Session 4: *An Integrated Approach to Gastro-intestinal Involvement*

S.4.1

GI: HOW TO EVALUATE, DIAGNOSE AND TREAT UPPER AND LOWER GI INVOLVEMENT

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Raynaud's phenomenon and skin sclerosis are the most common and prominent characteristics in patients with SSc, but recent data of the EUSTAR consortium and other SSc networks show that involvement of the GI-tract is much more frequent than expected. In addition, in the registry of the German Systemic Scleroderma Network, it could be shown that higher modified Rodnan Skin Score values were significantly associated with higher frequencies of upper gastrointestinal symptoms. Main symptoms of GI involvement are meteorism, dysmotility of the esophagus, heartburn and dysphagia. In severe cases, gastrointestinal manifestations can result in lethal complications such as severe intestinal pseodoobstruction and Barrett's cancer. In contrast to the idea that limited SSc is a more benign disease entity with respect to GI symptoms, both SSc subsets are affected. In diffuse SSc, the most frequent symptoms were meteorism (80%), daytime heartburn (80%), coughing/ sore voice (80%) and stomach ache (80%), followed by nighttime heartburn (73%), diarrhea (73%), and nausea (60%). When comparing diffuse and limited SSc, the most prominent differences -with lower prevalence in limited SSc- were nighttime heartburn (-24%), daytime heartburn (-15%) stomach ache (-15%), and diarrhea (-6%). In contrast, fecal incontinence (+14%) and meteorism (+7%) were more frequently reported by patients with limited SSc. Owing to the multiple organs and compartments, questionnaires and several technical methods had to be developed to evaluate of involvement of GI tract in systemic sclerosis including the search for infra-aortic oesophageal dilatation in high resolution CT as specific sign of oesophageal involvement, oesophageal manometry, 24-hour pH monitoring, endoscopic ultrasound, oesophagogastroscopy, small bowel barium follow-through x-ray (especially for cases of intestinal pseudoobstruction), D-xylose test, jejunal cultures and H2 glucose and lactose breath test for malabsorption and bacterial overgrowth. With respect to treatment, still no evidence-based disease-modifying regimen for systemic sclerosis exists although most of the available immunsuppressants and antifibrotics have been investigated at least in small series to inhibit overall disease activity but several therapeutic approaches for the individual organs of the GI-tract have proven to be effective, including proton pump inhibitors to counteract all reflux-associated problems, prokinetic drugs such as metoclopramide and domperidone, laser photocoagulation by neodymium yttrium-aluminum garnet (YAG) and argon plasma coagulation, bipolar electrocoagulation, heater probe coagulation, and injection sclerotherapy with 5% polidocanol foe water melon stomach and many more. However, managing the various problems of SSc-related gastrointestinal disease remain amongst the most challenging in the course of the disease.

S.4.2

NEW THERAPEUTIC APPROACHES

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Although the GI system is the second most frequently involved organ system and a major determinant of quality of life amongst patients with systemic sclerosis there is little published evidence or novel approaches available to guide clinicians on the best management for these patients. This presentation will outline evolving data on novel approaches for management, as well as outlining the new UK consensus best practice pathways for the management of the Gastrointestinal manifestations of systemic sclerosis.

S.4.3

MORTALITY, RECURRENCE, AND HOSPITAL COURSE OF PATIENTS WITH SYSTEMIC SCLEROSIS (SSC) RELATED ACUTE INTESTINAL PSEUDO-OBSTRUCTION

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Introduction. Acute intestinal pseudo-obstruction is a rare gastrointestinal manifestation of SSc with little data existing as to the demographics, clinical course, outcomes and mortality of this disease.
Methods. We undertook a retrospective chart review of patients admitted at two University Medical Centers in the city of Philadelphia over an 11.5 year period (1/2001-6/2012).Medical records were searched using ICD codes for SSc in combination with ICD codes for intestinal obstruction and fecal impaction. The medical records were then reviewed and those patients who were identified as true cases of pseudo-obstruction we collected demographic data. Continuous variables were analyzed by a student's unpaired two-tailed t test while categorical variables by the Fisher's exact test.
Results. A total of 1,733 admissions of SSc patients to the two hospitals were identified during the time period in question. 103 admissions had ICD codes matching our search criteria and from them 64 admissions were identified as true acute intestinal pseudo-obstruction cases in 37 unique SSc patients. From these cases 73% had spontaneous resolution with conservative measures of IV hydration and bowel rest, 11% underwent surgical resection and 26% required permanent total parenteral nutrition (TPN), Hospital course was for a mean of 12+12.5 days and there was 10% mortality. In a subgroup analysis of patients who had recurrent episodes of pseudo-obstruction this was more commonly seen in women (p=0.01), associated with symptoms of nausea at presentation (p=0.04) and resulted more often to the use of prolonged TPN (p<0.0001). Mortality was higher in male patients (p=0.014) who had low hemoglobin (p<0.00008) and serum albumin (p<0.001). Patients who underwent surgery were more likely to die (p<0.005). A prolonged hospital stay was more often related to the use of a nasogastric tube (p<0.05) and a surgical resection (p<0.05).
Conclusion. Acute intestinal pseudo-obstruction is a rare cause of hospitalization of SSc patients (64/1733 (3.7%) admissions). This is the largest study attempting to characterize this subpopulation of SSc patients. Based on our results most patients have spontaneous resolution with conservative measures such as bowel rest and IV hydration. Women were more likely to have recurrences and these patients were more likely to suffer from nausea symptoms at their presentation, and progressed to need permanent TPN. Mortality was higher in males especially in those patients with a low hemoglobin and serum albumin at presentation. Patients who underwent a surgical resection had a higher mortality and a more prolonged hospital stay.

S.4.4

PREVALENCE, CORRELATES AND OUTCOMES OF GASTRIC ANTRAL VASCULAR ECTASIA IN SYSTEMIC SCLEROSIS: A EUSTAR CASE-CONTROL STUDY

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Objective. To estimate the prevalence, determine the subgroups at risk and the outcomes of systemic sclerosis (SSc) patients with gastric antral vascular ectasia (GAVE).
Method. We queried the EUSTAR network for the recruitment of SSc-GAVE patients. Each case was matched for cutaneous subset and disease duration with 2 SSc controls recruited from the same centre, evaluated at the time the index case had the diagnosis of GAVE made. SSc characteristics were recorded at the

time of GAVE occurrence and the last observation was collected to define the outcomes.
Results. 49 cases of SSc patients with GAVE were included (24 with diffuse cutaneous SSc) and compared to 93 SSc controls. The prevalence of GAVE was estimated at about 1% of SSc patients. By multivariate analysis, SSc-GAVE patients exhibited more frequently a diminished (<75%) DLCO value (Odds Ratio, OR : 12.8; 95% confidence interval, CI, 1.9-82.8) despite less frequent pulmonary fibrosis (OR : 0.2; 95%, CI 0.1-0.6). GAVE was also associated with the presence of anti-RNA-polymerase III antibodies (OR : 4.6; 95%CI 1.2-21.1). SSc-GAVE was associated with anemia (82%) requiring blood transfusion (45%). Therapeutic endoscopic procedures were performed in 45% of GAVE cases. After a median follow-up of 30 months (range 1-113 months), survival was similar in SSc-GAVE patients, as compared to controls but a higher number of scleroderma renal crisis occurred (12% vs. 2%. p=0.01).
Conclusion. GAVE is rare and associated with a vascular phenotype including anti-RNA-polymerase III antibodies and a high risk of renal crisis. Anemia usually requiring blood transfusions is a common complication.

Session 5: *Links to Inflammation, Immunity and Vasclular Disease*

S.5.1

IMMUNOLOGICAL MECHANISMS OF FIBROSIS

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Macrophages are found in close proximity with collagen-producing myofibroblasts and play key roles in the mechanisms of wound healing and fibrosis. They produce growth factors and pro-fibrotic mediators that directly activate fibroblasts, including transforming growth factor beta, insulin-like growth factor, vascular endothelial growth factor, and platelet-derived growth factor. They also regulate extracellular matrix turnover by influencing the balance of various matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases. Macrophages also regulate fibrogenesis by secreting chemokines that recruit fibroblasts and other inflammatory cells and by producing various inflammatory and anti-inflammatory cytokines. With their potential to act in both a pro- and anti-fibrotic capacity at distinct stages of the wound healing response, macrophages and the factors they express are integrated into all stages of the fibrotic process. These various and sometimes opposing functions are performed by distinct macrophage subpopulations, the identification of which is a growing focus of fibrosis research. Although collagen-secreting myofibroblasts once were thought of as the master ''mediators" of fibrosis, in this presentation I will illustrate how macrophages function as the master ''regulators" of fibrosis.

S.5.2

PIGMENT EPITHELIUM DERIVED FACTOR SECRETED BY SSC FIBROBLASTS INHIBITS ANGIO AND VASCULOGENESIS IN VITRO

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Background. Systemic Sclerosis (SSc) is an autoimmune disorder characterized by tissue fibrosis and defective angio/vasculogenesis. There is scanty of studies investigating the molecular mechanisms linking the two processes in SSc. Recently, a proteomic analysis of SSc dermal fibroblasts (SScFBs) secretome, identified an increased secretion of Pigment Epithelium Derived Factor (PEDF) compared to healthy fibroblasts. PEDF produced by retinal-pigmented epithelium and melanocytes (HEMs), is the major endogenous inhibitor of intraocular angiogenesis. Here we aimed to validate the increased expression of PEDF in SSc and to determine whether PEDF might play a role in SSc vasculopathy.
Methods. PEDF expression was investigated in the involved skin and FBs of 4 early diffuse SSc patients and 4 healthy controls (HC) by immunohistochemistry (IHC) and rt-PCR. Functional effects of PEDF on angio/vasculogenesis were examined by Matrigel assays and organotypic co-culture assays of HUVECs or microvascular endothelial cells (MVECs), on either primary healthy FBs (HCFBs) or SScFBs or HCFBs silenced for Caveolin-1 (Cav-1). Endothelial cells were visualized by CD31 staining. Vascular tubule number, length and junctions were analyzed by Angiosys software (TCS CellWorks).
Results. In SSc skin 52% (+/-5.9) of dermal fibroblasts were positive for PEDF vs. 13% (+/-0.68) of FBs in HC skin ($p<0.05$). Furthermore, double IHC studies indicated that PEDF positive FBs showed a decreased Cav-1 expression in both HC and SSc skin. In-vitro studies confirmed that SScFBs showed on average a 5-fold increased PEDF expression when compared to HCFBs ($p<0.0162$). Additionally, consistent with IHC studies HCFBs silenced for Caveolin-1 showed on average a 2-fold increase in PEDF mRNA levels compared to control ($p<0.0055$). Matrigel studies indicated that recombinant PEDF protein inhibited vasculogenesis, suppressing the loop number by 20% ($p<0.05$). Consistently, co-culture assays indicated that PEDF inhibited tubulogenesis, suppressing both total tubule length by 42% ($p<0.005$), number of tubules by 55% ($p<0.005$) and