Scleroderma Overlap Syndrome

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ABSTRACT: **Background:** Overlap syndrome is an entity that satisfies the criteria of at least two connective tissue diseases (CTD). These conditions include systemic sclerosis (SSc), dermatomyositis or polymyositis, Sjogren's syndrome, rheumatoid arthritis and systemic lupus erythematosus. A combined pathology has impact on the clinical features, diagnosis and treatment.

Objectives: To analyze the features of SSc patients with overlap syndrome registered in the European (EUSTAR) database at our center and to review the literature focusing on clinical and diagnostic issues and new treatments.

Methods: We studied the medical records of 165 consecutive SSc patients and reviewed cases with scleroderma overlap syndrome. A PubMed search for the period 1977 to 2009 was conducted using the key words "overlap syndrome," "systemic sclerosis," "connective tissue disease" and "biological agents."

Results: Forty patients satisfied the criteria for scleroderma overlap syndrome. The incidence of additional connective tissue diseases in the whole group and in the overlap syndrome group respectively was: dermatomyositis or polymyositis 11.5% and 47.5%, Sjogren's syndrome 10.3% and 42.5%, rheumatoid arthritis 3.6% and 15.4%, and systemic lupus erythematosus 1.2% and 5.0%. Coexistence of SSc and another CTD aggravated the clinical course, especially lung, kidney, digestive, vascular and articular involvement. Coexisting non-rheumatic complications mimicked SSc complications. An additional rheumatic or non-rheumatic disease affected treatment choice.

Conclusions: The definition of scleroderma overlap syndrome is important, especially in patients who need high-dose corticosteroids for complications of a CTD. The use of novel biological therapies may be advocated in these patients to avoid the hazardous influences of high-dose steroids, especially renal crisis. In some overlap syndrome cases, biological agents serve both conditions; in others one of the conditions may limit their use. In the absence of formal clinical trials in these patients a cautious approach is preferred.

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KEY WORDS: overlap syndrome, systemic sclerosis, connective tissue disease, biological agents

Overlap syndrome is defined as an entity that satisfies the diagnostic criteria of at least two connective tissue diseases [1]. The most common combinations are systemic sclerosis with Sjogren's syndrome, dermatomyositis or polymyositis, rheumatoid arthritis, and systemic lupus erythematosus. Scleroderma may occur simultaneously with organ-specific autoimmune disease (e.g., autoimmune hepatitis). The development of new diagnostic tools allows the precise diagnosis of co-morbidities. Control of SSc, especially its diffuse form (DcSSc), is a challenge. In some patients standard therapies fail to control the disease.

In contrast to the wide use of biological therapies in other autoimmune diseases (for example, RA), the use of biological agents in SSc in controlled clinical trials has only recently been reported. In an open-label study, 16 DcSSc patients treated with infliximab achieved stabilization of skin disease but developed multiple adverse events [2]. In an open-label study (15 patients with DcSSc) rituximab was safe, depleted circulating and dermal B cells but had little effect on the levels of SSc-associated autoantibodies and skin thickness at 6 months [3]. In contrast, rituximab significantly improved lung function tests and skin score one year after treatment in eight patients compared to six patients treated with standard regimens [4]. While biological agents offer the opportunity to control at least one of the diseases, their influence on a coexisting pathology is not clear. The purpose of the present study was to determine the prevalence of other connective tissue diseases or organ-specific autoimmune diseases in patients with SSc and to review existing data on biological agents in SSc-overlap syndrome with emphasis on efficacy and safety issues.

PATIENTS AND METHODS

Our center has participated in the EULAR Scleroderma Trials and Research (EUSTAR) group since 2004 and collects prospective registry data in the Minimal Essential Data Sets (MEDS) on patients fulfilling the American College of Rheumatology criteria for SSc. Data entered in our EUSTAR database until December 2009 were analyzed. Patients with an additional systemic CTD and organ-specific autoimmune diseases were identified. Missing data were retrieved from

SSc = systemic sclerosis
CTD = connective tissue disease

RA = rheumatoid arthritis
DcSSc = diffuse form systemic sclerosis

the medical records. The diagnosis of an associated CTD was based on accepted criteria. The literature review is based on a MEDLINE (PubMed) search of the English literature from 1975 to 2009, using the keywords "systemic sclerosis," "overlap syndrome," "connective tissue disease" and "biological agents." Our local ethics committee approved a retrospective analysis of clinical data for this study.

RESULTS

PATIENTS' CHARACTERISTICS

Since 2004 a total of 165 consecutive SSc patients attended our center (DcSSc 25.4%). Of these, 40 (24.2%) fulfilled the criteria for overlap syndrome (33 females, 7 males; mean age 60.5 ± 15.2 years, mean disease duration 10.4 ± 7.5 years) [Table 1]. The prevalence of an additional CTD in the whole group and in the overlap syndrome group respectively was: DM/PM 19 patients (11.5%, 47.5%), Sjogren's syndrome 17 patients (10.3%, 42.5%), RA 6 patients (3.6%, 15.0%) and SLE 2 patients (1.2%, 5.0%). Three patients (1.8%, 7.5%) with high titer of antibodies to ribonucleoprotein and signs of SSc, SLE and myositis were defined as having mixed connective tissue disease. Twelve patients had more than two coexisting systemic CTDs (7.2%, 30.0%).

Analysis of the most common overlap syndrome in our group (SSc/myositis and SSc/SS) is presented in Table 2. Among patients with SSc/myositis overlap, myositis followed recent-onset SSc in 16; myositis appeared first in 2, and in one patient myositis developed 15 years after appearance of

DM/PM = dermatomyositis or polymyositis
SLE = systemic lupus erythematosus
SS = Sjogren's syndrome

Table 1. Characteristics of patients with scleroderma overlap syndrome

Gender	Age	Disease duration (yrs)	SSc subset	Overlap	Clinical features	Immune profile	Treatment	Follow-up
F	44	15	Lc	PM	RP, DU, GERD	ANA, ACA	PPI, fundoplasty, Il	Alive
F	46	12	Lc	MCTD,PBC	RP, arthritis, ILD, Sicca, GERD	ANA, ACA, SS-A, AMA	Cs, PPI, ursolit, Il	Alive
F	51	18	Lc	RA	RP, GERD, arthritis	RF, CCP, ANA, ACA	Cs, PPI, MTX, HCQ	Alive
M	70	5	Dc	PM, HyT	RP, DU, GERD, CMp, ILD, serositis	ANA, Scl-70	Cs, PPI, Il, CYC, Bos	Alive
M	72	4	Dc	PM	RP, DU, CMp, ILD, GERD, Int, PAH	ANA, Scl-70	Cs, PPI, Il, CYC, Bos	Died (pancreatic carcinoma)
F	70	12	Lc	SS	RP, Sicca	ANA, RF, SS-A	Cs, HCQ	Alive
F	83	28	Lc	SS, HyT	RP, Sicca, arthritis, GERD, ILD, PAH	ANA, RF, SS-A	Cs, HCQ, PPI, Bos	Alive
F	64	6	Lc	PM, HyT	RP, DU, arthritis, ILD, CMp, GERD, pneumatosis intestinalis	ANA, Scl-70	Cs, AZA, PPI, antibiotics	Died (aspiration pneumonia and sepsis)
M	80	8	Lc	DM, HyT	RP, DU, DM, calcinosis, ILD	ANA	Cs, AZA, PPI, Il	Alive
F	63	16	Lc	RA, SSs, HyT	RP, arthritis, ILD, Sicca, GERD	ANA, RF, SS-A, SS-B	Cs, CYC, CyA, HCQ, Enbrel	Alive
M	44	8	Dc	PM	RP, GERD, arthritis	ANA	Cs, PPI, IVIG, HCQ	Alive
F	72	14	Lc	SS, MCTD, HyT	RP, GERD, ILD, PAH	ANA, SS-A, SS-B, RF, RNP	Cs, PPI, HCQ, Il	Alive
F	61	6	Lc	SS	RP, Sicca	ANA	Cs. HCQ, PPI	Alive
F	73	7	Lc	RA	RP, arthritis, ILD, Sicca, GERD, CMp	ANA, RF, CCP	Cs, MTX, HCQ, PPI, Enbrel	Alive
M	27	2	Dc	PM	RP, GERD	ANA, Scl-70	Cs, MTX, IVIG, PPI	Alive
F	60	4	Lc	SS, PM, HyT	RP, GERD	ANA, SS-A	Cs, HCQ, PPI	Alive
F	28	7	Lc	SLE	RP, DU, GERD, ILD, PAH, nephritis, arthritis, serositis	ANA, anti-DNA, Scl-70, SS-A	Cs, HCQ, AZA, Il, CYC, PPI	Alive
F	31	4	Dc	RA	RP, DU, GERD, arthritis	ANA, Scl-70	Cs, MTX, HCQ, PPI	Alive
F	81	12	Lc	SS	RP, GERD, ILD, calcinosis	ANA, SS-B	Cs, HCQ, PPI	Alive
F	52	17	Lc	RA, SS	RP, Sicca, arthritis, GERD	ANA, RF, SS-A	Cs, HCQ, PPI	Alive
F	46	16	Lc	SS	RP, Sicca, arthritis, GERD, ILD	ANA, ACA, SS-B	Cs, HCQ, PPI, Il	Alive
F	70	4	Lc	Hepatitis C cirrhosis, vasculitis, SS	RP, Sicca, GERD, ILD, cryoglobulinemia	ANA, ACA, SS-B, Cryoglobulins	Cs, HCQ, PPI	Alive
F	62	27	Lc	SLE	RP, discoid lupus, ILD, CMp	ANA, anti DNA	Cs, HCQ, PPI	Alive
F	65	4	Dc	RA, PM, HyT	RP, DU, arthritis, GERD, ILD, PAH	ANA, RF	Cs, MTX, HCQ, PPI, IVIG, Bos, Il, Enbrel	Alive

Gender	Age	Disease duration (yrs)	SSc subset	Overlap	Clinical features	Immune profile	Treatment	Follow-up
F	83	25	Lc	SS	RP, arthritis, ILD, Sicca, GERD	ANA, ACA, SS-A, SS-B	Cs, HCQ, PPI, Il	Alive
F	64	9	Dc	PM, SS	RP, arthritis, ILD, Sicca, GERD, PAH	ANA, Scl-70, SS-A	Cs, CYC, HCQ, PPI, Bos, Il	Alive
M	68	7	Lc	Sarcoidosis	RP, erythema nodosum, ILD	ANA, ACA, ACE	Cs, PPI, Il, MMF	Alive
F	64	3	Lc	PM	RP, ILD, GERD, InT	ANA, Scl-70	Cs, AZA, PPI, IVIG	Alive
F	66	5	Lc	PBC	RP	ANA, ACA, AMA	PPI, ursolit	Alive
F	64	7	Lc	PM	RP, arthritis, ILD, calcinosis	ANA, RF	Cs, CYC, PPI	Alive
F	61	18	Lc	PM, SS, autoimmune hepatitis	RP, Sicca, GERD, sialoadenitis, ILD	ANA, ACA, SS-A, SS-B	Cs, HCQ, AZA, PPI	Alive
F	59	2	Dc	PM, HyT	RP, DU, GERD, InT, pericarditis, CMp, ILD, PAH	ANA, Scl-70	Cs, CYC, PPI, Bos, Epoprostenol	Died (pulmonary hypertension and sepsis)
F	78	18	Lc	PM, SS	RP, Sicca, GERD, pericarditis, CMp, ILD	ANA, RF, SS-A, SS-B	Cs, HCQ, AZA, PPI	Died (sudden)
F	72	18	Lc	PM, SS, HyT	RP, Sicca, GERD, monoclonal gammopathy	ANA, RF, SS-A, SS-B	Cs, HCQ, IVIG, AZA, PPI	Alive
F	56	3	Lc	PM, SS	RP, ILD, GERD, pneumatosis intestinalis	ANA, SS-A	Cs, HCQ, IVIG, PPI, antibiotics	Alive
F	31	1	Dc	PM	RP, arthritis	ANA, Scl-70	Cs, HCQ, CYC, IVIG, PPI	Alive
F	60	4	Lc	SS	RP, GERD, Int, ILD	ANA, SS-B	Cs, PPI, antibiotics	Alive
F	70	23	Lc	PBC	RP, GERD, ILD, CMp, calcinosis, PAH	ANA, ACA, AMA	PPI, inhaled Il, sildenafil, pacemaker, ursolit	Alive
F	36	2	Dc	MCTD, PM, SS	RP, sialoadenitis, trigeminal neuralgia, GERD, ILD, muscle atrophy, arthritis, PAH	ANA, SS-A, SS-B, RF, RNP	Cs, AZA, HCQ, PPI	Alive

F = female, M = male, SSc = systemic sclerosis, Lc = limited cutaneous, Dc = diffuse cutaneous, PM = polymyositis, DM = dermatomyositis, SS = Sjogren's syndrome, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, MCTD = mixed connective tissue disease, HyT = hypothyroidism, PBC= primary biliary cirrhosis, RP = Raynaud's phenomenon, DU = digital ulcers, GERD = gastroesophageal reflux disease, ILD = interstitial lung disease, CMp = cardiomyopathy, Int = intestinal involvement, PAH = pulmonary arterial hypertension, ANA = antinuclear antibodies, Scl-70 = antibodies to topoisomerase, RF = rheumatoid factor, CCP = anti-cyclic citrullinated peptide antibodies, RNP = antibodies to ribonucleoprotein, ACA = antibodies to centromere, AMA = antibodies to mitochondria, Cs = corticosteroids, HCQ = hydroxychloroquine, MTX = methotrexate, AZA = azathioprine, PPI = proton pump inhibitors, CYC = cyclophosphamide, MMF = mycophenolate mofetil, Il = iloprost, Bos = bosentan, IVIG = intravenous immunoglobulins

Table 2. Clinical data of patients with scleroderma/myositis and scleroderma/SS overlap syndrome

	Scleroderma/myositis (N=19)	Scleroderma/SS (N=17)
Diffuse skin involvement	9 (47.4%)	2 (11.8%)
Sjogren's syndrome	7 (36.8%)	–
Myositis	–	7 (41.2%)
DU	8 (42.1%)	2 (11.8%)
GIT	16 (84.2%)	15 (88.2%)
GERD	16 (84.2%)	15 (88.2%)
Intestinal involvement	5 (26.3%)	2 (11.8%)
ILD	13 (68.4%)	12 (70.6%)
Cardiomyopathy	5 (26.3%)	2 (11.8%)
PAH	5 (26.3%)	4 (23.6%)
Arthritis	8 (42.1%)	7 (41.2%)
Calcinosis	2 (10.5%)	1 (5.9%)
Scl-70	8 (42.1%)	1 (5.9%)
ACA	2 (10.5%)	3 (17.6%)
Death	4 (15.8%)	–

DU = digital ulcers, GIT = gastrointestinal tract, GERD = gastroesophageal reflux disease, ILD = interstitial lung disease, PAH = pulmonary arterial hypertension, Scl-70 = antibodies to topoisomerase, ACA = antibodies to centromere.

scleroderma. In this subgroup there was a high prevalence of DcSSc (47.4%), digital ulcers (42.1%), gastrointestinal tract involvement (84.2%), interstitial lung disease (68.4%), arthritis (42.1%), and antibodies to Scl-70 (42.1%). Four patients with overlap syndrome, who eventually died, had myositis (one died from pancreatic carcinoma). Most of the patients in the SSc/SS subgroup had limited scleroderma but a low incidence of anti-centromere antibodies (17.6%). Arthritis, upper GIT and lung involvement were common in this subgroup. Seven patients had scleroderma and both myositis and SS. Of six patients with SSc/RA overlap, four had LcSSc and five had rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies; all had destructive hand arthritis. Overlap between SSc and SLE was rare (two patients); in both, scleroderma developed years after active SLE with no kidney involvement. Both patients had pulmonary arterial hypertension. One developed PAH during SLE flare with excellent response to steroids and azathioprine and the other had PAH secondary to heart failure and cardiomyopathy. All MCTD

GIT = gastrointestinal tract
LcSSc = limited scleroderma
PAH = pulmonary arterial hypertension
MCTD = mixed connective tissue disease

patients had multiple autoantibodies, severe Raynaud's phenomenon, and lung and GIT involvement. One patient had sarcoidosis with lung involvement and erythema nodosum. There were no signs of antiphospholipid syndrome in our group. Among organ-specific autoimmune diseases, thyroid pathology was frequent: nine patients had hypothyroidism and one had hyperthyroidism. Six patients had liver disease: primary biliary cirrhosis (n=4), autoimmune hepatitis (n=1), and hepatitis C complicated with liver cirrhosis and an episode of cryoglobulimenic vasculitis (n=1). They all had LcSSc and positive ACA.

The overall mortality in our overlap syndrome subgroup did not differ from the whole SSc group: 16 SSc patients died during follow-up, including 4 with overlap syndrome (9.7%, 10.0%); in the SSc/myositis subgroup mortality was 21.6%.

All but four patients with SSc overlap needed steroids, different disease-modifying anti-rheumatic drugs and intravenous immunoglobulin to control serositis, arthritis, myositis and ILD. Three patients needed anti-tumor necrosis factor-alpha agents for uncontrolled arthritis. Six patients received cyclophosphamide infusions for ILD. Twelve patients needed recurrent iloprost infusions for treatment of ischemic skin ulcers. Seven patients received treatment for PAH: bosentan (n=6) and sildenafil (n=1). Sarcoidosis partially controlled with high steroid doses responded well to mycophenolate mofetil and IVIG.

LITERATURE REVIEW

SSC AND OTHER CTD OVERLAP SYNDROMES

- **Systemic sclerosis and myositis**

Sclerodema/myositis overlap has been described in adults and adolescents. In a Canadian cohort of 100 patients with inflammatory myopathy, 29% had features of SSc and constituted 42% of 24 overlap syndrome patients in this cohort [5]. Myositis may appear simultaneously, before or in already established SSc. DcSSc was more prevalent in this overlap syndrome and was associated with cardiomyopathy confirmed on magnetic resonance imaging [6]. Prominent GIT involvement and severe complications such as pneumatosis intestinalis and/or pseudo-obstruction were reported in SSc/myositis [7]. Scleroderma/myositis is associated with specific autoantibodies: anti-PM-Scl, anti-Ku, anti-U2 RNP and anti-U5 snRNP [8]. Positive antibodies to PM/Scl correlated with arthritis and a benign course of ILD. Unlike isolated polymyositis with arthritis and alveolitis, anti-Jo-1 autoantibodies did not occur in SSc/myositis. Also, antibodies to Ku in SSc/myositis patients were not associated with malignancy, unlike isolated inflammatory myopathies.

ACA = anti-centromere antibodies
ILD = interstitial lung disease
IVIG = intravenous immunoglobulin

In SSc/myositis, treatment is directed against alveolitis, muscle and skin damage: corticosteroids, cytotoxic drugs (methotrexate), azathioprine, mycophenolate mofetil and cyclophosphamide are widely used. Traditionally used for myositis, high-dose steroids may be problematic in DcSSc because of their potential to provoke renal crisis [9]. Effective treatment of myositis, joint or skin disease does not necessarily indicate control of alveolitis in SSc/myositis. Alveolitis may be a contraindication for methotrexate in SSc/myositis. The use of anti-TNFα therapy in patients with SSc/myositis is controversial because of its potential to aggravate ILD, particularly with concomitant methotrexate treatment [10]. In reported cases and open-label studies, treatment with rituximab was effective in most patients with uncontrolled myositis [11,12]. IVIG and mycophenolate mofetyl may be of interest in SSc/myositis as both drugs have been reported to improve skin and muscle manifestations, and to be effective also in cases of GIT involvement and alveolitis [13,14]. Control of severe Raynaud's phenomenon and digital ulcers in SSc/myositis may require the use of prostaglandins and endothelin receptor antagonists.

- **Systemic sclerosis and Sjogren's syndrome**

Sicca syndrome is common in SSc (68%), but only 14% of SSc patients fulfill the criteria of Sjogren's syndrome [15]. The main feature in primary SS is lymphocytic infiltration of the salivary glands. In contrast, half of SSc patients had salivary gland fibrosis that correlated with more severe SSc and higher mortality rate. Lower titers of anti-SS-A and/or anti-SS-B antibodies did not modify the severity of arthritis, neuropathy or cryoglobulinemia in SSc/SS overlap. Patients with SSc/SS mainly had LcSSc with a low frequency of lung fibrosis. In SS patients the development of scleroderma was preceded by the appearance of ACA for several years. In patients with SSc/SS, coexistence with primary biliary cirrhosis has been described. There are no data regarding biological therapy in SSc/SS overlap.

Experience with anti-TNFα drugs in SS revealed conflicting results. Rituximab was effective in open-label trials in the treatment of primary SS, interestingly mostly in the control of systemic (including ILD) features.

- **Systemic sclerosis and rheumatoid arthritis**

The precise incidence of this combination is unknown. The development of RF-positive erosive RA in established DcSSc with ILD and Scl-70 antibodies was reported. Longstanding RA was complicated with the occurrence of LcSSc. Cases of multiple overlap (RA/SLE/SSc/SS) have been reported. Joint erosions may reach 20% in SSc patients. RF and anti-CCP were found in 25.3% and 10.6% of SSc patients, respectively. The frequency of anti-CCP2 and anti-CCP3 antibodies in SSc was 14.8% and 13.5% compared to 79.1% and 77% in RA. In

TNFα = tumor necrosis factor-alpha
RF = rheumatoid factor

SSc, anti-CCP2 antibodies strongly correlated with arthritis and marginal erosions on X-rays [16]. The titers of anti-CCP antibodies were lower in patients with SSc/RA overlap compared to RA only.

Anti-TNF agents are widely used in RA patients with inadequate response to DMARDs. Safety issues are a concern, such as serious infections, tuberculosis and fibrosis (especially pulmonary fibrosis). Etanercept controlled arthritis in 15 of 18 SSc patients with a trend to improvement of skin score, although there was a case of lupus and abnormalities in lung function test in another case in this series. Despite an overall deterioration in lung function tests this reduction was not significantly different compared to a similar group of SSc patients not treated with etanercept [17]. Scleroderma-like skin changes complicating treatment with infliximab has been reported. Lupus-like disease was described in SSc where infliximab and etanercept were used for severe arthritis [18]. Fatal pneumonitis developed in two SSc patients treated with adalimumab [19]. In contrast to SLE-related antibodies, anti-TNF agents did not produce scleroderma-related antibodies in RA patients. Immunoglobulin M cardiolipin and thrombocytopenia were reported in a patient with SSc/RA overlap treated with infliximab. The presence of CD20+lymphocytes in scleroderma skin raises the possibility of using rituximab in the treatment of SSc-related conditions. Elevated levels of interleukin-6 were found in serum, peripheral blood mononuclear cells and T cell lines from SSc patients. Serum IL-6 levels correlated with severity of skin and lung fibrosis and with PAH in scleroderma patients. Considering the effectiveness of monoclonal antibodies to CD20+ and to soluble IL-6 receptor (tocilizumab) in RA trials, the option of using B cell-modifying drugs in SSc/RA overlap may be suggested.

- **Systemic sclerosis and systemic lupus erythematosus**

Several cases of SSc/SLE/discoid lupus overlap have been reported. SSc/SLE combination often had an uncontrolled course and even a fatal outcome. Polyserositis, pancreatitis, avascular bone necrosis, PAH and leukoencephalopathy have been reported in SSc/SLE overlap. SSc/SLE patients often developed PAH. SLE-driven PAH may require prompt immunosuppression with corticosteroids and cytotoxic drugs. In both conditions potent vasodilators (Iloprost, endothelin receptor antagonists) are effective. In SSc/SLE patients who develop renal failure and hypertension, it is essential to distinguish between lupus nephritis and scleroderma renal crisis because the treatment is completely different [20]. Serological markers are relevant in SSc/SLE overlap syndrome with a high incidence of antibodies to double stranded DNA and anti-PM/Scl. The presence of ACA in SLE patients does not necessarily indicate SSc. Concomitant DcSSc may limit the use of high steroid doses in SLE and may advocate early use of cytotoxic drugs. Possible exacerbation of SLE may limit the use of anti-TNFα agents in SSc/SLE overlap [18]. Clinical trials and case studies have reported the efficacy and safety of rituximab and MMF in SLE. It seems that in SSc/SLE overlap these therapies could be attractive for both conditions but as yet there are no data in the literature.

- **Systemic sclerosis and antiphospholipid syndrome**

The incidence of antiphospholipid antibodies in SSc patients is about 7–13%. The presence of lupus anticoagulant or anti-beta-2-glycoprotein-1 antibodies has not been reported in SSc patients. In contrast, other reports demonstrated the presence of anti-β2-GPI in SSc complicated with severe peripheral ischemia, PAH, digital loss, hemolytic-uremic syndrome, glomerular thrombosis, multi-organ thromboembolism, myocardial ischemia, and death [21]. Antiphospholipid antibodies or lupus anticoagulant were demonstrated in silica-related scleroderma and generalized morphea. Screening for procoagulability factors may be advocated in SSc, especially when complicated with severe peripheral, kidney or myocardial ischemia, and thromboembolism. In these cases anticoagulation may be considered (with caution because of possible gastric vascular ectasia). The use of aspirin in SSc patients with asymptomatic presence of antibodies to cardiolipin has not been clarified. IVIG and rituximab were successfully used in Hughes syndrome; their use in SSc/APL syndrome might be suggested.

- **Mixed connective tissue disease**

The term MCTD has been applied to a particular subset of patients with overlapping clinical signs of SSc, SLE and myositis and presence of antibodies to U1-RNP. Among 53 patients who developed drug-induced lupus during anti-TNF therapy, 3 had MCTD [22]. In severe MCTD refractory to prostanoids, steroids and cyclophosphamide, treatment with rituximab led to digital ulcer healing and prolonged the disappearance of anti-RNP antibodies. The use of biological agents in MCTD with refractory arthritis, myositis, cytopenias and nephritis may be promising.

- **Systemic sclerosis and vasculitides**

The coincidence of SSc and vasculitis is extremely rare, although there have been reports of scleroderma and polyangiitis, polyarteritis nodosa, Wegener's granulomatosis, Takayasu's arteritis, giant cell arteritis, D-penicillamine-induced Goodpasture-like syndrome, pulmonary hemorrhage and cryoglobulinemic vasculitis [23]. Similar lung and kidney manifestations and ischemic skin changes make the diagnosis difficult. Since both diseases could be life threat-

DMARDs = disease-modifying anti-rheumatic drugs
IL-6 = interleukin-6
MMF = mycophenolate mofetyl
anti-β2-GPI = anti-beta-2-glycoprotein-1

ening, an aggressive diagnostic approach (biopsy, immune tests) and urgent prompt treatment (steroids, cyclophosphamide, plasma exchange, IVIG) for both disorders are crucial. Successful use of anti-TNFα agents, rituximab and ERAs was reported in vasculitis resistant to standard therapy.

- **Systemic sclerosis and sarcoidosis**

The coexistence of these diseases is rare. Fever, weight loss and hilar adenopathy may raise the probability of sarcoidosis in SSc. The test for angiotensin-converting enzyme is useless. Lymph node biopsy is needed in unexplained hilar adenopathy. Sarcoid-induced myositis has been reported in SSc. The appearance of ILD in both diseases mandates lung biopsy in view of the different treatment options; in contrast to SSc, lung sarcoidosis generally responds well to steroids.

SSC AND OSAD OVERLAP SYNDROMES

- **Systemic sclerosis and liver diseases**

The prevalence of SSc in PBC patients is 7–12%, and about 15% of PBC patients will have SSc. SSc predated the diagnosis of PBC in 59% of patients [24]. PBC mostly (93%) accompanied LcSSc and generally was clinically silent despite elevation of cholestatic enzymes and presence of antimitochondrial antibodies and hyperglobulinemia (IgM). The incidence of ACA was higher in SSc/PBC than in LcSSc alone. Positive ACA in PBC patients indicates risk of future LcSSc. Liver biopsy specimens in SSc/PBC were similar to those in idiopathic PBC. Liver disease has a slower progression and better prognosis in SSc/PBC compared with PBC alone. In cases of PAH and signs of right heart failure (hepatomegaly and leg edema), concomitant PBC could easily be overlooked. Abnormal liver function may limit the use of ERAs (possible hepatotoxicity). There are no data regarding the biological treatment in SSc/PBC overlap. A patient with SSc/RA/PBC was treated with etanercept for RA with no changes in liver enzyme levels. The incidence of other liver diseases in SSc is extremely rare; only single cases of autoimmune hepatitis and a case of sclerosing cholangitis have been reported.

- **Systemic sclerosis and thyroid diseases**

Hypothyroidism and Grave's diseases have been reported (13% and 2.5% respectively) in SSc [25]. Positive antithyroid peroxidase antibodies may identify patients at risk of developing thyroid dysfunction. Screening for silent thyroid dysfunction in scleroderma overlap syndrome is important since there may be treatment implications.

- **Systemic sclerosis and celiac disease**

The coexistence of these two disorders has been described, especially in women with LcSSc. Chronic diarrhea, iron deficiency anemia and malabsorption are shared clinical manifestations. Tests for antigliadin and anti-endomysial antibodies and intestinal biopsy may be helpful, since a gluten-free diet is necessary in celiac disease.

ERAs = endothelin receptor antagonists
OSAD = organ-specific autoimmune disease
PBC = primary biliary cirrhosis

DISCUSSION

Our results indicate that scleroderma overlap syndrome is a relatively common condition. In our cohort SSc/myositis and SSc/SS were the most common combinations. In these patients DcSSc, digital ulcers, upper GIT and intestinal involvement, ILD, cardiomyopathy and PAH, but no renal involvement were prominent features. The mortality rate in the SSc/myositis subgroup was 21.1%, higher than in the entire SSc and overlap syndrome groups. It seems that myositis in scleroderma overlap syndrome patients reflects a more severe disease with potential for high morbidity and mortality. In our subgroup of overlap syndrome, the incidence of SS was higher than in reported data. As in other series, most patients in our cohort had LcSSc. Our data confirmed previous observations that patients with SSc/RA overlap had a high incidence of RF and/or anti-CCP antibodies and destructive arthritis. However, combined pathologies do not always result in a progressive or complicated course: LcSSc is less severe when it appears in SS patients; the course of PBC in patients with LcSSc is less severe than in those with idiopathic PBC; and patients with SSc/myositis overlap have a low incidence of malignancies compared to isolated myositis. Scleroderma/SLE overlap was rare in our patients. The occurrence and course of PBC in our overlap syndrome patients were similar to data from other cohorts. A high frequency of thyroid dysfunction was similar to previously reported data.

Most of our patients were treated with standard therapies. Frequent use of steroids, cyclophosphamide and DMARDs, as well as IVIG was prominent in scleroderma overlap syndrome patients. The use of vasodilators (calcium channels blockers, iloprost and bosentan) and proton pump inhibitors was similar in SSc patients with and without an additional CTD. In patients with severe co-morbidities, different drug combinations [Table 1] were needed including anti-TNF agents.

Shared clinical features between scleroderma and another CTD – such as arthritis in SSc/RA overlap, ischemic ulcers in SSc/vasculitis overlap, ILD in SSc/myositis or SSc/SS overlap, and renal involvement in SSc/SLE overlap – complicate the definition of the leading condition and dictate the use of additional diagnostic tools. Similar features between scleroderma and organ-specific autoimmune disease (liver cirrhosis, thyroid disorders, celiac disease) may mimic SSc complications. High steroid doses continue to be a major treatment in life-threatening SLE, myositis and vasculitis. In CTD overlap syndrome patients with diffuse skin involve-

ment the steroid dosage should be modified because of possible provocation of renal crisis. Reduction in steroid dose may be achieved with aggressive immunosuppression including novel biological therapies. In SSc overlap, anti-TNFα agents may serve both conditions (SSc and myositis, SSc and RA); in contrast, coexistence with ILD or SLE may limit their use. B cell-modifying therapies (rituximab, tocilizumab) could be another option. Since formal randomized controlled trials have not been conducted on subgroups of scleroderma overlap syndrome patients, a cautious approach is preferred. Patients with combined pathology are often treated with multiple drug regimens. Drug interaction and/or underlying liver disease will affect the drug choice (e.g., PBC and ERAs). With ongoing accumulation of clinical experience, the proper place of biological drugs in the treatment of scleroderma-overlap syndrome will be defined.

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"It is neither good nor bad, but thinking makes it so" (from *Hamlet*)

William Shakespeare (1564-1616), English poet and playwright, widely regarded as the greatest writer in the English language and the world's pre-eminent dramatist. His plays have been translated into every major living language and are performed more often than those of any other playwright

"No fathers or mothers think their own children ugly; and this self-deceit is yet stronger with respect to the offspring of the mind"

Miguel de Cervantes (1547-1616), Spanish novelist, poet and playwright. His magnum opus *Don Quixote*, often considered the first modern novel, is a classic of Western literature, and one of the best works of fiction ever written