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# Emerging Issues in the Immunopathogenesis, Diagnosis and Clinical Management of Primary Biliary Cirrhosis Associated with Systemic Sclerosis

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## 1. Introduction

### 1.1 Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by immune-mediated, chronic nonsuppurative cholangitis that affects interlobular and septal bile ducts (Kaplan & Gershwin, 2005). PBC is a rare disease, with prevalence ranging from 28 to 402 per million depending on geographical location (Table 1). PBC predominantly affects middle aged women, and is exceedingly rare in males (James et al., 1999). Familial clustering of PBC cases has been observed, which predominantly affects female family members. Several reports indicate that the prevalence and incidence of PBC is increasing globally (James et al., 1999). Concomitant autoimmune diseases are often found in patients with PBC (Kaplan & Gershwin, 2005). The serological hallmark of PBC is the presence of high-titer serum antimitochondrial autoantibodies (AMA), which are present in 90–95% of patients with PBC (Bogdanos et al., 2003; Bogdanos et al., 2008; Bogdanos & Komorowski, 2011; Kaplan & Gershwin, 2005). The presence of AMA in asymptomatic patients is considered predictive of eventual disease development (Metcalf et al., 1996). These autoantibodies are specific to the lipoylated domains within components of the 2-oxoacid dehydrogenase family of enzymes, particularly the E2 component of the pyruvate dehydrogenase complex, located within the inner mitochondrial membrane (Bogdanos et al., 2003; Bogdanos et al., 2008; Bogdanos & Komorowski, 2011; Kaplan & Gershwin, 2005). Indirect immunofluorescence using rodent liver, kidney and stomach sections as substrate are the most widely used screening assays for AMA in the

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routine setting (EASL 2009). Other techniques including immunoblotting and ELISA have a higher sensitivity, and the use of cloned mitochondrial antigens and bead assay testing systems allow for the identification of AMA in the sera of patients previously defined as AMA negative. In addition to AMA, PBC specific anti-nuclear autoantibodies (ANA) are also characteristic of PBC in approximately 30% of patients presenting with multiple nuclear dot (antibodies against Sp100) or nuclear membrane staining patterns (antibodies against gp210) (Bogdanos et al., 2008; Bogdanos & Komorowski 2011; Courvalin & Worman, 1997), which preferentially are identified using HEp-2 cells as substrate. The multiple nuclear dot pattern specific for PBC needs not to be confused with the nuclear dot pattern of anticentromere antibodies (ACA). The autoimmune pathogenesis of PBC is supported by a plethora of experimental and clinical data, such as the presence of autoreactive T cells in PBC patients, and serum autoantibodies characteristic of the disease (Bogdanos et al., 2003; Bogdanos et al., 2010; Bogdanos & Vergani, 2009; Shimoda et al., 1995).

The aetiology of PBC is unknown, however the current view is that both genetic susceptibility, and environmental factors are involved together, although these need further characterization. A number of chemicals and infectious agents have been proposed to induce the disease in genetically predisposed individuals (Bogdanos et al., 2010; Bogdanos & Vergani, 2009; Bogdanos et al., 2004a; Bogdanos et al., 2004b; Gershwin & Mackay, 2008; Smyk et al., 2011; Vergani et al., 2004). The presentation of PBC may include symptoms such as pruritus (the most specific symptom of PBC) and fatigue (the most common non-specific symptom), and/or jaundice (Kaplan & Gershwin, 2005). More severe patients may present with symptoms related to portal hypertension and its complications (Kaplan & Gershwin, 2005). However, a significant proportion of PBC patients are asymptomatic and diagnosed incidentally during treatment for other conditions, which are quite often other concomitant autoimmune conditions (Gershwin et al., 2005; Hudson et al., 2008). Currently, a definite diagnosis of PBC is made on a combination of abnormal serum enzymes indicating cholestasis (i.e. elevated alkaline phosphatase for at least six months), the presence of serum AMA (titre > 1:40), and characteristic liver histology with florid bile duct lesions (EASL 2009, Kaplan & Gershwin, 2005). The presence of two of the three criteria is indicative of a probable PBC diagnosis, but this definition is not globally accepted. Serum AMA may precede disease onset by several years, and many individuals found positive for these autoantibodies in the absence of other criteria eventually develop PBC (Metcalf et al., 1996).

The progression of PBC may extend over many decades, and is highly variable among patients. The final stages of this progression are characterised by cirrhosis, liver failure and death. However, the patterns of clinical disease and natural history have changed significantly in the last two decades after the introduction of medical treatment with ursodeoxycholic acid (UDCA). When UDCA is administered in early PBC at adequate doses (13-15 mg/kg/day), the progression of the disease is often altered, with many patients having a normal life expectancy without additional therapeutic measures.

## 1.2 Systemic sclerosis (SSc)

Systemic sclerosis (SSc) is a chronic systemic connective tissue disease characterized by vascular and immune dysfunction. The cardinal features are sclerosis of the skin with potential involvement of other organs (kidney, oesophagus, heart and lung are the most frequent targets), but involvement of the liver is relatively rare (Kalabay et al., 2002). The available data indicate a prevalence of scleroderma ranging from 50 to 200 per million (Table 1), with women

being at much higher risk for scleroderma than men (Chiffot et al., 2008). The poorly understood pathogenesis of SSc is complex. Familial clustering and the high frequency of other autoimmune disorders in families of patients with scleroderma, is suggestive of a genetic involvement (Kalabay et al., 2002). In addition, infectious agents have been suggested as possible contributing factors to the development and progression of SSc, through mechanisms of molecular mimicry and immunological cross-reactivity involving microbial/self homologues. SSc is extremely heterogeneous in its clinical manifestations, pattern of organ involvement, natural history, and survival. Survival is correlated with internal organ involvement and is inversely related to the severity of restrictive lung disease. In the kidneys, injury to the medium-sized arteries can precipitate scleroderma renal crisis with malignant hypertension, hyper-reninemia, microangiopathic hemolytic anemia, and rapidly progressive renal failure. Pulmonary arterial hypertension develops in 40% of SSc patients, and is a major SSc complication and a leading cause of death (Kalabay et al., 2002). Heart involvement in SSc may include cardiac fibrosis in addition to pulmonary hypertension.

The autoantibody profile in SSc appears specific and is useful for confirming the diagnosis, the disease subset, and for monitoring disease activity (Steen, 2005). Autoantibodies that characterize limited cutaneous SSc (lcSSc) include ACA, anti-Th/To, anti-U1-RNP, and PM/Scl. Diffuse cutaneous SSc (dcSSc) is characterized by anti-Scl 70 antibody (anti-topoisomerase I antibody, TOPO), anti-RNA polymerase III and anti-U3-RNP. Severe lung disease is the hallmark of anti-TOPO positive dcSSc patients. DcSSc patients with anti-RNA polymerase III appear to have the most severe skin disease and the highest frequency of renal crisis. Patients with the nucleolar antibody anti-U3-RNP have dcSSc with multiorgan involvement (Steen, 2005).

## 2. PBC/SSc

### 2.1 Epidemiology

The main features of PBC and SSc are shown in Table 1. PBC is the most common liver disorder in SSc patients (Abraham et al., 2004). One case from 1964 reports two patients with SSc and possible (but unconfirmed) PBC. Murray-Lyon et al reports two cases of SSc with PBC (Murray-Lyon et al., 1970). Despite several similar reports over the years, liver disease has not been considered a significant feature of scleroderma, and larger studies have demonstrated that liver disease was more common in the control groups. The association of lcSSc and PBC was first described in 1970 with two cases of PBC and limited scleroderma (Murray-Lyon et al., 1970). A further six cases were also reported, and several other case reports have found an association between lcSSc and PBC. The first case reporting an association of PBC and scleroderma, without features of lcSSc, was described in 1972. The prevalence of clinically evident PBC among patients with SSc was recently reported to be 2.5% in a registry of 1700 SSc patients (Norman et al., 2009), and 2% in a series of 817 patients with SSc (Assassi et al., 2009). On the other hand, the prevalence of SSc in patients with PBC is estimated to be around 8%. However, case reports and some series (Akimoto et al., 1999) reported wider range of prevalence (3-50%) of SSc, mostly lcSSc, in PBC patients.

Large epidemiological studies on PBC note a small number of patients who also have SSc. A large French study found SSc in 1% of a cohort of PBC patients, although 1% of their first degree relatives and 1% of controls also had scleroderma (Corpechot et al., 2010). Gershwin and colleagues found that 2% of PBC patients and 1% of their first degree relatives had scleroderma, which was not found in any of the controls (Gershwin et al., 2005). First degree

relatives with scleroderma were more often sisters, followed by daughters of PBC patients, in keeping with the high female predominance (Gershwin et al., 2005; Parikh-Patel et al., 2001). Twin studies in both conditions are scarce. One twin study for SSc found a concordance of 4.2% among monozygotic (MZ) twins, compared to 5.6% in dizygotic (DZ) twins, indicating a small genetic component to the disease (Feghali-Bostwick et al., 2003). However, there was a 90% concordance for ANA among MZ twins, compared to 40% among DZ (Feghali-Bostwick et al., 2003). The only twin study conducted in PBC demonstrated a concordance of 63% among MZ twins (Selmi et al., 2004). Although both twin studies note co-existing autoimmune disease, which was often the same condition in the twin, none have noted SSc in twins with PBC and *vice versa*. If one of the affected twins had SSc, it would be of interest to see whether the other would develop the disease, and within how many years after presentation of the first twin.

## 2.2 Immunopathogenesis

The immunopathogenesis of PBC has not been fully clarified, but it appears that the interaction between genetic predisposition, antigen-specific autoreactive T and B cells, the innate immune system, and environmental factors are critical in the development of the disease. Although PBC/SSc is relatively uncommon, several common factors found at the genetic and environmental levels may account for the development of the disease in this subgroup of patients.

### 2.2.1 Genetics

Genetic studies have recently implicated several gene loci in the pathogenesis of PBC (Hirschfield & Invernizzi, 2011). Strong associations between PBC and HLA DQB1, as well as at the IL12A, IL12RB2, STAT4 and CTLA4 loci were found in a large cohort of PBC patients from North America (Hirschfield & Invernizzi, 2011). The role of HLA in PBC is now believed to play a larger role that was previously suspected. Additionally, IRF5-TNPO3, 17q12-21, and MMEL1 loci have also been found to be associated with PBC. A cohort of Japanese PBC patients also showed an association with 17q12-21, however no association was found with IL12A, IL12RB2 or IRF5-TNPO3, and similar findings in an Italian cohort have also been reported. More recently, several new candidate genes have also been identified, including STAT4, DENND1B, CD80, IL7R, CXCR5, TNFRSF1A, CLEC16A and NFKB1. It should be noted that variability in gene associations have been observed between different ethnicities and/or geographical locations.

In regards to SSc, several HLA and non-HLA regions have been identified (Agarwal & Reveille, 2010). Positive HLA associations in whites and Hispanics include HLA-DRB1\*1104, DQA1\*0501, DQB1\*0301 (Assassi et al., 2009). Negative associations in those groups included DRB1\*0701, DQA1\*0201, DQB1\*0202, and DRB1\*1501 (Assassi et al., 2009). In African Americans, positive associations have been found with HLA-DRB1\*0804, DQA1\*0501, DQB1\*0301 (Assassi et al., 2009). That study also noted that ACA positivity was closely associated with HLA-DQB1\*0501 (Assassi et al., 2009), and another associated TOPO positivity with HLA-DRB1\*1104. Similar HLA findings to those noted above were also found in a Spanish cohort. Non-HLA regions have also been identified in SSc, and include STAT4 (Agarwal & Reveille, 2010), IRF5 (Agarwal & Reveille, 2010), BANK1, TNSF4, TBX21, IL-23R, and C8orf13-BLK among others (Agarwal & Reveille, 2010). Overlapping PBC/SSc genes include HLA-DRB1, DQA1, DQB1, IRF5, and STAT4, although it should be noted that DR11, which is positively associated with SSc, is considered protective in PBC (Agarwal & Reveille, 2010; Liu et al., 2010).



	PBC	SSc
Prevalence (highly variable geographically)	28-402/million	50-200/million
Incidence (highly variable geographically)	2.3-27/million	0.6-122/million
Male to Female Ratio	1:8	1 : 1.5-12 (highly variable geographically)
Peak Frequency Age	53 years	45-64 years
Autoantibodies	AMA, ANA	Limited disease: ACA, anti-Th/To, anti-U1-RNP Diffuse disease: TOPO, anti-RNA polymerase III, anti-U3-RNP
Genes (positive associations)	HLA: DRB1, DQA1, DQB1, DQA2 Non-HLA: STAT4, IRF5, SPIB, IKZF3-ORMDL3, IL12A, IL12RB, MMEL1, DENND1B, CD80, IL7, CXCR5, TNFRSF1A, CLEC16A, NKFB1	HLA: HLA-DRB1*1104, DQA1*0501, DQB1*0301, HLA-DRB1*0804, DQA1*0501, DQB1*0301 Non-HLA: STAT4, IRF5, BANK1, TNSF4, TBX21, IL-23R, and C8orf13-BLK

Table 1. Major features of primary biliary cirrhosis (PBC) and systemic sclerosis (SSc)

2.2.2 Cellular immunity

Autoreactive T cells are likely to be involved in the pathogenesis of PBC. Histologically, PBC is characterized by the presence of autoreactive T cells in the periductular spaces. CD4+ and CD8+ lymphocytes purified from biopsy samples of PBC patients recognize PDC-E2 epitopes, and sequence overlap has been demonstrated between PDC-E2 specific T and B cell epitopes (Shimoda et al., 1995). PBC appears to be unique among other classical autoimmune diseases as it seems that there is only one immunodominant CD4+ epitope within the major autoantigen (Shimoda et al., 1995). CD4+ T cell clones have also been shown to recognize other mitochondrial autoantigens, including OGDC-E2, BCOADC-E2, and E3BP (Shimoda et al., 2003). CD8+ T cells have been found to identify amino acids 159-167 and 165-174 of PDC-E2 (Shimoda et al., 1995). As well, a 10 fold increase in these CD8+ cells has been found in liver tissues compared to peripheral blood of PBC patients. In regards to PBC/SSc patients, it has been reported that this patient group has clonally expanded CD8+ T cells expressing one T-cell receptor beta chain variable region, TCRBV3, which may be involved in the disease pathogenesis (Mayo et al., 1999).

2.2.3 Humoral immunity

AMA has been found in approximately one-quarter of patients with scleroderma, and ACA in one-quarter of patients with PBC. Positive ACA is reported in 9-30% of PBC patients (Chan et al., 1994; Marasini et al., 2001; Mayes et al., 2009; Powell et al., 1984) and in 22-25% of all SSc patients, the majority of which have lcSSc. AMA positivity is found in 14-25% of SSc (Gupta et al., 1984). ACA positivity is greater in PBC/SSc than in either disease in isolation, but there is no cross reactivity between mitochondrial and centromere antigens

(Whyte et al., 1994). Because ACA have been detected not only in SSc but also in other autoimmune diseases (Kallenberg et al., 1982; Miyawaki et al., 2005) including PBC (Mayes et al., 2009), the clinical significance of ACA has been investigated. Three major centromere antigens have been recognized: centromere protein A (CENP-A, 18 kD polypeptide), centromere protein B (CENP-B, 80 kD polypeptide), and centromere protein C (CENP-C, 140 kD polypeptide). One study attempted to identify the major centromeric antigen of ACA in sera obtained from patients with PBC, and to classify the clinical characteristics associated with this. Forty one patients with PBC were studied: 10 out of 16 (63%) patients with ACA (all anti-CENP A) had one or more lcSSc feature. The higher incidence of Raynaud's phenomenon seen in ACA positive patients with PBC than in ACA negative patients with PBC suggested a close association of the presence of ACA with clinical features of lcSSc. This led to the proposal that there is a subset of PBC patients with scleroderma who are ACA positive, and differ from both ACA negative PBC/SSc and ACA negative PBC non-SSc patients, based on their clinical features and ACA epitope reactivity. As well, it has been suggested that there may be cross-reactivity between ACA and AMA epitopes, but no such link has been demonstrated (Whyte et al., 1994).

Immunological features of PBC/SSc patients were examined in a study by Akimoto and colleagues (Akimoto et al., 1998), and compared to patients with PBC and SSc alone. ACA positivity was observed in 80% PBC/SSc, 100% PBC/SSc spectrum, 25% PBC alone, and 100% SSc alone patients. AMA positivity was observed in 90% PBC/SSc, 75% PBC/SSc spectrum, 91.7% PBC alone, and 0% SSc alone patients (Akimoto et al., 1998). Interestingly, 100% of PBC/SSc spectrum patients showed reactivity to PDC-E1 $\beta$ , as did 90% PBC/SSc patients, but only 25% of PBC alone patients (Akimoto et al., 1998). Additionally, 70.6% of SSc alone patients showed reactivity to PDC-E2 compared to only 23.8% of controls, and 100% showed PDC-E3 reactivity, although this was also observed in 90.5% of controls (Akimoto et al., 1998). That study has suggested both clinical and immunological similarities in PBC/SSc and PBC/SSc spectrum patients.

#### 2.2.4 Infectious agents and molecular mimicry

Infectious agents have been implicated in the pathogenesis of both SSc and PBC, and pathogens implicated in both are of interest in the pathogenesis of PBC/SSc. *E. coli* has been strongly associated with PBC (Bogdanos et al., 2010; Burroughs et al., 1984), largely due to the high occurrence of recurrent urinary tract infections in women with PBC (Corpechot et al., 2010; Gershwin et al., 2005). Experimental data support the presence of cross-reactive immune responses between human and *E. coli* PDC-E2 at the CD4 and CD8 T-cell level (Shigematsu et al., 2000; Van de Water et al., 2001). Several studies have demonstrated cross reactivity between the human PDC-E2 autoepitope (GDLLEIETDKATI), and that of *E. coli* (EQSLITVEGDKASM) at the CD4 T cell level (Shimoda et al., 1995). As well, a shared motif, PDC-E2 (ExDK), was found to be critical for T cell epitope recognition (Shimoda et al., 1995). T cells specific for human PDC-E2 have also been shown to be activated by a motif sharing peptide of *E. coli* OGDC-E2 (Shimoda et al., 1995). In another study, 16 T cell clones specific for *E. coli* OGDC-E2 were tested for proliferation when stimulated by human OADC-E2 autoepitopes from PDC-E2, OGDC-E2 and BCOADC-E2. Activation was seen in 13/16 clones when stimulated by human OADC-E2. These studies have demonstrated that cross-reactivity between the highly conserved human and *E. coli* PDC-E2 epitopes may be a factor in the development of PBC, but there is currently no evidence to suggest the association between *E. coli* infection and the development of SSc.

*Helicobacter pylori* and Chlamydia have been implicated in both PBC and SSc (Grossman et al., 2011; Randone et al., 2008), however some studies indicate the Chlamydia are not involved in the pathogenesis of these diseases (Mayes et al., 2009). DNA of *H. pylori* and *H. hepaticus* have been isolated from livers of patients with PBC, leading to the suggestion that *Helicobacter* species may be involved in PBC pathogenesis. Anti-helicobacter antibodies have been detected in the serum and the bile of PBC patients. *Helicobacter* species have induced a PBC-like pathology in experimental models of the disease. In regards to molecular mimicry, it has been reported that a short *H. pylori* urease beta subunit sequence shares significant amino acid similarity with the human PDC-E2<sub>212-226</sub> autoepitope. The *H. pylori* urease beta subunit mimic has been implicated as a candidate for the initiation of cross-reactive immunity due to a high degree of sequence homology (13/15, 87%), and the fact that the mimic originates from the urease beta subunit, which is a major target antigen of anti-helicobacter immunity during infection. However, experimental studies have not demonstrated evidence of cross-reactive immunity involving *H. pylori* in PBC. *H. pylori* has more recently been implicated in the pathogenesis of SSc. *H. pylori* infection has been found in as many as 78% of SSc patients in one cohort, while another study notes that there is no difference between SSc and controls, although 90% of SSc patients had a highly virulent strain compared to only 37% of controls (Danese et al., 2000).

Other pathogens implicated in SSc include herpes-virus, parvovirus B19, retroviruses, and human cytomegalovirus. Sequence homology has been found between retroviral proteins and TOPO, which is the target of anti-Scl 70 antibodies in SSc patients (Jimenez et al., 1995). As well, fibroblast infection with retrovirus' has induced an SSc-like phenotype (Jimenez et al., 1995). It is possible that certain infectious organisms contribute the development of PBC or SSc in isolation, and that other organisms induce the disease in both conditions. Additionally, if common pathogens are implicated in both PBC and SSc, then the possibility of molecular mimicry in one disease may be applicable to the development of the other.

### 2.3 Screening and diagnosis of PBC in SSc patients and vice versa

Given the overlap between PBC with SSc and *vice versa*, including ACA positivity in PBC patients and AMA positivity in SSc patients, the major challenge remains to clarify which screening method would be best for early diagnosis of the associated conditions (Figure 1 and 2).

A recent study investigated the presence of antibodies against PBC disease-specific mitochondrial antigens and antibodies against the sp100 nuclear body antigen in 52 SSc patients using two commercially available ELISAs. In that study, AMA positivity was observed in 13%, ANA in 2% (anti-sp100), and one patient (2%) was diagnosed with symptomatic PBC. These figures were also found by Mytilinaiou et al., who confirmed 13.5% positive results with ELISA testing for antibodies against PBC disease-specific mitochondrial antigens in 37 SSc patients (Mytilinaiou & Bogdanos, 2009). However, this was not confirmed with the conventional indirect immunofluorescence based on unfixed rodent kidney, liver, stomach tissue sections or HEP-2 cells as antigenic substrates, and none of the ELISA positive patients showed features of PBC (Mytilinaiou & Bogdanos, 2009). The specificity of ELISA testing needs clarification in regards to whether it is less specific with false positive results, or that it simply represents a more sensitive method with respect to indirect immunofluorescence, which remains the technique of choice.



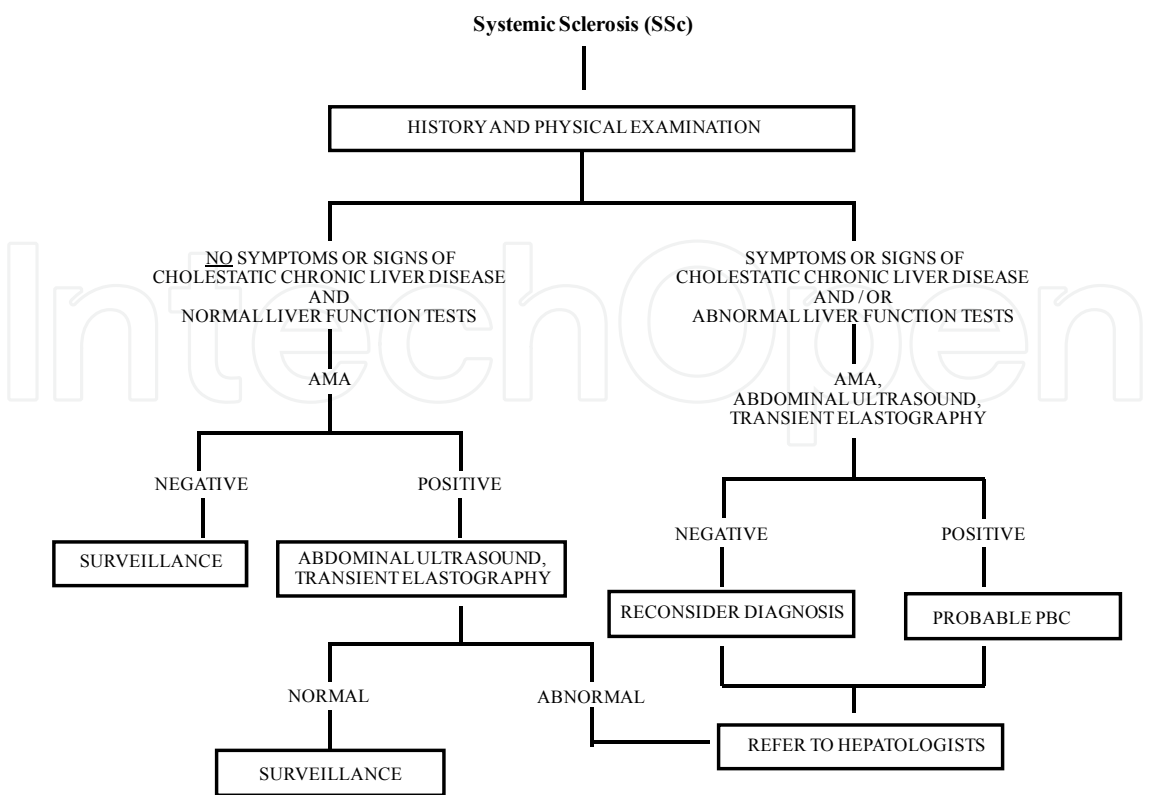


Fig. 1. Diagnostic algorithm for patients with SSc and suspected chronic liver disease

The presence of AMA can precede clinical symptoms of PBC. It has been demonstrated that the vast majority of AMA positive subjects have typical histological features of PBC despite being asymptomatic and having normal liver biochemistry (Metcalf et al., 1996). Furthermore, the study by Prince et al. suggested that 36% of initially asymptomatic PBC patients would become symptomatic within 5 years (Prince et al., 2004). Thus, SSc cases, and in particular those found to be positive for AMA, require urgent attention and long-term monitoring for early detection of symptoms, signs and liver biochemistry suggestive of chronic cholestatic liver disease. Routine follow-up of AMA positive SSc patients should include liver biochemical tests (alaninoaminotransferase, aspartateaminotransferase, gamma-glutamyltranspeptidase, alkaline phosphatase, albumin, bilirubin, international normalized ratio), thyroid function and possibly annual abdominal ultrasound scans. Since transient elastography of the liver has been emerging as a useful screening tool to detect undiagnosed chronic liver disease in apparently healthy subjects, this could be used to detect liver disease by evaluating liver stiffness on a yearly basis, and has the benefit of being non-invasive. In addition, transient elastography is reported to be reliable in the assessment biliary fibrosis. Figure 1 reports a proposed diagnostic and screening algorithm for PBC in SSc patients.

Screening PBC patients for ACA is mandatory. Nakamura et al. reported that in PBC patients, ACA positivity was significantly associated with more severe ductular pathology histologically, and was a significant risk factor for the development of portal hypertension (Nakamura et al., 2007). In another study, ACA positive PBC patients without clinical features of SSc were shown to have similar symptoms and signs at diagnosis. These findings need to be confirmed in large multicenter studies. Although ACA positivity is not pathognomic of SSc, it is associated with an increased risk of developing connective tissue disease. One review reported a sensitivity of 32% (17–56%) for SSc, 57% (32–96%) for lcSSc,

and specificity of at least 93%, while ACA positivity was present in 5% of patients with other connective tissue diseases, and less than 1% of disease free controls. Since ACA could be predictive of autoimmune rheumatological disorders, it has been suggested that an assessment of PBC patients should include careful questioning and evaluation for SSc related symptoms, such as Raynaud's phenomenon and CREST-related symptoms (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and teleangiectasia). The early diagnosis of SSc was recently defined into three domains containing seven items: skin domain (puffy fingers/puffy swollen digits turning into sclerodactyly), vascular domain (Raynaud's phenomenon, abnormal capillaroscopy with scleroderma pattern) and laboratory domain (ANA, ACA and TOPO antibodies) (Avouac et al., 2011). The use of nailfold video-capillaroscopy in patients suspected of having connective tissue disease may also be a useful indicator. It has been suggested that this assessment would need to be incorporated into the diagnostic and/or clinical management of patients with PBC and suspected SSc. Experimental and clinical observations suggest that endothelial dysfunction is present in PBC patients. One study found nailfold video-capillaroscopy abnormalities in 91% of patients with PBC, and 54% had capillary alterations characteristic of SSc (Fonollosa et al., 2001). Eleven out of the 22 PBC patients (50%) had extrahepatic signs of connective tissue disease with most being related to SSc, while patients with other types of chronic liver disease did not present with rheumatic manifestations (Fonollosa et al., 2001). The high prevalence of nailfold capillary abnormalities characteristic of SSc in patients with PBC, and correlation with sclerodermal manifestations, suggests that this capillaroscopic finding could be a useful indicator to investigate rheumatic manifestations in these patients (Fonollosa et al., 2001). Further clinical assessment of organ involvement (especially lung by spirometry) in association with evaluation of pulmonary artery pressure on echocardiography, should be considered in PBC patients diagnosed with SSc. A proposed diagnostic and screening algorithm for SSc in PBC patients is presented in Figure 2.

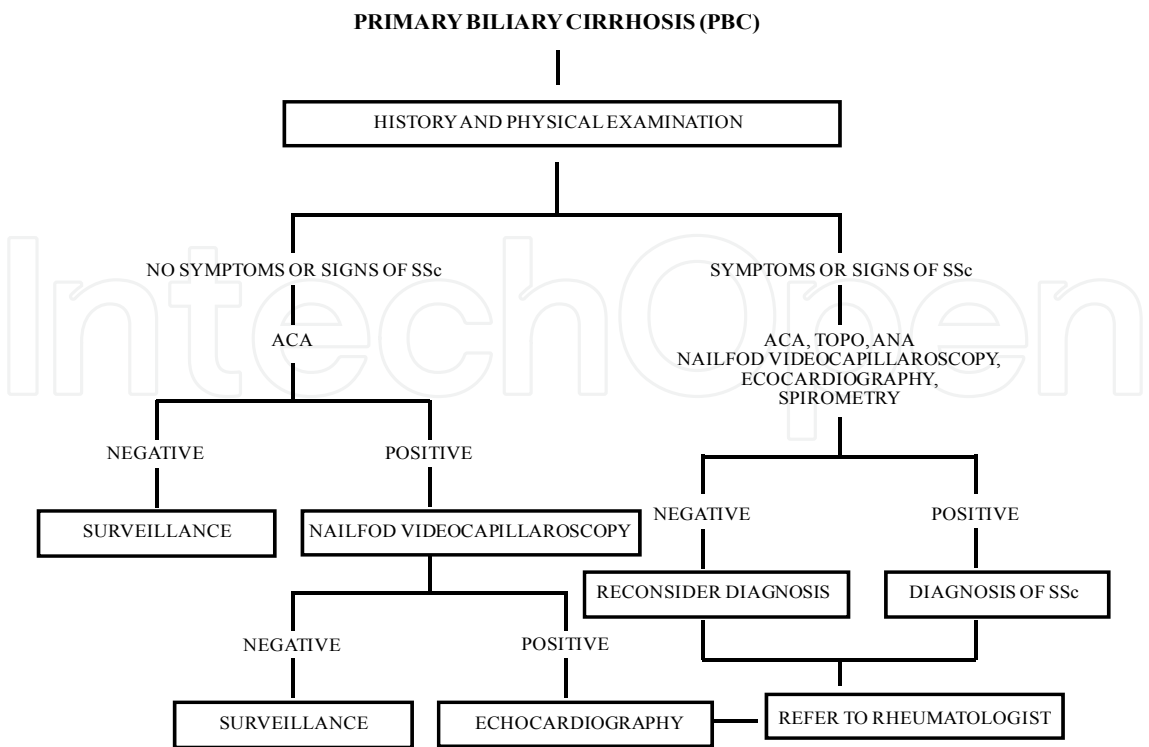


Fig. 2. Diagnostic algorithm for patients with PBC and suspected SSc

## 2.4 Clinical presentation and prognosis

The clinical presentation of SSc precedes that of PBC in approximately 60% of cases. The demographics of the disease in patients with overlapping features are not well-defined. For example, it is not clear whether in the diagnosis of PBC in the PBC/SSc group occurs at a lower age than in patients with PBC alone. In a study of 43 PBC/SSc patients (Rigamonti et al., 2006), the median age at diagnosis of PBC made after SSc diagnosis was lower (46.1 years) than in PBC diagnosed before SSc (51.1 years). This was lower than the diagnosis in PBC alone, with a median age of 53.2 years at diagnosis. The age difference at diagnosis in the PBC/SSc patients compared to patients with PBC alone, may be attributed to lead time bias (that is, screening for PBC in SSc patients and thus early diagnosis of asymptomatic PBC, since 56% presented with SSc alone).

A higher first incidence of spontaneous bacterial peritonitis is found in PBC/SSc patients, in addition to septicemia during follow up, when compared to patients with PBC alone. This is likely due to an increased risk of infection due to immune abnormalities and organ system manifestations associated with SSc.

Both SSc and PBC are associated with increased morbidity and mortality (Bryan et al., 1996). Among the disease-related causes of death in SSc patients, pulmonary fibrosis, pulmonary arterial hypertension and cardiac causes (mainly heart failure and arrhythmias) are reported to account for the majority. The most frequent non-SSc-related causes of death are infections, malignancies and cardiovascular causes (Tyndall et al., 2010). In PBC patients, liver-related causes account for roughly 50% of deaths, whereas cardio- and cerebrovascular causes together with malignancies are responsible for the non-liver related deaths. Some case reports suggest that PBC in association with SSc is associated with a more favourable prognosis than PBC alone, whereas increased mortality due to SSc has been reported in others. In the study, which included 43 PBC/SSc patients, liver disease had a slower progression in PBC/SSc compared to matched patients with PBC alone (Rigamonti et al., 2006). A lower rate of liver transplantation and liver related deaths was demonstrated in PBC/SSc patients compared to patients with PBC alone, and these differences were not due to earlier SSc related deaths. However, the improvement in liver related survival in the PBC/SSc cohort was outweighed by an increase in non-liver related deaths due to SSc, and thus overall survival was not different in PBC/SSc patients and those with PBC alone. Prince and colleagues observed an increase in non-hepatic deaths in asymptomatic PBC, even with a reduced liver related mortality, in comparison with symptomatic PBC (Prince et al., 2004). Since the causes of death in PBC/SSc patients are mainly due to SSc and not to liver disease, these patients may need different prognostic models in order to better predict their liver related survival. Prognostic models for PBC alone may not be applicable for PBC associated with SSc, or for other associated autoimmune diseases to assess the risk of liver related mortality and the need for liver transplantation.

## 2.5 Therapy

All PBC patients with abnormal liver biochemistry should be considered for specific therapy. UDCA at the dose of 13-15 mg/kg/day on a long term basis is currently considered the mainstay of therapy for PBC (EASL 2009). In the early stages of PBC, UDCA protects injured cholangiocytes against the toxic effects of bile acids. In later stages of the disease, UDCA stimulates impaired hepatocellular secretion, mainly by posttranscriptional mechanisms (Beuers, 2006). In addition, stimulation of ductular alkaline cholestasis, and inhibition of bile acid-induced hepatocyte and cholangiocyte apoptosis are included among the beneficial effects of UDCA in PBC (Beuers, 2006). UDCA has been demonstrated to

markedly decrease serum bilirubin, alkaline phosphatase, gamma-glutamyltranspeptidase, cholesterol and immunoglobulin M levels, and to ameliorate histological features in patients with PBC in comparison to placebo treatment (Poupon et al., 1991). However, no significant effects on fatigue or pruritus were observed in these large trials, nor were effects on survival. Favorable long-term effects of UDCA are observed in patients with early disease and in those with a good biochemical response, which should be assessed after one year from start of treatment (EASL 2009). A good biochemical response after one year of UDCA treatment is currently defined by a serum bilirubin  $\leq 1$  mg / dl (17 micro-mol/l), alkaline phosphatase  $\leq 3 \times$  ULN and aspartate aminotransferase  $\leq 3 \times$  ULN, according to the "Paris criteria". The "Barcelona criteria" indicate a good response with a 40% decrease or normalization of serum alkaline phosphatase.

The appropriate management of SSc is complex and includes early diagnosis of internal organ involvement, identification of patients who are at risk of progressive disease, and treatments tailored for each patient. Raynaud phenomenon and ischaemic digital ulcers are common in patients with SSc and are a cause of disease-related morbidity. The European League against Rheumatism (EULAR) recommended dihydropyridine-type calcium antagonists, such as oral nifedipine, as first-line therapy for Raynaud phenomenon and intravenous prostanoil iloprost for more severe forms (Avouac et al., 2009). The oral treatment with endothelin-1 receptor antagonist bosentan is the treatment of choice for SSc-related pulmonary artery hypertension (Avouac et al., 2009). The reportedly increased incidence of elevated aminotransferases with bosentan (Rubin et al., 2002) gives further support for the continual monitoring of liver function with this treatment, particularly in the special group of patients with associated PBC. Cyclophosphamide given orally should be considered for scleroderma interstitial lung disease (Avouac et al., 2009). Proton-pump inhibitors and prokinetic are used for the management of SSc-related gastrointestinal disease including gastroesophageal reflux, ulcers, strictures and motility disturbances. Scleroderma renal-crisis should be treated with Angiotensin converting-enzyme inhibitors (Avouac et al., 2009).

### 3. Conclusions

PBC-associated SSc is an intriguing autoimmune syndrome, which provides many challenges to hepatologists and rheumatologists in terms of early diagnosis and management, which should be shared between the two. A major effort should be made for continuing collaborative research in this field aimed at achieving a better understanding of the immunopathogenesis, genetic background, and demographic features of patients at higher risk of developing the associated conditions. Joint outpatient clinics between hepatologists and rheumatologists have been initiated in some large centers, and this may be a good start in the management of these complex patients.

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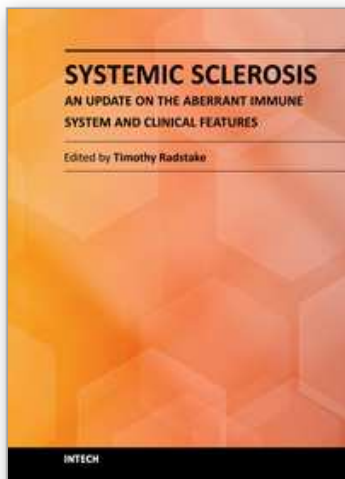
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## **Systemic Sclerosis - An Update on the Aberrant Immune System and Clinical Features**

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Systemic sclerosis (SSc), or often referred to as Scleroderma (tight skin), is characterized by an exaggerated formation of collagen fibers in the skin, which leads to fibrosis. Accumulating evidence now points toward three pathological hallmarks that are implicated in Ssc, the order of which has yet to be determined: endothelial dysfunction, autoantibody formation, and activation of fibroblasts. This current book provides up-to-date information on the pathogenesis and clinical features of this severe syndrome. It is our hope that this book will aid both clinicians and researchers in dealing with patients with this clinical syndrome. In addition, we hope to shed more light on this rare and severely disabling syndrome, ultimately leading to better research and successful therapeutic targeting.

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