Comment on: Anti-NOR90 antibody associated with paraneoplastic systemic sclerosis

Sirs,

We read with interest the recent article by Duffau *et al*. on the relationship between anti-NOR90 antibodies (anti-NOR90Ab) and cancer in systemic sclerosis (SSc) (1). In this paper, the authors present a 72-year-old woman with limited cutaneous SSc (lcSSc) and isolated anti-NOR90Ab who developed myelodysplastic syndrome at the same time as the onset of SSc, subsequently progressing to acute myeloid leukaemia (LMA).

Anti-NOR90Ab have been detected in around 6% of SSc and have also been associated with other rheumatic diseases (2-4). Nevertheless, its association with a specific clinical profile or prognostic significance in SSc is not clearly elucidated. With the aim of better understanding the clinical phenotype of anti-NOR90Ab, we conducted a retrospective study in patients with anti-NOR90Ab in our hospital. We selected patients with at least two positive serum determinations for anti-NOR90Ab separated in time, between January 2013 and December 2021. Autoantibody testing was done using a immunoblot assay (Euroimmun EUROLINE SSc profile IgG autoAb assay kit).

We identified 30 patients with anti-NOR-90Ab, most of them women (Table I). Twelve patients (40%) had been diagnosed with rheumatic diseases and only two patients were diagnosed with SSc, both with lcSSc and none with crucial organ damage. The most frequent clinical manifestation in all these patients was musculoskeletal involvement (n=14/30) and the most common SSc feature was Raynaud's phenomenon (n=6/30). Only one patient with anti-PL7 antibody associated developed vital organ involvement, consisting of mild interstitial lung disease (ILD). Interestingly, we found seven patients with cancer history: three solid organ tumours (bladder, kidney and lung), one multiple myeloma, one LMA, and two basal cell carcinomas. In three of them, the cancer was diagnosed after anti-NOR90Ab detection. None of patients with cancer had SSc, but two patients presented other SSc auto-antibodies (1 anti-centromere, and both of them anti-Ro52).

All subjects or their legal representatives were fully informed and provided written informed consent to use their clinical data for this research.

Published literature observe that anti-NOR-90Ab are not consistently associated with SSc (2-5) and, in accordance with our findings (12/30 patients with different rheumatic diseases, only two had SSc), previous reports have shown a higher association rate with other rheumatic diseases compared to SSc (2-5). Contrarily, a recent study by Yamashita *et al*. (6) reported a greater association of SSc in anti-NOR90Ab patients: 4/8 patients with SSc (3 lcSSc, 1 diffuse cutaneous SSc) and 2/8 patients had idiopathic interstitial pneumonia with SSc features but did not fulfill 2013 ACR\EULAR criteria for SSc. Three SSc patients had developed ILD, in contrast with our study. Liaskos *et al*. (2) also report a strong correlation with anti-NOR90Ab and ILD in SSc patients (6/8 positive cases had ILD). Nonetheless, in the case of Duffau *et al*. (1), the patient had lcSSc and no vital organ involvement, similar to what was detected in our patients.

Furthermore, we also observed an increased association between cancer and anti-NOR-90Ab (7/30 patients), in line with Yamashita's results (4/8 patients, 2 with concomitant lcSSc) (6) and Duffau *et al*. case (1), but none of our patients had coexistent SSc. In contrast, other studies in patients with anti-NOR90Ab have not been associated with malignancy (3-5). Additionally, a recent study from the Canadian Scleroderma Research Group registry observed an increased cancer risk with anti-topoisomerase I and anti-U1-RNP-positive patients, but none of the anti-NOR90-positive patients developed cancer during the 2-year follow-up (7).

Our study has several limitations, including its retrospective design, limited sample size and short period of follow-up. Therefore, robust conclusions could not be obtained.

In summary, in our case series, anti-NOR-90Ab positivity was highly associated with the presence of rheumatic diseases, including SSc, although no severe organ involvement was observed. The potential association of anti-NOR90Ab with cancer deserves further research and prospective studies with larger series are needed.

Table I. Demographic, clinical features and main diagnoses of patients with anti-NOR90 antibodies.

Clinical features	Anti-NOR90Ab positive patients (n=30)
Female sex, n (%)	23 (76.6)
Age (years), mean (SD)	60.5 (17.5)
Ethnicity, n (%)	
Asian	1 (3.3)
Hispanic	8 (26.6)
Caucasian	21 (70)
Follow-up (months), median [IQR]	22 [15.5-48]
Positive ANA (>1:160), n (%)	27 (90)
SSc-related autoantibodies, n (%)	17* (56.6)
Anti-Ku	7 (23.3)
Anti-U3RNP	6 (20)
Anti-RNA pol III	5 (16.6)
Anti-Th/To	4 (13)
Anti-centromere	4 (13)
Anti-topoisomerase I	2 (6.6)
Anti-PM-Scl	3 (10)
Underlying rheumatic disease, n (%)	12 (40)
Systemic sclerosis	2 (6.6)
Rheumatoid arthritis	1 (3)
SLE	2 (6.6)
Sjögren's syndrome	1 (3)
Antisynthetase syndrome	1 (3)
UCTD	3 (10)
Overlap syndrome	2 (6.6)
Other non-rheumatic diseases	18 (60)
Graft Versus Host Disease	2 (6.6)
Morphea	1 (3)
Autoimmune hepatitis	1 (3)
Raynaud's syndrome	2 (6.6)
No immune disease found up to now	12 (40)
Scleroderma features, n (%)	
Raynaud's phenomenon	6 (20)
Telangiectasia	3 (10)
Skin thickening	2 (6.6)
Puffy fingers	2 (6.6)
Calcinosis	0 (0)
Digital ulcers	0 (0)
Systemic organic involvement, n (%)	
Joints/tendons	12 (40)
Skeletal muscles	2 (6.6)
Gastrointestinal tract	4 (13)
Interstitial lung disease	1 (3)
PAH	0
Heart	0
Kidney	0
Cancer, n (%)	7 (23.3)

ANA: antinuclear antibodies; IQR: interquartile range; PAH: pulmonary arterial hypertension, not secondary to lung fibrosis; PM-Scl: polymyositis-scleroderma; SD: standard deviation; SLE: systemic lupus erythematosus; UCTD: undifferentiated connective tissue disease.
*The same patient may have several SSc-related autoantibodies.

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