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Systemic sclerosis: are anti-nuclear antibodies our guiding stars?

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Auto-antibodies and cancer in Systemic Sclerosis

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Dear Editor,

With interest we have read the article by Bernal-Bello et al., associating Pm/Scl antibodies with a higher risk of cancer in Systemic Sclerosis (SSc) (1). We appreciate the research this group performed as early detection of malignancies in Systemic Sclerosis patients is important in daily clinical practice.

Bernal-Bello et al. retrospectively analysed data of 432 consecutive SSc patients and found a cancer prevalence of 12.2% (n=53) with decreased survival for SSc patients with cancer. Pm/Scl antibody prevalence of 20.7% (n=6/29) amongst SSc patients with cancer diagnosis compared with 7.7% (n=19/247) amongst SSc patients not being diagnosed with cancer is shown, together with increased cancer prevalence amongst Pm/Scl patients (24%, n=6/25). The authors conclude that Pm/Scl antibodies are associated with malignancies in SSc and patients being Pm/Scl antibody positive might benefit from comprehensive cancer screening (1). The authors acknowledge the limitations of their design and suggest that their data should be replicated in other cohorts. For example, not all included patients were serologically evaluated for Pm/Scl positivity.

We took advantage of our prospective SSc cohort including all patients that participate in the multidisciplinary day-care program for SSc at the Leiden University Medical Center (LUMC) (2) in order to evaluate the association between auto-antibodies and cancer diagnosis. We re-evaluated 46 SSc patients with a history of malignancy amongst 305 SSc patients with recent follow-up and at least 2 visits to our care pathway available. Sera of 280 patients were tested for ANA screen, ENA (anti-SSA, anti-SSB, anti-centromere [ACA], anti-topoisomerase [ATA], anti-RNP70, anti-U1RNP, anti-Smith, anti-Jo), anti-U3RNP (fibrillarin), anti-Pm/Scl, anti-RNA polymerase III (RNAPIII), anti-Th/To and anti-Ku. In the remaining 25 patients, Th/To and Ku was not determined and RNAPIII, U3RNP and Pm/Scl status was only determined if ANA screening was positive and ENA screening did not reveal any disease-specific auto-antibodies, based on the result in the first 280 patients. Prevalence of ACA was 38.0% (n=116), ATA 25.9% (n=79), RNAPIII 6.6% (n=20), U3RNP 4.3% (n=13), U1RNP 9.2% (n=28), Pm/Scl 6.9% (n=21), anti-ThTo 1.6% (n=5), anti-Ku 2.0% (n=6), ANA-ENA- 4.3% (n=13), ANA+/ENA+, no specific SSc antibodies 9.5% (n=29), >1 SSc specific antibodies 8.9% (n=27).

We evaluated distribution of clinical features and SSc-specific auto-antibodies amongst SSc patients with and without malignancies (Tables 1 and 2). Patients with cancer history were older, had longer duration between first Raynaud phenomenon and first visit to the day-care program, less often diffuse cutaneous disease and more often pulmonary arterial hypertension (Table 1). There were no significant differences in auto-antibody status between patients with or without cancer history, although prevalence of anti-topoisomerase was numerically lower (15.2%, n=7 vs 24.3%, n=63) and RNA polymerase III (10.9%, n=5 vs. 5.0%, n=13) was numerically higher amongst patients with malignancy.

Table 1. Baseline characteristics of patients of the CCISS cohort with recent follow-up, auto-antibody status determined and at least 2 visits to the comprehensive care pathway

	no malignancy n=259	malignancy n=46	p
male, %(n)	16.2 (42)	15.2 (7)	0.865
age, mean (SD)	53.0 (14.1)	60.9 (13.7)	0.001
time since first Raynaud phenomenon, median (IQR)	9.3 (3.8-17.9)	13.6 (5.3-21.0)	0.024
time since first non-Raynaud phenomenon, median (IQR)	4.7 (1.6-11.1)	5.3 (2.1-11.7)	0.455
5 year-survival since first non-Raynaud phenomenon, %(n)	79.1(204)	80.4(37)	0.902
unknown, %(n)	17.1 (44)	15.2 (7)	0.767
dcSSc, %(n)	27.0 (70)	13.0 (6)	0.043
mRSS, median (IQR)	4.0 (1.3-6.0)	2.0 (0.0-4.5)	0.096
lung involvement on HRCT, %(n)	54.4 (141)	56.5 (26)	0.794
arrhythmia, %(n)	38.2 (95)	47.7 (21)	0.231
PAH, %(n)	2.7 (7)	13.0 (46)	0.001
>10% weight loss, %(n)	10.9 (28)	8.7 (4)	0.655
history of renal crisis, %(n)	4.3 (11)	2.2 (1)	0.503
DU, %(n)	23.2 (60)	23.9 (11)	0.912

CCISS cohort: Combined Care in Systemic Sclerosis cohort; Leiden University Medical Center
dcSSc - diffuse cutaneous Systemic Sclerosis, DU - digital ulcers, PAH - pulmonary arterial hypertension

Table 2. Auto-antibody prevalences of patients with and without cancer history of the CCISS cohort with recent follow-up, auto-antibody status determined and at least 2 visits to the comprehensive care pathway

	no malignancy n=259	malignancy n=46	p
anti-topoisomerase, %(n)	27.4 (71)	17.4 (8)	0.153
anti-centromere, %(n)	37.8 (98)	39.1 (18)	0.868
anti-RNA polymerase III, %(n)	5.8 (15)	10.9 (5)	0.200
anti-U1RNP, %(n)	9.3 (24)	8.7 (4)	0.902767
anti-U3RNP, %(n)	4.6 (12)	2.2 (1)	0.447
anti-Pm/Scl, %(n)	6.9 (18)	6.5 (3)	0.916
anti-ThTo, %(n)	1.2 (3)	4.3 (2)	0.116
anti-Ku, %(n)	1.9 (5)	2.2 (1)	0.913
>1 disease specific auto-antibody, %(n)	8.9 (23)	8.7 (4)	0.968
ANA/ENA negative, %(n)	4.6 (12)	2.2 (1)	0.447
ANA/ENA positive, no SSc specific auto-antibody, %(n)	8.9 (23)	13.0 (6)	0.375

Unfortunately, we could not replicate the finding of Bernal-Bello et al. of Pm/Scl being more prevalent in SSc patients with a diagnosis of cancer. For Pm/Scl frequencies were similar between patients with (6.5%, n=3) and without malignancy (6.9%, n=18, p=0.916).

Also, our research is limited in its design as it concerns a single center cohort with limited sample size, especially for auto-antibodies with lower prevalences in general. However, based on our data we cannot advocate comprehensive cancer screening for Pm/Scl positive SSc patients.

In addition, interestingly, the authors hypothesize that, as has been shown for RNAPIII antibodies (3), changed expression of the antigen targeted by Pm/Scl in cancer tissue, might trigger the auto-immune response, and result in Pm/Scl positive systemic sclerosis as a paraneoplastic phenomenon. However, a consequence of auto-antibodies directed against proteins that are highly or differently expressed in tumor tissue might also be relevant in preventing tumor progression and metastasis. In cancer, changed expression of proteins known as antigens in SSc, is described not only for RNAPIII and Pm/Scl, but is also described for anti-topoisomerase (ATA) and anti-centromere (ACA) (4-6).

Indeed, the incidence of cancer in SSc is known to be increased compared to the general population (7, 8). We therefore hypothesize that prevalence of auto-antibodies differ between SSc patients with and without cancer diagnosis according to their potency to fight cancer in a preclinical stage.

More research in the association of auto-antibodies and occurrence of cancer amongst SSc patients is warranted, as this may shine light on disease pathogenesis in both diseases. In our opinion, antibody status in its current form cannot help identifying which patients to screen for cancer in the daily clinical setting, therefore clinical manifestations should be leading in which patients to screen.

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