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Scleroderma: the role of serum autoantibodies in defining specific clinical phenotypes and organ system involvement

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Abstract

Purpose of review—To discuss recent advances in serologic testing for SSc-associated antibodies with respect to the diagnosis and prognosis of the disease.

Recent findings—The importance of SSc antibodies for diagnosis has become increasingly recognized, as evidence by incorporation into the 2013 ACR/EULAR clinical classification criteria for SSc. Two new SSc-associated antibodies and their clinical associations have been described. Multiple cohort studies have reported variable antibody frequency distribution based on geography, but the clinical associations remain much the same. New associations include anti-RNA polymerase III antibodies with gastric antral vascular ectasia, and a temporal association between SSc onset and RNA polymerase III antibodies.

Summary—The role and associations of SSc-associated antibodies for diagnosis and internal organ involvement is becoming increasingly accepted.

Keywords

antibodies; systemic sclerosis

Introduction

Systemic sclerosis (SSc) has long been clinically classified into limited or diffuse cutaneous disease, based on the extent of skin thickening. Clear prognostic and phenotypic associations with cutaneous subtype have been well recognized. In recent years the adjunctive benefit of serologic classification in predicting cutaneous subtype manifestations and internal organ involvement has become increasingly recognized. Simultaneously, serologic testing for SSc-associated antibodies has become more available. The purpose of this review is to discuss recent advances in serologic testing for SSc-associated antibodies in regard to diagnosis and prognosis of the disease.

In reviewing publications regarding autoantibodies in SSc, there are two important considerations. First, there are multiple testing methods for antibody detection, each subject to its specific limitations. The antigens presented may produce varied testing results based

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on the source of antigens (native versus recombinant) and the conformational changes in antigen presentation between the autoantibody testing methods. These differences affect the sensitivity and specificity of the results not only for the type of antibody detection methods (immunofluorescence, immunodiffusion, immunoprecipitation, immunobloting and enzyme-linked immune [ELISA] testing), but also in separate manufacturing kits available for the same method of antibody testing. For example, the sensitivity and specificity of the multiple ELISA kits available for anti-Scl 70 detection varies. Second, it has become increasingly clear that the frequency of specific SSc-associated autoantibodies varies in different countries and geographic regions. This may be related to genetic and/or environmental factors, which at this time remain to be elucidated. One must be aware of both these issues when assessing and attempting to aggregate the data of antibody prevalence and organ system association studies.

Diagnosis

LeRoy and Medsger first suggested the importance of SSc-associated specific autoantibodies in the detection of SScor scleroderma sine scleroderma[1]. This publication was an attempt to identify SSc patients with limited or no skin thickening who had Raynaud phenomenon with internal organ involvement and SSc-associated antibodies, but who would not have otherwise been classified as “definite SSc” by the 1980 American College of Rheumatology (ACR) criteria.

The new combined ACR/EULAR clinical classification criteria were designed to improve the shortcomings of the earlier 1980 ACR clinical classification criteria by using the advances in the diagnostic techniques for autoantibodies and nailfold capillaroscopy. The new criteria incorporate autoantibodies, specifically the presence of anti-Scl70, anti-RNA polymerase 3 (RNAP), and anti-centromere (ACA) which provide support for the classification of systemic sclerosis[2, 3]. This represents a clear transition in the evolution of thinking regarding the importance of serology and SSc.

New SSc-associated autoantibodies

In recent years there have been two newly discovered SSc-associated antibodies that account for a small percentage of the SSc population. In 2014 Kaji et al., reported on autoantibodies identified in both Japanese and American populations to RuvBL1/2 which are specific to SSc[4]. These autoantibodies were initially recognized by immunoprecipitation as a doublet at around 50 kilodaltons, and associated with a moderate titer, speckled pattern on ANA immunofluorescence testing. Identification of the antigens was made by purification, mass spectrometry and then further evaluated by immunoblot-based assay and identified as a complex containing both RuvBL1(pontin) and RuvBL2(reptin). These are conserved eukaryotic proteins implicated in many cellular processes including transcription, DNA repair and small nucleolar RNP assembly. Prevalences estimates were 1–2% in the American and Japanese populations. More than half the patients with this antibody had a SSc-overlap condition with skeletal muscle involvement. When anti-RuvBL1/2 patients were compared with other SSc overlap patients (PM/Scl, U1RNP) they were found to be older, more frequently male and have diffuse disease.

In 2012 Betteridge et al., described in abstract form a 30 kilodalton band on immunoprecipitation in 7 of 379 SSc patients [5]. Immunoprecipitation and mass spectrometry identified the antigen as EIF2, and this was confirmed by immunoprecipitation-Western blotting. Six of the 7 patients had interstitial lung disease (ILD). This autoantibody was not found in patients with other connective tissue diseases, interstitial lung disease (ILD) or healthy controls. This finding has yet to be confirmed in a second SSc population.

Prognosis

Since commercially available ELISA kits for the detection of anti-RNA polymerase III (RNAP) have been developed, there have been several studies reporting the prevalence and clinical associations of RNAP in different populations. Nikpour et al., examined a prevalent population of 451 Australian patients, of whom 15.3% were positive for RNA polymerase III antibodies. They confirmed an independent association with diffuse skin disease, increased risk of renal crisis (OR 3.6; 95% CI 1.2–11.5) and joint contractures (OR 2.5, 95% CI 1.2 – 5.3). Sobanski et al., examined another prevalent cohort of 133 French SSc patients, and demonstrated a lower prevalence of 6–9% (variable based on ELISA kit manufacturer) [6]. They then performed a systematic review and meta-analysis which included 8,437 SSc patients from the published literature. The overall pooled prevalence was 11%, but considerable heterogeneity was noted. Geographic factors (continent and country) partially explained the heterogeneity and variable prevalence. This is in accordance with prior publications, which have detected lower frequencies of RNAP in European populations compared to North American SSc populations. In a separate case-control study from European Scleroderma Trials and Research (EUSTAR) examining clinical and serologic correlates of gastric antral vascular ectasia (GAVE), 48% of patients with GAVE were anti-RNAP positive, compared to 16% of those without GAVE. This high proportion is clearly above the baseline prevalence rates of RNAP in other EUSTAR publications [7]. This confirms other observations made in published abstracts associating RNAP with the presence of GAVE[8]. The RNAP and other antibody prevalence and organ associations discussed below are summarized in Table 1.

Cohort Studies : Asia

Data on SSc in Asian countries is traditionally sparse, but there have been several cohort studies published recently. Sujau studied 31 consecutive Malaysian SSc patients[9]. The most common antibody affecting one-third of patients was anti-topoisomerase (topo I), and a low percentage were found to be ACA positive (9.7%). Anti-topo I was associated with ILD and anti-PM/Scl with an overlap presentation. There have been two small cohort studies published from Japan. Hashimoto et al., described 405 patients and confirmed associations of prior Japanese literature of anti-topo I in positivity associated with ILD and cardiac involvement, and anti-U1RNP with pulmonary hypertension (PH)[10]. In another Japanese cohort of 329 patients in which age of onset was examined, younger patients more frequently had anti-U1RNP and U3RNP antibody, and older age at onset patients more often had ACA and ILD [11].

Cohort Studies: European

Data on 2,489 patients enrolled in the Digital Ulcer Outcome (DUO) registry produced an interesting result, as nearly 90% of those tested were either anti-topo I (45.2%) or ACA antibody (43.6%) positive. Patients with anti-topo I tended to be younger, have twice the rate of ILD and experienced their first digital ulcer 5 years earlier in disease than ACA positive patients from the onset of Raynaud phenomenon. Prior to this study, literature had been conflicting regarding the association of digital ulcers and ACA. One must bear in mind, however, that in Europe the two most common SSc associated antibodies are anti-topo I and ACA.

A publication from the EUSTAR group describing the 7655 patients enrolled as of June 2011 reported an overall ANA positivity as 93.4% [7]. Anti-topo I was the most common (36.8%), followed by ACA (32.3%), anti-U1RNP (7.7%) and RNAP (2.4%). As expected, anti-topo I was seen more with diffuse disease and ACA with limited disease, although ACA comprised 7.2% of diffuse SSc patients and anti-topo I 23.2% of limited patients. Information on antibody testing methods was not provided.

Data from a Belgian SSc cohort [12]of 438 patients in which variable antibody testing was performed showed the following: 41% ACA, 24% anti-topo I, 6% RNAP, 4.5% anti-U1RNP and 4.9% other antibodies. This ACA frequency is higher than other European studies, but anti-topo I and RNAP frequencies were in accordance with other European mainland reports. The two largest antibody subsets (ACA and topo I) were compared, and anti-topo I was associated with ILD, diffuse skin thickening, joint or tendon involvement and peripheral vascular manifestations. RNAP was associated with diffuse skin thickening. These results support other publications.

Mireau et al., studied the prevalent serologies and clinical associations in the German SSc network of 863 consecutive SSc patients[13]. Ninety-four percent were ANA positive, 36% ACA, 30% anti-topo I, 5% anti-U1RNP, 5% anti-PM/Scl, 4% RNAP, and the remaining antibodies < 1.5%. These rates were similar to other European countries for ACA, anti-topo I, anti-U1RNP, although somewhat lower for RNAP. Cutaneous associations included: anti-U1RNP and anti-PM/Scl with an overlap presentation, ACA with limited skin thickening, and anti-topo I, RNAP and anti-U3RNP with diffuse skin thickening. Similar to DUO, digital ulcers occurred most frequently in ACA and anti-topo I positive patients. ILD was related with anti-topo I, but ACA was protective (similar to UK studies below). Synovitis and joint contractures were associated with anti-topo I. ACA was protective for synovitis, joint contractures, tendon friction rubs and elevated muscle enzymes. Anti-PM/Scl was associated with elevated serum muscle enzymes.

United Kingdom

The associations of ACA positivity with pulmonary function test (PFT) abnormalities in the setting of no clinically evident ILD or PH were examined in a retrospective study from the UK[14] which included 59 patients, 34 of whom were ACA positive. Patients with ACA had a higher forced vital capacity to total lung capacity ratio, which the authors interpreted as

suggestive of sub-clinical pulmonary vasculopathy. Further long-term follow-up is needed for confirmation.

In another UK study that compared patients with SSc patients with and without overlap reported different antibody frequencies between these two groups [15]. Patients with SSc-overlap had higher frequencies of anti-PM/Scl, anti-U1RNP, anti-Ku and anti-Jo1 antibodies, in support of previously existing data. Those with elevated serum muscle enzymes were most frequently PM/Scl positive followed by anti-U1RNP and anti-topo I antibodies.

Cohort studies: North American

The Canadian Scleroderma Research Group evaluated the clinical and serologic correlates of anti-PM/Scl antibodies in 764 patients. The prevalence of PM/Scl was 7.2%. Anti-PM/Scl was associated with SSc in overlap, skeletal muscle involvement, inflammatory arthritis, calcinosis and younger age. Interestingly, half had another positive SSc antibody, which raises the question of false positive ELISA tests, as this frequency is higher than reported in prior studies [16, 17].

Rodriguez-Reyna published on a Mexican Mestizo patient cohort of 139 patients[18]. In these patients 30% had ACA, 28% anti-topo I, 11% anti-U1RNP, 10% anti-Ku, 9% anti-PM/Scl and 1% RNAP. No Th/To, U3RNP or U11/U12 RNP positive patients were detected. Anti-topo I was associated with ILD and anti-Ku with cardiac involvement and PH. This antibody frequency distribution is distinct from other North American populations although the clinical-serologic associations were similar.

Role of antibodies in clinical risk prediction models—While cohort studies have clearly and consistently demonstrated an association between antibodies and internal organ involvement, predictive or risk stratification models have not always demonstrated this consistently and independent of SSc clinical subtype. Nihtyanova, et al. [19]developed within their large single center Royal Free Hospital cohort with long-term follow-up, separate clinical risk prediction models for the development of PH and clinically significant ILD (defined as abnormal chest CT and FVC or DLCO 55%, or a 15 decline in FVC or DLCO). In both the PH and ILD models, autoantibodies play a significant predictive role which is independent of clinical subtype. The presence of anti-topo I predicted the presence of clinically significant ILD (as expected), whereas the presence of ACA was greatly protective. The magnitude of ACA protection for ILD was greater than the risk of anti-topo I positivity. For PH, both anti-U3RNP and RNAP predicted PH, whereas anti-topo I was protective. U3RNP has been associated with PH in numerous cohort studies [20], although the effect of RNAP has not been previously appreciated. This may reflect the relatively larger percentage of RNAP patients in the Royal Free cohort, which is closer to North American frequencies than European. These models will need to be validated, but clearly support the concept that serologic profiling may augment clinical subtyping. Of note, this concept that autoantibodies may provide an equal or stronger association to the development of PH was also supported in a recent abstract presented at the 3rd World Congress on Scleroderma[21].

Anti-RNA polymerase III and malignancy—In the last three years there have been four important publications examining the potential relationship between RNAP and malignancy. While the overall data on the risk of malignancy associated with SSc has been conflicting, a more consistent message has been found in these RNAP publications, which have specifically examined the temporal relationship between SSc and malignancy. Shah et al., first reported on 23 patients with SSc and malignancy with available pathology specimens, of whom six were positive for RNAP. She found that patients with RNAP antibodies experienced SSc onset close to the time of their malignancy diagnosis (-2 to +1.3 years). Interestingly there was enhanced nucleolar RNA polymerase III expression in tumor pathology samples from RNAP patients only, supporting the hypothesis that there may be a link between malignancy and SSc-specific immune reponse in this subset. Shortly thereafter, Airo et al. described a series of consecutive SSc patients in which 360 tested positive for RNAP, anti-topo I or ACA[22]. Of these, 10.8% had a malignancy. Although an infrequent antibody, patients with RNAP had a significantly higher malignancy frequency (44%), compared to anti-topo I (11%) and ACA (9%). They likewise showed a clustering of malignancy close to SSc onset in the RNAP patients. Nikpour et al., performed a cross-sectional analysis of an Australian cohort of 451 patients to describe the characteristics associated with RNAP[23]. RNAP patients had a significantly higher frequency of malignancy within five years of SSc onset, but not an overall increase in malignancy rate. Additional regression analysis for the development malignancy within five years of SSc demonstrated that RNAP and age conferred significant risks. This further suggested a possible temporal relationship to RNAP and malignancy risk in a population subset. Finally, Moinzadeh and colleagues [24]then sought to independently confirm this temporal relationship in a large single-center UK cohort of 2,177 SSc patients. An overall malignancy rate of 7.1% during follow-up was found, with a statistically significant higher frequency in RNAP (26%) compared to those without RNAP (13%; $p>0.0001$. Similar to Shah et al., breast cancer was the most common cancer among RNAP patients. In multivariable Cox regression, the only autoantibody that was associated with increased cancer risk was RNAP. After age and gender adjustment, RNAP had an odds ratio of 2.55 (95% CI 1.75 – 3.74) for cancer. When malignancy within 36 months of SSc onset was examined RNAP positive patients had a increased risk of 5.83 times (95% CI 3.11 – 10.92).

In the general population, abnormal RNA polymerase activity in breast and lung adenocardcinoma cells has been reported. Recently Joseph et al., examined the biochemical reasons underlying this association, expanding on Shah et al.'s earlier work regarding cancer tissue RNAP expression[25]. They examined the tissues of 8 RNAP positive SSc patient with cancer, and 8 SSc-cancer patients with other SSc antibodies[26]. The RNAP patients had all developed cancer from 4 years before to 2.5 years after SSc, whereas those with other SSc-antibodies developed cancer between 2 years before and 37 years after SSc diagnosis. In 6 of 8 RNAP patients there was a somatic mutation in the antibody locus, which was not present in the non-RNAP malignancy patients. In the peripheral blood, T-cells reactive with the mutant forms of RNA polymerase III were identified in 2 of 3 patients tested. They propose that the tumor-associated antigen (mutant RNA polymerase III) may initiate an immune response in a subset of SSc patients, although other factors (genetic, environmental) may be required.

Conclusions

The role and associations of SSc-associated antibodies for diagnosis and internal organ involvement is becoming increasingly accepted. Serologies have now been incorporated into international collaborations for the development of clinical classification criteria. Multiple cohort studies have reported varying geographic rates of antibody prevalence in SSc which may be related to genetic or environmental factors. However, the cutaneous subtype and internal organ associations with specific antibodies continue to be affirmed. With the now commercially available RNAP testing, a new link between RNAP and GAVE has been described, and a temporal relationship between RNAP and cancer diagnosis in a subset of patients appears to be emerging. Finally, a new set of autoantibodies, anti-RuvBL1/2, has been associated with SSc in overlap with myositis in Asian and North American populations.

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Key Points

- The importance of SSc-associated antibodies in the diagnosis and classification of SSc is now recognized. Autoantibodies are incorporated into the 2013 ACR/EULAR clinical classification criteria for SSc.
- The prevalence of SSc-assoicated antibodies varies by geographic region, although the internal organ associations are similar across all populations, consistent with earlier studies. New associations include digital ulcers with ACA positivity, and GAVE with RNAP.
- Anti-RNA polymerase III antibodies have now been linked to malignancy in three separate SSc cohort studies, with the cancers occurring during the period close to the diagnosis of SSc.

Table 1

Autoantibody prevalence and clinical associations: now and before

Antibody	Prevalence		Clinical associations	
	Prior	New	Prior publications	New publications
Anti-centromere	16–39%	32% EUSTAR 41% Belgium 36% Germany 10% Malaysia 30% Mexico	Limited SSc PH	**Digital ulcers** (DUO registry)
Anti-topoisomerase I	9–39%	37% EUSTAR 24% Belgium 30% Germany 32% Malaysia 28% Mexico	Diffuse SSc ILD Digital ulcers Cardiac	Digital ulcers (DUO registry) ILD
Anti-RNA polymerase III	4–25%	2% EUSTAR 15% Australia 6–9% France 6% Belgium 4% Germany 7% Malaysia 1% Mexico	Diffuse SSc Renal crisis	Diffuse SSc Renal Crisis **Malignancy** **GAVE**
Anti-PM/Scl	0–6%	5%; Germany 7%; Canada 7% Malaysia 9% Mexico	Overlap Myositis ILD	Overlap Myositis
Anti U1RNP	5–35%	8% EUSTAR 5% Belgium 5% Germany	Overlap	Overlap Myositis PH
Anti-U3RNP (fibrillarin)	1–6%	10% Malaysia	Overlap Myositis Joint PH	
Anti-Th/To	1–7%		Limited SSc	
Anti-Ku	1–3%	1% Germany 7% Malaysia 10% Mexico	Overlap myositis	Overlap Myositis Dysphagia
Anti-U11/U12 RNP	1 – 5%		Severe ILD	
Anti-RuvBL1/2		1–2%; US, Japan		Overlap

PH = pulmonary hypertension; ILD = interstitial lung disease; GAVE = gastric antral vascular ectasia

Boldtype signifies new reported internal organ associations