ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2024.402
Asthma Allergy Immunol 2024;22:130-137

RESEARCH ARTICLE

Received: 17.08.2023 • Accepted: 10.01.2024
Online Published: 06.02.2024

Hepatic Involvement in Common Variable Immunodeficiency: a Single Center Experience

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ABSTRACT

Objective: Common Variable Immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency in adults. This study evaluates the clinical, immune, and immunohistological characteristics of hepatic involvement in CVID.

Materials and Methods: Medical records of 72 CVID patients, including 7 with liver biopsies, were retrospectively reviewed. Immunohistochemical staining was performed to identify immune cell infiltration.

Results: We enrolled 72 patients with a median age of 38 (22–77) years, and 47% (n = 34) were female. Elevated alkaline phosphatase (ALP) levels were found in 58.3% (n=42) of the patients. Hepatic involvement was more prevalent among females, and those with hepatic involvement displayed a higher incidence of autoimmune disease. Splenomegaly was identified in 85% of the patients with hepatic involvement. Notably, switched memory B cells (IgD- CD19+ CD27+) and the CD4+/CD8+ ratio were statistically lower in patients with hepatic involvement (p=0.031, p=0.047). Liver biopsies were performed on 7 patients, revealing minimal to severe chronic hepatitis. Immunohistologic analysis of these liver biopsies revealed varying degrees of positivity of CD8+, CD4+, and CD16+. However, staining for CD21, CD56, and CD138 yielded negative results.

Conclusion: Our findings suggest that immune cells, particularly CD8+, CD4+, and CD16+ cells, may play a role in developing hepatic involvement. Understanding the underlying causes and mechanisms of hepatic involvement in CVID patients can lead to early diagnosis and targeted treatments, ultimately improving the prognosis.

Keywords: Common variable immunodeficiency, nodular regenerative hyperplasia, hepatic involvement, T cells

INTRODUCTION

Common Variable Immunodeficiency (CVID) is adults' most common symptomatic primary immunodeficiency. Most CVID diagnoses occur between the ages of 20 and 40, but diagnostic delays are common due to the disease's heterogeneity (1). Frequent and recurrent infections are commonly characteristic of CVID. Other clinical manifestations, such as lymphoproliferative disorders, autoimmune diseases, malignancies, and gastrointestinal or hepatic involvement, can also be observed in CVID patients (2).

Although most CVID patients exhibit average circulating B cell counts, defects in B cell differentiation are characteristic. The decrease in plasma and memory B cell counts results in reduced levels of circulating immunoglobulins (3). Defects in T cells, such as a decrease in the counts of circulating naive CD4+ T cells, have been observed in individuals with CVID. These abnormalities

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are linked to an elevated risk of developing lymphoinfiltrative end-organ diseases, including liver disease (4). Intravenous immunoglobulin (IVIG) therapy has been the cornerstone of CVID treatment for the past 40 years. As chronic infections have declined with IVIG treatment and patient lifespans have increased, autoimmune symptoms have become more prominent (5). Because of the wide variety of clinical manifestations associated with CVID, the diagnosis of liver involvement is often delayed. This delay can result in significant organ damage and a poor prognosis for affected individuals (6).

Liver disease in CVID patients can result from infectious, neoplastic causes or immune dysregulation. Among these conditions, infections of hepatitis B and C (historically associated with transfusion of immunoglobulin (Ig) products from infected donors), autoimmune hepatitis, primary biliary cirrhosis (PBC), and B-cell lymphomas may be present (4). Additionally, CVID patients may develop Nodular Regenerative Hyperplasia (NRH) (7, 8).

NRH is typically regarded as the most common form of hepatic involvement in CVID (9). NRH, a common histopathological manifestation in various liver diseases, is believed to result from an intrahepatic vasculopathy that causes hepatocyte damage and regeneration (10). Although nodularity and heterogeneity in the liver parenchyma suggestive of NRH can be detected by magnetic resonance imaging or ultrasonography, histological confirmation is essential for diagnosis (11).

This study aimed to characterize liver disease in CVID patients by assessing the prevalence of abnormal liver function tests (LFTs) and analyzing the immunohistological features of patients who underwent liver biopsy.

MATERIALS and METHODS

Study Design

This retrospective cohort study was conducted at Necmettin Erbakan University Hospital. The study protocol was approved by the local ethics committee (approval number: 2023/4332). Due to the retrospective data scanning method of the study, it was optional to obtain informed consent after ethics committee approval. Therefore, informed consent was not obtained from the patients. We enrolled 72 patients with CVID, whom we had regularly followed for ten years. The diagnosis of CVID was made in accordance with the updated diagnostic criteria of the European Society for Immunodeficiencies (ESID) (12). We employed the histologic method to evaluate hepatic involvement in patients with CVID.

We systematically collected the following data from the medical records of the CVID patients: serum Ig levels, Complete Blood Count (CBC), LFTs, Peripheral Blood Lymphocyte (PBL) phenotype, hepatitis B virus (HBV), and HCV serologies, Polymerase Chain Reaction (PCR) results, rheumatoid factor, Coombs test, anti-nuclear and anti-tissue antibodies (anti-mitochondrial, -smooth muscle, -thyroid), results of abdominal CT scans or ultrasonography, and upper gastrointestinal endoscopy. Portal hypertension was defined by the presence of esophageal varices or portal hypertensive gastropathy observed on upper gastrointestinal endoscopy.

Flow Cytometry Analysis

PBL subsets were assessed using the BD FACS Canto II 8-color configuration flow cytometer system (New Jersey, USA) equipped with fluorescence-labeled antibodies. A low $CD4^+/CD8^+$ ratio was defined as ≤ 0.9 (13).

Histological Evaluation

Liver biopsy samples were collected from individuals with hepatic involvement and evaluated by two experienced histopathologists specializing in liver histology (HHE, NK). A liver biopsy was performed on seven patients (10%). The most common indications for liver biopsy were elevated transaminases (n=5), heterogeneity and lobulated contours in liver ultrasonography (n=4), and splenomegaly (n=4). Histochemistry was conducted on formalin-fixed, paraffin-embedded (FFPE) tissue sections using a Dako autostainer (Dako Artisan Link Pro, Denmark). NRH was defined through reticulin staining, which revealed regenerating liver cell plates (with widths of ≥ 2 hepatocytes) alternating with atrophic areas without significant portal fibrosis, bridging fibrosis, or definite cirrhosis (14). The degree of necroinflammatory activity was assessed using the Ishak grading system. In the Ishak system, piecemeal necrosis (0-4), focal necrosis (0-4), portal inflammation (0-4), and confluent necrosis (0-6) yield a final maximum necroinflammatory score of 18. Scoring was performed in this manner, and based on the final numerical score, biopsies were classified into one of four grades of necroinflammatory severity: minimal (scores of 1-3), mild (4-8), moderate (9-12), or severe hepatitis (13–18) (15).

Immunophenotyping

Immunohistochemistry was performed using an indirect immunoperoxidase method on FFPE tissue sections using a Dako OMNIS autostainer (Dako OMNIS, Denmark). The following markers were used after appropriate antigen retrieval: $CD4^+$ (clone 4B12, Dako), $CD8^+$ (clone C8/144B, Dako), $CD16^+$ (clone DJ13OC, Dako), $CD21^+$ (clone 1F8, Dako), $CD56^+$ (clone 123C3, Dako), and $CD138^+$ (clone MI15, Dako). These immunohistochemical stains were evaluated according to their percentage of staining.

Statistical Analyses

Continuous variables are presented as means ± standard deviation or medians (min-max), while categorical variables are presented as numbers with percentages. The independent samples t-test or Mann-Whitney U test was used to evaluate continuous data, while the chi-squared test or Fisher's exact test was utilized for categorical data. All analyses were conducted using the SPSS statistical package (ver. 22.0; IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

In this study, we included 72 patients with CVID. The median age was 38 (22-77) years, with 47% (n=34) of the participants being female. The median age at diagnosis was 29 (4-72) years, while the median delay in diagnosis was 60 (0-360) months. The initial presenting symptoms of the patients were as follows; 55 patients (76%) with recurrent infections, 32 patients (44%) presented with immune dysregulation, and 3 patients (4%) malignancy. Upon diagnosis, mean serum IgG levels stood at 3.3±1.7 g/L, and the percentage of switched memory B cells was 2.7 (0.1-57) (Table I). Elevated alkaline phosphatase (ALP), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) levels were observed in 42 (58.3%), 17 (23.6%), and 14 (19.4%) patients, respectively. Splenomegaly and autoimmunity were found in 34 (47.2%) and 32 (44.4%) patients.

A significant difference was found in the sex ratio between patients with and without hepatic involvement. Specifically, hepatic involvement was more frequent in females (p=0.047). Autoimmune diseases were more common in patients with hepatic involvement compared to those without (85.6% vs. 40%; p=0.041). Autoimmune complications of CVID included immune thrombocytopenic purpura (2/7 patients), Evans syndrome (2/7 patients), autoimmune hemolytic anemia (1/7 patient), and inflammatory bowel disease (1 patient). Splenomegaly was observed in 85% of patients with hepatic involvement. Switched memory B cells and low $CD4^+/CD8^+$ ratios were significantly different between patients with and without liver disease (p=0.031, p=0.047, respectively). Other examined parameters were similar in both groups (Table II).

Table I: Demographic, laboratory, and immunologic parameters of the study population.

Sex, female, n (%)	34 (47)	ALT (U/L)	19 (5-97)
Current age, years	38 (22–77)	GGT (U/L)	27 (8-320)
Age at diagnosis, years	29 (4–72)	$CD3^+$ T cells, %	77.4 ± 11.4
Diagnostic delay, months	60 (0–360)	$CD4^+$ T cells, %	34.9 ± 13.3
First Visit Complaints		$CD8^+$ T cells, %	40 (15–77)
-Recurrent Infections, n (%)	55 (76)	$CD4^+$ / $CD8^+$ ratio	0.91 (0.16-3.58)
-Immune Dysregulation, n (%)	32 (44)	$CD19^+$ B cells, %	7.3 ± 6.1
-Malignancy, n (%)	3 (4)	$CD16^+$–56^+ NK cells, %	7 (0.5–53)
IgG, g/L	3.3 ± 1.7	IgM- $CD27^+$ switched memory B cells, %	2.7 (0.1–57)
IgM, g/L	0.31 (0.06–5.7)	Albumin (g/dL)	4.1 (2.4-4.9)
IgA, g/dL	0.25 (0–1.9)	INR	1 (0.1-2)
IgE, IU/mL	17.8 (5–344)	Platelet count, mm3	208500 ± 101582
ALP (U/L)	119 (40-453)	Lymphocyte, mm3	1565 (200-8900)
AST (U/L)	20 (10-110)	Total bilirubin (mg/dL)	0.4 (0.1-2.5)

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, Total Bilirubin: 0.2 to 1.2 mg/dl, INR: 0.8 to 1.2. Continuous variables were presented as means ± standard deviation or median (min-max).

Liver biopsy was conducted in 7 patients (1 male, 6 females). Before liver biopsy, hepatobiliary ultrasound revealed normal findings in three patients, and heterogeneity, lobulated contours, and splenomegaly in four patients. The mean age of the patients with hepatic involvement was 37.8±11.2 years. Daily alcohol consumption was less than 30 g in men and 20 g in women. None of the patients had a history of drug abuse. Hepatitis B, hepatitis C, or autoimmune hepatitis was not detected in the patients. Portal hypertension was observed in 4 patients (57%), and ascites in 3 patients (42.8%). Esophageal varices were found in 3 patients (patients 1, 5, 6), and thrombocytopenia in 3 patients (patients 1, 3, 6) (Table III).

According to the Ishak system, liver biopsy specimens from 4 patients (57.1%) showed only minimal or mild chronic hepatitis, while one (14.2%) had moderate chronic hepatitis and two (28.5%) had severe chronic hepatitis (Table IV). NRH was detected in 3 of 7 biopsies (Figure 1). The percentages of $CD4^+$ $CD8^+$ T cells, $CD21^+$ B cells, $CD16^+$, $CD56^+$ NK cells, and $CD138^+$ plasma cell infiltration, determined by immunohistochemical techniques, are shown in Table IV. The immunohistological analysis of liver biopsies showed various levels of positivity for $CD4^+$ (Figure 2), $CD8^+$ (Figure 3), and $CD16^+$. In contrast, $CD21^+$, $CD56^+$, and $CD138^+$ were negative in all specimens.

DISCUSSION

This paper reports on the hepatic involvement of patients with CVID and the histopathological features of those who underwent a biopsy. Histologically proven liver disease was found in 9.7% of the patients. We detected that many patients with hepatic involvement had NRH. Immunohistochemical analysis showed that infiltrates mainly

Table II: Comparison of demographic, clinical, and immunologic parameters in CVID patients with and without hepatic involvement.

	CVID with hepatic involvement (n=7)	CVID without hepatic involvement (n=65)	P
Gender, n (%)			**0.047**
Female	6 (85.7)	28 (43.1)	
Male	1 (14.3)	37 (56.9)	
Current age, years	37 (24–57)	38 (22–77)	0.849
Age at diagnosis, years	32 (13–53)	29 (4–72)	0.143
Bronchiectasis, n (%)	2 (28.6)	27 (41.5)	0.694
Malignancy, n (%)	0 (0)	6 (9.2)	0.529
Splenomegaly, n (%)	6 (85.7)	28 (43.1)	**0.047**
Autoimmunity, n (%)	6 (85.7)	26 (40)	**0.041**
Mortality, n (%)	1 (14.3)	12 (18.5)	0.629
IgG, g/L	2.7 ± 1.4	3.3 ± 1.8	0.621
IgM, g/L	0.23 (0.08-2.1)	0.32 (0.06-5.7)	0.697
IgA, g/L	0.24 (0.07-0.49)	0.25 (0.01-1.9)	0.661
IgE, g/L	18.7 (5-22)	17.6 (5-344)	0.547
$CD3^+$ T cells, %	80.1 ± 12.3	77.1 ± 11.3	0.621
$CD4^+$ T cells, %	27.8 ± 13.5	35.7 ± 13.1	0.114
$CD8^+$ T cells, %	48.7 ± 16.8	40.7 ± 14.2	0.177
$CD19^+$ B cells, %	4.6 ± 3.5	7.6 ± 6.3	0.341
$CD16^+$–56^+ NK cells, %	8.2 (0.5-15)	7 (0.5-53)	0.761
IgM-$CD27^+$ switched memory B cells, %	0.9 (0.3-1.2)	3.3 (0.1-57)	**0.031**
$CD4^+$ / $CD8^+$ ratio	0.5 (0.2-2.3)	0.9 (0.1-3.5)	0.117
Low $CD4^+$ / $CD8^+$ratio, n (%)*	6 (85)	28 (43)	**0.047**

*Low CD4/CD8 ratio: CD4/CD8 ≤ 0.9

Table III: Clinical and biological characteristics of the 7 patients with hepatic involvement.

	S	Age	A	SM	EV	PH	ALP	AST	ALT	GGT	Alb	TB	INR	Platelets	CD27	CD4/CD8
1	M	26	+	+	+	+	226	73	67	70	2.5	1.4	2	33000	1	0.7
2	F	45	-	+	-	-	190	56	49	78	4	0.2	0.9	219000	0.3	0.3
3	F	57	+	+	-	+	294	54	18	67	3.6	1.7	1.4	97000	1.1	2.3
4	F	40	-	+	-	-	232	110	97	320	4.4	0.3	1	163000	1.2	0.2
5	F	37	-	+	+	+	141	27	26	54	3.4	0.3	1.1	155000	0.4	0.7
6	F	24	+	+	+	+	197	89	90	167	4.1	1.3	1.3	63000	0.9	0.5
7	F	36	-	-	-	-	453	106	63	262	4	1.7	1.1	155000	0.5	0.2

S: Sex, **F:** Female, **M:** Male, **A:** Ascites, **SM:** Splenomegaly, **EV:** Esophageal Varices, **PH:** Portal Hypertension, **ALP:** Alkaline Phosphatase, **AST:** Aspartate Aminotransferase, **ALT:** Alanine Aminotransferase, **GGT:** Gamma Glutamyl Transferase, **Alb:** Albumin, **INR:** International Normalized Ratio, **TB:** Total Bilirubin, CD27, IgM- CD27+ Switched Memory B Cells; CD4/CD8: Blood CD4/CD8 ratio at diagnosis; **-:** Absent; +, Present. (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, Total Bilirubin: 0.2 to 1.2 mg/dl, INR: 0.8 to 1.2.)

Table IV: Ishak necroinflammation scores and immune Cell infiltration percentages in hepatic biopsies.

The Ishak Score of Necroinflammation of Liver Biopsies						
Patients	**Piecemeal Necrosis/ 4**	**Confluent Necrosis /6**	**Focal Necrosis/ 4**	**Portal Inflammation/ 4**	**mHAI**	**NRH**
1	3	3	3	3	12	Y
2	1	0	2	1	4	N
3	3	4	3	3	13	Y
4	1	0	2	1	4	N
5	3	1	1	2	7	N
6	3	4	2	4	13	Y
7	1	0	1	1	3	N
The Percentages of Immune Cell Infiltration in Liver Biopsies						
Patients	**CD4 (%)**	**CD8 (%)**	**CD16 (%)**	**CD21 (%)**	**CD56 (%)**	**CD138 (%)**
1	10	30	5	0	0	0
2	10	40	5	0	0	0
3	20	30	10	0	0	0
4	10	50	2	0	0	0
5	15	60	2	0	0	0
6	30	50	20	0	0	0
7	20	30	10	0	0	0

NRH: Nodular Regenerative Hyperplasia, **mHAI:** Modified Hepatic Activity Index, **Y:** Yes, **N:** No.

comprised $CD8^+$ T cells and a small number of $CD4^+$ and $CD16^+$ cells. None of the patients tested positive for $CD56^+$, $CD21^+$, and $CD138^+$ cells.

Hepatic involvement is defined as a deterioration in liver function or portal hemodynamics, typically diagnosed using biochemical, clinical, imaging, and histologic methods (16). The prevalence varies significantly between studies, depending on the sampling method and detection strategy. In a cohort study that used a biochemical method, 43.5% of CVID patients had hepatic involvement (8), whereas two other studies found lower rates of histologically proven hepatic involvement (9.1% and 9.3%, respectively) (17, 18). In this study, a histological evaluation of patients' hepatic involvement was performed, revealing an incidence of 9.7%.

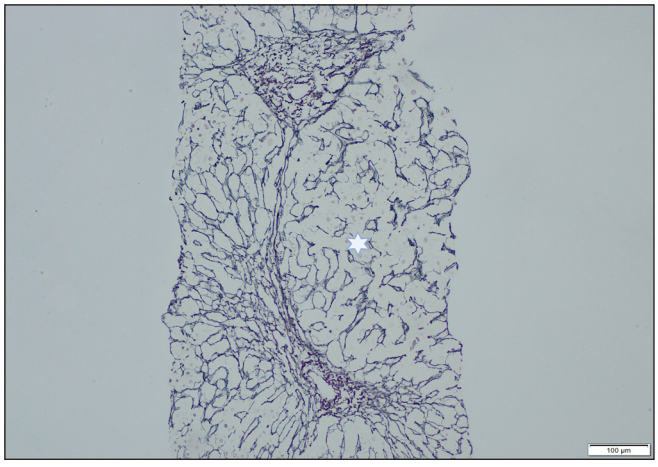

Figure 1. Image of nodular regenerative pattern in liver biopsy specimen with reticulin stain.

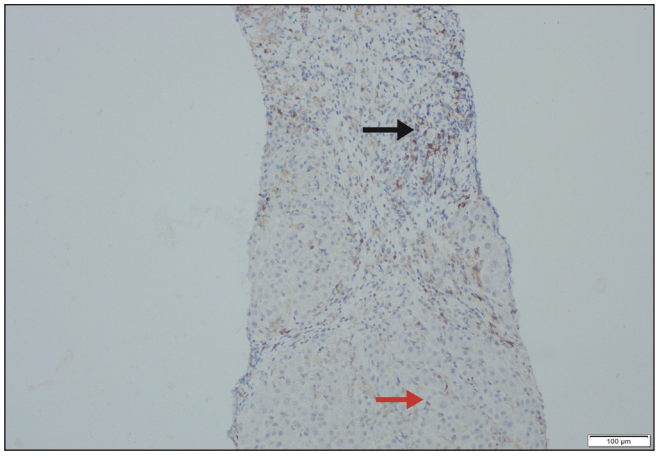

Figure 2. Liver biopsy specimen, Black arrow: Immunohistochemical CD4+ expressions in the periportal zone, Red arrow: CD4+ expression in the liver sinusoid (hematoxylin-eosin).

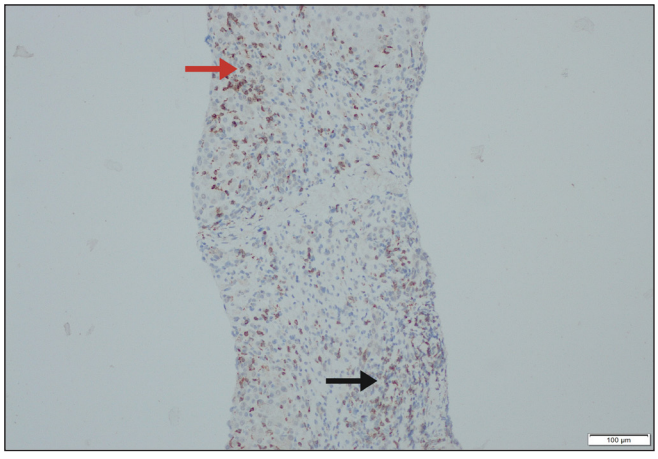

Figure 3. Liver biopsy specimen, Black arrow: Immunohistochemical CD8+ expressions in the periportal zone, Red arrow: CD8+ expression in the liver sinusoid (hematoxylin-eosin).

Autoimmune diseases secondary to CVID are more common in female patients compared to males (19, 20). The pathogenesis of autoimmunity in CVID has been associated with primary T-cell defects and an elevated presence of autoreactive B cells (20). However, no gender predominance has been observed in studies investigating the association between hepatic involvement and CVID (7, 8, 21). In this study, hepatic involvement was significantly higher in female patients than in males. This discrepancy may be due to the patients' higher prevalence of concurrent autoimmune diseases.

Typically, autoimmune diseases are found in 25-30% of CVID patients (22). This rate was 64% in CVID patients with hepatic involvement (7). Although the specific mechanisms of this increased susceptibility to CVID are unknown, it is thought to primarily stem from immune dysregulation (19, 22). In this study, autoimmunity was observed in 44.4% of CVID patients, while this rate was 85.7% in patients with hepatic involvement.

In patients with CVID, splenomegaly may occur due to granulomatous disease, lymphoproliferation, gastrointestinal disorders, and lymphoma (5). In a study of 224 CVID patients, splenomegaly was found in 26% (23). Another study observed splenomegaly in 22% of CVID patients, with this rate increasing to 54% in patients with hepatic involvement (24). In our study, splenomegaly was observed in 47% of CVID patients, increasing to 85.7% in patients with hepatic involvement.

Upon stimulation by an antigen and in the presence of appropriate costimulation, an immature B cell can transform into either plasma cells or memory B cells (25). Most studies have identified a significant association between low-switched memory B cells and both autoimmunity and splenomegaly (25, 26). However, this relationship could not be demonstrated in CVID patients with hepatic involvement (7, 8, 21). Our study observed that CVID patients with hepatic involvement had significantly lower levels of switched memory B cells.

In addition to B cell defects, $CD4^+$ and $CD8^+$ T cells, along with regulatory T (Treg) cells, are also implicated in the pathogenesis of CVID. Specifically, the number of $CD4^+$ and Treg cells decreases, while the number of $CD8^+$ T cells increases (27). In patients associated with chronic inflammation, a low $CD4^+/CD8^+$ ratio has been observed, similar to severe infections such as HIV (28). In a previous study, the $CD4^+/CD8^+$ ratio was lower in CVID patients

with hepatic involvement compared to controls (7). In our study, we found that the $CD4^+/CD8^+$ ratio was significantly lower in CVID patients with hepatic involvement than in those without (85% vs. 43%).

ALP is the liver enzyme most frequently elevated in CVID patients. ALP elevation in CVID patients is not solely linked to hepatic involvement, but may also be attributed to enteropathy, granulomatous disease, and osteomalacia. ALP usually increases gradually in CVID patients with NRH (8). In a study of CVID patients with NRH, the elevation in ALP levels was initially noticed 5-10 years after the diagnosis of CVID. Concomitantly, there were increases in ALT and AST levels, but to a lesser extent (29). While 58.3% of CVID patients had elevated ALP in our study, all patients with hepatic involvement in CVID showed elevated ALP levels.

NRH is diagnosed histologically by the presence of hepatocellular nodules smaller than 3 mm in diameter, which are not surrounded by significant fibrosis and without an inflammatory component. It can easily be missed unless specifically sought, and its detection necessitates reticulin staining. NRH may represent a nonspecific tissue response due to differential blood flow in different areas of the liver parenchyma (14). NRH is commonly found in the livers of CVID patients, potentially resulting in cirrhosis, chronic cholestasis, or non-cirrhotic portal hypertension (5). In a study of histological liver characteristics in CVID, NRH was found in 13 (81%) of 16 liver biopsies (8). According to the report by Malamut et al.(7), 84% of the cases exhibited non-fibrotic structural abnormalities consistent with NRH. In contrast to the high incidence of NRH in both studies, another study, which is the largest histological liver series in CVID to date, found the incidence of NRH to be 32% (n = 28/86) (24). In our study, the incidence of NRH was 43%. All patients with NRH developed cirrhosis.

Many studies have demonstrated that NRH is characterized by chronic $CD8^+$ T-cell infiltration in the sinusoidal endothelium of the liver in CVID patients. This leads to decreased hepatic parenchymal perfusion and increased portal pressure, resulting in altered blood flow through the portal system (7, 29, 30). In our study, B-lymphocytes and plasma cells were not detected in the immunohistochemical examination of liver biopsies. However, we found an increase in $CD8^+$ T lymphocytes in line with the literature.

Our study has several limitations. The retrospective design, the limited number of patients due to the rarity of the disease (1:50,000), and the single-center setting should be considered. These factors may limit the generalizability of our results. Despite these limitations, the prevalence of hepatic involvement in our study is consistent with that reported in the literature.

In conclusion, considering the heterogeneity of liver disease, each patient with CVID should be routinely evaluated for hepatic involvement. This approach may help detect hepatic involvement promptly, monitor its progression, and select patients for liver biopsy. Our study indicates that immune cells, particularly $CD8^+$, $CD4^+$, and $CD16^+$ cells, are likely involved in the pathogenesis of hepatic involvement. Understanding the etiology and pathophysiology of hepatic involvement in CVID patients could aid in early diagnosis and appropriate treatment, improving the prognosis.

Conflict of Interest

The authors have no conflicts of interest to declare.

Funding

None.

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