Thymus alterations and systemic sclerosis

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Objectives. The pathogenesis of systemic sclerosis (SSc) includes complex alterations to the immune system, possibly responsible for diffuse microvasculature and fibroblast dysfunction. Previous anecdotal observations suggest a possible role for thymus alterations in some autoimmune rheumatic diseases, including SSc. This study aimed to investigate the prevalence of radiological thymus alterations in SSc patients.

Methods. Thirty-four unselected patients [28 female and 6 male, mean age (± s.d.) 49.7 ± 9.5 yr, range 33–67 yr] and 34 age- and sex-matched controls were included in the study. The presence of major radiological thymus alterations, i.e. an abnormally enlarged or nodular thymus, were blindly investigated by means of unenhanced multidetector computed tomography.

Results. Abnormally enlarged or nodular thymuses were detected in a statistically significant percentage of SSc patients compared with controls (21 vs 0%, P = 0.011). More interestingly, radiological thymus alterations were invariably observed in patients with shorter disease duration (≤5 yr, 41% vs >5 yr, 0%; P = 0.007), frequently associated with serum anti-Scl70 antibodies (P = 0.017). Among patients with thymus alterations one developed myasthenia gravis while two others showed thymus hyperplasia at histopathological evaluation after thymectomy.

Conclusions. The present study suggests a possible role of thymic disorders, mainly thymus hyperplasia, in a significant number of SSc patients. Due to the limitations of radiological evaluation, the actual relevance of such an association might be underestimated. The relationship of thymus alterations with shorter disease duration, as well as with serum anti-Scl70, suggests that thymic dysfunction could play a pathogenetic role mostly in the early phases of the disease, and possibly in specific SSc patient subsets.

Key words: Systemic sclerosis, Scleroderma, Thymus, Thymus hyperplasia, Computed tomography.
The presence of interstitial lung involvement was investigated by standard chest X-ray, high-resolution computed tomography (HRCT) and spirometric evaluation.

The thymus alterations were evaluated in all patients and controls by unenhanced multidetector computed tomography (MDCT). Computed tomography exams were carried out at suspended end-inspiratory volume by means of a Somatom Volume Zoom 4 (Siemens, Germany). The technical parameters of MDCT examination, performed from apex to base without administration of contrast medium, were: 2.5 mm collimation, 5 mm thickness, 5 mm interval. Images of the thymus, reviewed at the mediastinal window, were then reconstructed using 3 mm thickness, 1 mm interval and a field of view small enough to include all the gland.

Radiological thymus alterations were evaluated according to the current methodology [15]: the most helpful value for thymus size was considered to be the ‘thickness’ measured perpendicular to the length, with 13 mm being the maximum normal value in adult subjects. A thymus thickness greater than 13 mm or a focal soft-tissue density of more than 7 mm can be considered specific for thymic hyperplasia or thymoma [15].

A trained radiologist evaluated, blindly and in random order, the MDCT scans of patients and controls. Radiological thymus features were classified as follows: 1, normal with complete or incomplete involution; 2, abnormally enlarged; 3, nodular thymus or mass-like or inhomogeneous in attenuation [15].

Group differences were tested for significance by Fisher’s exact test and a P value of <0.05 was considered significant.

Results
At the time of the study, the 34 SSc patients [28 female, six male, mean age (±s.d.) 49.7 ± 9.5 yr, range 33–67 yr] had a mean (±s.d.) disease duration of 8.4 ± 6.8 yr (range 1 to 33 yr). According to the skin involvement, they were classified as having limited (n = 16), intermediate (n = 11) or diffuse SSc (n = 7). The most frequent internal organ alterations were lung fibrosis (85%), and oesophageal (68%) and cardiac dysfunction (35%). Among serological markers, ANA were detected in 24/34 (71%) patients, ACA in 7/34 (21%), anti-Scl70 in 13/34 (38%) and ANoA in 1/34 (3%).

In SSc patients the MDCT revealed an abnormally enlarged thymus in 5/34 cases (15%), a nodular thymus in 2/34 (6%) and an incomplete organ involution in 9/34 (26%). This latter was detected in a comparable percentage of control subjects (29%), while neither abnormally enlarged nor nodular thymus was observed in the controls. Major radiological thymus alterations (abnormally enlarged or nodular thymus) were present in a statistically significant percentage of SSc patients compared with controls [7/34 (21%) vs 0/34 (0%), P = 0.011; Fig. 1a]. Interestingly, thymus alterations were invariably observed in patients with shorter disease duration [≤5 yr, 7/17 (41%) vs >5 yr, 0/17 (0%); P = 0.007; Fig. 1b]. Moreover, the seven patients with radiological thymus abnormalities showed the presence of serum anti-Scl70 in five and ANoA in one; while in the other patient serological markers were absent (Fig. 1c). The association between thymus abnormalities and anti-Scl70 was particularly relevant considering the subset of 15 patients with disease duration ≤5 yr: namely the prevalence of thymus alterations in anti-Scl70-positive patients was significantly higher compared with that found in anti-Scl70-negative subjects [5/6 (83%) vs 2/11 (18%); P = 0.017]. There were no significant correlations between thymus alterations and either cutaneous subsets or visceral organ involvement.

At the time of the study, 15 patients had been treated with immunosuppressive agents (cyclophosphamide, ciclosporin A and/or methotrexate); however, the prevalence of thymus alterations between two groups of treated and non-treated subjects was not statistical significant (26 vs 16%, respectively). In no cases had high doses of steroids been administered.

Case reports
Case 1. Since 1997 a 33-yr-old female (Fig. 2) had developed Raynaud’s phenomenon, arthralgias, melanodermia, diffuse cutaneous sclerosis, skin ulcers, oesophageal and pulmonary involvement, scleroderma capillaroscopic changes and serum anti-Scl70 antibodies. The MDCT demonstrated the presence of a nodular thymus. Given the severity and the progression of the disease a therapeutic attempt with thymectomy was decided upon.

![Fig. 1. Prevalence of radiological thymus alterations in (a) SSc patients and controls, (b) SSc patients with disease duration ≤5yr and >5yr and (c) SSc patients with different serological markers (for abbreviations see text). Considering the subset of 15 patients with disease duration ≤5yr, the prevalence of thymus alterations in anti-Scl70-positive patients was significantly higher than that found in anti-Scl70-negative subjects (5/6 = 83% vs 2/11 = 18%; P = 0.017).](https://academic.oup.com/rheumatology/article-abstract/45/1/72/1788513/1?search_type=abstract&fid=abstract445/727178513&guest=1)
Histological evaluation revealed thymic hyperplasia. However, the patient's clinical status did not change during the following 6-month period, while an improvement of the cutaneous sclerosis and stabilization of lung involvement were observed with a combined treatment with steroids, iloprost and oral cyclophosphamide.

**Case 2.** A 33-yr-old female (Fig. 2) who had been suffering from Raynaud's phenomenon since 1994 was referred to our rheumatology unit where a diagnosis of SSc, limited cutaneous variant, was made (Raynaud's, sclerodactyly, scleroderma capillaroscopic alterations, lung fibrosis and high-titre ANoA). An MDCT study demonstrated an abnormal enlargement of the thymus. Considering the presence of active disease (recurrent skin ulcers and interstitial lung involvement) and the possible pathogenetic role of the thymus, the patient underwent a thymectomy. Thymic hyperplasia was diagnosed by histological evaluation. Consequently, the patient showed clinical improvement of both cutaneous and lung involvement, which remained stable during the following 2-yr follow-up period.

**Case 3.** A 67-yr-old man, (Fig. 2) suffering since 1998 from Raynaud's phenomenon, sclerodactyly, and melanodermia, was diagnosed with SSc (sclerodactyly, Raynaud's, telangiectasias, typical capillaroscopic changes, oesophageal dysmotility, lung interstitial involvement). In 2000 he developed mild bilateral ptosis and progressive limb and neck fatigue. These latter symptoms suggested the diagnosis of myasthenia gravis, confirmed by the presence of antiacetyl-choline receptor antibodies, electromyographic alterations and positive prostigmine test. An MDCT examination revealed an abnormally enlarged thymus. The patient was treated with prostigmine, steroids (prednisolone 40 mg/day) and long-term selective plasmapheresis (protein A immunoadsorption, Immunosorba, Excotom, Fresenius Hemocare GmbH, StWendel, Germany). The patient's clinical status, particularly the myasthenic symptoms showed a clear improvement. One year later the patient died due to myocardial infarction.

**Discussion**

The results of the present study suggest a possible role for thymic disorders in a significant number of unselected SSc patients compared with control subjects; obviously, our preliminary data need to be confirmed in other patient series. Thymic hyperplasia seems to be the main pathological alteration, as suggested by radiological features and confirmed in two cases by histopathological evaluation. Moreover, we can hypothesize that the actual relevance of such an association might be underestimated due to the following considerations. Although the current methodology, based on the measurement of gland thickness and focal soft-tissue density, is considered as the best non-invasive diagnostic approach [15], we cannot exclude possible false-negative results. Previous studies on large series of patients with myasthenia gravis, comparing radiological findings with histopathological diagnosis after thymectomy, support this hypothesis [16]. Besides, incomplete thymus involution, as well as residual ectopic thymus, can...
hide small areas of functional tissue. On the other hand, the striking correlation between thymus alterations and shorter disease duration suggests that thymic dysfunction could play a pathogenic role mostly in the early phases of the disease. In addition, thymic dysfunction might be particularly involved in specific SSc subsets, as indirectly suggested by the frequent anti-Scl70 sero-
positivity in patients with thymus alterations and, vice versa, the constant absence of ACA. These autoantibodies are regarded as hallmarks of different clinico-prognostic SSc subsets, possibly related to specific aetiopathogenetic factors [1, 2, 14]. Thus, future studies should evaluate larger SSc series by stratifying patients according to disease duration and other clinico-epidemiological and serological features.

Thymus morphology varies considerably with age; gland involution proceeds from puberty to the age of about 25 yr [17]. Previous radiological investigations clearly demonstrated the absence of significant thymus abnormalities in normal subjects over the age of 30 yr [17]. If so, the possible relevance of false-positive results due to age-related residual thymus can be excluded in our patients series. Similarly, the possible effects of immuno-suppressive treatments on the MDCT findings can be reasonably ruled out.

The presence of thymic hyperplasia in SSc has been suggested on the basis of anecdotal observations, but not sufficiently investigated in large patients series [15, 17]. This is the first attempt to evaluate the possible involvement of the thymus in the SSc. The disease is characterized by a wide spectrum of clinical variants, suggesting a multifactorial and multistep pathogenetic mechanism, including complex alterations to the immune system. Different causative factors, i.e. infectious and/or toxic agents, have been proposed in the pathogenesis of SSc, although their exact role still remains to be definitively established [1, 2]. Moreover, the thymus exerts a key role in the balance between tolerance and immunity [3, 4]. The recognition of self and foreign peptides is fundamental in physiological conditions, while its failure may be crucial in the pathogenesis of various autoimmune disorders [3, 4]. The thymic stromal cells and hormones play a key role in modulating the immune reactions through their effects on T-lymphocyte differentiation of both helper and suppressor/cytotoxic cells. The role of thymic dysfunction has been investigated in both murine models [18] and autoimmune diseases of humans [19]. In SSc, different defects of T lymphocytes have been reported, even if their exact pathogenetic role remains largely obscure, probably due to the small number and the inhomogeneity of patient series investigated [2]. On the other hand, the lack of suitable animal models of scleroderma represents a further limitation. In rare conditions simulating the clinical features of SSc, such as in UCD L200 chickens, the presence of abnormalities of the thymic microenvironment might induce altered T-cell differentiation that may predispose to autoimmune disease [18]. Thymic dysfunction might be crucial in the inducing phase of the disease when the correct recognition of potentially triggering factor(s) is determin-

ant, with the possible contribution of a genetically driven immune reactivity [2]. Successively, we can hypothesize the presence of a self-perpetuating, thymus-independent mechanism of disease. Moreover, in patients with advanced SSc we can observe the natural involution of the thymus, probably accelerated by diffuse scleroderma organ fibrosis. The timing of thymus dysfunction during the natural history of SSc might be crucial; it can be indirectly suggested by the variability of radiological findings observed in our SSc patients, characterized by a wide range of disease durations. Finally variable polarization of thymus activity [5, 20] could explain the contrasting effects of thymectomy observed in our two patients.

The authors have declared no conflicts of interest.

References


