Association of RNA Polymerase III Antibodies with Scleroderma Renal Crisis

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To the Editor:

The study by Cordullo, et al investigated the prevalence of systemic sclerosis (SSc)-related autoantibodies among SSc patients with scleroderma renal crisis (SRC) in Italy. The authors report that the majority of the SRC patients had anti-topoisomerase I (anti-topo I) antibody (30/46, 65%), whereas a minority of patients (7/46, 15%) had anti-RNA polymerase III (RNAP)1.

Whereas a minority of patients (7/46, 15%) had anti-RNA polymerase III with SSc at the time of analysis. All patients fulfilled American College of Rheumatology preliminary classification criteria2 or had at least 3 of the 5 features of CREST (calcinosis, Raynaud’s phenomenon, esophageal dys- function, sclerodactyly, telangiectasia); the diagnosis was verified by medical record review. The Registry database included demographic features, clinical disease characteristics, including extent of skin involvement, and autoantibody results. In addition, date of disease onset, defined as the time of first non-Raynaud’s phenomenon symptom and time of SRC onset, was abstracted. Methods for detecting autoantibodies were indirect immunofluorescence on HEp-2 cells for antinuclear antibodies (ANA) and anticientromere (ACA) antibodies, immunodiffusion against calf-thymus extract for the presence of anti-topo I and anti-ribonucleoprotein (RNP) antibodies (Inova Diagnostics, San Diego, CA, USA), and commercially available enzyme-linked immunoassay for RNAP (MBL, Nagoya, Japan).

A total of 47 cases with SRC (5%) were identified in the Registry. Ethnicities of SSc patients with SRC were 35 (74%) Caucasian, 3 (6%) African American, and 8 (17%) Hispanic. As expected, there was a female predominance (F:M ratio 6:1). Further, the majority of patients had diffuse disease (39/47, 83%) and a positive ANA (39/47, 83%). Among patients with SRC, RNAP III was present in the majority of cases (25/47, 52%), while anti-topo I was detected in only 5 (11%) cases; further, only 2 (4%) patients had anti-RNP antibodies, while none had ACA.

The prevalence of anti-topo I and RNAP III in the Registry in SSc patients with SRC parallels other North American and European studies3,4. Using chi-square, SRC was associated with RNAP III (p < 0.001, OR 6.4, 95% CI 3.4–12.2), while anti-topo I did not show a correlation with SRC (p = 0.097) in the Registry, which is consistent with previous studies1,3,4. In fact, there was a trend toward anti-topo I being protective against SRC (OR 0.45, 95% CI 0.14–1.15), although this was not statistically significant. The median time between disease onset and occurrence of SRC was 12.97 months, with this time interval being shorter than 48 months in 69% of cases. In addition, using Cox proportional hazards regression, the time from disease onset to SRC was found to be shorter in patients with RNAP III [p < 0.001, hazard ratio (HR) = 7.5, 95% CI 4.0–13.9], while time to SRC was longer for patients with anti-topo I [p = 0.048, HR = 0.31, 95% CI 0.09–0.99]. This observation supports a similar finding by Cordullo, et al5 indicating SSc patients with RNAP develop SRC earlier in the course of their disease. However, our findings regarding prevalence of autoantibodies in SRC were divergent from the reported study. Cordullo, et al did not report any formal associations of these autoantibodies with SRC, possibly because their study was a case series and lacked a control group (SSc patients without SRC)5. The difference in prevalence of autoantibodies among SRC patients between the Italian and our population might originate from the lower prevalence of RNAP III among Italians as alluded to by Cordullo, et al5. Bardoni, et al reported a prevalence of 8% for anti-RNAP I-III autoantibodies in an Italian SSc sample6, which is lower than the 12% reported by Bunn, et al in a British population5, and 17% prevalence in our overall sample. It is conceivable that a large study of Italian SSc patients with a greater number of RNAP-positive cases would show a similar positive association of RNAP antibodies with SRC as observed by ourselves and other groups.

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