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Letters to the Editor

Long-term risk of cancer development among anti-Th/To antibody-positive systemic sclerosis patients: comment on the article by Mecoli et al.

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To the Editor:

We read the report by Mecoli et al on the relationship between cancer and anti-Th/To antibodies (AThAs) in patients with systemic sclerosis (SSc) (1). It is interesting that the presence of AThAs was reported to confer a protective effect against cancer development in those patients. However, cancer development in AThA-positive patients was significantly suppressed only within the first 3 years after SSc onset, and there was no significant difference in the number of deceased between the AThA-positive and AThA-negative patients.

We retrospectively screened 1,252 patients with various conditions from the Department of Dermatology, Nagoya University Hospital between 1994 and 2020, and 244 patients with idiopathic interstitial pneumonia (IIP) from the Department of Respiratory Medicine, Tosei General Hospital between 2007 and 2015. We investigated AThAs in serum samples by enzyme-linked immunosorbent assay and immunoprecipitation using the recombinant RPP25 and hPOP1 proteins produced by in vitro transcription/translation according to our established protocol (2). Seventeen patients had antibodies to RPP25 and/or hPOP1: 6 with SSc (6/249), 3 with IIP (3/244), 2 with overlap syndrome without overlapping SSc (2/12), 2 with systemic lupus erythematosus (2/141), 1 with primary Sjögren's syndrome (1/134), dermatomyositis (1/187), 1 with rheumatoid arthritis (1/33) and 1 with Raynaud's disease (1/23). These results demonstrate that AThAs are found in various autoimmune conditions. Table 1 shows the clinical features of our AThA-positive SSc patients. Two also had anti-centromere

antibodies, although none of the AThA-positive patients had other SSc-related anti-nucleolar (anti-PM/Scl, -U3RNP, or -NOR90 antibodies), anti-RNA polIII or anti-Topoisomerase I antibodies. Four of the AThA-positive SSc patients had interstitial lung disease (ILD), but the complication rate of ILD was not significantly higher in SSc patients with versus without AThA (4/6 vs. 74/196, P<0.215). Only 1 AThA-positive SSc patient developed cancer within 3 years after SSc onset; however, there was no significant difference in the cancer development rate within 3 years of disease duration between the AThA-positive and AThA-negative SSc patients (1/6 vs. 6/197, P<0.193). Moreover, 5 AThA-positive SSc patients had cancer histories, and cancer incidence was higher in the SSc patients with versus without AThAs (5/6 vs. 31/197, P<0.00072). The follow-up durations did not significantly differ between the two groups (AThA-positive, 3.3-31 years, median=10.8 vs. AThA-negative, 0.1-46 years, median=18.6, P<0.282). One AThA-positive SSc patient did not have cancer, although he had been followed up for only 2 years.

In our study, no AThA-positive SSc patients has died to date. Cancer is a major cause of death (8/29) in our SSc cohort. Our major concern is the causes of death in the AThA-positive SSc patients in the previous study. Our study suggests that AThA-positive patients need long-term follow-up.

AUTHOR CONTRIBUTIONS

All of the authors were involved in drafting the article or revising it critically

for important intellectual content, and all approved the final version for publication. Dr. Muro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of its analysis.

Study conception and design: Yamashita, Muro, Akiyama

Data acquisition: Yamashita, Yamano, Muro, Koizumi

Data analysis and interpretation: Muro, Takeichi, Kondoh, Akiyama

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TABLE 1. Clinical features of SSc patients with anti-Th/To antibodies

Pt	SSc subtype	Age	Sex	IIF pattern*	anti-RPP25/ anti-hPOP1	Other SSc-related antibodies	ILD/ PAH	Cancer (onset age)	Years from SSc onset to cancer development	Years of observation
1	limited	38	F	AC-3 AC-8	+/+	ACA	+/-	colon (55)	7	31
2	limited	44	F	AC-2 AC-8	+/+	-	-/-	breast (right: 44, left: 62)	right: 0, left: 18	27
3	diffuse	58	M	AC-8	+/+	-	-/-	-	-	2
4	limited	42	F	AC-8	+/+	-	+/-	lung (63)	21	23
5	limited	60	F	AC-3 AC-8 AC-21	-/+	ACA	+/-	lung (73)	13	13
6	limited	56	F	AC-2 AC-8	+/+	-	+/-	endometrial (54)	-2	4

* Evaluation of IIF pattern is based on the International Consensus on Antinuclear Antibody Patterns. ACA, anti-centromere antibody; IIF, indirect immunofluorescence; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; Pt, patient; SSc, systemic sclerosis.