Hypocomplementemia in systemic sclerosis

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Comment to the article

To the Editor,

We read with interest the paper recently published by Cuomo et al. (1) in your journal reporting on the associations between hypocomplementemia and disease status in systemic sclerosis (SSc).
In their report, these investigators found that 16.5% of their study subjects had hypocomplementemia and that those with hypocomplementemia had significantly greater disease activity, severity as well as disability.
In our own large, Canadian cohort of SSc patients, we have also found a rate of hypocomplementemia of approximately 14% (2) and were thus interested in replicating the results of Cuomo et al.
We used the same definitions of disease activity (European Scleroderma Study Group (EScSG) activity score), severity (Medsger Disease Severity Score for nine organ systems, divided as scores 0-1 and 2-4) and disability (Health Assessment Questionnaire-Disability Index (HAQ-DI) >0.5) used in the Cuomo study, except for one difference.
Since hypocomplementemia is one of the 10 variables in the EScSG activity score, we computed a score for our patients based on the other nine variables only, otherwise the outcome and predictor variables could be over-correlated. We ran crude and adjusted logistic regression models comparing SSc patients with hypocomplementemia to those with normal complementemia (Tab. II).
We could not use abnormal kidney severity in the models due to the fact that there were no patients with kidney disease severity scores >2 in the hypocomplementemic group.
After adjusting for multiple comparisons, we did not find any significant associations between complement levels and disease activity, severity and function in our cohort.

Table I - Baseline characteristics of the cohort.

	Whole cohort N. 440 N or SD		*Low C3/C4 N. 46 N or SD*		*Normal C3/C4 N. 394 N or SD*	
Female	86%	382	91%	42	86%	340
Mean age	56.0	12.3	52.0	12.6	56.5	12.2
Mean disease duration	11.0	9.3	11.4	8.4	11.0	9.4
Diffuse disease	42%	184	48%	22	41%	162
Anti-centromere antibody	31%	137	28%	13	32%	124
Anti-topoisomerase	19%	82	20%	9	19%	73
EScSG activity score						
Total	2.15	1.50	2.90	1.20	2.07	1.56
Without complements	2.05	1.50	1.90	1.20	2.07	1.56
HAQ-DI >0.5	56%	245	52%	24	56%	221
Medsger Disease Severity Score ≥2						
General	22%	95	35%	16	20%	79
Skin	27%	120	35%	16	26%	104
Lung	46%	204	51%	22	27%	182
Joints	28%	121	35%	16	27%	105
Muscles	8%	36	15%	7	7%	29
Heart	13%	57	13%	6	13%	51
Gastrointestinal	89%	393	85%	39	90%	354
Peripheral vascular	50%	220	54%	25	49%	195
Kidneys	4%	17	0	0	4%	17

Table 2 - Logistic regression models comparing patients with low to normal complements.

	Crude			Adjusted		
	OR	*95%*	*CI*	*OR*	*95%*	*CI*
Female	1.67	0.65	5.71	2.31	0.82	8.33
Age	0.97	0.94	1.00	0.97	0.94	0.99
Disease duration	1.01	0.97	1.04	1.02	0.98	1.05
Diffuse disease	1.31	0.71	2.42	1.01	0.41	2.36
EScSG activity score (without complements)	0.92	0.73	1.12	0.82	0.60	1.07
HAQ >0.5	0.85	0.46	1.58	1.06	0.34	3.27
General disease severity	2.13	1.08	4.05	2.17	1.00	4.59
Skin severity	1.49	0.76	2.81	1.59	0.58	4.56
Lung severity	1.07	0.58	1.97	1.17	0.60	2.27
Heart severity	1.01	0.37	2.34	0.89	0.30	2.31
Peripheral vascular severity	1.21	0.66	2.26	1.09	0.53	2.23
Muscle severity	2.26	0.86	5.25	2.05	0.64	5.99
Joint severity	1.47	0.75	2.77	1.30	0.58	2.80
Gastrointestinal severity	0.63	0.28	1.62	0.57	0.23	1.59
Kidney severity	NA	NA	NA	NA	NA	NA

Even after attempting more advanced model selection strategies, there was very little conclusive evidence of any association between complement level and disease status (data not shown).

Thus, we failed to replicate the associations identified by Cuomo et al.

There are some possible explanations for our discrepant results. First, our patients may differ in important respects. The Canadian cohort includes patients with a definite diagnosis of SSc according to the participating rheumatologist.

Thus, a patient with evidence of overlap disease could be included provided that the patient also had SSc. On the contrary, in the Cuomo study, patients with overlap were specifically excluded from the cohort.

However, we believe that the inclusion of patients with overlap should have resulted in stronger associations with hypocomplementemia since some of the overlap diseases are well known to be associated with hypocomplementemia, in particular systemic lupus erythematosus. Secondly, and probably as a correlate of the same exclusion criteria in the Italian cohort, the prevalence of anti-centromere and anti-topoisomerase antibodies in the Cuomo study was very high.

Indeed, the sum of patients with either antibody approached 90% and patients with anti-centromere antibodies were more likely to be hypocomplementemic (p 0.08).

This, too, may in part account for their findings since there have been studies suggesting that anti-centromere antibodies are capable of fixing complement (3). However, the high rates of antibody positivity in the Cuomo study stands in contrast to other large SSc cohorts that have found cumulative rates of anti-centromere and antitopoisomerase positivity closer to 40% (4) and to our cumulative rate of approximately 50%.

Thus, their findings may not be generalizable to other SSc cohorts.

For the most part, though, the discrepancies in our two cohorts remain unexplained and beg for further research to understand whether, and if so how and to what extent, complement contributes to the pathophysiology of SSc.

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