Review

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Autoantibody profile in a cohort of Algerian patients with systemic sclerosis

Profil en auto-anticorps dans un groupe de patients algériens atteints de sclérodermie systémique

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Abstract. *Aim*: To describe the autoantibody profile in a cohort of Algerian patients with systemic sclerosis (SSc) and to determine clinical associations between SSc-related autoantibodies, disease subtypes and specific clinical features. *Methods*: Consecutive Algerian patients with SSc were included in the present study. In addition to clinical characterization, all subjects underwent autoantibody testing using indirect immunofluorescence, immunoenzymatic, and line immunoblot assays. *Results*: A total of 150 patients were included in this study, 103 (68.7%) had limited cutaneous SSc (lcSSc), 42 (28%) had diffuse cutaneous SSc (dcSSc) and 5 (3.3%) had sine cutaneous scleroderma. One hundred thirty-five (90.0%) patients were positive for SSc-related autoantibodies, including 63 (42%) with more than one autoantibody. The two most frequent autoantibodies were anti-topoisomerase I (ATA) (76; 50.7%) and anti-SSA/Ro (49; 32.7%). Only 23 (15.3%) patients were positive for anticentromere; 9 (6%) were positive for anti RNA polymerase III; 5 (3.3%) for anti-U3 RNP; 3 (2%) for anti Th/To; 25 (16.7%) for anti-U1 RNP; 11 (7.3%) for anti-PM/Scl and 4 (2.7%) for anti-Ku. Anti-topoisomerase I was associated with dcSSc ($p < 0.0001$), interstitial lung disease (ILD) ($p < 0.0001$) and digital ulcers ($p < 0.0001$). Anti-U3 RNP was associated with pulmonary arterial hypertension (PAH) ($p=0.031$). *Conclusion*: Notable similarities and differences in the prevalence of SSc-related autoantibodies were found in our population when compared to other ethnic groups. ATA and anti-U3 RNP may be a reliable biomarker for ILD and PAH. Further studies should be conducted to better understand the ethnic influence on disease expression and autoantibody production.

Key words: *autoantibodies, clinical relevance, systemic sclerosis, Algeria*

Résumé. *Objectif* : Etablir un profil en auto-anticorps dans un groupe de patients algériens atteints de sclérodermie systémique (ScS) et évaluer les associations entre ces auto-anticorps et les différentes formes clinques et phénotypiques de la maladie. *Méthodes* : Une série de patients algériens diagnostiqués et suivis pour ScS ont été inclus dans cette étude. En plus d'une caractérisation clinique, tous les patients ont bénéficié d'une recherche d'auto-anticorps par des techniques d'immunofluorescence, immuno-enzymatiques et d'immuno-dots. *Résultats* : L'étude a porté sur 150 patients dont 103 (68,7 %) avaient la forme sclérodermie systémique cutanée limitée (ScScl), 42 (28 %) avaient la forme sclérodermie systémique cutanée diffuse (ScScd) et 5 (3,3 %) avaient la forme sclérodermie systémique sine scleroderma. Les auto-anticorps associés à la ScS étaient positifs chez 135 (90,0 %) patients et dont 63 (42 %) avaient plus d'un auto-anticorps. Les deux auto-anticorps les plus fréquents sont les anticorps anti-topo-isomérase I et les anti-SSA/Ro avec respectivement 76 (50,7 %) et 49 (32,7 %) des patients. Tandis que les anticorps anti-centromère, anti-RNA polymérase III, anti-U3 RNP, anti-Th/To, anti-U1 RNP, anti-PM/Scl et anti-Ku étaient notés respectivement chez 23 (15,3 %), 9 (6 %), 5 (3,3 %), 3 (2 %), 25 (16,7 %), 11 (7,3 %) et 4 (2,7 %) des patients. Les anticorps anti-topo-isomérase I

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étaient associés à la forme cutanée diffuse ($p < 0,0001$), à la pneumopathie interstitielle ($p < 0,0001$) et aux ulcérations digitales ($p < 0,0001$). De plus, les anti-U3 RNP étaient associés à l'hypertension artérielle pulmonaire ($p = 0,031$). *Conclusion* : De nombreuses similitudes et différences ont été observées dans la prévalence des auto-anticorps au cours de la ScS dans notre étude en comparaison aux autres populations. Les anticorps anti-topo-isomérase I et anti-U3 RNP pourraient constituer des marqueurs utiles pour l'atteinte pulmonaire. Des études supplémentaires sont nécessaires afin d'évaluer l'influence de l'origine ethnique dans l'expression de la maladie et la production des auto-anticorps.

Mots clés : auto-anticorps, associations cliniques, sclérodermie systémique, Algérie

Systemic sclerosis (SSc) is an idiopathic systemic autoimmune rheumatic disease (SARD) characterized by vascular damage, immune dysregulation and massive deposits of collagen and other matrix substances in the skin and many internal organs, including the lungs, gastrointestinal tract, and kidneys [1-3]. The estimated annual incidence is of 0.77 to 5.6 per 100 000 adult inhabitants [4]. Women are affected more frequently than men with the female-to male ratios ranging from 4:1 to 14:1 [5]. The clinical manifestations of SSc cover a broad spectrum, ranging from limited involvement of the skin and internal organs to diffuse skin involvement with fibrosis of internal organe [5]. Depending on the degree of skin involvement, SSc can be divided into three main groups: limited (lcSSc), diffuse (dcSSc) and sine cutaneous disease (scSSc) [6-8].

The presence of serum autoantibodies directed against a variety of intracellular and extracellular antigens is a serological hallmark of SSc. Autoantibodies are present in more than 95% of patients and are helpful biomarkers for diagnosis, classification and predicting specific clinical features of SSc [9]. Some of them are considered highly specific for SSc, including anti-topoisomerase I antibody (ATA) (or anti-Scl-70), anti RNA polymerase III antibody (anti-RNAP III) and anti-U3 RNP antibody (or anti-fibrillarin), which are generally detected in dcSSc patients, and anticentromere antibody (ACA) and anti Th/To antibody, usually associated with a limited cutaneous disease [9]. ATA, ACA and anti-RNAP III antibody were recently added to the 2013 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) SSc classification criteria [10]. In addition other autoantibodies although less specific were also associated to SSc. These include anti-U1 RNP, anti-SSA/Ro and anti-SSB/La, which can be found in other SARDs including Sharp's syndrome, Sjögren's syndrome (SS) and systemic lupus erythematosus, and anti-Ku and anti-PM/Scl, usually associated with overlap syndromes such as scleromyositis [9].

Autoantibody profile in SSc patients have been investigated in several cohorts. Notable differences were observed, highlighting the role of ethnic diversity. Most of the published reports are from Caucasian, Hispanic, African American or Asiatic patients, data from Arab and North African patients are scarce. The primary purpose of this study was to describe the autoantibody profile in a large cohort of Algerian SSc patients. A secondary goal was to determine clinical associations between SSc-related antibodies, disease subtypes and specific organ system involvement.

Patients and methods

Patients

This study has been approved by the local Committee of Ethics in Research and it conforms to the provisions of the World Medical Association's Declaration of Helsinki. A total of 150 Algerian patients all fulfilling the preliminary criteria of the American Rheumatism Association for SSc were included in this study [11]. The recruitment was done prospectively from June 2011 to July 2014 in a single rheumatology department at Specialized Medical Center of Ben Aknoun (Algiers, Algeria). Patients were classified according to the clinical subset of the disease in dcSSc, lcSSc or sine cutaneous scleroderma based on the extent of their skin involvement. They underwent multi-disciplinary clinical evaluation for the presence of peripheral vascular (i.e. Raynaud's phenomenon, digital pitting scars, digital tip ulcerations, and/or digital gangrene), joint; skeletal muscles, gastrointestinal tract and pulmonary involvement (interstitial lung disease (ILD) and/or pulmonary arterial hypertension (PAH)) as described previously [12, 13]. Patients with scleroderma-like fibrosing disorders or with Sharp's syndrome were excluded from the present study.

Antibody testing

Patient's sera were tested for a large panel of autoantibodies including: anti-topoisomerase I, anticentromere, anti-RNAP III, anti-U3 RNP, anti Th/To, anti-SSA/Ro, anti-SSB/La, anti-U1 RNP, anti-PM/Scl, anti-Ku, anti-NOR90 and anti-platelet-derived growth factor receptor

Table 1. Demographic data of Algerian SSc patients.

Variable	All (n=150)	dcSSc (n=42)	lcSSc (n=103)	p
Gender	F 140 (93.3)* M 10 (6.7)	F 39 (92.9) M 3 (7.1)	F 96 (93.2) M 7 (6.8)	NS
Age (years)	45.4 ± 13.7#	42.0 ± 14.9	46.6 ± 12.9	NS
Disease's duration (years)	12.0 ± 9.3	8.6 ± 5.5	13.8 ± 10.2	p <0.0001

dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; NS: not significant; *N (%); #numbers are expressed as mean ± SD.

(anti-PDGFR). Anti-nuclear antibodies (ANA) screening was performed by indirect immunofluorescence using HEp-2 cell line as substrate, according to the manufacturer's recommendations (INOVA Diagnostics, San Diego, CA, USA). Serum samples were tested at 1:80 dilution and nuclear staining patterns were read by two experts. Serum immunoglobulin G anti-topoisomerase I, anticentromere (CENP A & CENP B), anti-RNAP III, anti-U1 RNP, anti-SSA/Ro and anti-SSB/La antibodies were detected by immunoenzymatic assay (EIA) using commercial kits, according to the manufacturer's recommendations (INOVA Diagnostics, San Diego, CA, USA). IgG anti-U3 RNP, anti Th/To, anti-PM/Scl (75 & 100 KDa), anti-Ku, anti NOR90 and anti-PDGFR antibodies were detected by line immunoblot assay (LIA) according to the manufacturer's recommendations (Euroimmun AG, Lübeck, Germany). Briefly, diluted serum samples were first incubated with test strips coated with thin parallel lines of several purified antigens. In positive samples, the specific IgG antibodies have bound to the antigens coupled to the solid phase. A second incubation was carried out to detect the fixed antibodies using enzyme-labelled anti-human IgG which displayed a color reaction in the presence of the chromogen/substrate solution.

Statistical analysis

Clinical associations with the SSc antibodies were evaluated using chi-square or Fisher's exact test. Mann–Whitney U-test was used for continuous variables. The level of significance was taken as $p \leq 0.05$. The statistical analyses were performed using SPSS version 18 (software package (IBM), Chicago, IL, USA).

Results

Demographic data

A total of 150 Algerian SSc patients were included in the present study; 103 (68.7%) had lcSSc, 42 (28%) had dcSSc and 5 (3.3%) had sine cutaneous scleroderma (*table 1*). One hundred and forty were female (93.3%) and 10 (6.7%) were male. In the dcSSc group, 39 (92.9%) were female and 3 (7.1%) were male and in the lcSSc group, 96 (93.2%) were female and 7 (6.8%) were male. Patients were predominantly middle-aged, with a mean age of 45.4 ± 13.7 years; 42.0 ± 14.9 years in the dcSSc group and 46.6 ± 12.9 years in the lcSSc group. Mean duration of the disease (from first symptom attributed to SSc) was 12.0 ± 9.3 years; 8.6 ± 5.5 years in the dcSSc group and 13.8 ± 10.2 years in the lcSSc group (p <0.0001). Mean time since appearance of Raynaud's phenomenon was 11.9 ± 9.1 years; 8.5 ± 5.5 years in the dcSSc group and 13.5 ± 10.0 years in the lcSSc group (p <0.0001).

Table 2. Prevalence of organ system involvement in Algerian patients with SSc.

Organ system	All (n=150)	dcSSc (n=42)	lcSSc (n=103)	p
Vascular	149 (99.3)*	41 (97.6)	103 (100)	NS
Joint	109 (72.7)	31 (73.8)	74 (71.8)	NS
Skeletal muscles	27 (18.0)	5 (11.9)	20 (19.4)	NS
Gastrointestinal tract	117 (78.0)	33 (78.6)	81 (78.6)	NS
ILD	105 (70.0)	33 (78.6)	68 (66.0)	NS
PAH	16 (10.7)	6 (14.3)	9 (8.7)	NS
Kidney	1 (0.7)	1 (0.7)	0 (0)	NS

dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; NS: not significant;*N (%).

Clinical features

The clinical features of SSc patients are presented in *table 2*. All, but one (99.3%), had Raynaud's phenomenon; 93 (62%) had digital tip ulcerations; 84 (56.4%) had telangiectasia; 109 (72.7%) had join involvement, including 60 (40%) with arthritis; 117 (78%) had gastrointestinal involvement; 105 (70%) had interstitial lung disease; 16 (10.7%) had pulmonary arterial hypertension and one (0.7%) had renal involvement. Twenty-one (14%) SSc patients had Sjögren's syndrome.

Table 3. Frequency of autoantibodies according to disease's subtype.

Autoantibody	All (n=150)	dcSSc (n=42)	lcSSc (n=103)	p
SSc-specific autoantibody				
ANA	139 (92.7)*	41 (97.6)	95 (92.2)	NS
ATA	76 (50.7)	33 (78.6)	41 (39.8)	p <0.0001
ACA (IIF)	17 (11.3)	0 (0)	14 (13.6)	0.012
ACA (EIA)	23 (15.3)	2 (4.8)	19 (18.4)	0.034
Anti-RNA polymerase III	9 (6)	2 (4.8)	7 (6.8)	NS
Anti-U3 RNP	5 (3.3)	1(2.4)	4 (3.9)	NS
Anti-Th/To	3 (2)	0 (0)	3 (2.9)	NS
SSc-associated autoantibody				
Anti-SSA/Ro	49 (32.7)	7 (16.7)	42 (40.8)	0.005
Anti-SSB/La	12 (8)	4 (9.5)	8 (7.8)	NS
Anti-U1 RNP	25 (16.7)	5 (11.9)	19 (18.4)	NS
Anti-PM/Scl	11 (7.3)	1 (2.4)	10 (9.7)	NS
Anti-Ku	4 (2.7)	1 (2.4)	3 (2.9)	NS
Anti-NOR90	1 (0.7)	0 (0)	1 (1.0)	NS
Anti-PDGFR	0 (0)	0 (0)	0 (0)	NS

dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; ANA: anti-nuclear antibodies; ATA: anti-topoisomerase I antibody; ACA: anticentromere antibody; Anti-PDGFR: anti-platelet-derived growth factor receptor; NS: not significant; *N (%).

Prevalence and clinical relevance of autoantibodies

One hundred thirty-nine (92.7%) patients were positive for ANA screening by IIF using HEp-2 cells. Four main nuclear staining patterns were observed: homogeneous (62, 45%); speckled (31, 22%); centromere (17, 12%), and nucleolar (15, 11%). *Table 3* shows the prevalence of different autoantibodies in our patients. One hundred thirty-five (90.0%) sera were positive for at least one autoantibody, 72 (48%) were positive for one, 44 (29.3%) were positive for two, 16 (10.7%) were positive for three, and 3 (2%) were positive for four antibodies. The two most frequently detected autoantibodies were ATA (76; 50.7%) and anti-SSA/Ro (49; 32.7%).

SSc-specific autoantibodies

One hundred eleven (74%) patients were positive for at least one SSc-specific autoantibody (i.e. ATA, ACA, anti-RNAP III, anti-U3 RNP and anti Th/To); ninety-nine (66.0%) were positive for one, and 12 (8%) were positive for two SSc-specific autoantibodies. ATA were present in 76 (50.7%) patients while ACA was present in only 23 (15.3%) patients. Anti-RNAP III, anti-U3 RNP and anti Th/To autoantibodies were found at lower frequencies, 6%, 3.3% and 2% respectively (*table 3*). Clinical associations between autoantibodies, disease subtypes and specific organ system damage are shown in *table 4*. ATA-positive patients had significantly higher frequency of dcSSc (43.4% in ATA-positive patients *vs.* 12.2% in ATA-negative patients, p <0.0001), ILD (82.9% *vs.* 56.8%, p <0.0001) and digital ulcers (77.6% *vs.* 45.9%, p <0.0001). ACA-positive patients had lower frequency of dsSSc compared to ACA-negative patients (8.7% *vs.* 31.5%, p=0.025). Patients with anti-U3 RNP antibody had higher frequency of PAH (40.0 vs. 9.7, p=0.031). No significant associations were found with anti-RNAP III and anti-Th/To.

SSc-associated autoantibodies

In spite of their lack of specificity for SSc, anti-SSA/Ro and antti-U1 RNP antibodies were detected at relatively high frequencies (32.7% and 16.7% respectively) (*table 3*). Patients with anti-U1 RNP had higher frequency of musculoskeletal involvement although this association did not reach statistic significance (24.0% vs. 12.8%; p=0.148). The anti-SSA/Ro anti-SSB/La antibodies did not show any significant correlation with clinical features but their positivity was associated to the presence of Sjögren's syndrome in SSc patients (anti-SSA/Ro: 26.5% *vs.* 9.9%, p=0.008; anti-SSB/La: 50.0% *vs.*12.3%, p=0.001).

Autoantibody profile in sine cutaneous scleroderma patients

Anticentromere antibody had the highest frequency in the scSSc group; 3(60%) patients were positive by IIF and 2 (40%) by EIA. ATA was positive in two patients (40%) and anti-U1 RNP antibody in one (20%). We did not detect any other antibodies.

Table 4. Clinical associations between autoantibodies, disease subtypes and specific organ system involvement.

	ATA#	ACA (EIA)	U3 RNP	SSA/Ro	SSB/La
dcSSC	43.4% + vs. 12.2% –* p <0.0001	8.7% + vs. 31.5% – p=0.025	NS	NS	NS
lcSSc	53.9% + vs. 83.8% – p <0.0001	NS	NS	NS	NS
Vascular	NS	NS	NS	NS	NS
Joint	NS	NS	NS	NS	NS
Skeletal muscles	NS	NS	NS	NS	NS
GI tract	NS	NS	NS	NS	NS
ILD	82.9% + vs. 56.8% – p <0.0001	NS	NS	NS	NS
PAH	NS	NS	40.0% + vs. 9.7% – p=0.031	NS	NS
Kidney	NS	NS	NS	NS	NS
Sjögren's syndrome				26.5% + vs. 9.9% – p=0.008	50.0% + vs. 12.3% – p=0.001

dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; NS: not significant; *frequency in positive (+) and negative (-) patients for the specific antibody; #only autoantibodies with significant(s) clinical association(s) are shown.

Discussion

This is the first study that investigates the autoantibody profile in Algerian SSc patients and one of the few existing published reports from North Africa where data on SSc are scarce. Our study that included 150 patients of two main racial backgrounds (i.e. Berber and Arab origins), showed some distinctive features regarding the clinical expression (i.e. disease subtypes distribution and specific organ system damage prevalence), and the serological profile.

Differences in the prevalence of SSc subsets between different ethnic groups were previously highlighted by several studies [14-20]. Our patients showed predominance of lcSSc subtype consistent with other studies including Caucasian patients [15, 16]. In contrast, dcSS appears to be more common in Hispanics, African Americans, and patients from some Asiatic countries [14, 21-24]. Contrasting with the EUSTAR study we did not find significant difference between dcSSc and lcSSc patients regarding the age of patients and organ damage prevalence; nevertheless, our lcSSc patients had significantly longer duration of the disease compared to patients with dcSSc [15].

High prevalence of vascular and gastrointestinal involvement was noted in our patients, consistent with previous studies in which the frequencies of vascular damage and gastrointestinal involvement ranged from 89% to 100% and 65% to 83% respectively [14-16, 18, 25, 26]. The frequency of joint involvement (72.7%) is higher in our cohort than in the EUSTAR study (18%) but lower than in the US study (i.e. African American: 85%; Caucasian: 79%) [15, 25]. Skeletal muscle involvement is low in our patients (18%) when compared to the European (30%) and the Mexican patients (27%), but lower frequency of musculoskeletal damage was observed in Caucasian patients (12%) from the US study [15, 25, 26]. Higher prevalence of ILD was observed in our patients (70%), compared to Caucasian (38%) [25], African American (54%) [25], Mexican (41%) [26], and Chinese patients (58.1%) [24]; nevertheless, the frequency of pulmonary artery hypertension (10.7%) and renal involvement (0.7%) were lower than those reported in other cohorts [15, 25, 26].

We evaluate the prevalence and the clinical significance of large panel of autoantibodies in Algerian SSc patients using different immunoassays: IIF, EIA and LIA. One hundred thirty-nine (92.7%) patients were positive for ANA by indirect immunofluorescence using HEp-2 cell line as substrate, 135 (90.0%) were positive for one or more autoantibody and 111 (74%) were positive for at least one SSc-specific autoantibody. Our series showed a relatively high proportion of patients with more than one positive autoantibody; indeed, 63 (42%) were positive for two or more autoantibodies, including 12 (8%) with more than one SSc-specific autoantibody. Early literature [27, 28], and even some recent reports [29], suggested that

Table 5. Frequency of SSc-related autoantibodies in different ethnic groups [14, 15, 18, 19, 24-26].

	Algerian (this study)	Caucasians [14, 15, 25]	African American [14, 19, 25]	Mexican Mestizo [26]	Japanese [18, 19]	Chinese [24]
Anti-topoisomerase I (%)	50.7	13-17	14-26	28	25-28	59.9
Anti-centromere (%)	15.3	22-32	4-11	29	16	13.4
Anti-RNA polymerase III (%)	6	8-21	11-14	1.4	5	1.3
Anti-U3 RNP (%)	3.3	3-4	17-45	NA	4	NA
Anti-Th/To (%)	2	5-6	0-5	NA	2	NA
Anti-U1 RNP (%)	16.7	5-10.5	18-32	11	8-35	18
Anti-PM/Scl (%)	7.3	2-4	0-3	9	0	NA
Anti-Ku (%)	2.7	2	8-9	10	3	NA

NA: data non-available.

autoantibodies are remarkably monospecific in SSc. However, with the use of recent multiplexed immunoassays, this perception is changing [9].

Our study showed notable similarities and differences in the frequency of SSc-related autoantibodies when compared to other cohorts from other ethnic groups (*table 5*). In particular, anti-topoisomerase I antibody was found at higher frequency (50.7%) in our patients compared to Caucasian, African American, Japanese and Hispanics patients. Higher frequency of ATA was seen in the Chinese cohort (50.7% *vs.* 59.9%); however, in the analysis according to disease subtype, the dcSSc group in our cohort showed higher frequency of ATA compared to the findings from the Chinese study (78.6% vs. 64.4%) [24]. Consistent with other studies, ATA was found to be associated with diffuse form of SSc ($p < 0.0001$), interstitial lung disease ($p < 0.0001$) and digital ulcers ($p < 0.0001$) [15, 16, 24, 30, 31].

Anticentromere antibody was positive in 17 (11.3%) patients by IIF and 23 (15.3%) patients by EIA. The frequency of this autoantibody was lower than in Caucasian (22%-32%) and Hispanic (18%-29%) patients buts higher than in African American (4%-11%), Tunisian (6.5%) and Malaysian patients [15, 25, 26, 30, 31]. While ACA is usually seen in limited cutaneous disease [9], it was only detected in 14 (13.6%) (by IIF) and 19 (18.4%) (by EIA) patients with lcSSc and did not show any significant associations with specific organ system involvements. Interestingly, patients with sine cutaneous SSc were more likely to have ACA (IIF: 60%, EIA: 40%) compared to patients with lcSSc and dcSSc. Analysis of greater number of patients with scSSc should be performed to confirm this finding.

Nine (6%) patients were positive for anti RNA polymerase III antibody; a prevalence within the range reported in previous studies [31-34]. The presence of this antibody has been associated with the development of scleroderma renal crisis (SRC) in patients with early dcSSc [9]. In our cohort, the only SSc patient with renal involvement was negative for anti-RNAP-III but had no evidence of SRC. Moreover, the patient's clinical presentation was notable for some definite features of ANCA-associated vasculitis (i.e. severe lung disease with probable alveolar hemorrhage, rapidly progressive kidney disease, high inflammatory markers and positive anti-neutrophil cytoplasmic antibody (strong anti-myeloperoxidase positivity)) (data not shown) [35].

Anti-U3 RNP antibody was found in 5 (3.3%) patients. Similar frequency was previously reported in Caucasian (3-4%) [14, 25], and Japanese (4%) patients [18], but higher prevalence was observed in African American patients (19%) [25]. PAH was increased in frequency in our anti-U3 RNP-positive patients (40.0% in anti-U3 RNP positive patients *vs.* 9.7% in anti-U3 RNP negative patients; p=0.031)). This latter finding is consistent with the findings from a previous US study in which an increased frequency of PAH among anti-U3 RNP-positive patients was found in both African Americans and Caucasians [25]. We found lower frequency of anti Th/To (2%) in our patients compared to the frequencies reported in Caucasians [14, 15, 25]. Anti-PM/Scl and anti-Ku autoantibodies were detected in 11 (7.3%) and 4 (2.7%) patients respectively. Comparable frequencies were observed in Caucasians but higher values were reported in Mexican patients [14, 15, 26]. Contrasting with previous studies, we did not find any significant association of these autoantibodies with disease subtype or specific clinical features [36, 37].

Anti-SSA/Ro (Ro52 and Ro60) antibody was the second most common autoantibody (second to ATA) in our cohort with a prevalence of 32.7%. Similar frequency was reported in the Malaysian cohort (32.2%) but the one reported in a large Canadian cohort was lower (20%) [30, 38]. In this later study, anti-SSA/Ro52-positive patients were mores likely to be older, to have interstitial lung disease and to have a coincident autoimmune condition. In our series, we did not find such associations; nevertheless, analysis according to disease subtype revealed that anti-SSA/Ro antibody was more prevalent in lcSSc group. Moreover, increased frequency of Sjögren's syndrome among anti-SSA/Ro-positive patients was noted (p=0.008), consistent with the findings from

a previous study of Japanese patients that suggested that anti-SSA/Ro may be a serological marker for the presence of Sjögren's syndrome in SSc patients [39]. Anti-SSB/La antibody was found in 12 (8%) patients, its presence was associated with increased frequency of Sjögren's syndrome (p=0.001). The frequency of U1 RNP in our cohort (16.7%) was higher than in Caucasian (5%-10.5%) and Hispanic (11%) cohorte [25, 26]; however, similar or higher frequencies were reported in African American (18-32%) and Chinese (18%) patients [24, 25]. Contrasting with results from a previous Japanese study we did not find a significant difference in the frequency of this antibody among disease subtypes [20]. However, patients with anti-U1 RNP had higher frequency of musculoskeletal involvement although this association did not reach statistic significance (24.0% *vs*. 12.8%; p=0.148).

Conclusion

The present study represents the first report of autoantibodies in a cohort of Algerian SSc patients. Notable differences in the prevalence of SSc-related autoantibodies between our population and other ethnic groups were observed. Indeed, our patients had lower frequency of ACA and anti Th/To than Caucasians and Hispanics despite the predominance of limited cutaneous subtype. On the other hand, we noted higher frequency of ATA compared to Caucasian, Hispanic, African American, and Japanese patients and similar frequencies of anti-RNAP III, anti-U3 RNP, anti-PM/Scl and anti-Ku when compared to Caucasians. Our study confirms certain associations previously described in other ethnic groups such as the association of ATA with ILD and digital ulcers, and anti-U3 RNP with PAH; however, some other correlations have not been established in our patients. The finding of distinctive characteristics in Algerian SSc patients supports the impact of genetic factors. In this context, a growing body of evidence has shown that the major histocompatibility complex (MHC) genes influence the antibody profile in SSc; indeed, HLA-DRB1*1104 and HLADPB1*1301 alleles have been associated with ATA positivity, whereas DQB1*0501 is more common in ACA-positive SSc patients and *HLA-DRB1*08:04* allele was strongly associated with the severe antifibrillarin [14, 40]. Further studies should be conducted to determine the distribution of these alleles in our patients, and thus elucidate the influence of major histocompatibility complex class II genes on disease expression and autoantibody production in Algerian SSc patients.

Conflict of interest: none of the authors has any conflict of interest to disclose concerning this article.

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