

Squamous cellular carcinoma immunocomplexed is increased in scleroderma patients with lung fibrosis

Sirs,

In the last few years, the need for serologic markers to follow the development of interstitial lung fibrosis has emerged, but none of the biomarkers currently available satisfy this requirement.

Squamous cellular carcinoma antigen (SCCA), a protein physiologically expressed in the suprabasal layer of the skin, is a member of the high molecular weight family of serine protease inhibitors (serpins) (1). It has been reported to be expressed in a number of different epithelial malignancies, including those of the larynx, cervix, lung and, more recently, the liver. Recently, the SCCA immunocomplexed form SCCA (IC) has been detected and, together with SCCA, used as a marker for hepatocellular carcinoma diagnosis (2, 3).

The aim of this study is to investigate the expression of SCCA and SCCAIC in the serum of SSc patients and to correlate it to the clinical outcome.

Serum SCCA and SCCAIC were determined as described (4) in 88 SSc patients (5) and 29 healthy donors (HD) (6), Table I. SCCA levels were 1.9 ± 1.7 ng/ml and 1.48 ± 0.9 in the whole group of SSc patients and of HD, respectively, this difference not being statistically significant ($p > 0.05$). On the contrary, SCCAIC serum levels were 263 ± 447 AU/ml and 23 ± 16 in the whole group of SSc patients and HD, respectively, showing a statistically significant difference ($p < 0.05$).

To further study the clinical significance of SCCA and SCCAIC, SSc patients were stratified according to the different types of clinical involvement. Specifically, SCCA levels were 1.9 ± 1.7 in the limited cutaneous subset, 1.3 ± 1.0 in the diffuse cutaneous subset, 1.5 ± 0.8 in SSc with associated PAH, 2.1 ± 1.8 in lung fibrosis SSc and 1.9 ± 1.9 in SSc without lung involvement ($p > 0.05$). Consistently, SCCAIC was evaluated in the same subsets of SSc patients and the following results were obtained: 265 ± 456 in the limited cutaneous subset, 249 ± 370 in the diffuse cutaneous

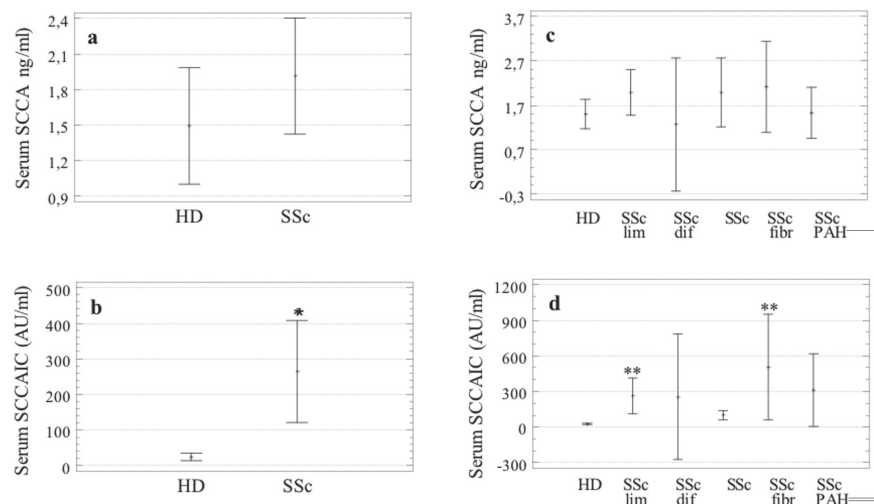


Fig. 1. SCCA and SCCAIC levels in HD and the whole group of systemic sclerosis (SSc) patients (panel a, b). SCCA and SCCAIC in HD and different clinical subsets of systemic sclerosis (SSc) patients: limited and diffuse cutaneous (SSc lim, SSc dif, respectively), without lung involvement (SSc), with interstitial lung fibrosis (SSc fibr), with pulmonary arterial hypertension (SSc PAH), panel c, d respectively. The values are expressed as mean $\pm$ 1 SD, * $p < 0.05$; ** $p < 0.01$.

subset, 309 ± 431 in SSc with associated PAH and 555 ± 694 in lung fibrosis SSc, these differences being statistically significant (lung fibrosis versus HD and SSc without lung involvement, $p < 0.01$; limited SSc versus HD $p < 0.01$) (Fig. 1). However, SCCAIC serum levels did not correlate with lung function test, neither with forced vital capacity nor with diffusion CO test. Furthermore, no correlations were found between SCCA and SCCAIC and the duration of the disease, age, gender, erythrocyte sedimentation rate (ESR, mm/1st hour), ANA, ACA and Scl-70 titers.

The only proposed marker to investigate lung fibrosis in SSc patients is KL-6, that has been shown to be associated with the presence and severity of interstitial lung fibrosis in SSc patients (7). However, this marker has been reported mainly in Japanese studies and not further confirmed in larger cohorts. SCCA has been reported to be increased in several epithelial malignancies including lung, cervix, and lately, liver, and so proposed as a diagnostic marker of cancer (2, 4, 8). In this study, SCCA and SCCAIC are investigated in the course of a systemic disease characterized by fibrosis in different parts of the body. Surprisingly, for the first time SCCAIC was found to be significantly increased in the group of patients with lung fibrosis, although a similar (but not statistically different) trend was observed also in patients with diffuse skin involvement. SCCA levels also showed a similar pattern, although the differences are not statistically significant, likely because of the limited number of patients investigated. This hypothesis seems also to be supported by the fact that SCCA is up-regulated in SSc with fibrotic but not vascular lung involvement, suggesting that this protein is likely related to “fibrotic” tissue remodeling. However, in

the case of scleroderma, the increased fibrosis is also associated with an abnormal immune response, thus explaining the increase of SCCAIC. What the biological role of SCCAIC may be is still unknown and we cannot rule out the possibility that it represents a marker of activated fibrotic-immune cell interactions.

In conclusion, longitudinal studies are needed to investigate whether SCCA and SCCAIC could be used as additional markers, together with the conventional diagnostic tools, in the long-term follow-up of patients with lung fibrosis.

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Table I. Patients demographic characteristics (PAH: pulmonary arterial hypertension), mean $\pm$ 1SD.

Total number of patients	88 (80 females, 8 males)
Age (years)	51 $\pm$ 13
Disease duration (years)	9.3 $\pm$ 6
Limited SSc	81
Diffuse SSc	7
Patients with PAH	18
Patients with pulmonary fibrosis	24

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Chloroquine and QTc interval

Sirs,

Chloroquine is a medication commonly used in rheumatology because it is cheap, easy to use and has a wide spectrum of therapeutic indications.

One of our patients using chloroquine and methotrexate for rheumatoid arthritis complained of an unspecific chest pain and underwent an electrocardiogram. A prolongation of QTc interval (0.45sec) was found to be reverted to normal when chloroquine was suspended. This can be explained by the fact that chloroquine belongs to the pharmacological group of quinidine (a Ia antiarrhythmic drug known to have a prolongation effect on QT interval (1)).

Prolongation of QT interval has already been described with chloroquine in healthy volunteers (2), *in vitro* with feline myocytes (3), and in cases of treatment for resistant malarial infection with halofantrine (4). On the other hand, Wosniaka *et al.* studied 28 lupus patients using chloroquine but did not find arrhythmias, conduction disturbances, nor alterations in QTc interval (5).

We decided to study the QTc interval on the electrocardiogram of 46 patients using antimalarials for rheumatoid arthritis (8 patients), systemic lupus (28 patients), erosive hand osteoarthritis (8 patients), Sjögren's syndrome (1 patient) and cutaneous lupus (1 patient). All included patients gave informed consent. These patients had been on antima-

Table I. QTc intervals in patients before and after stopping antimalarial.

PATIENT	Chloroquine dosing	Time of chloroquine use (months)	Concomitant drugs	QTc interval (in seconds)	
				With antimalarial	After stopping antimalarial
ALF, 77 years	120mg/day	4	Hydrochlorthiazide; paracetamol	0,463	0,431
IMV, 29 years	240mg/day	43	Paracetamol	0,448	0,381
OV, 30 years	240mg/day	50	Prednisone, azathioprine	0,472	0,395
TMN, 30 years	240 mg/day	26	Prednisone, methotrexate	0,452	0,407
EP, 44 years	240 mg/day	29	None	0,474	0,431
ESG, 62 years	240mg/day	32	Paracetamol	0,447	0,419
LV, 38 years	240 mg/day	6	None	0,446	0,406
EA, 30 years	240 mg/day	38	None	0,443	-

larials from 1 to 84 months (median = 27.24 months; SD $\pm$ 19.76). All but 2 patients were female; 42 were using chloroquine (Cloroquina[®], Far-Manguinhos, RJ, Brazil) and 4 were using hydroxychloroquine (Reuquinol[®]-Apsen). We considered the maximal value for a normal QTc to be 0.440 sec (6).

We found a prolongation in the QTc interval in 8 patients (17.39%). All of them were female and had been using chloroquine from 4 to 50 months (mean 28.5 ± 16.42). None of the four hydroxychloroquine users had a QTc prolongation. None of the patients with QTc prolongation previously had other heart conditions except for one with mild arterial hypertension. Concomitant medications used by this group of patients are shown in Table 1. We could not find a difference in the groups of patients using 240 mg/day or 120 mg/day of chloroquine (Fisher's test; $p = 0.574$); nor a relationship with time of use (Fisher's test; $p = 0.09$).

The 8 patients with prolongation of QTc interval were advised to stop the drug and seven of them agreed upon repeating the electrocardiogram within 2 weeks. In these patients, the QTc interval returned to normal (Table I).

Having observed the return to normal of QTc interval after withdrawal of medication and that there was no use of other drugs in these patients that could explain this prolongation, we think chloroquine may be implicated in causing this abnormality.

Although this is a small, uncontrolled study, we would like to call attention to the findings, because prolongation of QT interval can induce "torsade de points" ventricular tachycardia which may cause syncope and even sudden death.

We would like to advise taking an ECG in all patients using antimalarials. Studies with a larger number of patients and also specifically addressing the role of hydroxychloroquine are needed for a better understanding of QTc prolongation with these medications.

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