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Review

Lung cancer in scleroderma: Results from an Italian rheumatologic center and review of the literature ☆

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ABSTRACT

The association between systemic sclerosis (SSc) and cancer was widely described, particularly with breast and lung carcinoma; while, data regarding possible associations between cancer and SSc features are still scarce. We retrospectively evaluated the prevalence of lung cancer in our SSc patient cohort (318 SSc patients, 31 M and 287 F, age 51.5 ± 14.5SD years, disease duration 10.3 ± 6.5SD years) and clinico-serological factors potentially associated to the development of this malignancy. A review of the world literature about this topic was also done. We found that lung cancer complicated 16/318 (5%) SSc patients; namely 11/287 females (4%) and 5/31 males (16.1%). Median age of SSc patients with lung cancer was 54 (range 38–72) years for female patients, and 63 (range 40–73) for males; 13/16 patients died because of the neoplasia. Considering the incidence of lung carcinoma in sex/age-matched general population of the same geographical area, the percentages of lung cancer in our SSc series are about 2.5 and >5 times higher for male and female patients, respectively. The presence of lung cancer significantly correlated with male sex ($p = 0.011$), presence of anti-Scl70 antibodies ($p = 0.0007$), cyclophosphamide therapy ($p = 0.0001$), forced vital capacity (FVC) <75% ($p = 0.0001$), and lung fibrosis ($p = 0.0127$); moreover patients with cancer have a significantly lower age at the diagnosis of SSc ($p = 0.009$) and longer disease duration ($p = 0.0175$). The logistic regression analysis confirmed a significant association with the anti-Scl70 antibodies (OR 6.4, 95%IC 1.7–24.1; $p = 0.006$) and the reduction of FVC (OR 6.7, 95%IC 2.2–20.7; $p = 0.001$) only. Overall, the prevalence of lung cancer in the subset of SSc patients with anti-Scl70 antibodies was 12/105 (11.4%), 9/40 (22.5%) in patients with FVC% reduction, and 7/22 (31.8%) in patients with both. In literature, the median prevalence of lung cancer in SSc series was 2.4% (range 0–4.2%); even if sporadic, associations with lung involvement or antiScl70 autoantibodies were raised, according to our findings.
Our study confirmed the higher frequency of lung cancer among SSc patients compared to general population, particularly within patients' subset with serum anti-Scl70 antibodies and lung involvement.

Contents

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1. Introduction

The possible complication of connective tissue diseases with certain site-specific malignancies has been well-recognized over the years; in a few cases, the rheumatic disorder may represent the consequence of ongoing neoplastic process and may be classified as "paraneoplastic" [1–4]. With regard to systemic sclerosis (SSc), several previous studies have evidenced an increased incidence of malignancies, particularly lung and breast cancers [5–7]. Therefore, malignancies should be considered relevant causes of death in SSc patients, reaching almost 10% of cases [8].

On the basis of these considerations, careful assessment of lung involvement and clinical monitoring are mandatory in all SSc patients, not only for the early treatment of interstitial lung disease but also to identify potential neoplastic lesions as soon as possible.

Up to date, cyclophosphamide (CYC) is the first-line therapy for SSc alveolitis, given its capability to slow disease progression and to improve the overall prognosis [9]. However, a wide use of CYC for long-term treatment is not recommendable because of possible toxic adverse events and its carcinogenic potential [10]. In the last years, we occasionally observed some patients with SSc-related alveolitis developing lung cancer after CYC treatment. Therefore, we decided to evaluate the whole series of SSc patients followed at our Rheumatology Unit in order to define the actual incidence of lung cancer, and to identify the possible risk factors, including CYC treatment.

2. Cohort analysis

The study retrospectively evaluated 318 consecutive SSc patients (31 M and 287 F, age 51.5 ± 14.5SD years, disease duration 10.3 ± 6.5SD years), followed at our Rheumatology Unit from January 1999 to December 2011, and classified according to the American College of Rheumatology 1980 preliminary criteria [5]. All patients were Caucasian subjects from a region of about 5 million residents (Emilia-Romagna, Northern Italy). Table 1 summarizes clinico-epidemiological, serological, and instrumental data from SSc patients' records. We considered the age of patients at the SSc diagnosis, while the disease duration was calculated at the time of patient's last control (December 2011 or to the date of diagnosis of lung cancer): it was 10.3 ± 6.5 SD years, comprising 3270 patient-years (285 male patient-years plus 2985 female patient-years). The mean follow-up period was quite shorter (8.4 ± 4.8 SD years), since a small group of SSc patients referred to our center few months/years after the diagnosis; however, the clinical histories (particularly, eventual previous lung cancer) of these subjects were known and reported in clinical records.

The lung study had been performed in all patients as previously described [11], including pulmonary function tests, chest X-ray, and high-resolution computed tomography (HRCT). In particular, the presence of lung fibrosis was defined by the finding of basal symmetrical fibrosis of the pulmonary interstitium and/or presence of ground-glass areas in prone position at HRCT, independently from its severity. In addition, patients with signs of active lung involvement, i.e. deterioration of lung function and increase of the areas of interstitiopathy, underwent long-term CYC treatment (mean cumulative dosage 25.4 ± 11.7 SD g in 21.1 ± 9.5 SD months).

All cases of lung cancer diagnosed and recorded during the follow-up were compared with the remaining patients. In particular, the main clinico-serological features were carefully evaluated in order to find possible risk factors for pulmonary cancer, including both disease-related symptoms and other potential oncogenetic factors such as family history, smoke habit, as well as occupational and residential environments.

The observed incidence of lung cancer in our SSc patients was compared with that reported in the general population of the same geographic area (Emilia-Romagna), using sex- and age-matched data from AIRTUM, the Italian Association of the Registries of Tumors [12].

Statistical analysis was performed in order to investigate the possible correlations between SSc parameters and complicating lung cancer, as well as the role of well-known oncogenetic factors. Values are given as mean ± SD for normally distributed variables, or as median (range) for not normally distributed variables. Group proportions were compared by the chi-square test or Fisher's exact test. A logistic regression (stepwise forward) was performed considering lung cancer, as a dependent variable, and the other parameters statistically significant in bivariate analysis.

Data collected in the present retrospective study were judged exhaustive for the statistical analysis, since less than 3% of the whole data amount was missing.

3. Results

Among 318 SSc patients series 16 (5%) cases of lung cancer were recorded, including 11/287 females (3.8%) and 5/31 males (16.1%). The age at the diagnosis of cancer was <65 years for female patients with the exception of one (median 54, range 38–72 years), and 63 (range 40–73 years) for males. Table 1 shows the clinico-serological features of all SSc patients' series and of two subgroups with/without complicating lung cancer.

The observed incidence of lung cancer in our SSc patients was markedly higher compared with that reported in the general population of

Table 1
Clinico-serological features of scleroderma patients with/without lung cancer.

	All patients	Patients with lung cancer	Patients without lung cancer	p value°
	No = 318	No = 16	No = 302	
Age (mean ± SD)	51.5 ± 14.5	42.3 ± 15.4	51.9 ± 14.2	0.0094
M/F	31/287	5/11	26/276	0.011
Dis. duration (years) (mean ± SD)	10.3 ± 6.5	14 ± 9.6	10.1 ± 6.3	0.0175
Smoke habit	97 (30.5%)	5 (31.2%)	92 (30.5%)	ns
Cutaneous subsets (L/D)^	278/40	14/2	264/38	ns
Skin ulcers	123 (38.7%)	6 (37.5%)	117 (38.7%)	ns
ACA	140 (44%)	1 (6.2%)	139 (46%)	0.0042
Anti-Scl70	105 (33%)	12 (75%)	93 (30.8%)	0.0007
ANoA	45 (14%)	3 (18.7%)	42 (13.9%)	ns
Interstitial lung disease (X-ray)	152 (47.8%)	13 (81.2%)	139 (46%)	0.0127
FVC% (mean ± SD)	96.4 ± 22.9	71 ± 24.6	97.9 ± 21.9	<0.0001
FVC<75%	40 (12.6%)	9 (56.2%)	31 (10.3%)	0.0001
Paps > 35 mm Hg	54 (17%)	5 (31.2%)	49 (16.2%)	ns
Therapy with CFX*	36 (11.3%)	7 (43.7%)	29 (9.6%)	0.0001

^L = limited; D = diffuse; *CFX = cyclophosphamide.
Serology: Scl70 = anti-Scl70, ACA = anticentromere, ANoA = anti-nucleolar, ANA = anti-nuclear autoantibodies.
°Statistical evaluations between patients with and without lung cancer.