through biological tests such as Fibromax, liver elastography, the Acoustic Radiation Force Impulse Shear wave method, or Fibroscan (also known as transient elastography)[2].

Over the last decade, multiple studies in the literature have mentioned the coexistence of various liver disorders. Alcoholic liver disease, the most frequently detected liver disease, may overlap with other liver diseases such as viral chronic B or C hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, hemochromatosis, or Wilson disease[3,4]. In order to diagnose the possible overlapped pathologies mentioned above, it is mandatory for each patient to undergo specific tests such as HbS antigen, viral hepatitis C antibodies[5], antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies, anti-liver kidney antibodies, anti-liver cytosol antibodies, ferritin, ceruloplasmin, urinary and serum copper[6].

Autoimmune hepatitis is a chronic inflammatory and non-contagious hepatic disease that is determined by autoantibody-mediated liver cell injury[7,8]. Depending on the profiles of the serum autoantibodies, autoimmune hepatitis is classified into three different types. However, all types have a common

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characteristic – the presence of Ig G hypergammaglobulinemia[9]. 80% of the cases are represented by type 1 autoimmune hepatitis, which is defined by the presence of antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (ASMA)[10,11]. The other 20% is represented by type 2 and type 3 autoimmune hepatitis. Type 2 serum profile is distinguished through the presence of liver kidney microsomal antibodies 1 (anti-LKM1) and/or liver cytosol antibodies 1 (anti-LC1), whereas type 3 is exclusively represented by the presence of soluble liver antigen/liver pancreas antibodies[12,13].

Detecting autoimmune hepatitis is often a diagnosis of exclusion whenever continuous liver inflammation cannot be explained by alcohol consumption, chronic viral infections, or ingestion of hepatotoxic medication. Whereas in the case of non-alcoholic fatty liver disease, having genetic involvement and long-standing chronic inflammation might lead to hepatocellular carcinoma[14]. Hence, each and every parameter should be thought carefully before reaching the final diagnosis, as treatment plans may vary accordingly.

Usually, the biomarkers, especially the non-invasive ones, play a major role in diagnosing and staging chronic liver diseases. Fibrosis 4 (FIB-4) and aminotransferase to platelet ratio index (APRI) can be considered as economical alternatives[15]. Similarly, acoustic radiation force impulse (ARFI) relies on the principle of generating waves that are shear acoustic, which are silently affected by the force exerted by a bean of ultrasonic radiation[16]. This elastography technique is on the rise for the early diagnosis of fibrosis of the liver. Liver stiffness measurement (LSM) is another tool of diagnostic importance in cases of liver cirrhosis[17].

This article exhibits a case report in which alcoholic liver disease was the initial misdiagnosis. Due to the chronic alcohol consumption of the patient, other causes of liver cirrhosis were missed[18]. Fortunately, the overnight remission of the scleral jaundice while the patient was receiving corticotherapy for an asthmatic exacerbation raised the suspicion of an autoimmune liver disorder, and further tests were performed[19].

Case Presentation

We present the case of a 45-year-old female patient with a past medical history of chronic alcohol consumption (according to the patient, she had no alcohol consumption in the past 2 years ago), moderate to severe asthma without the use of chronic medications, and on selective serotonin reuptake inhibitors SSRI (Citalopram) treated clinical depression. She was first consulted by her regional general practitioner, where routine blood tests for liver disorders were performed. Because the patient resided in a remote area, no elastography was available to be executed in order to establish the grade of liver fibrosis. The general practitioner resumed only calculating APRI and FIB-4 scores. Both indicated liver cirrhosis. The patient was then referred to our clinic, where she was further investigated thoroughly.

The patient presented recurrent scleral jaundice, extreme fatigue, appetite loss, bloating, and mild abdominal pain. No fever, passage of pale stool, vomiting, or diarrhea were noted. However, she declared a similar episode of jaundice 7 months before the presentation that oddly resolved after receiving oral corticotherapy during a severe episode of asthma. A physical exam revealed cachexia, scleral jaundice, mild ascites, bilateral pedal edema, and tachycardia. Viral markers of hepatitis B and C (HbsAg, HbeAg, AntiHbe, AntiHbc total, AntiHCV) were negative. Routine blood tests, such as coagulation tests, total and differential blood counts, hemograms, biochemical tests, and urinalysis, were also performed. Moreover, an abdominal ultrasound was carried out at our facility, which revealed an accentuated and micronodular echotexture on a normal-sized liver; intra and extrahepatic bile ducts within normal limits; enlarged spleen with normal echogenicity; enlarged portal vein; normal-shaped kidneys with regular size and moderate ascites. ARFI-SW elastography was also performed, and it showed stage 4 fibrosis (cirrhosis).

A diagnosis of liver cirrhosis was made. In this case, chronic alcohol consumption could have easily been labeled as the main cause of cirrhosis. However, the rapid remission of jaundice while the patient was on oral corticosteroid therapy for asthma indicated that an autoimmune hepatitis can also be a possible cause of cirrhosis. Thus, further specific testing was requested (Table I).

Blood work excluded viral hepatitis (non-reactive hepatitis B surface antigen and core antibodies, non-reactive hepatitis C antibodies), hemochromatosis (normal ferritin levels), and Wilson's disease (copper levels in 24 h urine were normal) as a possible cause for liver cirrhosis and indicated macrocytic anemia, elevated liver enzymes, cholestasis and positive serology for autoimmune hepatitis. Liver biopsy was not performed because of the cirrhotic status of the patient,

Table I. Patient's laboratory test results.

Tests	Normal range	Laboratory results
ALT	10-50 U/L	360 U/L
AST	14-50 U/L	182 U/L
ALP	38-126 U/L	173 U/L
Total bilirubin	0.2-1.3 mg/dl	4.6 mg/dl
Conjugated bilirubin	0.0-0.4 mg/dl	3.1 mg/dl
Total protein	6.3-8.2 g/dl	5.9 mg/dl
Albumin	3.5-5 g/dl	2.8 g/dl
Platelets	150-350x10^3/mm^3	81.000/mm^3
Mean corpuscular volume	79-92 fl	103 fl
Hematocrit	38-46%	36%
Prothrombin time	10-13.2 s	17 s
INR	0.80-1.15	2.1
Urine bilirubin	-	Positive
ANA	-	Positive
ASMA	-	Positive
Anti-LKM 1	-	Negative
Anti-LKM 3	-	Negative
Anti-LC1	-	Negative
Serum IgG	700-1,600 mg/dl	2,156 mg/dl
Ferritin	30-400 ng/ml	68 ng/ml
Ceruloplasmin	19-31 mg/dl	27 mg/dl
Copper, serum	63-140 µg/dl	Not performed
Copper, urine 24 h	3-50 µg/24 hours	23 µg/24 hours
Hepatitis B surface antigen	Non-reactive	Non-reactive
Hepatitis B core antibodies	Non-reactive	Non-reactive
Hepatitis C antibodies	Non-reactive	Non-reactive

Liver kidney microsomal antibodies 1 (anti-LKM1), liver cytosol antibodies 1 (anti-LC1), antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), alkaline phosphatase (ALP).

thrombocytopenia, and elevated international normalized ratio (INR) and prothrombin time.

The final diagnosis was autoimmune hepatitis-related cirrhosis in a patient with alcohol dependence. The patient initially received 60 mg of Prednisolone, which was tapered off to 20 mg over 4 weeks. Other medications were considered but not recommended: Budesonide was not an option for treatment because it undergoes extensive first-pass hepatic metabolism, and neither was Azathioprine because of the patient's low platelet count. On follow-up one-month post-treatment, the patient was found to be stable and without jaundice, ascites, or pedal edema.

Discussion

This case report highlights the challenges of a difficult-to-diagnose case of autoimmune cirrhosis, especially in a situation where the medical history of the patient included chronic alcohol consumption and SSRI (Citalopram) treatment for clinical depression. Alcohol cirrhosis and drug-induced liver injury from the SSRI intake could have been two of the alternative diagnoses. Fortunately, detailed anamnesis, together with specific blood tests, revealed the four main diagnostic leads of this case.

Initially, according to the patient, she stopped alcohol intake 18 months before the first episode of jaundice. During this time, two blood samples were tested, and both showed only macrocytic anemia, with all liver enzymes in the normal range. Afterward, the oral corticosteroid therapy used to treat the patient's asthmatic exacerbation (which was only two weeks away from the first episode of jaundice) fully resolved the yellow discoloration of the sclera and mucous membranes. Additionally, the elevated liver enzyme levels returned to the normal range after the first week of treatment with steroid medication. Lastly, the most common causes of liver cirrhosis, alcohol consumption, chronic viral infections, and drug-induced liver injury were excluded, after which the patient was tested for hemochromatosis, Wilson's disease, and autoimmune hepatitis.

According to the American Association for Study of Liver Diseases (available at: https://

www.aasld.org/practice-guidelines/management-autoimmune-hepatitis), the diagnosis of AIH is based on clinical characteristics, laboratory findings [elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and increased serum IgG concentration], histological abnormalities (interface hepatitis) and the presence of characteristic autoantibodies. Autoantibodies detection holds high clinical importance, and as stated by the International Autoimmune Hepatitis Group (IAIHG)[20], since the clinical and para-clinical picture mimics largely other diseases, the more tests we do, the more the chances of gaining accuracy of diagnosis in case of autoimmune hepatitis. Establishing the right diagnosis also requires the exclusion of other diseases that may resemble autoimmune hepatitis (e.g., viral hepatitis, drug-induced liver injury, Wilson's disease, hereditary hemochromatosis)[4,21]. Among the five different types of hepatitis, hepatitis B and hepatitis C are considered to have devastating effects[22].

Based on the specific autoantibodies that can be detected in a patient's serum, autoimmune hepatitis is divided into 3 types. 80% of the cases are type 1 autoimmune hepatitis, defined by the presence of antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (ASMA). The other 20% is represented by type 2 and type 3 autoimmune hepatitis. Type 2 serum profile is characterized by the presence of liver kidney microsomal antibodies 1 (anti-LKM1) and/or liver cytosol antibodies 1 (anti-LC1), whereas type 3 is exclusively represented by the presence of soluble liver antigen/liver pancreas antibodies.

Our patient tested positive for ANA and ASMA autoantibodies, leading to the final diagnosis of type 1 autoimmune hepatitis-related cirrhosis with alcohol dependence. Unfortunately, she was not an appropriate candidate for Budesonide and Azathioprine due to her cirrhotic status and low platelet count. The final medical decision was to treat her initially with 60 mg of Prednisolone and to taper off the dose from 60 to 20 mg over 4 weeks. After the first month of corticosteroid therapy, the overall symptomatology improved (ascites, jaundice, or pedal edema were absent) as well as the laboratory findings (normal liver enzymes and no cholestasis).

In case of no response to the treatment, the final option remains to undergo liver transplantation. However, even this choice brings along a number of complications, which need to be properly weighed before making a decision. Various guidelines have been set in order to help the treating clinicians reach a diagnosis that is beneficial to the patient[23].

Conclusions

This case report highlights the challenges that our medical team encountered when diagnosing autoimmune-related liver cirrhosis in a patient with a history of alcohol dependence. The patient's medical history, presentation symptoms, and biochemical markers led to further investigations that established the right diagnosis. We conclude from this case report that even though alcoholic liver disease and non-alcoholic fatty liver disease are amongst the most common causes of liver disease, clinicians should still look for subsequent liver pathologies in order to avoid delay in the diagnoses and to ensure optimal treatment as early as possible.

Conflict of Interest
The authors declare no conflict of interest.

Ethics Approval
Ethics approval was obtained under the reg. No. 11607/16.12.2019 from the Ethical Board Committee of the Emergency University Hospital, Bucharest, Romania.

Informed Consent
Written informed consent was obtained as a routine procedure during admission to our university hospital for publishing the data.

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Data Availability
Data will be made available upon request.

Authors' Contributions
R.C-N: Conceptualization, investigation, data curation, Writing—Original Draft Preparation. V.A.: Investigation, data curation. B.E.I.: Formal Analysis, Writing—Review & Editing. D.N.: Visualization, Writing—Original Draft Preparation. E.M.: M.P.: Editing and final revision. Writing—Original Draft Preparation. P.M.: Conceptualization, Writing—Review & Editing. I.A.M.S: supervision, validation.

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