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Cryptogenic cirrhosis and Common variable immunodeficiency: an unrecognized relationship

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ABSTRACT

Objectives: This study investigates the prevalence of Common Variable Immunodeficiency (CVID) in patients with cryptogenic cirrhosis. It aims to highlight CVID's role in liver involvement and raise awareness of its potential as an underlying cause of cryptogenic cirrhosis.

Methods: This retrospective cohort study, approved by the ethics committee, included patients diagnosed with cryptogenic cirrhosis at a university hospital. Comprehensive evaluations were performed to exclude other causes of cirrhosis, and patients were screened for CVID based on the European Society for Immunodeficiencies (ESID) criteria.

Results: This study included 30 patients with cryptogenic cirrhosis, among whom 6.7% (n=2) were diagnosed with CVID. Both CVID patients had low immunoglobulin levels and abnormal immune cell profiles, leading to recurrent infections in one case and suspicion due to low total protein levels in the other. IVIG treatment was initiated for both, and liver biopsy findings in one patient suggested CVID-related liver involvement.

Conclusions: Determining the underlying causes of chronic liver diseases is crucial for guiding treatment and follow-up, potentially preventing cirrhosis progression and influencing liver transplantation eligibility. CVID screening in patients with cryptogenic cirrhosis should be considered, with appropriate treatments initiated as needed.

Keywords: Common variable immunodeficiency, cryptogenic cirrhosis, nodular regenerative hyperplasia

Common Variable Immunodeficiency (CVID) is the world's most common symptomatic primary immunodeficiency. Inadequate immunoglobulin (IgG, IgA/IgM) synthesis and poor response to antigens are the leading causes of CVID formation. It is a heterogeneous group of diseases. In this disease, quite different clinical findings are seen due to lymphocytic end-organ damage and recurrent infections. The basic pathophysiology of CVID is the impairment of humoral immunity resulting from impaired B cell

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maturation and loss of plasma and memory B cells [1, 2]. In CVID, in addition to B cell impairments, T cell defects (decrease in naive $CD4^+$ T cells and increase in $CD8^+$ cytotoxic T lymphocytes) lead to lymphoinfiltrative involvement in organs such as the liver [3]. Although precise data on the prevalence of CVID are lacking, it is estimated to range between 1 in 100,000 and 1 in 10,000. However, the prevalence of CVID varies significantly across different regions [4]. CVID is typically diagnosed between the ages of 20 and 40, with no sex preference. Common presentations include recurrent infections and respiratory or gastrointestinal diseases. In some cases, autoimmune and lymphoproliferative disorders may occur, complicating the diagnosis [2, 5]. The clinical manifestations of CVID can affect multiple organ systems, and diagnosis is often delayed due to low disease awareness. Patients presenting without significant infections but with inflammatory or autoimmune complications can further complicate the diagnostic process. As a result, a delay of 4-6 years in diagnosis is typical [4].

Histologically confirmed liver involvement in CVID has been reported in approximately 10% of cases in various studies [6, 7]. Cryptogenic cirrhosis is a type of liver cirrhosis with an undetermined etiology despite comprehensive evaluation, and it is considered a diagnosis of exclusion. With the increasing accumulation of knowledge and technological advancements, the incidence of this condition is steadily decreasing [8].

This study aims to investigate the prevalence of CVID in patients with cryptogenic cirrhosis and to raise awareness of CVID liver involvement, thereby increasing awareness of CVID in cryptogenic cirrhosis.

METHODS

Study Design and Patient Selection Process

This retrospective cohort study was conducted at the Nacmettin Erbakan University Hospital. The local ethics committee approved the study protocol, with approval number 2023/4251. The study was conducted on patients diagnosed with cryptogenic cirrhosis who were followed at the Gastroenterology Clinic of our hospital. These patients were referred to the Adult Allergy-Immunology Clinic for screening for underlying CVID. The patient's medical records were retrospectively reviewed, and Child-Turcotte-Pugh and MELD (Model for End-Stage Liver Disease) scores and immunological parameters were obtained from the patient files. Height and weight were measured using standard measuring devices, and body mass index (BMI) was calculated. CVID was diagnosed based on the latest criteria established by the European Society for Immunodeficiencies (ESID) [9].

Inclusion Criteria:

•Patients diagnosed with cryptogenic cirrhosis following a detailed evaluation by the Gastroenterology department.

•Evaluations performed to exclude other causes of cryptogenic cirrhosis, including:

•Hepatitis B and C serology and PCR were evaluated.

•Laboratory tests to investigate metabolic causes included serum ceruloplasmin, 24-hour urinary copper excretion, iron and ferritin levels, and tests to exclude Wilson's disease, hemochromatosis, and storage diseases.

•Serological tests for autoimmune hepatitis included antinuclear antibody, smooth muscle antibody, liver-kidney microsomal antibody, and soluble liver antigen antibody to rule out autoimmune hepatitis and related conditions.

•Assessment of Metabolic Associated Fatty Liver Disease (MAFLD)

•Celiac Disease was excluded by evaluating anti-tissue transglutaminase antibodies (tTG), anti-endomysium antibodies (EMA)

•History of hepatotoxic injury, especially alcohol use, drug exposure, and methotrexate usage.

•Cirrhosis diagnosis confirmed by histological examination. For patients who did not undergo liver biopsy, the clinical diagnosis was based on the presence of portal hypertension signs and a cirrhotic appearance of the liver.

•Patients aged >18 years.

Exclusion Criteria:

•Patients with BMI ≥30 kg/m² (due to the high prevalence of MAFLD in cryptogenic cirrhosis).

•Patients with Type 2 diabetes mellitus.

•Patients with missing data.

Serum Immunoglobulin Measurements

Serum immunoglobulin levels were measured using nephelometric methods with the Siemens BNII System (Erlangen, Germany).

Flow Cytometry

Peripheral blood lymphocyte subsets were analyzed by flow cytometry using a panel that included $CD3^+$ (T cells), $CD3^+CD4^+$ (helper/inducer T cells), $CD3^+CD8^+$ (cytotoxic T cells), $CD19^+$ (B cells), CD3-$CD16^+CD56^+$ (NK cells), and IgM-$CD27^+$ switched memory B cells.

Statistical Analysis

The analysis performed in this study was mainly descriptive. Data were processed using SPSS software, version 22.0. Descriptive statistics included the frequency of occurrences (n) and percentages (%). The normality of numerical data was examined using the Shapiro-Wilk test, which is more appropriate for small sample sizes (<50). Data not conforming to normal distribution were presented using median, minimum, and maximum values.

RESULTS

The study included 30 patients, with a predominance of females (76%). The median age of the participants was 57.5 years (range: 26-70 years). The median follow-up duration was 13.5 months (3-240 months). Among the study population, 6.7% (n=2) were diagnosed with Common Variable Immunodeficiency (CVID).

The clinical, laboratory, and demographic characteristics of cryptogenic cirrhosis patients with and without CVID are summarized in Table 1. Based on the Child-Pugh classification at the time of cirrhosis diagnosis, 26 patients were classified as Class A, three as Class B, and one as Class C.

The medical histories of the two CVID patients are briefly summarized below.

Case 1

A 56-year-old male patient presented approximately four years ago with complaints of fatigue, weakness, and abdominal distension. Initial evaluations at the referring center revealed pancytopenia, diffuse ascites, and splenomegaly on abdominal ultrasonography and esophageal varices on endoscopy. The patient refused a liver biopsy. Investigations for known causes of cirrhosis yielded negative results, leading to a diagnosis of cryptogenic cirrhosis.

During follow-up, the patient experienced recurrent infections and required hospitalization for pneumonia four times in the past year. Given this history, he was referred to the Adult Allergy and Immunology Department for further evaluation. A detailed immunodeficiency workup revealed the following results: IgG < 1.5 g/L, IgM < 0.05 g/L, IgA < 0.05 g/L, CD3 = 79%, CD4 = 23%, CD8 = 59%, CD4/CD8 ratio = 0.39, CD16 = 9%, and CD27+ switched memory B cells = 2%, albumin = 3.2 g/dL, total protein = 5.3 g/dL. Based on the clinical findings and laboratory investigations, including absent isohemagglutinins and/or poor response to vaccines, the patient was diagnosed with CVID. The patient was started on intravenous immunoglobulin (IVIG) treatment every three weeks.

Case 2

A 25-year-old woman presented to the emergency department with abdominal bloating. Abdominal ascites and elevated liver function tests were detected, and she was admitted to the Gastroenterology clinic. Evaluations revealed pancytopenia, a cirrhotic appearance of the liver on abdominal ultrasonography, splenomegaly, and esophageal varices. A liver biopsy showed chronic hepatitis (stage 4).

Investigations into all known possible causes of liver cirrhosis were conducted, but no etiology was identified. The attending physician noted that the patient's total protein level was 4.7 g/dL and albumin level was 3.7 g/dL and suspected that the low total protein might be due to immunoglobulin deficiency. Immunoglobulin levels were measured, and significant decreases were found (IgG: 2.5 g/L, IgM: 0.36 g/L, IgA: <0.24 g/dL). The patient was referred to the Adult Allergy and Immunology clinic for further evaluation.

The detailed immunodeficiency panel revealed the following results: CD3 = 82%, CD4 = 29%, CD8 = 51%, CD16 = 8%, and $CD27^+$ switched memory B cells = 0.9% with a CD4/CD8 ratio of 0.5. The patient's HIV serology test was negative. Despite the ab-

Table 1. **Clinical, laboratory, and demographic characteristics between cryptogenic cirrhosis patients with and without CVID**

	Non-CVID Patients (n=28)	CVID Patients (n=2)		Non-CVID Patients (n=28)	CVID Patients (n=2)
Sex (female), n (%)	22 (78)	1 (50)	**GGT (U/L)**	42 (10-278)	89 (58-120)
Current age (years)	55 (30-70)	41 (26-56)	**$CD3^+$ T cells, n (%)**	71 (54-79)	80 (79-82)
Follow-up (months)	13.5 (3-240)	30 (12-48)	**$CD4^+$ T cells, n (%)**	40.5 (32-54)	26 (23-29)
BMI (kg/m²)	24.7 (16.5-29)	23.2 (23.1-23.4)	**$CD8^+$ T cells, n (%)**	23 (15-32)	55 (51-59)
MELD Score	8.5 (6-20)	14 (12-16)	**$CD4^+$ / $CD8^+$ ratio**	1.8 (1.1-3.6)	0.4 (0.3-0.5)
Child-Pugh Score, n (%)	5 (5-8)	9 (7-11)	**$CD19^+$ B cells, n (%)**	14 (8-31)	2
IgG (g/L)	15.3 ± 3.7	1.9 (1.5-2.4)	**$CD16^+$–56^+ NK cells, %**	9 (5-28)	8.5 (8-9)
IgM (g/L)	1.1 (0.2-2.7)	0.1 (0.05-0.3)	**Switched memory B cells, n (%)**	5.3 (2-21)	1.5 (1-2)
IgA (g/L)	3.7 ± 1.8	0.1 (0.05-0.24)	**Albumin (g/dL)**	3.9 ± 0.6	3.5 (3.2-3.7)
IgE (IU/mL)	24 (15-349)	18	**Total Protein (g/dL)**	7.1 ± 0.7	5 (4.7-5.3)
ALP (U/L)	106 (42-241)	219 (188-250)	**INR**	1.2 (1.1-1.4)	1.4 (1.2-1.6)
AST (U/L)	24.5 (13-61)	133 (34-233)	**Platelet count ($\times 10^3/\mu L$)**	127 (76-432)	174 (121-227)
ALT (U/L)	18.5 (11-40)	71 (26-116)	**Lymphocyte (mm^3)**	0.9 (0.6-2.5)	1.9 (1.8-2)

Data are shown as means±standard deviation or median (min-max) or n (%). CVID=common variable immunodeficiency, BMI=body mass index, MELD= Model for End-Stage Liver Disease, Ig=immunuglobin, ALP= alkaline phosphatase, AST= aspartate aminotransferase, ALT= alanine transaminase, GGT= gamma-glutamyl transferase, INR=international normalized ration.

Normal values - AST=0 to 41 U/L, ALT=0 to 40 U/L, ALP=40 to 110 U/L, GGT=0 to 45 U/L, Albumin=3.5 to 5.2 g/dl, INR=0.8 to 1.2.

sence of a history of recurrent infections, the clinical and laboratory findings, including absent isohemagglutinins and/or poor response to vaccines, led to the diagnosis of CVID. IVIG treatment was started every three weeks.

The patient's liver biopsy was re-evaluated for CVID-related liver involvement. The biopsy results revealed nodular regenerative patterns in the liver sinusoids, accompanied by infiltration of $CD4^+$ T helper cells, $CD8^+$ cytotoxic T lymphocytes.

DISCUSSION

Numerous studies have examined the specific clinical and histopathological aspects of liver involvement in CVID [2, 7, 10]. However, the relationship between cryptogenic cirrhosis and CVID in the adult population remains insufficiently explored. In our study, CVID was identified in 6.7% of patients with cryptogenic cirrhosis.

In a retrospective analysis of patients with CVID, approximately 10% were reported to have non-infectious liver disease [11]. This study highlighted that liver involvement in CVID can present across a wide spectrum, ranging from isolated alkaline phosphatase (ALP) elevations to cirrhosis. Another study reported persistent abnormalities in liver function tests (LFTs) in 44% of patients with CVID [10]. Nodular regenerative hyperplasia (NRH) is commonly observed in patients with CVID and may lead to conditions such as cirrhosis, chronic cholestasis, or non-cirrhotic portal hypertension. Studies have reported the incidence of NRH in CVID to range between 32% and 84% [12, 13]. Mechanisms of liver involvement in CVID include microvascular disturbances caused by microthrombosis, periportal lymphocytic infiltration, and chronic disruption of blood flow due to $CD8^+$ T cell activity. Additionally, impaired intestinal barrier function, leading to microbial translocation and autoimmune processes, such as seronegative autoimmune hepatitis, may contribute to liver damage. These mechanisms are critical in developing NRH associated with CVID [14]. Most CVID patients with liver involvement are reported to exhibit an inverted CD4/CD8 ratio [2, 7, 12]. In the biopsy of Case 2 included in our study, an increase in CD8+ cytotoxic T lymphocytes was observed, consistent with the literature. Additionally, an inverted CD4/CD8 ratio was detected in both cases.

Liver disease in CVID can result from various causes, including infections, autoimmune reactions, or neoplastic conditions. These causes include hepatitis B and C infections, autoimmune hepatitis, primary biliary cholangitis, sclerosing cholangitis, and B-cell lymphomas [2]. Liver involvement is a determining factor in the outcome and prognosis of CVID patients; mortality is higher in those with liver disease compared to those without liver involvement [14]. In CVID patients with hypogammaglobulinemia, specific autoantibody levels are often low or undetectable, complicating the diagnosis of certain liver diseases. This frequently makes liver biopsy necessary. If autoimmune hepatitis is suspected, a biopsy should be performed even if AMA, ASMA, and LKM tests are negative [15, 16]. Additionally, liver biopsy is recommended in CVID patients who exhibit a significant (more than twice the upper limit of the range) unexplained elevation in one or more liver enzymes persisting for more than six months [15] Also in particular the diagnosis of PBC which presents with elevated alkaline phosphatase and relies on the anti-mitochondrial antibodies (AMA) for diagnosis, should be considered despite negative AMA testing in CVID [6].

CVID can present with symptoms affecting multiple organ systems, and due to low awareness, delays in diagnosis may occur. In 5-10% of patients, a history of frequent infections may be absent, and these patients are more likely to present with inflammatory or autoimmune complications [4]. In our study, Case 2 had no history of recurrent infections, and the patient's initial presentation was with signs of liver failure. While investigating the etiology of liver cirrhosis in this case, a low total protein/albumin ratio was noted, raising suspicion for immunoglobulin deficiency. The patient, with observed immunoglobulin deficiency, was diagnosed with CVID following immunological evaluations conducted at our clinic. In the other case, the patient was referred to our clinic due to a history of frequent recurrent infections, and CVID was diagnosed.

Cryptogenic cirrhosis is defined as cases of liver cirrhosis in which the definitive cause cannot be identified despite comprehensive clinical, laboratory, and

histological evaluations. It is essentially a diagnosis of exclusion. To reach this diagnosis, the patient must have negative viral infection markers (HBsAg, HBV-DNA, anti-HCV, HCV-RNA), no history of parenteral blood exposure, alcohol use, or hepatotoxic drug exposure, normal metabolic parameters (ceruloplasmin, alpha-1 antitrypsin, ferritin levels), and negative autoimmune markers (ANA, AMA, anti-LKM-1). Over the past 40 years, with the accumulation of knowledge regarding liver diseases and advancements in technology, the definition of "cryptogenic cirrhosis" has changed, and a significant reduction in its prevalence has been observed [17]. MAFLD is considered a significant cause of chronic liver disease in the Western world, and it has been suggested that many cases of cryptogenic cirrhosis may be attributed to MAFLD. This view is based on the higher frequency of risk factors such as type 2 diabetes (DM), obesity, and metabolic syndrome in cryptogenic cirrhosis patients. Therefore, in our study, patients with type 2 diabetes and obesity (body mass index [BMI] ≥30) were excluded to minimize the possibility of MAFLD-related cryptogenic cirrhosis.

The observation of a close relationship between CVID and Immune Thrombocytopenia (ITP) has led to the inclusion of CVID screening in the diagnostic process and its incorporation into clinical guidelines, marking a significant development [18]. This highlights the critical role of immunodeficiencies in ruling out secondary causes and emphasizes the necessity of comprehensive evaluations to achieve an accurate diagnosis. Similarly, the findings of our study indicate that CVID can be observed in 6.7% of patients with cryptogenic cirrhosis, suggesting a potential relationship between these two conditions. To our knowledge, this is the first study to address the relationship between CVID and cryptogenic cirrhosis. Larger-scale and multicenter studies will contribute to a better understanding of the potential link between cryptogenic cirrhosis and CVID.

Limitations

Our study has certain limitations. First, the small sample size and selection bias may affect the reliability of the findings. Second, the study was conducted in a single center. These factors make it challenging to provide robust evidence regarding the prevalence of CVID in cryptogenic cirrhosis.

CONCLUSION

Determining the underlying causes of chronic liver diseases is essential, as this information can directly shape treatment and follow-up processes. Initiating appropriate treatment at an early stage may prevent the progression to cirrhosis, and, in some cases, the etiology may play a decisive role in evaluating eligibility for liver transplantation. Therefore, we recommend conducting CVID screening in patients diagnosed with cryptogenic cirrhosis and initiating necessary treatments accordingly.

Ethical Statement

Ethics committee approval was received for this study from the Ethics Committee of Necmettin Erbakan University Meram Medical Faculty, who approved this study protocol (17.03.2023/4251). The study followed the guidelines and principles of the Declaration of Helsinki.

Authors' Contribution

Study Conception: RE, MB, ŞA; Study Design: FÇ, FSA; Supervision: RE, MB, TA; Funding: EY, TA; Materials: MK, MEG; Data Collection and/or Processing: MK, FSA; Statistical Analysis and/or Data Interpretation: RE, FÇ; Literature Review: FSA, EY; Manuscript Preparation: RE and Critical Review: ŞA, MB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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