Research Article

Patterns and Features of Cholestatic Liver Diseases: Experience of a Tertiary Academic Center in Saudi Arabia

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Abstract

Background: Autoimmune cholestatic liver diseases (ACLDs) are recognized risk factors for liver cirrhosis and end stage liver disease. Data on ACLD from Saudi Arabia and other Middle Eastern countries are limited to case reports. The aim of this study was to evaluate the patterns, laboratory findings and long term outcomes of ACLD patients treated at a tertiary academic medical center in Saudi Arabia. **Methods:** This was a retrospective study of all patients diagnosed with ACLD from January 2016 to January 2020. For all patients, demographic data, laboratory data, and the Fibrosis score assessed by Transient elastography using the Fibroscan device were obtained. We also evaluated treatment response and long term outcomes for all patients. **Results:** Eighteen patients were diagnosed with ACLD during the study period. This included 9 patients with primary biliary cirrhosis (PBC), 3 patients with primary sclerosing cholangitis (PSC), and 3 patients with autoimmune hepatitis (AIH)-PBC overlap. Anti-mitochondrial antibody was positive in all PBC patients. One third of patients had cirrhosis. Treatment with ursodeoxycholic acid (UDC) was able to achieve disease control in about 90% of PBC patients for approximately 10 years. Only one patient without PBC had complete response to treatment with UDC and immunosuppression medication. Two patients (11%) with advanced PSC died. **In conclusion:** ACLDs are an important cause of chronic liver disease. Early recognition of PBC and initiation of treatment can delay disease progression in the majority of PBC patients. Achieving disease control with treatment is more difficult in patients with PSC and overlap syndromes.

Keywords: Autoimmune cholestatic liver disease; Clinical features; Follow up

Introduction

Autoimmune cholestatic liver disease (ACLD) refers to a group of chronic hepatic disorders that can progress to liver cirrhosis and end stage liver disease. [1] Primary biliary cholangitis (PBC) is the commonest ACLD, followed by primary sclerosing cholangitis (PSC). [2,3] Other less common forms of ACLD include variant forms of these diseases that are generally referred to as overlap syndromes. [4]

Primary biliary cholangitis is a progressive immune-mediated cholestatic disease that leads to destruction of the intrahepatic bile ducts and which can progress to liver cirrhosis. [2,5] Clinically, PBC tends to affect middle age females and presents with fatigue, pruritis, jaundice, xanthomas, osteoporosis, and dyslipidemia. [6]

Biochemically, PBC is characterized by elevated cholestatic liver markers including a serum alkaline phosphatase (ALP) level ≥ 2-fold the upper limit of normal (ULN) or a serum gamma-glutamyltransferase (GGT) level ≥5-fold ULN. Typical histologic features of PBC include nonsuppurative destructive cholangitis and destruction of interlobular bile ducts, [7,8] and 95% of patients are positive for anti-mitochondrial antibodies (AMA). In approximately 5% to 10% of patients, AMA is absent or present only in low titer (≤1/80). [8] Antinuclear antibody and anti-smooth muscle antibody (SMA) are positive in nearly half of patients. The aim of PBC therapy is to reverse injury from bile duct inflammation and relieve symptoms, prevent disease progression, improve laboratory abnormalities, and prevent the consequences of chronic cholestasis, including pruritus, fatigue, osteoporosis, and fat-soluble vitamin deficiencies. Ursodeoxycholic acid (UDCA) was the first therapy approved by the United States Food and Drug Administration for the treatment of PBC. It plays a role in the protection of cholangiocytes, stimulation of biliary secretions of bile acids, and decreases rates of liver transplantation and mortality. [9] In PBC patients who have an inadequate response to UCDA, obeticholic acid is the preferred second line treatment. [10]

PSC is a chronic progressive cholestatic liver disease that can progress to end stage liver disease. The majority of

How to Cite this Article: Khatib HA, et al. Patterns and Features of Cholestatic Liver Diseases: Experience of a Tertiary Academic Center in Saudi Arabia. Ann Med Health Sci Res. 2020;10: 1168-1172.

patients with PSC are asymptomatic at initial presentation. Among the symptomatic patients, fatigue, fever, jaundice, pruritus, and vague upper abdominal discomfort are the most commonly described symptoms. [11] Elevated ALP ≥ 3 fold is a characteristic feature of PSC that is present in 95% of patients. Serum alanine (ALT) and aspartate aminotransferase (AST) levels are also usually elevated up to 2–3 times ULN. Serum bilirubin level is typically normal at diagnosis in the majority of patients. [12,13] PSC is also associated with positive titers of auto-antibodies, including ANA, SMA and perinuclear anti-neutrophil cytoplasmic antibodies in up to 94% of patients, but these are not specific for PSC. [13,14] Radiologically, PSC shows cholangiographic findings of bile duct stenoses and dilatations, and histology shows mild to moderate portal infiltration and preductal fibrosis. [4]

At present, there is no standardized definition of the overlap syndromes. However, patients with overlap syndromes present with both hepatitic and cholestatic serum liver function tests and have histological features of autoimmune hepatitis (AIH) and PBC or PSC. PBC and AIH are the most frequent autoimmune hepatopathies. [15] The transition from PBC to AIH-PBC overlap syndrome has been reported. The Paris criteria are used to diagnose PBC-AIH overlap and include criteria for both PBC and AIH in addition to histologic evidence of interface hepatitis. [16] The diagnosis of AIH-PSC overlap requires the presence of both AIH-PSC features plus histological evidence of biliary changes which are more common than interface hepatitis. [13]

Transient elastography (Fibroscan) is a non-invasive method that is used to measure the degree of fibrosis in chronic liver disease. It is a simple and acceptable test with great accuracy for the assessment of the stage of fibrosis in cholestatic liver diseases including PSC and PBC. [17,18] However, the validity of the Fibroscan for evaluation of cholestatic liver disorder has been less established than for viral hepatitis. [18]

This study was conducted at King Abdulaziz University hospital, a tertiary academic medical center in Jeddah Saudi Arabia, and the aim was to evaluate the clinical and laboratory features of patients with ACLD.

Methodology

This was a retrospective analysis of all adult patients diagnosed with ACLD based on clinical, laboratory, and immunological features. The study protocol was approved by the research ethical committee of the faculty of medicine at King Abdulaziz University Jeddah (NO 443-20 on August/31/2020). The study duration was from January 2016 to January 2020.

Inclusion criteria were all patients with a diagnosis of ACLD who underwent assessment of liver fibrosis at the hepatology and gastroenterology unit of King Abdulaziz University hospital Jeddah. Only patients who had active regular follow up were included.

Patients were excluded if their clinical and laboratory data were not available on the hospital information system and or if they were lost to follow-up after the initial diagnosis.

Definitions

The diagnosis of PBC was based on clinical features (ie. itching); laboratory values, namely an ALP ≥1.5 times ULN; and AMA positivity at a titer of 1:40 or higher. [7]

The diagnosis of PSC was based on elevated cholestatic serum enzyme levels (ALP>3 times ULN), and typical cholangiographic findings of bile duct stenosis. [12]

The diagnosis of PBC-AIH overlap was based on the Paris criteria which includes criteria for both PBC and AIH. AIH-PSC overlap was diagnosed based on the presence of both AIH-PSC features. [13]

Autoimmune cholangiopathy was diagnosed based on the presence of cholesteric derangement of liver enzymes and immunological features similar to that of AIH and negative AMA.

The electronic medical records of patients, which were held on the database of the unit of gastroenterology and hepatology at King Abbdulaziz University hospital, were reviewed for data collection. For all patients, we obtained demographic data on age, sex, and nationality (Saudi or non-Saudi). We also collected data on the duration of follow up from the time of diagnosis until the last visit or death.

We collected data on the following laboratory data at the time of diagnosis: complete blood count including white blood count, hemoglobin, and platelet levels; and liver function tests (AST, ALT, ALP, GGT, albumin, total bilirubin). We also obtained the result of the patient's autoimmune profile at the time of diagnosis or whenever available (antinuclear antibody, ANA; SMA; AMA; immunoglobulin IgG and IgM).

The results of liver fibrosis assessment using Fibroscan examination was collected from the gastroenterology and hepatology unit. The standards for an acceptable Fibroscan at KAUH are 10 successful readings with a success rate of at least 70% and an IQR of less than 30%. We obtained the stiffness measurements in KPa. We then categorized the fibrosis score for all patients according to the stiffness measurement into F1= 6-7.1, F2=7.2-9.2, F3=9.2-17.2, and F4 > 17.3. [18]

Outcomes

We evaluated treatment response, defined as improvement of symptoms and normalization of liver enzymes and bilirubin at the last follow up. We also analyzed liver related mortality.

Statistical analysis

All the data were analyzed using the Statistical Package for Social Sciences software (SPSS, version 16.0; SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean and standard deviations. Tukey post-hoc test was used for calculating the significant difference between healthy and diseased sites for each clinical and biochemical parameters. Spearman's correlation coefficient was applied to determine the relationship between the clinical parameters and biochemical parameters (calprotectin and NTx). A p-value of less than 0.05 was considered significant.

Results

Eighteen patients fulfilled the inclusion criteria for ACLD during the study period. The majority of patients were female (15, 83.3%) and Saudi Arabian (13, 72.2%). The mean age was 51.2 years (standard deviation: 11 years, 24-65). There was no difference in the age between males and females (p=.47). There was no significant difference in the age of patients with PBC and those with other diagnoses. Table 1 presents the demographic data of the study population.

The most common diagnosis was PBC (9 patients, 50%) [Table 2]. Laboratory test results showed cholestatic or mixed pattern of elevation of liver enzymes [Table 3]. PBC patients had significantly lower serum ALP and serum AST levels compared to non-PBC patients. Alkp 139 SD 92 and 432 SD304 P=.03; and AST of 30 SD: 24 and 91.5 SD: 50.2 P=0.01 respectively. There was no significant difference in the other liver parameters between patients with and without PBC. Table 3 presents the laboratory results of all patients.

All PBC patients had a positive AMA of variable strengths (strongly positive in 6 patients and mildly to moderately positive in 3 patients). Among patients without a diagnosis of PBC, only one patient with AIH-PBC overlap syndrome had a strongly positive AMA (P = .025). ANA was weakly positive in 2 patients, moderately positive in 2 patients, and strongly positive in 2 patients without PBC and weakly positive in only 2 PBC patients (P=.016).

There was no statistically significant difference in the mean stiffness score, measured using the fibroscan, between PBC patients and other patients (9.1 KPa, SD (6.7) and 15.7 KPa, SD (8.4), respectively; P=0.086). Approximately 40% of patients had mild fibrosis (F1), and 50% of patients had severe fibrosis (F3) or cirrhosis (F4). Age older than 60 was associated with a higher fibrosis score compared to younger age (13.2 KPa, SD (8.4) and 8.6 KPa, SD (6), respectively; P=0.32). Table 4 shows the number of patients according to the stage of fibrosis and diagnosis using Fibroscan.

The mean duration of follow-up was longer for PBC patients compared to non-PBC patients, but this difference was not statistically significant (9.7 years, SD 3 years and 6.1 years, SD 4.6 years, respectively; P=.07).

All of the patients with PBC and PSC in this study were treated with UCD. All AIH-PBC overlap and AIH-PSC patients were

Table 1: Demographic data of all patients.

Variables		Number and % of patients out of 18	Age (Years, Standard deviation)
Sex P=0.47	Male	3 (16.7%)	56.33 SD (11.7)
	Female	15 (83.3%)	50.2 SD (11)
Nationality P= 0.13	Saudi	3 (16.7%)	54.1 SD (9.8)
	Non Saudi	15 (83.3%)	43.8 SD (11.6)

Table 2: Number and percent of patients according to diagnosis.

Diagnosis	Number of patients	Percent of patients
PBC	9 *	50.0
PSC	3*	16.7
PBC-AIH overlap	3	16.7
AIH-PSC	1*	5.6
Familial Cholestasis	1	5.6
Autoimmune Cholangiopathy	1	5.6
Total	18	100.0

*One male patient in this group.
PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis; AIH: Autoimmune Hepatitis

Table 3: Laboratory results for all patients.

Parameters	Normal Values	Minimum	Maximum	Mean	Std. Deviation
WBC	4.5-11.5 K/ul	2.00	11.40	6.7775	2.49242
Hb	12-15 g/dl	7.50	199.00	23.4938	46.85680
Platelets	150-450 K/ul	12.20	431.00	254.6375	108.29673
albumin	35-50 g/L	16.00	42.20	32.7625	6.14675
ALP	50-136 U/L	59.00	980.00	294.2500	257.50249
AST	15-37 U/L	3.00	167.00	63.0000	47.70744
ALT	30-65 U/L	23.00	149.00	67.5000	40.78235
GGT	5-85 U/L	3.00	1256.00	286.5625	362.76144
bilirubin	0-17 umol/L	3.50	182.00	30.0313	50.42964
IgG	5.4-16.1g/L	11	44	19.05	8.964
IgM	.5-1.9 g/L	1.50	4.42	2.6467	1.00349
stiffness	< 6	3.00	29.10	12.1688	7.67409

WBC: White Blood Cell; Hb: Hemoglobin; ALP: Alkaline Phosphatase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma-Glutamyltransferase; Ig: Immunoglobulin

Table 4: Stages of fibrosis according to diagnosis.

Diagnosis	Fibrosis score				Total
	1.00	2.00	3.00	4.00	
PBC	4	2	1	2	9
PSC	0	0	1	2	3
PBC-AIH overlap	1	0	0	2	3
AIH-PSC	0	0	1	0	1
Familial Cholestasis	1	0	0	0	1
Autoimmune Cholangiopathy	1	0	0	0	1
	7	2	3	6	18

P=0.6 Non-Significant
PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis; AIH: Autoimmune Hepatitis

immunosuppressed with steroids with or without azathioprine and UCD. Patients with autoimmune cholangiopathy were treated and maintained on both steroids and azathioprine.

At the end of the follow up or data collection period, there was a significant difference in the response to treatment among all 18 patients (P=.047). Among 9 patients with PBC, 8 had a complete biochemical response and 1 had a sub-optimal response, and the latter patient is scheduled for treatment with obeticholic acid. Alternatively, complete biochemical response was achieved in only 1 of 9 patients without PBC. This patient had familial cholestasis and her liver enzyme and bilirubin levels normalized after cholecystectomy and treatment with UCD. During the follow-up period, none of our patients developed hepatocellular carcinoma. We reported mortality in two female patients with PSC, accounting for 11.1% of all patients in the study group, approximately two year from the time of diagnosis.

Discussion

Viral hepatitis is the most common cause of chronic liver disease; less common causes include alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), and ACLD, which are nonetheless important causes of liver-related morbidity and mortality. [19,20] Previous local data has demonstrated that ACLD represents less than 2% of all causes of chronic liver disease. [21] However, data from Europe and North America have reported that 10% of liver transplantations were due to autoimmune liver diseases. [22] The data on ACLD from Saudi Arabia and other Middle Eastern countries are limited. Therefore, epidemiological data and the clinical features of ACLD in our region are not well defined compared to other countries from Europe and North America. To the best of our knowledge, this is the first study of its kind on ACLD among adults from Saudi Arabia or other regional countries. Consistent with previous reports on the prevalence of ACLD, PBC was the most common form of ACLD in our study population. [1-3] However, Lamba et al. [23] demonstrated that during 8 years of observation, PSC had a higher prevalence and incidence compared to PBC. Similarly, Webb et al. [24] demonstrated that PSC was the most common indication for liver transplantation among patients with autoimmune liver disease.

In our study population, PBC and AIH-PBC overlap were most common in female patients compared to PSC and AIH-PSC. This finding is consistent with the sex distribution of ACLD described in previous reports. [2-4,23] Recently, Tanaka et al. [25] showed that there is an increasing trend in the prevalence and male to female ratio of PBC and PSC.

The liver function tests showed a significantly higher ALP in non-PBC patients compared to PBC patients. Since PSC is characterized by marked elevation in serum ALP, which is presumed to reflect progressive biliary obstruction due to strictures, this observation may be explained by the presence of 3 PSC patients and one AIH-PSC overlap patient in the non-PBC group. [12]

Anti-mitochondrial antibody positivity is pathognomonic for PBC, and is detected in up to 95% of PBC patients and PBC-specific ANAs are found in 25%-40% of patients. [1] This is slightly different to our study which showed that all PBC patients had a positive AMA while ANA was positive in only 22% of PBC patients.

Transient elastography had shown promising results in the assessment of liver fibrosis in patients with autoimmune liver disease. [26] Our study showed that cirrhosis was less frequently diagnosed on Fibroscan among PBC patients compared to non-PBC patients. This finding can be explained by the aggressive nature of PSC, which if untreated, will inevitably progress to cirrhosis, and by the more severe disease in patients with AIH-PBC overlap compared to patients with isolated PBC. [3,4,24]

Early recognition of PBC can lead to early treatment that may delay the progression to advanced liver disease [8,9] In our study, approximately 90% of PBC patients had a complete response to treatment with UCD. This finding was similar to internationally reported data. [8,9,27] PSC tends to be a progressive disease with suboptimal response to treatment with UCD and immunosuppression, [11,12] and AIH-PBC is less responsive to treatment compared to PBC. [4,15] In our cohort, patients with AIH-PBC overlap and AIH-PSC were treated with both immunosuppression with steroids with or without azathioprine, and only one patient (11%) without PBC had a complete response.

Long term follow up of PBC patients who had treatment response is associated with a reduced chance of progression to decompensated cirrhosis and hepatocellular carcinoma. [8] At the end of follow up, none of our PBC patients progressed to decompensated liver disease or died.

A previous long term follow up study of patients with chlolestatic liver disease showed an increased rate of liver related mortality. [28] We reported mortality in only two patients with PSC, comprising 11.1% of all patients in the study group, approximately 2 years after diagnosis. They were both females. This may reflect the aggressive nature of PSC, especially if diagnosed once the patient is already symptomatic.

Conclusion

PBC was the most common cholestatic liver disease among our cohort and it is associated with remarkable treatment response to ursodeoxycholic. On the other hand, PSC and overlap patients have less chance of disease control on treatment with ursodeoxycholic with or without immunosuppression.

Competing Interests

The authors declare that they have no competing interests.

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