Radiological incomplete thymus involution in systemic sclerosis

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Objective. Thymus plays a crucial role in immune system homeostasis, and thymic abnormalities have been previously reported in many autoimmune diseases, including SSc. The aim of this study is to evaluate the frequency of radiological thymus abnormalities in SSc patients and its relationship with various clinical and laboratory features.

Methods. Sixty-three female SSc patients (diffuse/limited: 49/14), all having pulmonary high-resolution CT (HRCT) scans, taken previously for evaluating lung involvement were included. At the time of the scans, mean age and disease duration of the patients were 50.1 ± 8.5 and 10.2 ± 7.8 years, respectively. As the control group, 45 age-matched female patients, having normal pulmonary HRCT scans taken previously for evaluating non-specific symptoms, were included.

Results. Frequency of incomplete thymus involution was significantly higher in SSc patients (12/63; 19%) compared with the control group (2/45; 4.4%; P = 0.022). In SSc patients with pulmonary fibrosis, incomplete thymus involution was significantly lower (3/38; 7.9%) than those without pulmonary fibrosis (9/25; 36%; P = 0.007).

Conclusion. The present study shows significantly higher frequency of radiological incomplete thymus involution in SSc compared with normal controls. Furthermore, less common occurrence of pulmonary fibrosis in SSc patients with incomplete thymus involution deserves attention. These findings may have some implications regarding the possible role of thymic abnormalities at least in some patients with SSc.

Key words: Systemic sclerosis, Scleroderma, Thymus, Incomplete thymus involution.

Introduction

SSc is a connective tissue disease characterized by widespread fibrosis of skin and visceral organs and affecting especially females [1]. Although its pathogenesis is unknown, various immunological abnormalities such as activation of T lymphocytes and production of various autoantibodies and cytokines are believed to cause vascular endothelial damage and increased collagen synthesis [1].

The thymus is a primary lymphoid organ that supports the differentiation and selection of T cells. In the unique microenvironment of the thymus, lymphoid progenitor cells derived from the bone marrow and fetal liver, encounter a variety of specialized stromal cells and undergo multiple rounds of proliferation, differentiation, and positive and negative selection that comprise the T-cell development pathway [2–4]. Hence, thymus plays a crucial role in immune system homeostasis [2–4], and thymic abnormalities have been previously reported in many autoimmune diseases including SSc [5–12].

Physiologically, the activity of the thymus decreases in time; in normal subjects, thymic atrophy generally starts after puberty and complete involution is expected at the age of ~25 years [13]. As shown in previous radiological investigations, thymus gland normally involutes completely over the age of 30 years [13].

However, in some pathological conditions radiological thymic alterations including incomplete thymus involution, thymic hyperplasia or nodular thymus may be observed. The presence of radiological thymic alterations, mainly in the form of enlarged or nodular thymus was recently shown by Ferri et al. [12] in 34 SSc patients. However, they could not find significantly higher frequency of incomplete thymus involution in their SSc series. In the present study, we aimed to evaluate the frequency of radiological incomplete thymus involution in our larger series of SSc patients, all having pulmonary high-resolution CT (HRCT) scans, taken previously to evaluate SSc lung involvement. We also aimed at comparing the SSc patients with and without incomplete thymic involution to find out whether incomplete thymic involution might have any effect on various clinical and laboratory features of SSc.

Patients and methods

In this retrospective study, 63 female SSc patients whose pulmonary HRCT scans had been taken previously for evaluating possible lung involvement were included. All these patients were being followed up by Ege University Hospital Rheumatology Department, and all of them gave informed consent to enter the study, which was approved by the local ethical committee. Forty-five age-matched female patients (mean age: 47.6 ± 7.7 years), having normal pulmonary HRCT scans taken previously for evaluating non-specific symptoms, but otherwise healthy, were included as the control group. The clinicians had ordered these pulmonary HRCT scans, in order to exclude pneumonia or embolism and bronchiectatic changes in these patients. These normal pulmonary HRCT scans were randomly chosen from the archive records of the Ege University Hospital Radiology Department and served as normal control pulmonary HRCT scans in our study.

All the SSc patients included in this study were classified according to the ACR 1980 preliminary criteria [14]. In case of doubt, they were called back for further evaluation. These patients were divided into two groups based on the skin involvement. In case of the skin sclerosis involving the fingers and the distal parts of the extremities with or without the presence of facial and/or neck skin sclerosis, the patients were diagnosed as having lcSSc. In the presence of skin sclerosis involving proximal parts of the extremities, i.e. regions proximal to the knees and/or elbows, and the chest wall, the patients were diagnosed as having dcSSc. According to this definition, 49 patients had dcSSc and 14 patients had lcSSc.

Since in normal subjects the thymus gland involution proceeds from puberty to the age of ~25 years, and as shown in previous radiological investigations, thymus gland involutes completely over the age of 30 years [13], we accepted the age of 30 years as the cut-off point at the time when pulmonary HRCT scans had been taken. In other words, SSc patients <30 years were not included in this study. Mean age and mean disease duration of

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the SSc patients when pulmonary HRCT scans had been taken were 50.1 ± 8.5 (32–65) years and 10.2 ± 7.8 (1–40) years, respectively. In SSc patients, the disease duration was calculated on the basis of the age at which the first signs and symptoms compatible with the disease appeared, namely RP with digital ischaemic lesions, puffy hands, sclerodactyly with or without proximal scleroderma, dyspnoea and/or dysphagia.

All the SSc patients included in this study had detailed medical records and all the data were closely evaluated. Due to a special protocol applied to all our SSc patients, visceral involvement had been investigated in all cases. The presence of interstitial lung involvement had been investigated in all the patients by standard chest X-ray, pulmonary HRCT and respiratory function tests including carbon monoxide diffusion capacity. Oesophagus motility examinations using an oesophagus manometer and echocardiographic investigations were also available in all the SSc patients.

Autoantibody profiles, namely ANAs and anti-nucleolar antibodies (ANoAs), ACAs and anti-ENA antibodies, including anti-Scl70, anti-Sm, anti-RNP and anti-SSA/SSB were also noted.

Previous treatments including steroids and immunosuppressive agents that SSc patients had received before the pulmonary HRCT scans had been taken, were also noted.

All the pulmonary HRCT scans were taken using spiral CT scanner (Siemens, Somatom Plus 4, Erlangen, Germany). Technical parameters used were 140 kVp, 200 mA and a field of view small enough to include thymus. Examinations were performed in end-inspiration from apex to base of the lungs without contrast administration. The 1-mm slice thickness and 10-mm slice interval were used. Images were reconstructed with high spatial frequency algorithm. Images were reviewed on mediastinal window settings. All the scans of the 65 SSc patients and 45 control cases were retrospectively re-evaluated by a single and trained pulmonary radiologist (S.B.). Incomplete involution of thymus was accepted when thymus tissue could be observed as nodular or linear structure (Fig. 1). Complete involution of thymus was accepted in the presence of gland with fat density (Fig. 2). Due to technical limitations, thymus thickness measurements could not be performed.

Statistical package program (SPSS; version 11.0.0) was used to analyse the data. Values were expressed as the mean ± s.d. unless indicated otherwise. Chi-square analysis and Fisher’s exact test were used for the comparison of grouped variables. For parametric variables, Student’s t-test and Mann–Whitney U-test (in the subgroup analysis) were used. P-values <0.05 were accepted as significant.

Results

All the demographic characteristics of 63 female SSc patients included in this study as well as the frequencies of major internal organ involvements and autoantibody positivities are given in Table 1. At the time that the pulmonary HRCT scans had been taken, the mean age and mean disease duration of the SSc patients were 50.1 ± 8.5 years (range 32–65 years) and 10.2 ± 7.8 years (range 1–40 years), respectively. No cases had received high doses of steroids before the pulmonary HRCT scans. There were no significant differences between dcSSc and lcSSC patients, and between SSc patients with and without pulmonary fibrosis, with respect to previous immunosuppressive treatments including cyclophosphamide, AZA and/or MTX.

In SSc group, re-evaluation of the pulmonary HRCT scans revealed incomplete thymus involution in 12 patients (12/63; 19%);
however, among the control group, incomplete thymus involution was present only in two cases (2/45; 4.4%). Hence, frequency of incomplete thymus involution was significantly higher in SSc patients compared with the control group (P = 0.022). Among the SSc group, the frequency of incomplete thymus involution was higher in the lcSSc subgroup (5/14; 37.5%) than in the dcSSc subgroup (7/49; 14.3%), but without significance at P = 0.083.

In the next step, we analysed whether significant differences existed between SSc patients with and without radiological incomplete thymus involution. The most striking finding was the inverse relation between incomplete thymus involution and the pulmonary fibrosis. Among 63 SSc patients 38 had pulmonary fibrosis, relation between incomplete thymus involution and the pulmonary fibrosis. Among 38 SSc patients 38 had pulmonary fibrosis, the most striking finding was the inverse relation between incomplete thymus involution and the pulmonary fibrosis. Among 63 SSc patients 38 had pulmonary fibrosis, the most striking finding was the inverse relation between incomplete thymus involution and the pulmonary fibrosis.

In summary, unlike Ferri et al. [12], unenhanced multidetector CT was used to evaluate thymic alterations in 34 unselected SSc patients. If the thymus thickness was >13 mm, or if there was a focal soft-tissue density of >7 mm, they accepted these findings to be specific for thymic hyperplasia or thymoma. Among 34 SSc patients, they found that abnormally enlarged thymus was present in 5 (15%), nodular thymus in 2 (6%) and incomplete thymic involution in 9 (26%) patients. Incomplete thymus involution was also detected in a comparable percentage of control subjects (29%), whereas neither abnormally enlarged nor nodular thymus was observed in the controls. They concluded that only major radiological thymus alterations such as abnormally enlarged or nodular thymus, rather than incomplete thymus involution were significantly higher in SSc patients compared with controls. Ferri et al. [12] also reported that major radiological thymus alterations were invariably observed in SSc patients with shorter disease duration and frequently associated with serum anti-Scl70 antibody positivity. We also confirmed that SSc patients with incomplete thymus involution had shorter disease duration, but this did not reach statistical significance in our study.

In summary, unlike Ferri et al. [12], we found incomplete thymus involution to be significantly higher in our series of SSc patients. This difference may be due to several factors. While they made prospective volumetric measurements using unenhanced multidetector CT, our analysis was based upon retrospective analysis of pulmonary HRCT scans. More importantly, genetic and environmental factors may obviously explain the difference. We believe that thymus involution and thymic alterations in general may not be the same in different geographies and ethnic origins. Since infections are common in our country, one may speculate that even infection frequency may also retard thymus involution. Since we retrospectively analysed pulmonary HRCT scans with 1-mm slice thickness and 10-mm slice intervals, we could not make any comment on the presence and frequency of abnormally enlarged or nodular thymus in our SSc patients. Indeed it should be preferable to acquire specific scans of the thymus with 3-mm slice thickness and 1-mm slice interval to minimize false-negatives. Hence, we confess that the difference of incomplete thymic involution between SSc patients and controls might have been underestimated in our study.

From technical point of view, volumetric analysis such as measuring thymus thickness would have been unreliable in our study. For similar reasons, we might have misinterpreted abnormally enlarged thymus gland as incomplete thymic involution. We readily accept that this is a limitation of our study. We also accept that while evaluating thymus, the radiological findings may not always be consistent with the histopathological findings. A thymus gland that seems to be completely involuted, may indeed hide small areas of functional thymic tissue. In other words, morphological abnormalities of the thymus may not always suggest a 'thymic dysfunction': furthermore, the thymic alterations, complete or incomplete involution, could at least be in part a consequence of the SSc pathological process.

On the other hand, before drawing conclusions regarding thymus involution, one should also consider the age of the patients and the previous treatments that they received. Since all the participants in our study were >30 years of age at the time the scans had been taken, we excluded the effect of age on thymus involution. Similarly, the previous treatments including steroids and immunosuppressive agents that SSc patients had received before the pulmonary HRCT scans were carefully noted. There were no significant differences between dcSSc and lcSSC patients, and between SSc patients with and without pulmonary fibrosis in this aspect.

Besides the aforementioned pioneering study of Ferri et al. [12], the literature data about thymic abnormalities in SSc are scarce and confined to post-mortem histopathological examinations performed in a limited number of SSc patients [11], as well as a few case reports of thymoma in SSc [7–10]. Based upon post-mortem histopathological examination of three SSc patients, an old study reported that thymus glands showed a greater degree of atrophy than would be expected at that age [11].

Despite some differences involving methodology and results, both the present study and the previous study performed by Ferri et al. [12] might suggest a possible role for thymic disorders in SSc patients. We readily accept that SSc is a very complex disease and the whole pathogenesis cannot be explained solely based upon thymic abnormalities. However, we know that various immunological abnormalities occur in SSc, causing vascular endothelial damage and increased collagen synthesis.

Since thymus has a crucial role in immune system homeostasis [2–4], thymic abnormalities might readily contribute to SSc pathogenesis. One should also remember the role of the thymus in shaping the peripheral T-cell repertoire and self-tolerance. Not only positive and negative selection processes take place in the unique microenvironment of thymus, but thymus is also involved in the generation of regulatory T cells [15]. Furthermore, the importance of the thymus extends well beyond the initial seeding of the peripheral T-cell pool. As long as thymus goes on functioning, it serves as a source of new T-cell specificities. However, during the thymus atrophy, the export of new T cells dramatically reduces and this reduction predisposes an individual to impaired T-cell function, reduced T-cell immunity and increased autoimmunity [4]. Since SSc is an autoimmune disease where T-cell abnormalities readily exist, contribution of thymus abnormalities in SSc pathogenesis seems reasonable.
Some experts speculate that, in the future, thymic regeneration might become a feasible and potentially powerful approach to rejuvenating a depleted peripheral T-cell pool [4]. So, one really wonders whether the presence of incomplete thymic involution is an advantageous or disadvantageous condition in SSc. Interestingly, we found that the frequency of incomplete thymic involution was significantly higher in lcSSc, which may be accepted as a relatively milder form of SSc, compared with dcSSc. Furthermore, significantly more frequent incomplete thymic involution in the absence of pulmonary fibrosis also seemed to be an interesting finding. On the other hand, previous speculation raised by Ferri et al. [12] also sounds attractive. They speculated that thymic dysfunction might be crucial in the inducing phase of SSc and later self-perpetuating, thymus-independent mechanisms might contribute to the pathogenesis.

In conclusion, the present study shows significantly higher frequency of radiological incomplete thymus involution in SSc compared with normal controls. Furthermore, less common occurrence of pulmonary fibrosis in SSc patients with incomplete thymus involution deserves attention. These findings may have some implications regarding the possible role of thymic abnormalities at least in some patients with SSc. Currently, it remains unknown whether these thymic abnormalities might play a role in the pathogenesis of SSc. Further studies are obviously needed to clarify this issue.

Disclosure statement: The authors have declared no conflicts of interest.

References