Prevalence of Systemic Sclerosis in Primary Biliary Cholangitis Using the New ACR/EULAR Classification Criteria

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ABSTRACT. ***Objective.*** Systemic sclerosis (SSc) is a well-established disease associated with primary biliary cholangitis (PBC). However, the original 1980 American College of Rheumatology (ACR) criteria have poor sensitivity, especially for the detection of earlier SSc in previous studies. The objective was to evaluate the prevalence of SSc in patients with PBC using more sensitive 2001 LeRoy and Medsger criteria and the 2013 ACR/European League Against Rheumatism (EULAR) classification criteria. The secondary objective was to evaluate the frequency of individual clinical features.

Methods. One hundred consecutive patients with PBC without previously diagnosed SSc were recruited between 2005 and 2007 from a tertiary care gastroenterology clinic. All patients underwent a complete clinical examination, determination of SSc-specific antibodies, and a nailfold capillary microscopy. Fulfillment of the 3 different criteria sets was analyzed, along with individual disease features.

Results. Of 100 patients with PBC, 1% met the ACR 1980 criteria, 22% met the 2001 LeRoy and Medsger criteria for early SSc, and 17% the 2013 ACR/EULAR criteria. Raynaud phenomenon, SSc-related antibodies, and SSc capillaroscopic patterns were the most prevalent findings, with the highest sensitivities to help guide future screening.

Conclusion. Our data show a high prevalence of SSc in patients with PBC with probable underestimation by previous studies using the original ACR criteria. Comorbid SSc should be actively searched for based on newly described criteria to improve detection and increase benefits of earlier treatment.
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Key Indexing Terms:
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Primary biliary cirrhosis, recently renamed primary biliary cholangitis (PBC), is a chronic hepatic disease leading to cholestasis and cirrhosis[1]. Its strong autoimmune component is characterized by antimitochondrial antibodies (AMA) and its coexistence with other autoimmune disorders, one of the most frequent being systemic sclerosis (SSc)[2]. Both diseases feature abnormal fibroblast function and fibrosis with increased mast cells and profibrotic transforming growth factor-β and interleukin 6 cytokines[3,4,5,6]. Although no common etiology has been identified, genetic changes that have been described for both diseases may be contributive[7] and include the HLA-DRB1, DQA1, DRB1, interferon regulatory factor 5, and signal transducer and activator of transcription 4 complexes. SSc is also characterized by prominent cutaneous and vascular involvement, causing skin thickening and Raynaud phenomenon (RP). Both limited and diffuse cutaneous forms of SSc show visceral organ involvement, including the lungs, heart, kidneys, and gastrointestinal tract. Certain disease features may be shared by both SSc and liver cirrhosis, such as telangiectases, characteristically described as spider angiomas in cirrhosis, gastric antral vascular ectasia (GAVE), and pulmonary arterial hypertension, as well as possible renal failure states.

Estimates of SSc prevalence in PBC vary widely and some place it at 3%-15%[2,8,9,10]. The majority of previous studies used the highly specific but not sensitive 1980 American College of Rheumatology (ACR) SSc criteria[11]. New criteria proposed by LeRoy and Medsger in 2001[12] and validated by

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Koenig, *et al*[13], allowed for greater sensitivity and diagnosis of earlier disease by incorporating advances in nailfold capillary microscopy (NCM) and SSc-specific antibodies.

In 2013, recognizing previous flaws, the ACR and the European League Against Rheumatism (EULAR) jointly developed new weighted-point criteria endorsed for use in SSc inclusion studies[14]. Compared to LeRoy and Medsger's triad, the new set of criteria requires the addition of at least a clinical or radiological feature to be positive, as summarized in Table 1.

The aim of our study was to evaluate the prevalence of SSc in patients with PBC using both the newer and more sensitive criteria and to evaluate the prevalence of individual clinical features and characteristics to help guide screening.

MATERIALS AND METHODS

Patients. One hundred consecutive adult patients with PBC without previously diagnosed SSc were recruited from the Centre Hospitalier de l'Université de Montréal (CHUM) hepatology clinic between 2005 and 2007 for evaluation of SSc features. PBC was defined[15] by the presence of 2 of the following: elevated phosphatase alkaline, AMA, and compatible liver biopsy changes. All participants were studied prospectively until 2010; they underwent evaluation by an experienced internist (Dr. F. Joyal) over 2 visits. The project was approved by the CHUM Research and Ethics Committees, project approval number HD 05-019.

Evaluation at baseline and followup visits. A medical history was obtained and a physical examination was performed according to a standard protocol. RP was defined as a history of at least 2 of 3 phases of color change (white, blue, red) induced by cold exposure, and involving at least 1 finger of each hand[16]. A modified Rodnan skin score based on the degree of skin binding/tethering (scored on a scale of 0–4) was determined. Objective clinical signs included puffy fingers, digital ulcers, pitting scars, loss of distal finger pad, visible telangiectases, calcinosis, and synovitis. Auscultation of heart and lungs was performed at both visits. Chest radiography and transthoracic cardiac ultrasound were performed based on clinical suspicion, to screen for pulmonary fibrosis and pulmonary hypertension (systolic pulmonary artery pressure exceeds 35 mm Hg or tricuspid regurgitation velocity ≥ 2.9[17]). Presence of esophageal varices and GAVE during past hepatologic investigations were recorded from the patients' medical records. PBC severity was assessed by calculating the PBC Mayo score[18].

Nailfold capillary microscopy. Quantitative NCM was performed at baseline and followup visits. All digits except thumbs were examined on both hands with a Canon G5 camera coupled with a stereomicroscope (Carl Zeiss) at 8–50× magnification using a cool source of illumination. Pictures were recorded and then analyzed with ImageJ software to determine degree of capillary enlargement and capillary density. Noted were SSc NCM pattern, defined by the presence of at least 2 megacapillaries (≥ 90 μm) on 2 different digits and capillary density < 15 capillaries[19,20] per mm^2. NCM was also performed on hand telangiectases to assess their capillary origin.

Immunoassays. Serum samples obtained at baseline and followup visits were coded and stored at –80°C. All sera were tested blindly. ANA were determined by indirect immunofluorescence on HEp-2 cells (Antibodies Inc.; performed by J.L. Senécal). SSc-specific autoantibodies were determined as follows: anti–CENP-B and anti–topo I antibodies were detected by ELISA; anti–RNAP III antibodies were detected by ELISA using a kit from MBL; anti-Th/To antibodies were determined in sera displaying a nucleolar pattern of ANA using protein A–assisted immunoprecipitation for nucleic acid analysis from nonradiolabeled HeLa cells (M. Koenig). PBC-specific antibodies were detected using addressable laser bead immunoassay (M.J. Fritzler).

Classification of patients with PBC at the first visit. Based on clinical, antibody determination and capillaroscopic pattern at first visit, all 100 patients were retroactively evaluated for fulfillment of each of the 3 SSc criteria, blinded to diagnoses.

Statistical analysis. A protocol database encompassing 215 variables including all the features required by the different criteria sets was collected. Frequencies were compared using a 2-tailed Fisher's exact test. Differences between continuous variables were analyzed by t test or Mann-Whitney U test. $P < 0.05$ was considered statistically significant. GraphPad Prism 6.0 software package was used for statistical analysis.

RESULTS

The demographics and baseline characteristics of the study population are reported in Table 2. Of the 100 patients with PBC[15], 80 were also biopsy-proven. There were 91 female patients. Mean age at first visit (± SD) was 57 ± 10.3 years and an average of 8.18 ± 6.4 years elapsed since PBC diagnosis. Mean PBC Mayo score of disease severity and survival was 4.14 ± 1.06.

A total of 23 patients satisfied at least 1 set of criteria, with 22 being positive for LeRoy and Medsger criteria, 17 for

Table 1. SSc criteria sets definition.

ACR 1980[11]	Leroy and Medsger 2001[12]	ACR/EULAR 2013[14]	
Major criteria: Scleroderma proximal to MCP/MTP joints Minor criteria: Sclerodactyly, digital ulcers, bibasilar pulmonary fibrosis on chest radiograph	Presence of RP and (1) SSc-type nailfold capillary pattern and/or (2) SSc-related antibodies (ACA, anti Scl-70, anti-PM-Scl, anti-fibrillin, anti-RNA polymerase III, anti-Th/To)	Items	Score
		Bilateral skin thickening proximal to the MCP joints	9
		Skin thickening of whole finger distal to MCP or puffy fingers	4 or 2
		Fingertip lesions: digital ulcers or pitting scars	2 or 3
		Telangiectasia	2
		Abnormal nailfold capillaries	2
		Pulmonary arterial hypertension or interstitial lung disease	2
		RP	3
		SSc-related antibodies (ACA, anti Scl-70, anti RNA polymerase III)	3
Requires 1 major or 2 minor criteria	Requires either (1) or (2) if RP is objectively documented. Requires (1) and (2) if RP is subjective	Requires a total score of 9 or more	

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; SSc: systemic sclerosis; RP: Raynaud phenomenon; ACA: anticentromere antibodies; MCP: metacarpophalangeal; MTP: metatarsophalangeal.

Table 2. Initial characteristics of all PBC patients and comparison between those with and without SSc. Values are expressed as mean ± SD or n (%).

Characteristics	All Patients, n = 100	PBC without SSc, n = 77	PBC with SSc[#], n = 23	p, PBC without vs with SSc
Demographic variables				
Female	91 (91)	68 (88.3)	23 (100)	0.12
Age 1st visit, yrs	57 ± 10.3	57.4 ± 10.7	55.1 ± 8.2	0.30
PBC duration since dx, yrs	8.2 ± 6.4	7.3 ± 5.5	11.1 ± 8.2	0.012
RP present	39 (39)	17 (22.0)	22 (95.6)	< 0.001
RP duration	15.6 ± 9.1	11.6 ± 9.2	18.5 ± 7.9	0.017
PBC characteristics				
Mayo score	4.14 ± 1.06	4.2 ± 1.08	3.89 ± 1	0.32
Phosphatase alkaline, u/l	178.8 ± 108.7	180.1 ± 118.8	174.8 ± 66.8	0.84
Total bilirubin, umol/l	17.7 ± 16.1	18.8 ± 17.8	14.0 ± 6.8	0.23
AST, u/l	37.1 ± 13.3	43.3 ±28.2	37.1 ± 13.3	0.33
ALT, u/l	36.2 ± 19.9	45.2 ± 33.4	36.2 ± 19.1	0.22
Alb, g/l	38.1 ± 7.5	38.4 ± 6.6	36.1 ± 11.2	0.22
INR	1.37 ± 1.8	1.38 ± 1.8	1.34 ±1.6	0.92
Esophageal varices*	16/61 (19.7)	12/46 (26.1)	4/15 (26.7)	0.73
GAVE*	2/58 (3.4)	1/44 (2.3)	1/14 (7.1)	0.43
AMA-positive	97 (97)	75 (97.4)	22 (95.6)	0.54
IgM, g/l	3.09 ± 2.2	3.17 ± 2.4	2.85 ± 1.2	0.54
Spider angioma	29 (29)	23 (29.9)	6 (26.1)	0.79
Comorbidities				
Sjögren syndrome	5 (5)	3 (3.9)	2 (8.7)	0.32
Thyroid disease	16 (16)	13 (16.8)	3 (13.0)	0.75
SLE	1 (1)	1 (1.3)	0	1
RA	3 (3)	3 (3.9)	0	1
Celiac disease	1 (1)	1 (1.3)	0	1
Psoriasis	3 (3)	3 (3.9)	0	1
SSc features				
RP	39 (39)	17 (22.1)	22 (95.6)	< 0.001
Abnormal capillaroscopy	20 (20)	3 (3.9)	17 (73.9)	< 0.001
Antibodies present	26 (26)	4 (5.2)	22 (95.6)	0.12
ACA present	19 (19)	0	19 (82.6)	< 0.001
Puffy fingers, sclerodactyly	14 (14)	3 (3.9)	11 (47.8)	< 0.001
Ulcers	1 (1)	0	1 (4.3)	0.23
Capillary telangiectasia	17 (17)	1 (1.3)	16 (69.6)	< 0.001
Skin telangiectasia	23 (23)	7 (9.1)	16 (69.6)	< 0.001
Pulmonary hypertension**	9/25 (36)	3/14 (21.4)	6/11 (54.5)	0.12
Pulmonary fibrosis on CXR	5 (5)	2 (2.6)	3 (13.0)	0.0783

[#] All PBC patients who were positively classified by ≥ 1 classification criteria. * Expressed as a proportion (%) where the denominator represents total patients with data available. ** Screened by cardiac ultrasound (systolic pulmonary artery pressure exceeds 35 mm Hg or tricuspid regurgitation velocity ≥ 2.9). PBC: primary biliary cholangitis; SSc: systemic sclerosis; RP: Raynaud phenomenon; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GAVE: gastric antral vascular ectasia; Alb: albumin; AMA: antimitochondrial antibodies: IgM: immunoglobulin M; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; ACA: anticentromere antibodies; CXR: chest radiograph.

ACR/EULAR criteria, and only 1 for the ACR 1980 criteria. An individual breakdown of the features associated with SSc-positive patients is shown in Table 3. The most frequent SSc-associated features observed in the study population were RP (39%), SSc antibodies (26%), abnormal NCM (20%), and capillary telangiectases (17%). Being LeRoy and Medsger's central criteria, all 22 of those patients had RP, while its sensitivity and specificity for ACR/EULAR-positive SSc was 94.1% and 72.2%, respectively. SSc antibodies were found in 26 patients with PBC, with sensitivity and specificity at 100% and 89.1%, respectively. Abnormal NCM was present in 20 patients with PBC with sensitivity and specificity at 88.2% and 94.1%, respectively. The singular ACR 1980 positive person was also positive for both subsequent criteria. All ACR/EULAR positive patients also fulfilled the 2001 criteria except one, in whom RP was absent. This patient, however, had anticentromere antibodies (ACA) NCM changes and SSc-patterned NCM changes, telangiectases, and sclerodactyly. Clinically evident skin changes were the rarest major defining features and were found in 14 patients, of whom 10 and 11 were LeRoy and Medsger and ACR/EULAR positive, respectively. As expected, all 10 LeRoy and Medsger–positive patients with visible skin changes were also ACR/EULAR positive.

The patients' comparative characteristics according to the presence or absence of PBC-associated SSc are reported in the last columns of Table 2. The duration of PBC since diagnosis shows a longer average evolution time in patients

Table 3. Individual patterns of systemic sclerosis criteria–positive patients.

Pt. #	ACR 1980	ACR/EULAR 2014 (score)	LeRoy 2001	RP	SSc Antibodies	Abnormal NCM	Skin Telan.	Puffy Fingers	Sclerodactyly	Pitting Ulcers	PH	PF
16	+	+ (18)	+	+	ACA	+	+	-	+	+	+	+
98	–	+ (14)	+	+	Anti-Th/To ACA	+	+	+	+	–	–	–
38	–	+ (10)	+	+	ACA	+	–	+	–	–	–	–
34	–	+ (10)	+	+	ACA	+	+	–	–	–	–	–
32	–	+ (14)	+	+	ACA	+	+	+	+	–	–	–
44	–	+ (14)	+	+	ACA	+	+	–	+	–	–	–
14	–	+ (14)	+	+	ACA	+	+	+	+	–	–	–
54	–	+ (10)	+	+	ACA	+	+	–	–	–	–	–
71	–	+ (12)	+	+	ACA	+	+	–	–	–	+	–
73	–	+ (14)	+	+	RNA poly III	+	–	–	+	–	+	–
42	–	+ (12)	+	+	ACA	+	+	–	–	–	+	–
83	–	+ (14)	+	+	ACA	+	–	–	+	–	+	–
80	–	+ (12)	+	+	ACA	+	+	–	–	–	–	+
36	–	+ (10)	+	+	ACA	–	+	+	–	–	–	–
67	–	+ (10)	+	+	ACA	–	–	+	–	–	+	–
15	–	+ (10)	+	+	ACA	+	+	–	–	–	–	–
75	–	– (6)	+	+	ACA	–	–	–	–	–	–	–
7	–	– (8)	+	+	Anti Th/To	–	+	–	–	–	–	–
59	–	– (8)	+	+	Anti Th/To	–	–	–	–	–	–	+
10	–	– (8)	+	+	ACA	–	+	–	–	–	–	–
84	–	– (8)	+	+	ACA	+	–	–	–	–	–	–
39	–	– (7)	+	+	–	+	+	–	–	–	–	–
6	–	+ (11)	–	–	ACA	+	+	–	+	–	–	–
Total	1	17	22	22	22	17	16	6	8	1	6	3

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; RP: Raynaud phemonenon; SSc: systemic sclerosis; ACA: anticentromere antibodies; RNA poly III: RNA polymerase III; NCM: nailfold capillary microscopy; Telan.: telangiectasias; PH: pulmonary hypertension on echocardiography; PF: bibasilar pulmonary fibrosis on chest radiograph.

with PBC with SSc, at 11.1 years vs 7.3 years (p = 0.01). Duration of RP, when present, was also noted in both groups, with a longer average presence of RP in PBC patients with SSc, at 18.5 years compared to 11.6 years (p = 0.02). However, no differences were observed in liver biochemistry, PBC-related antibody, esophageal varices, and GAVE. Autoimmune comorbidities, obtained based on patient file history, were not significantly different. Mayo score was 4.21 ± 1.08 in SSc-negative and 3.89 ± 0.98 in SSc-positive patients (p = 0.32).

A flowchart of relevant clinical, serological autoantibody, and capillaroscopic findings of our study population was created (Figure 1) based on a modified algorithm for the screening and diagnosis of SSc in PBC first proposed by Rigamonti, *et al*[21]. The use of RP as the sentinel symptom of SSc, with SSc-specific antibodies and NCM as screening tools, allowed us to identify all the patients who eventually satisfied the ACR/EULAR criteria.

DISCUSSION

While previous studies have established that SSc is significantly more frequent in patients with PBC than in other patient groups[2,8,9,10], ours is the first study, to our knowledge, to compare all 3 criteria sets, to better estimate the prevalence of SSc in patients with confirmed PBC. Using more sensitive criteria, we found a generally higher prevalence rate than those previously reported in large cohort studies[2,8,10], at 17% prevalence using the ACR/EULAR criteria and 22% with LeRoy and Medsger's 2001 criteria.

Compared to previous studies, our prevalence rate using ACR 1980 criteria is similar, albeit lower, at 1% compared to 2%–3%[8,10]. With the inclusion of "possible SSc" based on their own defined criteria, the prevalence rate in 1 study then approached 8%[8], similar to patients with PBC cross-referenced with preestablished SSc[9]. In the only study applying LeRoy and Medsger's 2001 criteria in patients with PBC[22], 18.8% satisfied the criteria, having RP and either SSc antibodies or NCM changes. A significantly lower 6.25% had definite ACR 1980 criteria SSc. This is in line with our 22% prevalence rate based on the 2001 criteria. Comparatively, our slightly higher rate may also be due to the inclusion of RNA polymerase III and anti-Th/To antibody detection. Although patients were evaluated prior to the 2013 ACR/EULAR criteria, there are no expected biases in this respect because all clinical criteria were systematically searched for at the initial visit.

Foremost, it is the large prevalence gap between the original 1980 ACR and 2013 ACR/EULAR criteria that is revealing, especially because our gastroenterology patients had no prior SSc diagnosis and there was no rheumatologic

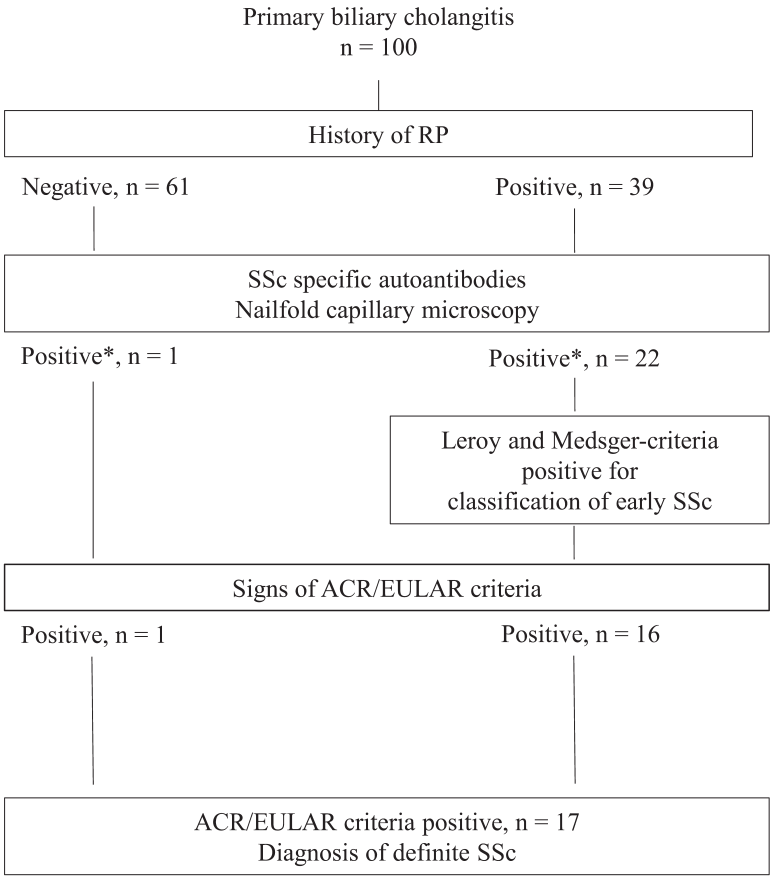

Figure 1. Diagnostic flowchart leading to SSc classification based on differing criteria. * Positive for SSc-specific antibodies and/or NCM changes. SSc: systemic sclerosis; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; NCM: nailfold capillary microscopy; RP: Raynaud phenomenon.

referral bias. While this may underestimate total SSc prevalence in PBC, it is interesting to note that the reverse association, PBC prevalence in established SSc, is lower, at only 2%[23]. More importantly, knowing the poor ACR 1980 criteria sensitivity, it is highly probable that SSc prevalence in PBC was underestimated in the past, similarly to previous SSc estimates among the general population with RP[24]. This is important because new ACR/EULAR classification criteria have reported both sensitivity and specificity upward of 90%[14,25,26]. Nevertheless, confirmation will still require expert diagnosis and exclusion of other causes.

In our cohort, SSc-positive patients seem to have a slightly longer PBC disease evolution and may have RP predating initial PBC symptoms, with an average duration of RP of 18 years, although this is susceptible to eternity bias and is an inadequate surrogate for SSc disease duration. Nevertheless, these are indications that SSc is a progressive disease[13], with prominent features of RP, which often precedes clinical SSc, as a "sentinel" sign[27].

One limitation is the lack of thoracic high-resolution computed tomography (HRCT) scanning in our patients. Only plain chest films were performed in all patients according to 1980 ACR SSc criteria for pulmonary fibrosis. As a much more sensitive examination, use of HRCT over plain films would only have led to a higher ACR/EULAR criteria SSc prevalence, especially in the group already LeRoy and Medsger–positive. Likewise, screening for pulmonary arterial hypertension (PAH) with cardiac ultrasound was performed in only 25 patients owing to clinical suspicion. No patient underwent right heart catheterization. One patient with a positive PAH screen required this as the additional criterion to be ACR/EULAR-positive. This may be another source of underestimation, although PAH may also be independently associated with cirrhosis[28].

Patients with PBC are also more likely to show nailfold abnormalities than other cirrhotic patients[29,30], ranging from typical SSc modifications to nonspecific changes. Whether these reflect early SSc in PBC or are PBC-related changes is unclear. In 1 study, no PBC patient with NCM abnormalities was classified with 1980 criteria SSc[30], although RP and ACA appeared significantly more frequently[29,30]. This would be interpreted as fulfilling LeRoy and Medsger criteria in our

study, although only specific NCM changes, as described in the methods, were accepted, excluding nonspecific findings such as increased capillary tortuosities. Also possibly confounding is the presence of telangiectasia in liver cirrhosis, generally as spider nevi. An attempt was made to objectively distinguish these by looking for nailfold capillary telangiectasias, an unvalidated technique. Compared to using the criterion of cutaneous telangiectasia, this resulted in 1 patient (patient 15 in Table 3) losing sufficient scoring on ACR/EULAR criteria, but remaining Leroy and Medsger–positive. The presence of clearly distinguishable spider angiomas was not different between SSc- positive and SSc-negative groups.

SSc is a major source of comorbidity in PBC from vascular and systemic involvement. While we see a non-statistically significant tendency of lower Mayo scores in our PBC-SSc patients, in accord with past evidence suggesting that these patients may have a slower rate of liver disease progression and related deaths, the overall survival benefit seems to be neutralized by increased SSc-related mortality[9]. The strong interest in earlier immunomodulatory options during the "window of therapeutic opportunity" before morbid organ fibrosis, paired with the significant SSc prevalence and morbidity, highlights the importance of early detection.

RP followed by SSc antibodies and NCM abnormalities were the most frequently detected trio of SSc features in our patients with PBC, and their successive presence greatly increased specificity while sacrificing some sensitivity. This highlights the value of LeRoy and Medsger's 2001 criteria, previously validated, wherein 79.5% of these patients eventually developed definite 1980 criteria SSc[13]. However, there is now a new subset of patients who are LeRoy and Medsger–positive but ACR/EULAR-negative, as recently reported by the Canadian Scleroderma Research Group[31], and that applies to 6 patients in our study. Opinion suggests these patients should be labeled as the new "early" SSc or pre-scleroderma[32] and we agree, having recognized the importance of LeRoy and Medsger features over time with accumulated clinical experience and experimental data[13,33]. We were not, on the other hand, able to evaluate the recent evolution of these patients, and so, especially with research focusing on the "very early" diagnosis and treatment options[34], screening criteria remain to be determined more rigorously.

We reaffirm the significant SSc prevalence in PBC, with probable underestimation in the past. A total of 23% of our patients with PBC were positively detected by more sensitive SSc criteria. Given the benefit of earlier detection and treatment of SSc, patients with PBC should be screened for RP and SSc antibodies, and have nailfold capillaroscopic microscopy where available, to identify those with or at risk for SSc. Clinicians need to remain alert for this sometimes insidious comorbidity.

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