

Session 2: Miscellaneous and Differential Diagnosis of SSc

S.2.1

HOW TO DIFFERENTIATE SSC FROM SCLERODERMA-LIKE DISORDER?

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The new American College of Rheumatology/European League Against Rheumatism classification criteria will enable earlier diagnosis and, therefore, the use of newer treatment modalities for systemic sclerosis (SSc). It is therefore critical to exclude non-SSc causes for diffuse skin thickening as early as possible. The recently described gadolinium-induced nephrogenic systemic fibrosis may mimic SSc as may other conditions which require a different treatment strategy. Recently, treatment with immunoablation and autologous stem cell transplantation has been shown to significantly benefit some patients with conditions such as scleromyxoedema and SSc. The more accurate measurement of SSc-specific autoantibodies such as topoisomerase 1, centromere and RNA polymerase has recently allowed a more precise subclassification of SSc with implications for treatment and prognosis. Skin thickening is a nonspecific manifestation of many different processes including (rarely) early scleroderma, which is mostly symmetrical and associated with Raynaud's phenomenon, nailfold capillaroscopic changes and antinuclear antibodies. If the latter three factors are absent, then other conditions must be excluded, the commonest being eosinophilic fasciitis. Skin biopsy (looking for eosinophil infiltration, increased mucin or amyloid deposition), SSc-specific autoantibodies or paraproteins in blood and a careful medical history and system screening will exclude nonscleroderma conditions.

S.2.2

GENDER EFFECTS ON SYSTEMIC SCLEROSIS PHENOTYPE: A LONGITUDINAL EUSTAR STUDY BASED ON MORE THAN 10 000 PATIENTS

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Introduction. In agreement with other autoimmune diseases, systemic sclerosis (SSc) is associated with a sex bias (up to 8 affected women for one man). However, unlike lupus, the effects of gender on disease characteristics and outcomes are poorly known. Thus, we set out to investigate (i) gender effects on SSc phenotype and (ii) the impact of gender on disease outcomes including severe damages and mortality in a large European population.

Patients and Methods. We used the latest 2013 data extract from EUSTAR cohort. We looked at gender influence on disease onset, disease phenotype looking in particular at organ involvement, auto-antibodies, age of death and cause of death using the baseline data. For the patients with follow-up, we focused on those with at least 2 years of follow-up to estimate disease progression. Data at baseline were statistically analyzed using chi-square tests and the Student's t-test. A multivariate stepwise logistic regression analysis was also performed for all variables identified with $p < 0.10$. We applied a Bonferroni correction for multiple comparisons (adjusted probability value = 0.003).

Results. 10675 SSc-patients were included (1455 males). 701/1417 (49.5%) SSc-men and 2583/9053 (28.5%) SSc-women had a diffuse cutaneous subtype ($p < 0.001$). Mean age at onset of the disease was 46.98 (± 14.28) in males and 45.98 (± 14.34) years in female ($p = 0.02$). In univariate analysis, a large number of characteristics were associated with male gender. In multivariate analysis, male gender was independently associated with renal crisis (OR: 5.04, CI 95% [1.98-12.84]; $p = 0.0007$) and CK elevation (OR: 3.30 [2.10- 5.20]; $p < 0.0001$). Conversely, they had less frequent intestinal involvement (OR: 0.41 [0.26-0.65]) and anti-centromere positivity (OR: 0.37 [0.25- 0.54]) ($p < 0.0001$ for both comparisons). After a mean follow-up of 3.5 years, 915/1922 patients had died and 525 new onset of lung fibrosis and 39 new renal crisis were recorded. Regarding death, they occurred in 209/1098 (19%) males and 706/6715 (10.5%) females; $p = 0.007$; HR: 1.53 CI 95% [1.29-1.83]. Mean age and disease duration at death were 60.37 and 8.46 in males and 63.96 and 12.38 years in female ($p < 0.01$ for both comparisons). Predictors of new organ damage are under investigations.

Conclusion. Although more common in women, SSc appears strikingly more severe in males. Indeed, our results obtained through the largest worldwide database, demonstrate a higher mortality in affected men. Other outcomes are still under investigation, but our results raise the point of including male gender in the management and the decision making process.

S.2.3

EPIDEMIOLOGY OF CANCER IN SYSTEMIC SCLEROSIS. SYSTEMATIC REVIEW AND META-ANALYSIS OF CANCER INCIDENCE, PREDICTORS AND MORTALITY

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Background/Purpose. To improve our understanding of the epidemiology of cancer in systemic sclerosis (SSc) by evaluating the incidence, prevalence, relative risk of overall and site-specific malignancies in comparison with the general population, and cancer-attributable mortality.

Methods. MEDLINE, CINAHL, EMBASE and Cochrane Library (inception-May 2012) were searched. Estimates were combined using a random effects model. Consistency was evaluated using the I² statistic.

Results. 4,876 citations were searched to identify 59 articles. The average incidence of malignancy in SSc was 14 cases/1000 person-years; the prevalence ranged between 4%-22%. Cancer was the leading cause of non-SSc related deaths with a mean of 38%. Overall SIR for all-site malignancy risk was 1.85 (95% CI 1.52, 2.25; I²76%). There was a greater risk of lung (SIR 4.69, 95% CI 2.84, 7.75; I²93%) and haematological (SIR 2.58, CI 95% 1.75, 3.81; I²100%) malignancies, including non-Hodgkin's lymphoma (SIR 2.55, 95% CI 1.40, 4.67; I²100%). SSc patients were at a higher risk of leukemia (SIR 2.79, 95% CI 1.22, 6.37; I²100%), liver (SIR 4.75, 95% CI 3.09, 7.31; I²100%), cervical (SIR 2.28, 95% CI 1.26, 4.09; I²54%) and oropharyngeal (SIR 5.0, 95% CI 2.18, 11.47; I²58%) cancers. Risk factors include a-RNAP I/III positivity, male sex, and late onset SSc. Smoking and longstanding interstitial lung disease (ILD) increase the risk of lung cancer; longstanding gastroesophageal reflux disease with Barrett's esophagus and a positive family history of breast cancer, respectively, increase the risk of esophageal adenocarcinoma and breast cancer.

Conclusion. SSc patients have a two-fold increase in malignancy, and greater risk of lung and haematological malignancies that contribute significantly to mortality. Vigilance should be considered in SSc patients with a-RNAP I/III antibodies, male sex, smokers, late disease onset, a positive family history of breast cancer, long duration of ILD, Barrett's esophagus.

S.2.4

JOINT AND TENDON INVOLVEMENT PREDICT SEVERE DISEASE PROGRESSION IN SYSTEMIC SCLEROSIS: A EUSTAR PROSPECTIVE STUDY

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Objective. To determine whether inflammatory joint involvement (synovitis and tendon friction rubs) may predict the progression and severity of systemic sclerosis (SSc) in a large cohort with longitudinal follow-up.

Methods. We included patients from the EUSTAR database (MEDS online) with disease duration less than 3 years and with a follow-up of at least two years. We extracted data regarding the presence or not of synovitis (tender and swelling joints) and tendon friction rubs (rubbing sensation detected as the tendon was moved) and data related to disease progression. Skin progression was defined by a >10% worsening of the modified Rodnan skin score (mRSS). Lung progression was defined by the new onset of pulmonary fibrosis on high resolution CT scan, or the deterioration of lung volume (>10% of forced vital capacity, FVC). Cardiovascular worsening was defined for skin by new ischemic digital ulcers (DU), for lung by pre-capillary pulmonary arterial hypertension (PAH) on right heart catheterization, and for heart by the reduction of the left ventricular ejection fraction below 50% on echocardiography. Renal progression was defined by the occurrence of scleroderma renal crisis.

Results. From the 9165 patients included in the database, 1301 patients (1079 females) met our inclusion criteria (mean \pm SD age of 55 \pm 15 years, mean \pm SD follow-up: 4.5 \pm 2.2 years).

In univariate analysis, synovitis and tendon friction rubs were identified as predictors of skin progression (Log-rank test, $p=0.0008$ and $p=0.0002$ respectively). In multivariate analysis, after stratification for disease subset and autoantibody status, synovitis and tendon friction rubs remained predictive of skin progression (Hazard Ratio, HR: 1.69, 95% confidence interval, CI: 1.09-2.63 and 1.68, 95%CI: 1.04-2.72 respectively). No impact on lung outcomes was identified. In multivariate analysis, synovitis independently predicted cardiovascular progression both for the occurrence of new ischemic DU (HR: 1.36, 95%CI: 1.01-1.83) and left ventricular dysfunction (HR: 2.20, 95%CI: 1.06-4.57). Tendon friction rubs independently predicted in multivariate analysis scleroderma renal crisis (HR: 3.78, 95%CI: 1.01-6.19).

Conclusion. This first report of the prospective follow-up of EUSTAR patients identified for the first time the merit of inflammatory joint involvement in early SSc patients. These results obtained through the largest worldwide database support the use of these easily detected clinical findings for the risk stratification of SSc patients. These parameters might be used in the future to select high-risk patients, guide therapies and might be regarded as potential surrogate markers for severity.

Session 3: The Great Debate

S.3.1

THE GREAT DEBATE - "THE PLACE OF CORTICOSTEROIDS IN SSC"

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The potent anti-inflammatory effects of corticosteroid (CS) therapy find clinical application in (1) early inflammatory diffuse cutaneous SSc; (2) arthritis/tenosynovitis; (3) myositis; (4) pleuritis/pericarditis; (5) rare presentations of myocarditis; and (6) management of inflammatory manifestations of various overlap syndromes. CS therapy remains widely used although there is little hard evidence of clinical efficacy. A recent survey of > 1700 SSc patients in Germany revealed that 41.3% were receiving CS therapy with 16.1% receiving daily doses of 15 mg prednisone equivalents or more.

Adverse effects of CS are numerous and well known to rheumatologists and include fluid retention, weight gain, hypertension, diabetes mellitus, cataracts, increased risk of infection, osteopenia, avascular necrosis of bone and others. A disease-specific complication of CS is thought to be an increased risk of scleroderma renal crisis (SRC). A widely accepted case control study demonstrated an odds ratio of 4.37 for development of SRC associated with CS doses at or above the 15 mg threshold. Similar data suggested that >30 mg per day increased risk of normotensive SRC. Prednisone exposure and dose were subsequently associated with SRC in large French and Italian series.

This clinical scenario is biologically plausible. Glucocorticoids suppress endothelial production of both prostacyclin and nitric oxide and enhance arterial contractile sensitivity to catecholamine. Bradykinin-influenced prostacyclin release is sensitive to CS while influence on arachidonic acid and COX-2 mediated effects are absent. However, CS do exert a protective effect on renal ischemia-reperfusion injury through stimulation of ERK 1/2 phosphorylation and inhibition of caspase release.

Risk factors for SRC independent of CS include a rapid rate of skin thickness progression, palpable tendon friction rubs and the presence of anti-RNA polymerase III antibody. A key question remains unanswered. Is SRC a drug-related toxicity or is the clinical setting in which the CS is employed the dominant risk factor? In a retrospective analysis of early diffuse SSc in the US study of D-penicillamine, measures of disease activity/severity were strongly associated with SRC (skin scores >20; large joint contractures). If these features were lacking, there was no association of prednisone therapy with SRC. The highest risk of SRC was in patients with high disease activity AND corticosteroid.

Question 1: Would you use CS, and, if so, at what dose, in a 38-year-old woman with severe skin thickening (MRSS 25 after only 6 months of disease) who also has definite synovitis and inflammatory myopathy (proximal weakness, CPK 4X normal)?

Question 2: Would you use CS, and, if so, in what dose, in the following clinical scenarios? (a) a patient with progressive interstitial lung disease (FVC declined from 78% to 53% predicted with worsened extent of disease on HRCT). This patient has anti-topoisomerase I antibody and mild skin involvement (MRSS 12). (b) A anti-U1RNP positive patient with limited cutaneous disease who presents with acute pericarditis with increased effusion unresponsive to NSAID (c) a 67 year old patient is anticentromere positive with limited cutaneous SSc. She is postmenopausal, osteoporotic and receiving PPI for reflux esophagitis. She presents with Sjogren syndrome and a rheumatoid-like arthritis.

In the absence of more robust data, we conclude that early active diffuse scleroderma has a high risk of SRC and these high risk patients are more likely to receive CS. In turn, CS appears to further increase risk of SRC in this clinical setting. Alternate strategies for control of inflammatory features should be considered. If CS remains clinically indicated, efforts should be made to limit dose and exposure