Disease Subsets, Antinuclear Antibody Profile, and Clinical Features in 127 French and 247 US Adult Patients with Systemic Sclerosis

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ABSTRACT. ***Objective***. To investigate the specificities of antinuclear antibodies (ANA) associated with systemic sclerosis (SSc) disease classification and internal organ involvement among patients with SSc of different origins (European and American).

Methods. Serum samples from 374 adult patients diagnosed with SSc were studied: 127 French patients (Paris) were compared with 247 US patients (Pittsburgh). Patients were classified into diffuse cutaneous (dc) and limited cutaneous (lc) SSc subsets. Antibodies associated with SSc were determined by protein and/or RNA immunoprecipitation, indirect immunofluorescence, and immunodiffusion.

Results. SSc classification differed significantly in the 2 cohorts: lcSSc and overlap patients with lcSSc combined made up 76% of the French series versus 52% of the US group ($p < 0.0001$). The frequency of anti-RNA polymerase III antibody was significantly increased in US patients compared with French patients ($p < 0.0001$). The frequency of anti-topoisomerase I (topo I) antibody was significantly increased among French patients ($p < 0.0048$). Anti-topo I-positive French SSc patients were less likely to have dcSSc (38% vs 65%) and more likely to have milder disease than US anti-topo I-positive patients. The French dcSSc patients had lower proportions of joint/tendon manifestations and renal crisis (7% vs 17%), but more often had radiographic evidence of pulmonary fibrosis (57% vs 30%). French lcSSc patients had a lower frequency of pulmonary arterial hypertension than US lcSSc patients (9% vs 31%; $p = 0.002$).

Conclusion. There are disease classification and SSc-related serum autoantibody differences between French and American patients with SSc. These differences help to explain variations in clinical features reported from different geographic regions. (First Release Nov 15 2006; J Rheumatol 2007;34:104–9)

Key Indexing Terms:
SYSTEMIC SCLEROSIS ANTI-TOPO I ISOMERASE ANTICENTROMERE
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Systemic sclerosis (scleroderma or SSc) is a systemic connective tissue disease characterized by microvascular injury and abnormalities of the immune system leading to fibrosis of the skin and major internal organs, including the digestive tract, lungs, heart, and kidneys. SSc is characterized by the occurrence of serum antinuclear antibodies (ANA), with prevalence varying from 80% to 98%[1]. ANA specificities are associated with certain clinical and laboratory features of the disease. For example, scleroderma renal crisis is most frequent in patients with anti-RNA polymerase III antibody[2], and pulmonary fibrosis is most common in patients with anti-topoisomerase I (topo I)[3,4] and anti-Th/To antibody[5]. Certain antinucleolar autoantibodies, such as anti-PM-Scl, and anti-uridine-rich ribonucleoprotein autoantibodies, such as anti-U1-RNP, have been associated with myositis and overlap syndromes[6].

ANA results from various ethnic groups have shown differences in the frequencies of ANA specificities[7-9]. Such variations may also exist among Caucasian patients with SSc from different geographic locations or origins. To explore this possibility, we examined whether the frequencies of SSc-related autoantibodies and their associations with disease classification and internal organ involvement differed between 2 cohorts of SSc patients, one from France and the other from the United States.

MATERIALS AND METHODS

Patients. We studied clinical manifestations and autoantibodies in serum samples from patients diagnosed as having SSc at 2 sites. French patients were consecutively evaluated at the Division of Rheumatology, Bichat University School of Medicine, Paris, during the period 1975-2002, and

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US patients were consecutively evaluated at the Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, during the period 1986-88.

Patients were classified into disease subsets based on the extent of skin thickness. Patients with diffuse cutaneous (dc) involvement must have had skin thickening proximal to the elbows or knees (affecting upper arms, thighs, or trunk) at some time during their illness. In contrast, individuals with limited cutaneous (lc) involvement either had no skin thickening (SSc sine scleroderma[10]) or skin thickening only distal to the elbows and knees throughout their course. Facial skin thickening was permitted in patients classified as lcSSc. Patients diagnosed with SSc in overlap had either dc or lcSSc and features of one or more other connective tissue disease(s) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PM/DM), or Sjögren's syndrome (SS). SSc subset classification was verified by 2 authors (OM for French and TAM for US patients) based on either personal observation or medical record review.

For the US patients, clinical and laboratory data were collected prospectively using a standard data collection form for the initial and all followup visits. For French patients, data were collected prospectively and abstracted for this study retrospectively from available medical records, using a standardized data form designed by OM, who personally supervised the process. Some clinical and laboratory features were not compared since the collected data were not comparable between groups.

SSc patients with disease onset during childhood (age < 16 yrs) were excluded. Disease onset was defined as the first symptom attributable to SSc. A serum sample was obtained from each patient within 1 year of the first visit and stored frozen until use.

Laboratory methods. Antibodies for both the French and US patients were determined in the same laboratory (Pittsburgh), as described, by protein immunoprecipitation[2] (anti-RNA polymerase III and anti-Ku); RNA immunoprecipitation[5] (anti-Th/To); both protein and RNA immunoprecipitation (anti-aminoacyl tRNA synthetases, anti-U1RNP, -U2RNP, and -U3RNP); and indirect immunofluorescence of a 1/40 dilution of patient sera on HEp-2000® substrate[5] (anticentromere; Immunoconcepts, Sacramento, CA, USA). Anti-topo I, anti-PM-Scl, anti-U1RNP, and anti-Jo-1 were confirmed by immunodiffusion[11].

Definition of clinical findings. SSc clinical features were considered to be present if predefined criteria were met during the course of the illness and were not attributable to other diseases. Both centers adhered strictly to these criteria for retrospective medical record review and prospective patient evaluation. Data on many clinical features were collected but not included in the analysis. They included digital pitting scars, digital tip ulcers, and digital tip gangrene. Few of the patients in either group had had high resolution computerized tomography scans of the lung or radiographs of small bowel. In other instances, data were available from one center but not from the other, precluding comparison. SSc clinical features included the following: (1) Cutaneous: skin thickening either absent (SSc sine scleroderma) or in a typical lc or dc distribution as described above; or calcinosis seen either radiographically or on physical examination. (2) Peripheral vascular: Raynaud's phenomenon by history. (3) Joint or tendon: inflammatory arthralgias or arthritis of the small joints of the hands with prominent morning stiffness; or one or more palpable tendon friction rubs. (4) Gastrointestinal tract: distal esophageal dysmotility by esophagram or motility study. (5) Lung: pulmonary fibrosis on plain chest radiograph or high resolution computerized tomograph (HRCT) or mean pulmonary artery pressure > 30 mm Hg on cardiac catheterization or echocardiographic evidence of increased pulmonary artery pressure. (6) Heart: estimated left ventricular ejection fraction < 50% on echocardiogram; or arrhythmia requiring treatment. (7) Kidney: "renal crisis," defined as the abrupt onset of accelerated arterial hypertension or rapidly progressive oliguric renal failure. (8) General: hemoglobin concentration and erythrocyte sedimentation rate (ESR).

Statistical analysis. Student's t test was used to detect significant differences between distributions of continuous data. Chi-square analysis was used to determine significant differences between sets of categorical data, with Fisher's exact test utilized when appropriate. Due to the number of variables being evaluated, the Bonferroni correction factor was used, with the specific p value denoting significance listed below each table.

Compliance with research ethical standards. Although retrospective, the protocol had been approved by the local institutional review board, the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (CCPPRB) of Bichat University and the Institutional Review Board of the University of Pittsburgh. All analyses were conducted using blinded data.

RESULTS

Demographic features and disease classification. We studied a total of 374 patients with SSc, 127 from France and 247 from the US. Of the patients who had all elements available for the American College of Rheumatology criteria for definite SSc[12], 199/240 (83%) of the US and 76/87 (87%) of French patients satisfied these criteria. The demographic and clinical subsets of the patients from both cohorts are described in Table 1. The mean age at the time of diagnosis (48.4 and 47.2 yrs) was similar in the French and US groups, respectively, as was the percentage of female patients (83% and 81%) and Caucasians (91% and 92%). Fifty-six percent of the French patients resided within 60 miles of Paris and 42% of the US patients lived within 100 miles of Pittsburgh (NS).

French and US patients were diagnosed as having SSc a mean of 5.1 and 5.1 years after disease onset (first symptom attributable to SSc), respectively. The mean time from first physician diagnosis to last followup was shorter in the French than in the US patients (6.0 vs 10.3 yrs, respectively), in part because of incomplete longterm followup for the French patients. Disease onset was before age 40 years in 58 (46%) French patients and 117 (47%) US patients.

The distribution of patients according to SSc disease classification differed significantly in the 2 cohorts. Limited cutaneous SSc and overlap patients with lcSSc combined made up 76% of the French series, compared with 52% of the US group ($p < 0.0001$; Table 1). As expected, almost all overlap patients had lcSSc. The frequency of overlap diseases was similar. Among the 34 French patients with overlap, 20 had PM/DM, 9 SLE, 4 RA, and 1 SS. Among the 27 US overlap patients, 10 had PM/DM, 12 SLE, 2 RA, 2 PM/DM and SLE, and 1 PM/DM and RA.

Serum ANA distribution. Serum ANA profiles for the 2 SSc patient cohorts are shown in Table 2. Three hundred seventy of the 374 sera (99%) were positive for ANA, leaving only 4 ANA-negative patients (2 French, 2 US). The frequency of anti-RNA polymerase III antibody was significantly increased in US patients compared with French patients (25% vs 4%, respectively; $p = 0.0001$). In contrast, the frequency of anti-topo I antibody was significantly increased among French patients compared with US patients (35% vs 22%, respectively; $p = 0.0048$). The pro-

Table 1. Demographic features and disease classification in the French and US systemic sclerosis cohorts.

	French, n = 127 (%)	US, n = 247 (%)	p
Mean age at first physician diagnosis, yrs	48.4 ± 15.6	47.2 ± 13.7	NS
Sex female	105 (83)	183 (81)	NS
Ethnicity			
Caucasian	116 (91)	226 (92)	
African-American	6 (5)	13 (5)	NS
Other	5 (4)	6 (2)	
Unknown	0 (0)	2 (1)	
Disease duration			
From onset to diagnosis, mean yrs ± SD	5.1 ± 9.1	5.1 ± 7.7	NS
From diagnosis to last followup, mean yrs ± SD	6.0 ± 6.1	10.3 ± 6.5	< 0.001*
Total, mean yrs ± SD	11.1 ± 10.5	15.4 ± 9.9	< 0.0011*
Disease classification			
Diffuse cutaneous (dc) alone	24 (19)	116 (47)	
Limited cutaneous (lc) alone	69 (54)	104 (42)	< 0.0001*
Overlap	34 (27)	27 (11)	
dc in overlap	6	3	< 0.0001*
lc in overlap	28	24	

* Using the Bonferroni correction, a statistically significant p value is < 0.0063. NS: nonsignificant.

Table 2. ANA profile in the French and US systemic sclerosis cohorts.

	Autoantibody	France, n = 127 (%)	US, n = 247 (%)	p
One autoantibody	Anti-RNA polymerase III	5 (4)	61 (25)	0.0001*
	Anti-topoisomerase I	45 (35)	54 (22)	0.0048*
	Anticentromere	23 (18)	52 (21)	NS
	Anti-Th/To	1 (1)	9 (4)	NS
	Anti-U1RNP	12 (9)	18 (7)	NS
	Anti-U3RNP	2 (2)	6 (2)	NS
	Anti-PM-Scl	8 (6)	7 (3)	NS
	Anti-Ku	3 (2)	2 (1)	NS
More than one autoantibody		4 (3)†	9 (4)††	NS
None of the above autoantibodies	ANA positive	22 (17)	27 (11)	NS
	ANA negative	2 (2)	2 (1)	NS

* Using the Bonferroni correction, a statistically significant p value is < 0.005. † French combinations: anti-topoisomerase I + anti-Ku (2); anti-topoisomerase I + anticentromere (1); anti-U1RNP + anti-Th/To (1). †† US combinations: anti-RNA polymerase III + anticentromere (2); anti-U1RNP + anti-U3RNP (2); anti-topoisomerase I + anti-Ku (1); anticentromere + anti-Th/To (1); anti-Th/To + U3 RNP (1); anti-Th/To + anti-Ku (1); U3RNP + anti-Ku (1). NS: nonsignificant.

portion of lcSSc patients with anti-topo I antibody was 29% in the French series and 15% in the US series (p < 0.014). The frequencies of other SSc-related ANA were similar in both groups of patients, either alone or in combination (more than one SSc-related ANA). Undefined ANA specificities were present in 17% of French and 11% of US patients (NS).

In data not shown, anti-U1RNP antibody was associated with SSc in overlap in French patients. Twelve of 34 French overlap patients had this autoantibody compared with 0/93 French patients without overlap (p < 0.0001). Similarly, anti-PM-Scl antibody correlated with overlap classification among French patients (6/34 vs 2/93; p = 0.0045). Conversely, anti-topo I and anticentromere antibodies (ACA) were less frequent in French patients with SSc in overlap (6/34 vs 40/93; p = 0.0085 and 0/34 vs 23/93; p = 0.0005, respectively). In the French series, anti-U1RNP antibody was more prevalent in SSc patients whose symptoms began before age 40 compared with patients who were 40 years or older at onset (16% vs 5%; p = 0.0005). A similar nonsignificant trend was found for US SSc patients (10% vs 4%; NS).

Comparison of clinical features according to disease classification. The presence of clinical findings in French com-

pared to US patients with dc or lcSSc is shown in Table 3. French dcSSc patients differed from US dcSSc patients in several respects. They had a higher proportion with radiographic evidence of pulmonary fibrosis (57% vs 30%) and lower frequencies of arthralgias or arthritis (70% vs 98%; p = 0.0001) and palpable tendon friction rubs (28% vs 60%; p = 0.003). French lcSSc patients had a significantly reduced frequency of pulmonary arterial hypertension compared with US lcSSc patients (9% vs 31%; p = 0.002). Among those with lcSSc, French patients had a lower frequency of arthralgias or arthritis but, paradoxically, a higher frequency of tendon friction rubs than US patients.

When all patients in both cohorts were compared (right column, Table 3), a significantly lower proportion of French patients had arthralgias or arthritis. Although not significant using the Bonferroni correction, renal crisis was less common in French patients (2% vs 9%; p = 0.005).

Comparison of clinical features according to ANA specificity. Clinical findings were also examined according to SSc related ANA (Table 4). French patients with ACA were less likely to have isolated pulmonary arterial hypertension than US patients with this antibody (6% vs 38%; p = 0.04). As with the French and US lcSSc comparison, ACA-positive French SSc patients less frequently had arthralgias or arthri-

Table 3. Clinical findings in French and US systemic sclerosis patients with diffuse and limited cutaneous disease.

Organ System	Clinical Findings	Diffuse Cutaneous			Limited Cutaneous			All Patients		
		French, n = 30 (%)	US, n = 119 (%)	p	French, n = 97 (%)	US, n = 128 (%)	p	French, n = 127 (%)	US, n = 247 (%)	p
Skin	Calcinosis	4/25 (16)	19/83 (23)	NS	26/73 (36)	39/93 (42)	NS	30/98 (31)	58/176 (33)	NS
Peripheral vascular	Raynaud's phenomenon	30/30 (100)	116/119 (97)	NS	96/97 (99)	127/128 (99)	NS	126/127 (99)	243/247 (98)	NS
Joint or tendon	Arthralgias or arthritis	19/27 (70)	117/119 (98)	0.0001*	62/96 (65)	100/128 (78)	0.034	81/123 (66)	217/247 (98)	0.0001*
	Tendon friction rub	8/28 (28)	71/119 (60)	0.0030*	15/82 (18)	9/128 (7)	0.015	23/110 (21)	80/247 (32)	0.027
GI	Esophageal dysmotility	23/29 (79)	68/102 (67)	NS	56/89 (63)	62/93 (67)	NS	79/118 (67)	130/195 (67)	NS
Lung	Chest x-ray fibrosis	16/28 (57)	33/109 (30)	0.014	24/81 (30)	42/113 (37)	NS	40/110 (36)	75/222 (34)	NS
	Isolated pulmonary hypertension	3/24 (12)	1/41 (2)	NS	6/69 (9)	17/54 (31)	0.002*	9/93 (10)	18/95 (19)	NS
Heart	EKG arrhythmia	3/29 (10)	10/90 (11)	NS	13/91 (14)	19/100 (19)	NS	16/120 (13)	29/90 (15)	NS
	Reduced LVEF	4/27 (15)	8/41 (20)	NS	9/77 (12)	3/48 (6)	NS	13/114 (11)	11/89 (12)	NS
Kidney	Renal crisis	2/30 (7)	20/119 (17)	NS	0/95 (0)	3/128 (2)	NS	2/125 (2)	23/247 (9)	0.005
General	Hemoglobin†, mean g/dl	12.7 ± 1.8	12.6 ± 1.8	NS	12.7 ± 1.7	13.2 ± 1.9	NS	12.70 ± 1.8	12.9 ± 2.1	NS
	ESR†, mean mm/h	28.6 ± 23.1	27.8 ± 23.1	NS	28.6 ± 29.9	27.9 ± 29.3	NS	28.6 ± 28.1	27.9 ± 26.3	NS

Parentheses indicate percentage positive or abnormal.* Using the Bonferroni correction, a statistically significant p value is < 0.0036. † First recorded. GI: gastrointestinal tract; EKG: electrocardiogram; LVEF: left ventricular ejection fraction; ESR: erythrocyte sedimentation rate; NS: nonsignificant.

Table 4. Comparison of clinical findings in French and US systemic sclerosis patients grouped according to autoantibody profile.

Organ System	Clinical Findings	Anti-Topoisomerase I			Anti-centromere			Anti-RNA Polymerase III		
		French, n = 45 (%)	US, n = 54 (%)	p	French, n = 23 (%)	US, n = 52 (%)	p	French, n = 5 (%)	US, n = 61 (%)	p
Skin	Diffuse skin changes	17/45 (38)	35/54 (65)	0.009	1/23 (4)	5/52 (10)	NS	4/5 (80)	52/61 (85)	NS
	Calcinosis	5/32 (15)	9/37 (24)	NS	7/18 (38)	21/36 (58)	NS	0/3 (0)	6/40 (15)	NS
Peripheral vascular	Raynaud's phenomenon	44/45 (97)	54/54 (100)	NS	23/23 (100)	52/52 (100)	NS	5/5 (100)	60/61 (98)	NS
Joint or tendon	Arthralgias or arthritis	30/43 (69)	50/54 (92)	0.006	11/23 (47)	38/52 (73)	0.037	3/4 (75)	58/61 (95)	NS
	Tendon friction rub	12/40 (30)	24/54 (44)	NS	3/19 (15)	0/52 (0)	0.016	1/5 (20)	43/61 (70)	NS
GI	Esophageal dysmotility	34/42 (80)	33/45 (73)	NS	12/21 (57)	29/35 (83)	NS	1/5 (20)	27/51 (53)	NS
Lung	Chest x-ray fibrosis	18/36 (50)	21/48 (44)	NS	2/18 (11)	8/44 (18)	NS	0/4 (0)	16/56 (29)	NS
	Isolated pulmonary hypertension	1/31 (3)	0/17 (0)	NS	1/15 (6)	6/16 (38)	0.04	0/5 (0)	1/14 (7)	NS
Heart	EKG arrhythmia	3/44 (6)	11/47 (23)	0.04	1/20 (5)	4/33 (12)	NS	0/5 (0)	1/45(2)	NS
	Reduced LVEF	4/36 (11)	3/16 (19)	NS	2/21 (9)	1/14 (7)	NS	0/5 (0)	1/14 (7)	NS
Kidney	Renal crisis	1/44 (2)	3/54 (6)	NS	0/23 (0)	0/52 (0)	NS	1/5 (20)	15/61 (25)	NS
General	Hemoglobin, mean g/dl†	13.1 ± 1.6	12.8 ± 1.6	NS	12.6 ± 1.4	13.4 ± 1.8	NS	12.3 ± 2.0	12.6 ± 2.1	NS
	ESR, mean mm/h†	24.1 ± 19.2	34.2 ± 27.3	NS	27.1 ± 24.4	16.1 ± 16.7	NS	11.8 ± 6.5	24.1 ± 20.9	NS

Parentheses indicate percentage positive or abnormal. *Using the Bonferroni correction, a statistically significant p value is < 0.0033. † First recorded. GI: gastrointestinal tract; EKG: electrocardiogram; LVEF: left ventricular ejection fraction; ESR: erythrocyte sedimentation rate; NS: nonsignificant.

tis but more often had tendon friction rubs. The number of French anti-RNA polymerase III antibody-positive patients was too small for meaningful comparison with US patients.

There were several differences between French and US anti-topo I antibody-positive patients. Anti-topo I antibody was associated with radiographic evidence of pulmonary fibrosis in French SSc patients ($p = 0.0381$) more than in US patients ($p = 0.0992$). French patients with this autoantibody less often were classified as having diffuse skin involvement (38% vs 65%; $p = 0.009$) and significantly less frequently experienced arthralgias or arthritis (69% vs 92%; $p = 0.006$). Arrhythmias on electrocardiogram were less frequent in French patients with anti-topo I antibody (6% vs 23%). The mean first recorded value of ESR was lower (24.1 vs 34.2) and the mean hemoglobin level was higher (13.1 vs 12.8 g/dl) in French compared with US anti-topo I patients.

DISCUSSION

Subset classification differed between the French and US patients with SSc in several respects. The proportion with lc changes was higher among the French compared with US patients (97 or 76% vs 128 or 52%, respectively, including overlap patients; Table 1). To examine whether selective referral of dcSSc patients to Pittsburgh contributed to this difference, we examined only patients residing within 100 miles of Pittsburgh. In the latter subgroup, the proportion with dcSSc was 37% and with lcSSc 63%. Thus although there was some disproportionate referral of dcSSc patients to Pittsburgh, it did not completely explain the classification differences between the cohorts. Based on a previous incidence study of SSc in Pittsburgh and Allegheny County, Pennsylvania[13], we determined that over 80% of all patients with SSc diagnosed in this geographic region are seen at the University of Pittsburgh Scleroderma Center. Thus, significant underrepresentation of lcSSc in this population, for insurance or other reasons, is unlikely.

Because the Bichat Hospital patients were enrolled over a prolonged period of time (28 yrs), we compared the 58 patients first evaluated before 1989 and the 69 seen in or after 1989. There were no significant differences in demographic features, disease classification including the proportion with overlap, clinical findings including organ system involvement, or autoantibody status. Thus, there were no apparent secular trends in occurrence or severity of SSc in the French findings during 1975-2002 that might have biased the results of this comparison.

The proportion of SSc patients with overlap features was higher in the French (27% vs 11%; $p < 0.001$). This difference could be explained by the longstanding interest in overlap syndromes such as mixed connective tissue disease at the Bichat University Rheumatology Department. Most (60–80%) SSc patients with overlap have lc skin changes, which may contribute to the lc compared to the dc differences in clinical findings that were detected. It is possible that the significant differences in longterm followup (Table 1) account in part for the lc versus dc discrepancy. For example, some French lcSSc patients followed for an additional 5 years could have evolved to dcSSc, thus altering the ratio of dc to lcSSc among the French patients. Finally, subtle differences in physical examination interpretation of skin thickness could account for some patients being classified as lcSSc in France who might have been classified as dcSSc in the US. No interobserver difference data are available to examine this possibility. Similarly, tendon friction rubs, arthralgias/arthritis, and Raynaud's phenomenon in French and US patients could be influenced by differences in history taking and physical examination in the 2 sites. Since few patients had right-heart catheterization, the presence of isolated pulmonary hypertension was most often based on clinical findings and echocardiogram results. It remains possible that methodologic or data collection differences explain the increased frequency of SSc in overlap patients in the French cohort. A prospective study with a strict definition of "overlap" and pre-study training of reporting physicians would be necessary to confirm these differences.

In Pittsburgh, virtually all SSc patients are seen in the Rheumatology Division. At Bichat University, about one-third of SSc patients are seen in the Dermatology Department. A comparison of Bichat Rheumatology and Dermatology patients with SSc seen during 1980-99 was performed in 2003, and it identified no differences in demographic features, disease classification, or prevalence of either ACA or anti-topo I antibodies. There were significantly higher frequencies of pulmonary fibrosis, gastrointestinal symptoms, cardiovascular involvement, and use of corticosteroids and immunosuppressive drugs in the Rheumatology Department patients (unpublished data). Thus it is likely that our finding of milder disease among French compared with US SSc patients is accurate.

In this study, the serologic profile of French patients differed significantly from the profile in US patients in 2 respects (Table 2). French patients had a lower frequency of anti-RNA polymerase III antibody (4% vs 25%) and a higher frequency of anti-topo I antibody (35% vs 22%). These findings may account for the lower frequency of scleroderma renal crisis (2% vs 9%; $p < 0.005$) among French patients. However, pulmonary fibrosis was not significantly more frequent among French patients (36% vs 34%; Table 3), as would have been expected with increased anti-topo I frequency.

Evaluation of the 2 populations according to serum autoantibody type shows some expected and some unexpected results (Table 4). French ACA-positive patients less often developed "isolated" pulmonary arterial hypertension than US patients. It is possible that differences in patient selection for echocardiography or lack of longterm followup in the French patients contributed to this difference.

In other respects, the profile for ACA-positive patients was similar in both groups, with low frequencies of pulmonary fibrosis and heart disease and no instances of renal crisis.

Anti-topo I-positive patients differed somewhat in the French and US cohorts. French anti-topo I patients were more likely to have limited skin involvement (62% vs 35%) and less joint or tendon involvement and cardiac arrhythmia than US anti-topo I patients, suggesting that, overall, they had a milder form of SSc. In keeping with this interpretation, French anti-topo I patients had a higher mean first-recorded hemoglobin concentration and lower mean ESR than US anti-topo I-positive patients. Longterm followup and survival data are being collected, but are not yet available to compare the natural history of SSc in these 2 patient populations.

Genetic factors may influence the frequency of autoantibodies specific for SSc such as anti-topo I or anti-RNA polymerase III antibodies. Since over 90% of patients are Caucasians in both series, we can assume that both populations share a genetic background different from patients of Japanese[8], Thai[7], Hispanic, or African American[9] ethnic origin. However, Caucasian SSc patients from France might differ from US patients since the majority of the latter are of Anglo-Saxon extraction.

Reports concerning the prevalence of anti-RNA polymerase III antibody in patients with SSc in different European countries suggest decreasing prevalence from north to south continental Europe: 22% in Sweden[14], 12% in England[15], 8% in Italy[16], and 5% or less in Poland. The 4% prevalence of anti-RNA polymerase III antibody in the French subgroup of 116 Caucasian patients with SSc is consistent with such a north to south gradient. Similar differences have been reported among European Caucasians for ACA and anti-topo I autoantibodies[17]. The methodology for determination of anti-RNA polymerase III antibody in the studies cited above differed, but our sera were all tested by the same method and by the same laboratory technician (NF).

Our data show that SSc cohorts from France and the US have many similar clinical and serologic manifestations. There is a disease classification difference in that French patients are more likely to have limited cutaneous involvement and SSc in overlap compared with US patients. Also, there are significant differences in the frequencies of anti-RNA polymerase III autoantibody and anti-topoisomerase I autoantibody between the 2 populations. Anti-topoisomerase I antibody is associated with lcSSc in French patients, and these individuals tend to have milder disease than US patients with this serum autoantibody. These differences help to explain variations in the clinical and laboratory features and natural history of SSc that are reported from different geographic regions.

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