

Clinical significance of concomitant extrahepatic autoimmune disease in patients with autoimmune liver disease

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Abstract

Background and Aim: This study aimed to determine the presence of concomitant extrahepatic autoimmune disease (EAD) in patients with autoimmune liver disease (ALD) and the efficacy of the treatment response of ALD with the presence of any EAD.

Materials and Methods: Between January 2001 and November 2017, 241 patients with ALD were included in the study.

Results: Of the 241 patients, 88, 134, and 19 had autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and overlap syndrome (OS), respectively. Thirty-one patients had cirrhosis: 77% and 23% had compensated and decompensated disease, respectively. The presence of at least one EAD was defined in 38.6% of the patients with ALD (n=93), and 12% of them had ≥ 1 EAD. EAD was most commonly seen in patients with OS and PBC compared with those with AIH (p=0.036). Autoimmune thyroid disease was the most common association (20%), followed by Sjogren syndrome (12.0%). At the end of the follow-up period, 165 patients (72%) had biochemical response. The presence of EAD did not affect the biochemical response.

Conclusion: EAD is most frequently seen in patients with ALD. The presence of EAD is not associated with the treatment response.

Keywords: Autoimmune liver disease; extrahepatic autoimmune disease.

Introduction

Autoimmune liver disease (ALD) consists of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC).^[1] ALD may be associated with more than one subgroup as an overlap syndrome (OS). The term of OS is used to define the co-

existence of AIH with PBC or PSC. Autoimmune diseases are chronic, progressive conditions initiated by the loss of immunologic tolerance to self-antigens as a result of interactions of genetic, epigenetics, and environmental factors.^[2-4]

Polyautoimmunity is defined as the presence of more than one autoimmune disease in a single patient.^[1,2,4-8] Approximately, one in three patients with ALD has a concomitant extrahepatic autoimmune disease (EAD), including endocrinologic, rheumatologic, dermatologic, or pulmonary diseases.^[4-8] This is mostly caused by the antigenic similarity in the hepatocyte or bile duct epithelial cell and the extrahepatic tissues, which activates innate and adoptive immune responses to similar antigenic structures.^[1,2,4-8] This study aimed to determine the presence of concomitant EAD in patients with ALD and the efficacy of the treatment response of primary disease with the presence of any EAD.

Materials and Methods

Patients: This is a single-center observational study. The medical data of patients diagnosed with ALD between January 2001 and November 2017 in the Liver Disease Outpatient Clinic, Department of Gastroenterology, Ankara University School of Medicine, were retrospectively evaluated. ALD was defined clinically, biochemically, and histologically when available. ICD-10 codes were used to identify disease and its complications. The patients were categorized as AIH, PBC, and OS using ICD-10 diagnostic codes. A diagnosis of ALD was established based on the international criteria,^[9,10] without any other cause of chronic liver disease. Patients with AIH were treated conventionally with corticosteroids and azathioprine. Prednisolone or prednisone was tapered to a maintenance dose of 5–7.5 mg/day.^[9] Patients with PBC were treated with ursodeoxycholic acid (UDCA) at a dose of 10–15 mg/kg/day.^[10] Complications of cirrhosis, including ascites, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, and hepatocellular carcinoma (HCC), were evaluated. Data were collected from outpatient visit charts. This study was approved by the local ethical committee of Ankara University School of Medicine.

Methods: Serum alanine aminotransferase, aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, and complete blood cell counts were measured by our central laboratory. Serological markers for viral infections (anti-HAV IgM, HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgG, anti-HCV, anti-HEV, anti-cytomegalovirus, anti-herpes simplex virus, and anti-Epstein-Barr virus), serum iron, ferritin, ceruloplasmin, and alpha-1 antitrypsin levels were measured, and serological studies for

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Table 1. Baseline characteristics of the 241 patients

	ALDs	AIH	PBC	OS
Age (years)	54.7±14.6 57 (18–90)	49.9±16.5 51 (18–90)	58.1±12.8 58 (23–86)	53.7±10.2 53 (34–71)
Sex (%) (Female/male)	92/8	85/15	95/5	100/0
Disease duration months (median, range)	95.1±71.4 84 (1–432)	90.8±74.8 72 (1–355)	98.1±70.3 84 (1–432)	94.4±64.5 78 (12–240)
Baseline cirrhosis, n (%)	31 (12.9)	16 (18.2)	15 (11.2)	–
Baseline ALT (U/L)	117.4±208.9 50 (5–1577)	193.6±302.8 68 (5–1577)	62.3±66.1 46 (11–573)	141.6±213.7 62.5 (13–918)
Baseline AST (U/L)	105.6±195 45 (13–1096)	174.4±279.7 47 (13–1096)	58.6±91.4 43 (13–1025)	107.4±140.4 53 (16–574)
Baseline GGT (U/L)	134.1±132.4 93(8–760)	109.5±121.6 66 (8–760)	154.9±141.4 108 (9–676)	103.9±85 90 (11–308)
Baseline ALP (U/L)	178.1±163 134 (16–1360)	130.5±93.8 114 (24–724)	212.2±195.6 153 (16–1360)	168.2±110.0 130 (73–528)
Baseline total bilirubin (mg/dL)	1.72±3.57 0.75 (0.2–32)	2.73±4.43 1.09 (0.2–22)	1.14±2.93 0.6 (0.2–32)	0.86±0.41 0.7 (0.29–1.7)
Baseline INR	1.05±0.24 1 (0.80–2.60)	1.13±0.29 1.05 (0.84–2.60)	0.99±0.15 0.99 (0.80–1.70)	1.04±0.31 0.96 (0.80–2.19)
Baseline platelet count (10 ⁹ /mm)	256.5±98.6 260 (33–686)	241.1±105 242 (33–686)	264.2±98.1 262 (34–676)	273.5±56.8 273 (170–400)

Data are presented as mean±SD, median (min, max). AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; OS: Overlap syndrome; AST: Aspartate aminotransferase; GGT: Gamma glutamyl transpeptidase; ALP: Alkaline phosphatase.

anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney membrane-1, and anti-mitochondrial antibodies were performed. All patients underwent abdominal sonography confirming the presence of cirrhosis, its complications, and HCC. Laboratory tests were performed at diagnosis and during the follow-up period.

Definitions: EAD was defined as patients with at least one or more of the following conditions including autoimmune thyroid disease (autoimmune thyroiditis, Hashimoto's disease, Graves' disease), Sjogren's syndrome, diabetes mellitus type 1, autoimmune skin disease (alopecia, vitiligo, psoriasis, dermatitis herpetiformis), systemic lupus erythematosus, celiac disease, vasculitis, rheumatoid arthritis (RA), connective tissue disease, inflammatory bowel disease, polymyositis, uveitis, systemic sclerosis, PSC, Churg–Strauss syndrome, autoimmune thrombocytopenia and autoimmune hemolytic anemia.^[5–8]

Biochemical response in patients with AIH was defined as a complete normalization of serum aminotransferases and immunoglobulin G levels.^[9] In patients with PBC, the response criteria are based on the improvement of serum ALP, AST, and bilirubin levels after 12 months of UDCA treatment based on Paris-II criteria (ALP <1.5 × upper limit of normal [ULN], AST <1.5 × ULN, normal bilirubin).^[10]

Follow-up: Patients were seen at regular intervals in an outpatient clinic during the follow-up period. Cirrhosis and its complications were evaluated. Further investigations included surveillance for HCC with radiological imaging and alpha-fetoprotein determinations every 6 months. If necessary, dynamic computed tomography or magnetic resonance imaging was performed.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and percent were used for descriptive statistics. Categorical variables

were assessed using the chi-squared test. Comparison between two groups was assessed using the Mann–Whitney U test for non-normally distributed variables. A $p < 0.05$ was considered significant.

Results

This study included 241 patients (female/male: 92%/8%), with a median age of 57.0 years (range: 18–90 years): 88 patients (median age: 51.0 years, range: 18–90 years) with AIH, 134 patients (median age: 58.0 years, range: 23–86 years) with PBC, and 19 patients (median age: 53.0 years, range: 34–71 years) with OS. Female sex was predominant (92%). Thirty-one patients (12.9%) had cirrhosis (16 AIH, 15 PBC). Among 31 patients with cirrhosis, 24 (77.4%) and 7 (22.6%) had compensated and decompensated disease. The median disease duration was 84 months (range: 1–432 months). Table 1 shows the patients' baseline characteristics.

The presence of at least one EAD was defined in 38.6% of the patients with ALDs (n=93). EAD was most frequently seen in patients with OS (52.6%) and PBC (43.3%) compared with patients with AIH (28.1%, $p=0.036$). Autoimmune thyroid disease was the most common association (20.3%, 49/241), followed by Sjogren syndrome in 29 patients (12%), RA in 8 (3.3%), celiac disease in 7 (2.9%), diabetes mellitus type 1 in 6 (2.5%), autoimmune skin disease in 5 (2.1%), and miscellaneous (inflammatory bowel disease, uveitis, systemic lupus erythematosus, systemic sclerosis, PSC, Churg–Strauss syndrome, and autoimmune thrombocytopenia) in 28 patients (11.6%) (Table 2). Concomitant autoimmune thyroid disease was more commonly observed in patients with OS compared with patients with AIH (36.8% vs 13.6%, $p=0.04$), whereas Sjogren syndrome was slightly more common in patients with PBC (16.4% vs 6.8% in AIH and 5.3% in OS, respectively, $p=0.06$). In addition, 29 patients (12%) had ≥1 EAD. The frequency was not significantly different among the groups (13.6% in AIH, 11.2% in PBC, and 10.5% in OS) ($p=0.6$).

Table 2. Frequency of EAD in patients with ALD

	ALDs (n=241)		AIH (n=88)		PBC (n=134)		OS (n=19)	
	n	%	n	%	n	%	n	%
Autoimmune thyroid disease	49	20.3	12	13.6	30	22.4	7	36.8
Sjogren syndrome	29	12	6	6.8	22	16.4	1	5.3
Rheumatoid arthritis	8	3.3	3	3.4	5	3.7	0	0
Celiac disease	7	2.9	3	3.4	3	2.2	1	5.3
Diabetes type 1	6	2.5	1	1.1	5	3.7	0	0
Skin disease	5	2.1	4	4.5	0	0	1	5.3
Miscellaneous	23	9.5	10	11.4	11	8.2	2	10.5

EAD: Extrahepatic autoimmune disease; ALD: Autoimmune liver disease; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; OS: Overlap syndrome.

Table 3. Biochemical response rate with univariate analysis

	Biochemical response	Biochemical non-response	p
Age (years)	57	57	0.572
Gender (%) (Female/male)	71/82	29/18	0.313
Baseline ALT (U/L)	49	52.5	0.691
Baseline AST (U/L)	43	52	0.03*
Baseline GGT (U/L)	82.5	138.5	0.024*
Baseline ALP (U/L)	123.5	160	0.001*
Baseline total bilirubin (mg/dL)	0.7	0.7	0.394
Baseline platelet count (10 ⁹ /mm)	263	239	0.3
Cirrhosis (%)	60	40	
No cirrhosis (%)	73.5	26.5	0.126
Presence of EAD (%)	78.3	21.7	
Without EAD (%)	67.4	32.6	0.073
AIH (%) / PBC (%) / OS (%)	76.5/69.2/68.4	23.5/30.8/31.6	0.49

*: Significant p-values as <0.05. Data are presented as median. EAD: Extrahepatic autoimmune disease; ALD: Autoimmune liver disease; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; OS: Overlap syndrome; AST: Aspartate aminotransferase; GGT: Gamma glutamyl transpeptidase; ALP: Alkaline phosphatase.

At the end of the follow-up period, 165 patients had biochemical response, 65 had non-response, and 11 patients (7 AIH, 4 PBC) died. The biochemical response rates in patients with AIH, PBC, and OS were 76.5%, 69.2%, and 68.4%, respectively. Of the remaining 230 patients (21.7%), 50 had cirrhosis (18 AIH, 28 PBC, and 4 OS). Among them, 68% (n=34) and 32% (n=16) had compensated (10 AIH, 21 PBC and 3 OS) and decompensated disease (8 AIH, 7 PBC, and 1 OS). At end of the follow-up period, cirrhosis developed in 30 patients without cirrhosis at baseline (8 AIH, 18 PBC, and 4 OS). Of the 30 patients, decompensated cirrhosis developed in 7 (23.3%, 3 AIH, 3 PBC, and 1 OS).

Among baseline patients' characteristics include age, gender, liver injury and cholestatic tests, type of ALD, the presence of cirrhosis, the presence of EAD, with univariate analysis, baseline low AST, GGT, and ALP levels were associated with biochemical response (Table 3). However, this was not statistically significant in multivariable analysis.

Discussion

The present study investigated the frequency, type, and clinical significance of concomitant EAD in patients with ALD in a single tertiary center. The presence of at least one EAD was found in 39% of the pa-

tients with ALD, and ≥ 1 EAD was observed in 12% of the patients. Female sex was predominant (96%). EAD was most commonly seen in patients with OS and PBC compared with those with AIH (p=0.036). Among the EAD, autoimmune thyroid disease was most commonly encountered (20%), followed by Sjogren syndrome (12%). This finding is compatible with previous studies,^[5,7,8,11-13] which reported a close association between EAD and ALD, and autoimmune thyroid disease was most frequently encountered. Because the association between AIH and EAD is well known, these results indicate that high frequency of concomitant EAD was also seen in patients with OS and PBC.

The prevalence and pattern of concomitant EAD in patients with ALD vary due to different geographical areas, genetic background, and study populations. Floreani et al.^[5] reported a high prevalence of EAD (61%) in Italian patients with PBC. Several investigators previously reported the prevalence of EAD in patients with ALD between 28.3% and 43.6%.^[8,11,13] In the present study, the overall prevalence of EAD in patients with ALD was 38.6%, whereas it was 43.3% in patients with PBC. These results were compatible with previous reports^[8,11,13] but lower than those of the Italian group. Autoimmune thyroid disease was the most frequently observed, with a prevalence of 10% and 15%,^[5,8,11-13] which was similar to our results (20%). The differences mostly seen

in the pattern of the EAD. Some centers reported a high prevalence of Sjogren syndrome with/without Raynaud phenomenon and autoimmune skin disease,^[5,11] the other centers did not.^[8,13] The prevalence of Sjogren syndrome, Raynaud phenomenon, and autoimmune skin disease was 34%, 18%, and 5% in Italian patients with PBC, respectively. In the present study, the prevalence of Sjogren syndrome in patients with PBC was 16.4%, which was lower than that of their Italian counterparts, whereas autoimmune skin disease was not observed in patients with PBC. Unfortunately, Raynaud phenomena was not evaluated. This discrepancy may be explained by the heterogenous study population and different geographical distributions. Of note, 2.2% frequency of celiac disease was observed in patients with PBC, similar to the Italian study, which reported 1.4%.^[5]

Several investigators reported that the presence of EAD was not associated with treatment response, did not affect disease outcome, and were not related with the onset of major events during the follow-up period.^[5,11–14] Teufel et al.^[12] reported that the presence of EAD in patients with AIH did not affect treatment response and relapse rate. In the present study, no statically significant differences among the patient groups in the treatment response based on biochemical response. The presence of EAD in patients with AIH, PBC, and OS did not affect biochemical response, disease progression, and patient survival. This finding confirms that of previous studies.^[11–14]

In conclusion, EAD was most frequently seen in patients with ALD. The presence of EAD was not associated with treatment response and disease progression. Asymptomatic patients with ALD may be identified as a result of the presence the EAD.

Ethics Committee Approval: This study was approved by the local ethical committee of Ankara University School of Medicine (Approval date: 05.09.2016, approval number: 14-671-16).

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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