Overlap syndromes in systemic sclerosis

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Abstract

Introduction: It is known, that course of the disease differs between overlap syndromes (OS) and systemic sclerosis (SSc) group.

Aim: To compare the prevalence of OS in limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous SSc (dcSSc) and to analyze the presence of different manifestations in the SSc and OS group.

Material and methods: The study included 126 European Caucasian SSc patients (99 females and 27 males) hospitalized consecutively in the Department of Rheumatology and Connective Tissue Diseases. Patients fulfilled the American College of Rheumatology (ACR) classification criteria of SSc (57 – dcSSc and 69 – lcSSc). The study groups were determined according to the subtype of SSc, coexistence of other connective tissue diseases (CTDs), and incidence of clinical and serological manifestations.

Results: In our SSc study group, 28/126 patients (22%) were affected by more than one CTD. The prevalence of OS was significantly higher in the lcSSc group – 33% (23/69) compared to the dcSSc group – 8% (5/57). We found that mortality and digital ulcers were significantly higher, whereas kidney involvement and arthritis were significantly lower in the SSc group compared to the OS group. The prevalence of anti-topoisomerase I (a-Scl-70) was significantly higher, and prevalence of anti-PM/Scl, anti-Ro-52 antibodies was significantly lower in the SSc group compared to the OS group.

Conclusions: Overlap syndromes were more common in lcSSc than in dcSSc. The course of the disorder and internal organ involvement were different in OS compared to SSc patients.

Key words: systemic sclerosis, overlap syndrome.

Introduction

Overlap syndromes (OS) are autoimmune disorders in which classification criteria of at least two connective tissue diseases (CTDs) are fulfilled. The most common combinations are systemic sclerosis (SSc) and Sjögren syndrome (SS), dermatomyositis (DM) or polymyositis (PM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) [1–4]. Occasionally, three or more CTDs overlap or other non-rheumatic autoimmune diseases occur, such as autoimmune thyroiditis (AT), autoimmune hepatitis, primary biliary cirrhosis (PBC), as well as autoimmune thrombocytopenia, coeliac disease or vitiligo [2, 3, 5]. In the course of SSc, 20–30% of patients develop OS [1–3]. The clinical presentation of OS patients is very heterogeneous and that diversity depends on the kind and subtype of diseases that overlap [6]. According to LeRoy et al., there are two different subtypes of SSc – limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) [7]. The course of the disease and prevalence of organ involvement differs in SSc and in OS. Moreover, there are some data describing differences in the prevalence of OS between the two subtypes of SSc [6].

Aim

The aim of the present study was to compare the prevalence of OS in patients with lcSSc and dcSSc, as well as to compare different manifestations of SSc in patients with SSc and with OS.

Material and methods

The study included 126 (99 female and 27 male) European Caucasian SSc patients hospitalized consecutively in the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin. All patients provided written informed consent to participate in the study according to the Declaration of Helsinki. The study design was approved by the ethical committee. All patients fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification.
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Characteristics of the systemic sclerosis and overlap syndrome group

Table 1. Characteristics of the systemic sclerosis and overlap syndrome group

| Parameter                  | Systemic sclerosis | Overlap syndromes (systemic sclerosis/connective tissue diseases) |
|----------------------------|--------------------|-----------------------------------------------------------------|
| Number of patients:        | 98                 | 28                                                              |
| dcSSc                      | 52                 | 25                                                              |
| lcSSc                      | 46                 | 23                                                              |
| Gender:                    |                    |                                                                |
| Female                     | 75                 | 24                                                              |
| Male                       | 23                 | 4                                                              |
| Age [years]                | 53.5 ±13.9 (18.0–81.0) | 54.1 ±10.4 (22.0–71.0)                                          |
| Duration of disease [years]| 6.3 ±1.1 (0.0–23.0) | 6.1 ±5.8 (0.0–22.0)                                             |
| Time from onset of Raynaud’s phenomenon to diagnosis [years]| 5.6 ±6.2 (0.3–30.0) | 6.2 ±4.8 (1.0–20.0)                                             |

Data were presented as number.
patients (7.1%, 32.1%) (2 patients dcSSc/SS and 7 patients lcSSc/SS); SSc/RA coexisted in 8 patients (6.3%, 26.6%) and all patients had lcSSc/RA; SSc/PM was found in 7 cases (5.5%, 25%) (5 patients lcSSc/PM and 2 dcSSc/PM); SSc/SLE coexisted in 2 patients (1.6%, 7.1%) and SSC/APS in another 2 cases (1.6%, 7.1%). Five patients developed more than two CTDs (3.9%, 17.8%).

In our study group, it was found that mortality and presence of digital ulcers was significantly higher in the SSc group in comparison with the OS group (21.4% vs. 3.6% respectively, \(p = 0.043\) and 21.4% vs. 3.6% respectively, \(p = 0.043\)). On the other hand, the prevalence of kidney involvement and arthritis was significantly higher in the OS group in comparison with the SSc group (67.8% vs. 29.9% respectively, \(p = 0.003\) and 68% vs. 20% respectively, \(p < 0.001\)). There were no significant differences in the prevalence of lung, heart, gastrointestinal or muscle involvement between SSc and OS groups.

The incidence of anti-Scl-70 antibodies was significantly higher in the SSc group in comparison with the OS group (43% vs. 14%, \(p = 0.005\)); however, the incidence of other antibodies (anti-PM/Scl and anti-Ro-52) was significantly lower in the SSc group in comparison with the OS group (10% vs. 25% respectively, \(p = 0.039\) and 21% vs. 42% respectively, \(p = 0.024\)). No significant differences in the prevalence of ACAs, anti-RNA pol III, anti Th1/Th0, anti-Ku and anti-NOR 90 antibodies were found between the study groups (Table 2). In our study group, there were no patients with the presence of ANCA.

Considering organ-specific autoimmune diseases we found that 30/126 patients (23%) had AT and 10/126 patients (8%) developed PBC. There were no significant differences in the prevalence of AT in the SSc group when compared with the SSC/CTDs group (21/98 (21%) vs. 9/28 (32%), NS). In AT, 12/30 patients had dcSSc and 18/30 patients had lcSSc. Interestingly, the prevalence of PBC was markedly lower in the SSc group when compared with the SSc/CTD group (5/98 (5%) vs. 5/28 (17%), \(p = 0.04\)). Additionally we observed that the incidence of PBC was significantly higher in lcSSc than in dcSSc (8/10 patients had lcSSc and 2/10 patients had dcSSc, \(p = 0.01\)).

**Discussion**

In our study group of 126 patients with SSc, 28 (22%) presented features of OS. The prevalence of OS was found to be significantly higher in patients with lcSSc than in patients with dcSSc. Concurrently, the incidence of lcSSc was significantly higher in OS than in SSc patients with no other CTDs.

In the OS group, the most prevalent concomitant CTDs included SS, RA and PM. Overlap of SSc and SLE or APS was quite rare. Results of our study indicate that SSc/PM seems to be the most severe type of OS. In our SSc/PM group, 6/7 patients developed gastrointestinal tract involvement and ILD, as well as 2/7 deaths occurred in that group. Additionally in our SSc patients we found symptoms of AT and PBC, with more common lcSSc subtype, both in PBC and AT.

The comparison of patients with OS and SSc (with no concomitant CTD) revealed a significantly higher prevalence of kidney involvement and arthritis, as well as significantly lower digital ulcers and mortality rate in the OS group, suggesting a more favourable course of the disease in OS patients. It is likely that a lower mortality rate in the OS group was also associated with a less severe course of lcSSc, which occurred more often in OS patients.

In serological tests, in patients with OS the prevalence of anti Ro-52 and anti PM/Scl was significantly higher and prevalence of anti-Scl-70 significantly lower, when compared with SSc patients (with no concomitant CTD). There was no significant difference in the presence of other assessed antibodies. Anti-Scl-70 are the most typical antibodies for SSC. As is well known, anti-Ro and anti-La antibodies are specific for SS. Anti Ro-52 and anti PM/Scl antibodies may occur in SSc, however they are usually detected in other CTDs such as SS, SLE that could explain their prevalence in OS patients.

The data from the literature are similar to our results. Balbir-Gurman and Braun-Mascovici demonstrated that 40/165 (24.2%) SSc patients fulfilled the criteria of OS [1]. According to Caramaschi et al., 32.2% of cases showed one autoimmune disease in association with SSc [2]. In another large study, 332 out of 1700 patients with SSc (20%) had OS [3]. Reports considering the prevalence of SSc subtypes in OS are diverse. Some studies reported that dcSSc seemed to be more prevalent in SSc/PM (47.4%) in comparison with other OS. However most patients with SSc/SS had lcSSc [1] and the vast majority of SSc/RA patients suffered from lcSSc [14]. According to the large study including 123 SSc/RA patients, 81.2% of patients were af-
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Our results are comparable to the data from the literature regarding SSC/SS and SSC/RA groups. In our study, all patients with SSC/RA had the lcSSc subtype and 78% of cases with SSC/SS had lcSSc. The results of our observations in the SSC/PM group differ from those in the literature. Most of our patients in the SSC/PM group developed lcSSc subtype.

Data from the literature indicate that SSC/myositis and SSC/SS were the most common combinations. Furthermore, the clinical course of SSC/SS was reported to be less severe in comparison with SSC without SS. Simultaneously, SSC/PM was found to have a more severe course of the disease with potentially higher morbidity and mortality [1]. Systemic sclerosis/polymyositis was associated with digital ulcers, gastrointestinal tract involvement, ILD, arthritis and cardiomyopathy [1, 3, 14]. According to the literature, overlaps of SSC and SLE or SSC/APS were quite rare combinations, often associated with an uncontrolled course and even a fatal outcome [1]. The prevalence of SSc/APS ranges from 7% to 13% [15].

Some studies compared clinical and serological parameters in SSC and OS groups. According to one study, fewer patients with OS suffered from digital ulcers, as compared with SSC patients (18.2% vs. 33.3%, p < 0.0001) [6]. According to our findings, the incidence of digital ulcers was higher in the SSC group than in the OS group. Interestingly, the incidence of kidney involvement was found to be lower in the SSC group compared to the OS group. An explanation of the result is quite difficult. The hypothesis that a more prevalent kidney involvement in the OS group could be associated with typical renal manifestations of other CTDs (e.g. lupus nephritis, Sjögren’s syndrome-associated interstitial nephritis, or vasculitis) seems too weak. In our study group there were no patients with SSC/ANCA-associated vasculitis and the prevalence of SLE was very low. Moreover, arthritis was observed most commonly in the OS group. We take into consideration the fact that patients with

Table 2. Comparison of the prevalence of internal organ involvement and selected antibodies between the systemic sclerosis groups “without” and “with” overlap syndrome

| Clinical markers                      | Systemic sclerosis | Overlap syndromes | P-value |
|---------------------------------------|---------------------|------------------|---------|
|                                       | (systemic sclerosis/connective tissue diseases) |                  |         |
| Scleroderma renal crisis              | 6 (6%)              | 1 (4%)           | 0.6     |
| Kidney involvement                    | 29 (30%)            | 19 (68%)         | 0.003   |
| Decreased DLCO                        | 53 (58%)            | 13 (46%)         | 0.3     |
| Decreased TLC                         | 27 (27%)            | 4 (14%)          | 0.1     |
| Pulmonary arterial hypertension (echo)| 26 (27%)            | 4 (14%)          | 0.2     |
| Gastrointestinal tract involvement    | 59 (63%)            | 17 (61%)         | 0.8     |
| ILD (HRCT)                            | 60 (61%)            | 13 (46%)         | 0.2     |
| Heart involvement                     | 38 (39%)            | 8 (29%)          | 0.3     |
| Arterial hypertension                 | 43 (44%)            | 11 (39%)         | 0.6     |
| Calcinosis                            | 17 (21%)            | 6 (21%)          | 0.9     |
| Arthritis                             | 19 (20%)            | 19 (68%)         | < 0.001 |
| Arthralgia                            | 80 (84%)            | 27 (96%)         | 0.09    |
| Myalgia                               | 17 (18%)            | 8 (29%)          | 0.2     |
| Digital ulcers                        | 21 (21%)            | 4 (4%)           | 0.04    |
| Death                                 | 21 (21%)            | 4 (4%)           | 0.04    |
| ACAs                                  | 18/98 (18%)         | 6/28 (21%)       | 0.7     |
| Anti-Scl 70                           | 43/98 (43%)         | 4/28 (14%)       | 0.005   |
| Anti-RNA polymerase III               | 8/98 (8%)           | 2/28 (7%)        | 0.3     |
| Anti-Ku                               | 3/98 (3%)           | 1/28 (3%)        | 1.0     |
| Anti-Pm/Scl                           | 10/98 (10%)         | 7/28 (25%)       | 0.04    |
| Anti-Ro 52                            | 21/98 (21%)         | 12/28 (43%)      | 0.02    |
| Anti-Th/To                            | 2/98 (2%)           | 0/28 (0%)        | 0.4     |
| Anti-NOR90                            | 3/98 (3%)           | 2/28 (7%)        | 0.3     |

Data were presented as numbers and percentages. P-value of < 0.05 was considered statistically significant.
OS use NSAIDs quite frequently due to arthritis and that could aggravate renal function. Our results are similar to data in the literature. According to one study, musculoskeletal involvement was the most frequent organ manifestation in OS [16].

According to the literature, the prevalence of AT in SSc was 14–30% and mostly accompanied lcSSc [2, 17], whereas PBC occurred in about 15% of SSc cases, most commonly in lcSSc subtype [1, 5]. Our results are similar.

The serological results of our study are consistent with data in the literature. In the large cohort, Pakozdi et al. demonstrated that patients SSc/PM or DM carried anti-PM/Scl antibodies in 33.1% of cases [3]. According to this study, anti-Ro/SSA and anti-La/SSB antibodies were reported in 38.8% SSc/SS cases [3]. In a large German cohort, the prevalence of ACAs was similar (37.3% vs. 36.4%), but prevalence of anti Scl-70 antibodies was lower in SSc/SS than in SSc patients [16]. Interestingly, anti-RNA Pol III antibodies were infrequently observed in SSc/SS compared to SSc [3].

The limitations of our study include a small number of patients in the different subtypes of OS as well as lack of follow-up observation.

Conclusions

In the entire group of patients with SSc, the prevalence of OS was significantly higher in patients with lcSSc than in patients with dcSSc. Moreover, the clinical symptoms and course of the disease as well as serological markers differed between OS and SSc groups [18–20]. The findings of our study and data in the literature suggest that patients with OS should be carefully evaluated and considered as a separate subset of patients with SSc.

Conflict of interest

The authors declare no conflict of interest.

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