Association of circulating CXCL10 and CXCL11 with systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune disorder defined 'vascular' disease[1] due to early defective angiogenesis ending in severe multiorgan fibrosis.[2] Biomarker(s) mirroring early microvascular derangements in SSc,[3] potentially useful for very early diagnosis, are lacking.

C-X-C angiostatic chemokines induced by interferon-γ, like CXCL10 and CXCL11, are involved in vasculopathy and associate with more severe SSc.[4 5] We investigated whether the shift from very early diagnosis of SSc (VEDOSS), when vasculopathy and fibrosis are at very low degree, to definite SSc elicits serum CXCL10/CXCL11 modifications.

CXCL10/CXCL11 were measured by multiplatform bead array in 26 healthy subjects; 62 sera from women admitted to the Scleroderma Clinic of Policlinico Umberto I, Sapienza University of Rome: 34 sera were from VEDOSS[6] (mean age 50.50±13.66 years, mean disease duration 11.1±4.2 months) and 28 sera from patients with SSc (mean age 56.56±12.45 years, mean disease 91.3±11.73 months) fulfilling the new American College of Rheumatology/European League Against Rheumatism 2013 classification[7]; table 1 reports patient characteristics.

Within VEDOSS, 29 subjects had a second blood sample collected during follow-up (T1, 40.67±5.46 months); for each one, we compared baseline (T0) and T1 serum chemokines. Informed consent was obtained.

Table 1 Demographic and clinical characteristics of patients with very early diagnosis of systemic sclerosis (VEDOSS) and systemic sclerosis (SSc) (whose sera sample collection was used in the study).

Characteristics	SSc (n=28)	VEDOSS (n=34)
Age (years)	56.56±12.45	50.50±13.66
Male	–	–
Female	28	34
lcSSc subsets	25 (89%)	–
dcSSc subsets	3 (11%)	–
Disease duration (months)	91.3±11.73	11.1±4.2
ANA	26 (93%)	31 (91%)
ACA	16 (57%)	17 (50%)
Anti-topoisomerase I (Scl-70)	4 (14%)	5 (15%)
Digital ulcers	4 (14%)	–
Normal NVC pattern	1 (4%)	13 (38%)
Early NVC pattern	6 (21%)	11 (32%)
Active NVC pattern	13 (46%)	9 (26%)
Late NVC pattern	8 (29%)	1 (3%)
Interstitial lung disease	6 (21%)	–

Age and disease duration were expressed as mean±SD/SE; disease duration was calculated since the first Raynaud phenomenon in VEDOSS and non-Raynaud symptom of SSc. Patients were not receiving corticosteroids, immunosuppressant or other disease-modifying drugs; patients with cardiac disease, pulmonary artery hypertension or active diseases other than SSc were excluded. Interstitial lung disease was determined by high-resolution computed tomography CT scan. ACA, anti-centromere antibodies; ANA, antinuclear antibodies; dcSSc, diffuse cutaneous SSc; lcSSc, limited cutaneous SSc; NVC, nailfold videocapillaroscopy.
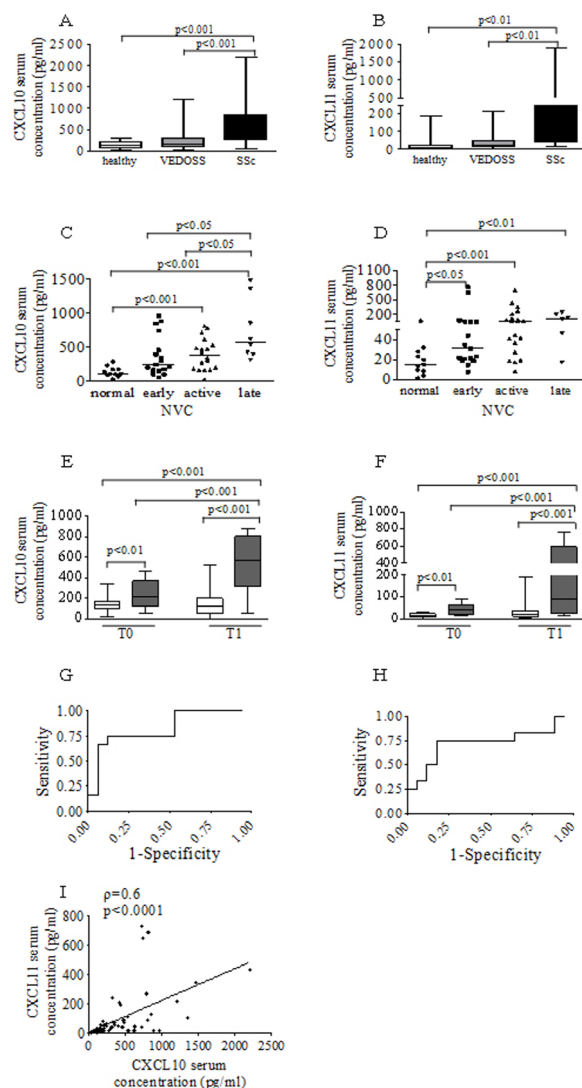
Figure 1 CXCL10 and CXCL11 serum-level modifications associated with very early diagnosis of systemic sclerosis (VEDOSS) and systemic sclerosis (SSc) condition. Baseline serum CXCL10 and CXCL11 levels in VEDOSS versus SSc and healthy subjects (A, B); CXCL10 and CXCL11 serum concentration according to capillaroscopic patterns in VEDOSS and SSc (C, D)—normal, early, active and late; CXCL10 and CXCL11 baseline (T0) and follow-up (T1) determination in sera of VEDOSS subjects shifted (grey boxes) or not (empty boxes) to SSc (E, F); receiver operating characteristic (ROC) curves constructed using chemokine baseline levels (**T0**) to identify CXCL10 and CXCL11 threshold (cut-off value) capable of discriminating VEDOSS subjects shifting or not to SSc (G, H); CXCL10 and CXCL11 serum-level correlation (**I**). GraphPad Prism V.5 software (GraphPad Software, La Jolla, California, USA) and SPSS V.24.0 software (SPSS) were used for statistical analysis. The Kolmogorov-Smirnov test was used for normal distribution of the data. Groupwise comparisons were performed using the Mann-Whitney U test. ROC curves were to give a graphic representation of the relationship between true-positive fraction (sensitivity, SE) and false-positive fraction (1 – specificity, Sp); ROC curves were assessed by plotting the values of 1 – Sp against Se in a squared box, where the ROC's area under the curve (AUC) is used to measure the performance of a diagnostic test. The AUC lies in the interval 0.5–1.0, so that the greater the area, the better the performance of the variable being examined. Chemokine association was determined using Pearson's correlation coefficient. For all tests, a two-sided p value <0.05 was considered significant. NVC, nailfold videocapillaroscopy.

CXCL10/CXCL11 were significantly higher in SSc (median: CXCL10 497.70 (range: 48.49–2206) pg/mL; CXCL11 107.20 (15.00–882) pg/mL) versus VEDOSS (CXCL10 168.70 (21.66–1202) pg/mL; CXCL11 23.30 (1.47–217.20) pg/mL) or healthy subjects (CXCL10 145.40 (15.86–310.30) pg/mL; CXCL11 10.90 (4.30–189.20) pg/mL) (figure 1A, B). All patients showed serum chemokines stratification according to capillaroscopic patterns (figure 1C, D), while chemokine levels did not significantly differ when related to anti-centromere antibodies or anti-topoisomerase positivity (not shown). VEDOSS subsequently shifted to SSc showed higher baseline chemokines (T0: CXCL10 217 (53.68–469.00) pg/mL; CXCL11 40.57 (15.74–92.04) pg/mL) versus subjects persistent in VEDOSS condition (T0: CXCL10 137.70 (21.66–339) pg/mL; CXCL11 17.47 (1.47–32.03) pg/mL) (figure 1E, F). Only VEDOSS shifted to SSc showed CXCL10/CXCL11 increase at T1 (570.80 (53.25–875.20) pg/mL). Both chemokines were able to discriminate VEDOSS subjects developing SSc (figure 1G, H) with the following cut-off values, identified by receiver operating characteristic (ROC) analysis: CXCL10 ≥165 pg/mL, area under the curve (AUC)=0.70 (95% CI 0.52 to 0.94, p<0.01) with 0.75 sensitivity and 0.70 specificity; CXCL11 ≥29.67 pg/mL, AUC=0.80 (95% CI 0.67 to 0.99, p<0.01) with 0.75 sensitivity and 0.88 specificity. Serum CXCL10 and CXCL11 positively correlated (ρ=0.6, p<0.0001) (figure 1I).

Due to CXCL10/CXCL11 detrimental effects on vessel homeostasis,[5 8 9] their higher baseline concentration in VEDOSS thereafter developing SSc likely mirrors the earliest vascular bed alteration(s)/modification(s)/rearrangement(s) occurring when vasculopathy is still at low degree. With vascular damage progression, serum chemokines increased, as suggested by level stratification according to the capillaroscopic patterns. VEDOSS subjects retaining lower CXCL10/CXCL11 overtime (at T0 and T1) did not evolve to definite SSc and maintained normal capillaroscopic pattern.

The small sample size investigated did not allow more robust combined analysis, completed by several validation stages, required by studies on functional biomarkers.[10] Result confirmation needs larger sample size, including more clinical variables and closer follow-up. This preliminary cross-sectional/retrospective analysis encourages further and larger works to ascertain if chemokines may be really the turning point from VEDOSS to definite SSc.

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