REVIEW

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Extrahepatic Manifestations of Primary Biliary Cholangitis

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Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by progressive destruction of the intrahepatic bile ducts, leading to cholestasis. PBC is known to have both hepatic and extrahepatic manifestations. Extrahepatic manifestations are seen in up to 73% of patients with PBC, with the most common being Sjogren's syndrome, thyroid dysfunction and systemic sclerosis. It is thought that patients with PBC are at increased risk of developing these extrahepatic manifestations, almost all of which are autoimmune, because patients with autoimmune disease are at higher risk of developing another autoimmune condition. Due to the high prevalence of extrahepatic diseases in patients with PBC, it is important to complete a thorough medical history at the time of diagnosis. Prompt recognition of extrahepatic disease can lead to improved patient outcomes and quality of life. The following review summarizes the most common extrahepatic conditions associated with PBC. **(Gut Liver 2017;11:771-780)**

Key Words: Primary biliary cholangitis; Liver diseases

INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by progressive destruction of the intrahepatic bile ducts leading to cholestasis. This leads to fibrosis, which can lead to liver cirrhosis and failure. Data from the United Network for Organ Sharing shows that since ursodeoxycholic acid (UDCA) was Food and Drug Adminstration approved to treat PBC in 1997, the absolute number of liver transplantations performed for PBC decreased steadily by a mean of 5.4 cases per year, while the absolute number of liver transplantation increased by a mean of 249 cases per year between 1995 and 2006.[1] It has been shown that initiating UDCA in early stages of disease improves transplant-free survival and that overall survival is similar to the general population.[2]

The diagnosis of PBC can be established when two of the following three criteria are met: (1) biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation; (2) presence of antimitochondrial antibody; and (3) histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular ducts.[3] Antimitochondrial antibody is a highly disease-specific autoantibody found in 90% to 95% of patients with PBC and in less than 1% of controls.[4] PBC, similar to other autoimmune diseases has a female predominance, with a female-to-male ratio of 10 to 1.[3,5] Most patients are diagnosed between 40 and 60 years of age.[4] A systematic review of population-based epidemiological studies reported that PBC incidence rates range from 0.9 to 5.8 per 100,000 inhabitants/year and prevalence rates range from 1.9 to 40.2 per 100,000 inhabitants/year.[6] Given the high concordance rate among monozygotic twins and high level of PBC aggregates in families, there appears to be a genetic predisposition towards this disease.[7,8]

Fatigue is the most common clinical manifestation of PBC. It is present in up to 80% of patients and fluctuates independently of disease activity or stage.[9] Interestingly, it is not alleviated by UDCA, and has even been found to persist after liver transplantation.[10] Although the etiology of fatigue present in PBC is not entirely clear, one theory is that cholestasis causes accumulation of substances toxic to the brain which can lead to autonomic dysfunction, sleep disturbance, impaired concentration and memory problems.[11,12] Pruritus is the second most common symptom in PBC and affects 40% to 80% of patients.[11] Severity of symptoms can vary and fluctuate, and are not related to disease stage or activity.[13] Hyperlipidemia affects around 75% to 80% of patients with PBC and is a result of many complex processes related to biliary cholestasis.[14] Because high-density lipoprotein cholesterol is disproportionally elevated compared to low-density lipoprotein cholesterol, these patients are not at increased risk for developing coronary artery disease.[15,16] There

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Table 1. Direct Cholestatic-Related Manifestations of Primary Biliary Cholangitis[9-18]

Fatigue
Pruritus
Hyperlipidemia
Fat-soluble vitamin malabsorption
Metabolic bone disease

is decreased bile acid secretion in PBC, so vitamin deficiencies can be present as there is increased risk of malabsorption of fat-soluble vitamins.[17] Although its pathogenesis in relation to PBC is not completely clear, metabolic bone disease is another common complication of PBC and osteoporosis is seen in 20% to 44% of patients (Table 1).[18,19]

The aforementioned clinical manifestations are well studied and recognized. However, there are additional extrahepatic manifestations unrelated to the hepatic manifestations caused by chronic cholestasis responsible for such symptoms as fatigue, pruritus, vitamin and metabolic bone disease. These extrahepatic manifestations are likely mediated by immunological mechanisms explaining why they all appear to be autoimmune-related. Of note, these symptoms and syndromes can present before the diagnosis of PBC and the complications related to chronic cholestasis. The following review summarizes the most common extrahepatic conditions associated with PBC including Sjogren's syndrome (SS), thyroid disease, systemic sclerosis and rheumatoid arthritis (RA).

METHODS

1. Search strategy and identification of studies

We searched the database PubMed for all studies on various extrahepatic diseases reported in patients with PBC. We searched PubMed from its inception until July 22, 2016. We used a combination of the keywords, "primary biliary cirrhosis," "primary biliary cholangitis," "Sjogren's syndrome," "sicca complex," "thyroid disease," "Hashimoto's disease," "grave's disease," "systemic sclerosis," "scleroderma," "crest syndrome," "rheumatoid arthritis," "systemic lupus erythematosus," and "celiac disease." Bibliographies of all identified studies were also searched for relevant articles.

2. Inclusion and exclusion data

We included all studies published in scientific journals that provided prevalence data for the various extrahepatic manifestations of PBC, including: SS, thyroid disease, systemic sclerosis, RA, systemic lupus erythematosus (SLE), and celiac disease. No studies were excluded based on cohort size alone in order to be as inclusive as possible. Articles not in the English language were excluded.

EXTRAHEPATIC MANIFESTATIONS

1. Sjogren's syndrome

SS is one of the most frequently encountered extrahepatic manifestations seen in PBC, affecting between 3.5% and 73% of patients (Table 2).[20-29] SS is a progressive autoimmune disorder characterized by a lymphocytic infiltration of the exocrine glands. Over time, this leads to decreased exocrine secretions, with the lacrimal and salivary glands most commonly affected, manifesting as ocular and oral dryness.[30] The reason that SS is one of the most common extrahepatic manifestations seen in PBC likely has to do with the fact that both diseases manifest signs of chronic autoimmune epithelitis, which can explain the destruction of both bile ducts as well as certain exocrine glands.[13] SS can be classified into two groups: primary and secondary SS. Primary SS presents as an entity by itself without an underlying autoimmune condition whereas secondary SS occurs in conjunction with an underlying autoimmune condition.[31] The prevalence of SS ranges from 0.2% to 3% in the general population, and, similar to other autoimmune diseases, is more frequent in women with a 9:1 female to male ratio, and presents more commonly in middle age.[32]

1) Symptoms

Given the decrease in exocrine secretions seen in SS, patients most commonly present with dry eyes and oral complications which often include dry mouth, difficulty tasting and swallowing, gingivitis, and dental caries. Fatigue is also another common symptom in these patients. Less common symptoms include arthralgias, vasculitis and glomerulonephritis.[31] Non-Hodgkins lymphoma (NHL) is a well-recognized complication of SS and affects between 5% and 10% of SS patients. A recent study has confirmed that although the absolute risk is small, concomitant SS and PBC places patients at increased risk for NHL with standardized incidence ratios of 4.9 and 3.9, respectively.[33-35]

2) Diagnosis and treatment

The diagnosis of SS is based on clinical symptoms, serological markers and histology. Anticentromere antibody is positive in approximately 80% of patients, while anti-Ro/Sjogren syndrome type A antigen (SSA) and anti-La/Sjogren syndrome type B antigen (SSB) are found in approximately 60% and 40% of SS patients, respectively.[36] Diagnosis can also be made histologically by labial salivary gland biopsy.[30] The Schirmer's test is a less invasive and objective measurement of tear production and is highly sensitive for the diagnosis of SS.[37] It is important for patients diagnosed with SS to be referred to rheumatology and followed closely. Treatment of SS involves control of the numerous symptoms associated with exocrine gland infiltration. For xerophthalmia, artificial tears are recommended and saliva substitutes can be used for xerostomia and dysphagia. In refrac-

tory patients, cholinergic agonists such as pilocarpine or cevimeline can be used.[3] These patients also benefit from specialized dental care to prevent complications related to decreased saliva production.[38]

2. Thyroid disease

Thyroid disorders are present in 5.6% to 23.6% of patients with PBC (Table 2).[21,23,25,39,40] In the United States, hypothyroidism is found in 4.6% of patients and hyperthyroidism in 1.3% of the population.[41] The reason for the increased incidence of thyroid disorders in patients with PBC is unknown, although the mechanism is likely autoimmune, similar to the other extrahepatic manifestations of PBC. One hypothesis to explain this increased incidence is that there is cross-reactivity of antithyroid autoantibodies in the presence of autoreactive T cells or similar epithelial antigens in both the liver and the thyroid.[42]

There have been several studies that have investigated thyroid dysfunction in PBC, and all studies suggest an increased incidence and prevalence of thyroid dysfunction in patients with PBC compared to the general population.[39,40,43] Hypothyroidism

Table 2. Prevalence of Extrahepatic Manifestations of Primary Biliary Cholangitis[20-29,39,40,44,45]

Reference	Region	No. of patients	Cohort	Prevalence, %
Sjogren's syndrome				
20	Italy	170	Consecutive patients with PBC evaluated at the University of Milan	3.5
21	United States	1,032	Patients with PBC at 23 tertiary referral medical centers for liver diseases	10
22	Japan	874	Patients with PBC included in a national multicenter survey	20.8
23	United States	67	Patients with PBC evaluated at the Mayo Clinic in Rochester, MN	24
24	United States	38	Outpatients with PBC seen at the National Institute of Diabetes and Digestive and Kidney Diseases	47.4
25	Italy	361	Patients with PBC at a referral tertiary care center	56.1
26	United States	113	Patients with PBC participating in a therapeutic trial of D-penicillamine at the Mayo Clinic	66
27	Canada	95	Patients with PBC evaluated at The Toronto Hospital either on the phone or as outpatients	68.4
28	United Kingdom	18	Patients with PBC attending hospital at the London, St Bartholomew's and Southampton general hospitals with less than 10 mm moistening of the filter paper during Schirmer's type I and II tests together with corneal or conjunctival staining with rose bengal	72
29	Sweden	26	Consecutive patients with PBC who were evaluated at the University of Umea with the presence of a Schirmer's test of less than 5 mm and corneal staining with rose bengal and/or radiological findings of sialectasia	73
Thyroid disease				
39	United Kingdom	95	Patients with PBC at the King's College Hospital	13.7
40	United States	58	Patients with PBC at New England Medical Center Hospital	12
22	Japan	874	Patients with PBC included in a national multicenter survey	5.6
21	United States	1,032	Patients with PBC at 23 tertiary referral medical centers for liver diseases	9
23	United States	67	Patients with PBC evaluated at the Mayo Clinic in Rochester, MN	13
25	Italy	361	Patients with PBC at a referral tertiary care center	23.6
Systemic sclerosis				
22	Japan	874	Patients with PBC included in a national multicenter survey	1.4
21	United States	1,032	Patients with PBC at 23 tertiary referral medical centers for liver diseases	2
44	Japan	5,805	Cross-sectional study of patients with PBC registered to receive public financial aid from the Ministry of Health, Labour and Welfare	2
45	United States	558	Patients with PBC and scleroderma seen at the Mayo Clinic	3.9
25	Italy	361	Patients with PBC at a referral tertiary care center	9.9
20	Italy	170	Patients with PBC seen consecutively at the University of Milan	12.3

PBC, primary biliary cholangitis.

is most commonly seen in patients with PBC with the most common subtype being Hashimoto's thyroiditis. In one study, 9% of patients with PBC were diagnosed with nonspecified thyroid disorders.[21] Another study of patients with PBC noted that 20.4% of all patients had Hashimoto's thyroiditis while 3.2% had Grave's thyroiditis.[25] The findings of a study looking at 67 patients with PBC showed that at initial evaluation, thyroid disease was detected in 13.5% of patients with 10.5% of having hypothyroidism and the remainder having hyperthyroidism. During follow-up, 31% of patients were noted to have an abnormal thyroid-stimulating hormone (TSH), resulting in a proposed incidence of 2.9 people per year. Interestingly, this study found that patient age and severity of disease according to the Mayo Risk Score was not predictive of the development of thyroid disease.[23]

1) Hashimoto's thyroiditis

The most common thyroid disorder seen in PBC is Hashimoto's thyroiditis. It is also the most common autoimmune disorder and the most common cause of hypothyroidism. The incidence of Hashimoto's thyroiditis is 1 per 1,000 people per year and the prevalence is 8 to 26 per 1,000 people per year.[46,47] These patients tend to present in the fifth decade of life. Women are at least eight times more likely to have the disease. It has also been shown to be more common in Caucasians and Asians compared to African-Americans.[48] Diagnosis is based on clinical features, the presence of either thyroperoxidase antibody (found in 95% of Hashimoto's thyroiditis patients) and less commonly, thyroglobulin antibody (found in 60% to 80% of Hashimoto's thyroiditis patients), in addition to the appearance of the thyroid on ultrasound.[48] The signs and symptoms are variable and can include constipation, dry, cold skin, bradycardia, oligomenorrhea, inability to concentrate, memory loss, and depression.[48] Treatment is with levothyroxine.

2) Grave's disease

Hyperthyroidism associated with PBC has only been reported in a few cases and Grave's disease is the most common disorder seen in these patients.[49] Grave's disease, which is the most common cause of hyperthyroidism, is seen in 20 to 30 per 100,000 people. It is an autoimmune thyroid disorder caused by stimulating antibodies to the thyrotropin receptor on thyroid follicular cells.[50] It often presents between 30 and 60 years of age and diagnosis is made by clinical presentation, elevated levels of thyroxine (T4) and triiodothyronine (T3), and undetectable levels of TSH. Grave's disease can also be diagnosed by serum TSH receptor antibody levels, radioactive iodine uptake, and thyroid ultrasound. Symptoms are variable and include palpitations, tremulousness, heat intolerance, weight loss, diarrhea, tachycardia and anxiety.[51] Treatment varies and includes use of antithyroid drugs to normalize thyroid hormone production, destruction of the thyroid using radioactive iodine and/or surgical removal of the thyroid.

3. Systemic sclerosis

Systemic sclerosis (SSc) is another extrahepatic manifestation of PBC with a prevalence rate ranging between 1.4% and 12.3% (Table 2).[20-22,25,44,45] SSc is a chronic, heterogeneous disorder whose pathogenesis is characterized by obliterative and proliferative microvascular involvement, activation of the immune system and increase of extracellular matrix deposition in the skin and internal organs. It is a multisystem autoimmune disease characterized by organ fibrosis that can involve the skin, lungs, gastrointestinal (GI) tract, heart or musculoskeletal system. There are two major disease subsets, defined by the degree and extent of skin involvement and include limited cutaneous SSc (lSSc) (formerly known as CREST syndrome) and diffuse cutaneous SSc (dSSc).[52] Multiple studies have suggested that the lSSc subtype is more common in patients with PBC, with one study demonstrating 93% of patients with PBC with SSc having the lSSc subtype.[20,45,53,54] lSSc is characterized by fibrosis of the skin limited to the hands, forearms and less commonly the face.[52] Patients with lSSc usually have a long-standing history of Raynaud's phenomenon and low prevalence of lung involvement.[52,55] On the other hand, dSSc is a progressive disorder that affects the extremities and trunk, and is characterized by a short duration of Raynaud's phenomena, involvement of multiple internal organs and unfavorable prognosis.[52,56-58]

Based on multiple studies, PBC seems to be much more highly correlated with limited SSc and is rarer in dSSc.[20,45,53,54,59] In the general population, the incidence of SSc ranges from 2.3 to 22.8 cases per million and prevalence ranges from 50 to 400 cases per million, respectively.[60,61] Similar to other autoimmune diseases, SSc is more common in women, with a female to male ratio ranging from 3–14:1.[61] Anticentromere antibodies (ACA) are found in approximately 90% of lSSc patients, although ACA titers do not appear to be associated with disease severity.[52,62,63] Studies have also shown ACA to be present in 9% to 30% of patients with PBC.[64-67] As the prevalence of ACA is higher than patients with PBC with SSc, this indicates that ACA can be present in PBC without the diagnosis of SSc.

1) Symptoms

The clinical manifestations of SSc are variable, with the majority of patients having skin thickening and varying degrees of internal organ involvement. Raynaud's phenomenon, which is cold and stress induced vasospasm of the digital arteries and cutaneous arterioles involved in body thermoregulation, is the most common initial symptom of SSc.[68] After its onset, patients may be asymptomatic for years or rapidly develop other signs of disease.[69] Another common finding of SSc is fatigue, which is usually seen early in the disease course.[70,71] GI involvement is also seen in SSc, with esophageal dysfunction being the most common, leading to dysphagia, regurgitation and heartburn.

Other GI complications of SSc include malabsorption, weight loss, bleeding, early satiety and fecal incontinence.[72,73]

Pulmonary involvement can also be present in SSc, and is a concerning finding, given that it is the leading cause of death in SSc. Approximately 50% of patients with dSSc and 30% of patients with lSSc develop interstitial lung disease.[74,75] Pulmonary vascular disease is more commonly seen in patients with lSSc, with isolated pulmonary arterial hypertension present in 8% to 12% of patients.[76-78] Cardiac manifestations of SSc include pericardial effusion, myocardial inflammation, conduction abnormalities, and heart failure.[79-82] In addition, there may be renal involvement in SSc. The most concerning disease presentation is scleroderma renal crisis (SRC). SRC is an example of accelerated arterial hypertension and/or rapidly progressive oliguric renal failure that is more common in patients with dSSc. Seventy-five percent of cases occur within the first 4 years of disease onset.[83]

2) Diagnosis

Given the complex pathology of SSc, both diagnosis and treatment can be difficult. In 2013, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed a joint proposal for new classification criteria for SSc, shown in Table 3.[84] It is important to note that these criteria are not applicable to patients that have another disorder that can better explain their manifestations or in patients with skin thickening sparing their fingers. Patients having a total score of 9 or more are classified as having definite systemic sclerosis.[84] When there is suspicion for SSc in PBC patients, these patients should be referred to a rheumatologist for evaluation.

3) Treatment

Given the heterogeneity of SSc, and the different number of organs involved, there are currently no single agent medications that treat the various manifestations of this disease. Therefore, treatment is often targeted, and even then, only a few therapies have shown modest benefits.[85] Patients with Raynaud's symptoms are encouraged to avoid cold exposure and smoking with first-line pharmacotherapy being calcium channel blockers. In patients who are refractory to first line treatment, phosphodiesterase-5 inhibitors can be given.[86]

Proton pump inhibitors are used in the treatment of esophagitis and gastritis, and promotility agents can be used to treat dysmotility issues.[69] Methotrexate is used to treat early diffuse skin disease, and treatment can be transitioned to immunosuppressants such as mycophenalate mofetil and cyclophosphamide when there is concern for worsening skin disease and well as lung involvement.[87-89] Biological agents such as Rituximab have also shown to improve and stabilize both skin scores and pulmonary function tests in patients with diffuse SSc.[90]

Treatments used for interstitial lung disease have only shown modest benefit. Cyclophosphamide is generally used as first line treatment in patients with SSc-interstitial lung disease.[91] Mycophenolate mofetil is often used as maintenance therapy in patients who have already undergone induction with cyclophosphamide.[92] Azathioprine has been used as an alternative agent to

Table 3. Diagnostic Criteria for Systemic Sclerosis[67]

Item	Subitem	Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers (Only count the highest score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to MCP and proximal to the PIPs)	4
Fingertip lesions (Only count the highest score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease (Maximum score is 2)	PAH	2
	ILD	
Raynaud's phenomenon		3
Scleroderma related antibodies	Anti-centromere	3
	Anti-topoisomerase1	
	Anti-RNA polymerase III	
		Total score:

Total score >9 indicates definite systemic sclerosis.
MCP, metacarpophalangeal joints; PIP, proximal interphalangeal; PAH, pulmonary arterial hypertension; ILD, interstitial lung disease.

cyclophosphamide as well as a maintenance regimen after cyclophosphamide induction.[93,94]

In patients with pulmonary arterial hypertension, agents such as phosphodiesterase-5 inhibitors, endothelin receptor antagonists and prostacyclin analogues have proven efficacious in improving symptoms, delaying disease progression. They can also be used in combination, if indicated.[95,96] Caution must be taken when using high-dose glucocorticoids to treat interstitial lung disease, as the use of these steroids can lead to an increased risk of SRC.[97] In patients who develop SRC, ACE inhibitors have been shown to improve kidney function and decrease mortality among patients with SRC.[98]

LESS COMMON EXTRAHEPATIC MANIFESTATIONS

There are other, less recognized diseases that have higher prevalence among patients with PBC including RA, SLE, and celiac disease. Although several studies have pointed towards an association between PBC and RA, epidemiological data only suggests a prevalence rate between 1.8% and 5.6%.[20,99] One of the factors that has made it difficult to assess the true prevalence is the fact that most published studies appear to use different classification criteria for RA instead of the standardized ACR/EULAR criteria. SLE is another disease that has been associated with PBC. Studies documenting the incidence of SLE in PBC show a prevalence that is generally less than 2%, but ranging between 0% and 3.7%.[20,25,54,100] One study that looked at 1,032 patients with PBC showed that 2.61% of these patients also had SLE, and that the incidence is higher than that in controls which was 0.48%.[21] An association between PBC and celiac disease has also been suggested. Data from national Danish and Swedish registers have shown an association between PBC and celiac disease. A Welsh study reported a prevalence of 6% in Welsh patients with PBC.[101,102] In contrast, other European studies from Poland and Italy have shown no prevalence greater than that seen in the general population.[103-105] Despite the high percentage of primary sclerosing cholangitis patients who also have inflammatory bowel disease, usually ulcerative colitis, an association between PBC and IBD is not widely recognized.[106,107] Larger, prospective studies are needed to assess if there are statistically significant associations between PBC and these other diseases.

CONCLUSIONS

To date, there is no known pathogenic mechanism for the extrahepatic manifestations of PBC. Extrahepatic manifestations of PBC are generally autoimmune in nature and occur between 32% and 63% of patients.[21,25,108] It is well known that people with one autoimmune disease are more prone to developing other autoimmune diseases. These patients are thought to have an underlying immunological dysfunction and the interplay between genetic, immunological, environmental and hormonal factors plays a role in the development of disease. It is also likely that the interaction between these factors accounts for the variability seen in the prevalence rates of extrahepatic manifestations. In patients with PBC, extrahepatic manifestations do not influence the incidence of end-stage liver disease complications, nor does it correlate with the onset of malignancies. Survival was also shown to be unchanged.[25]

Table 4. Laboratory Screening Recommendations for Extrahepatic Manifestations of Primary Biliary Cholangitis

Extrahepatic manifestation	Screening recommendation
Sjogren's syndrome	Anti-Ro/SSA, anti-La/SSB
Thyroid disease	Thyroid panel
Systemic sclerosis	Anticentromere

SSA, Sjogren syndrome type A antigen; SSB, Sjogren syndrome type B antigen.

Given the propensity for patients with PBC to develop extrahepatic manifestations, almost all of them being autoimmune, awareness and close screening is imperative. A summary of screening recommendations can be seen in Table 4. Upon initial diagnosis, a thorough review of systems should be obtained. It would also be prudent to conduct targeted serologic screening including a thyroid panel, anti-Ro/SSA, anti-La/SSB and anti-centromere antibody. Based on patient symptoms, more specific testing may be considered, such as Schirmer's test and pulmonary function tests. The patient care team should include practitioners in rheumatology, endocrinology, pulmonology and cardiology when indicated. Patients should follow regularly with their primary care physicians. As some of these extrahepatic manifestations can lead to diseases with a poor prognosis, vigilant screening and close follow-up will lead to prompt identification and treatment.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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