CONCOMITANT AUTOIMMUNE DISEASES IN PATIENTS WITH SARCOIDOSIS

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Introduction: Sarcoidosis is a chronic granulomatous disease characterized by non-caseating granuloma formation. It can mimic many autoimmune diseases and/or may be coexist with them. There are limited data in the literature about the association of sarcoidosis with autoimmune diseases. Aim: The purpose of this study is to determine the frequency and characteristics of autoimmune diseases associated with sarcoidosis patients. Material and method: One hundred and thirty-one sarcoidosis patients followed-up in single rheumatology center were included in the study. Demographic, clinical, laboratory and radiological data of these cases were evaluated retrospectively. The characteristics of autoimmune diseases associated with sarcoidosis (sarcoidosis-overlap group) patients and isolated sarcoidosis (isolated sarcoidosis group) were analyzed and compared. Results: Autoimmune disease was detected in 15 (11.5%) of 131 patients with sarcoidosis (15Sjögren syndrome, 3rheumatoid arthritis, 1Still disease, 1scleroderma, 4ankylosing spondylitis, 1familial Mediterranean fever, 1gut arthritis, 1immune trombocytopenic purpura, 1Hashimoto thyroiditis and 1Graves disease). Most of these diseases occurred before (such as RA, AS, Still, FMF) and others after sarcoidosis diagnosis. Among 15 sarcoidosis patients with autoimmune disease 10 were female and 5 were male, the mean age was 50.8 years and mean disease duration was 3 months (1-30 months). When compared with isolated sarcoidosis patients, more hand finger joint involvement, RF positivity, higher ESR and less NSAIDs usage were found in patients with sarcoidosis-overlap group (p=0.035, p=0.049, p=0.015, p=0.018 respectively). There was no statistically significant differences between the two groups when evaluated for demographic, clinical parameters and DMARDs used. Conclusions: Concomitant autoimmune diseases in patients with sarcoidosis may be often seen. This patients are characterized with more hand finger joint involvement, RF positivity, higher ESR and less NSAIDs usage. Multicenter, prospective studies involving large numbers of patients are needed to understand whether the association of sarcoidosis-autoimmune diseases is based only on coincidence or on a common etiopathogenesis.

Clinical significance of serum autoantibodies in patients with sarcoidosis.

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OBJECTIVE Sarcoidosis is a systemic granulomatous disease of unknown etiology. The association of sarcoidosis and autoimmunity has been reported. Sarcoidosis shares common features with several systemic and organ-specific autoimmune diseases. Also, various autoantibodies have been reported in sarcoidosis. However, the significance of autoantibodies in sarcoidosis is not well understood. There are no established autoantibodies that can be used as serologic biomarkers to diagnose, monitor the state of the disease and predict prognosis of patients. We performed comprehensive analysis of serum autoantibodies and examine their association with clinical features of sarcoidosis patients.

PATIENTS AND METHODS. Twenty-three patients with sarcoidosis who visited our hospital between December 2015 and May 2019 were enrolled to the study. Patients complicated with systemic autoimmune rheumatic diseases and those with sarcoid reaction due to malignancy were excluded. Autoantibodies in the sera were tested by indirect fluorescence (antinuclear antibodies, ANA, HEp-2 cell), enzyme linked immunosorbent assay (ELISA) using recombinant proteins (Ro60, Ro52, CENP-A, CENP-B, Jo-1, thyroglobulin, thyroid peroxidase) and immunoprecipitation (35S-methionine-labeled K562 cell). Their association with clinical and laboratory features of sarcoidosis was analyzed.

RESULTS. Nine out of 23 patients (39%) had one or more known serum autoantibody specificities; antibodies to Ro52 (n=3), Ro60 (n=2), Ago2/Su (n=2), CENP-A (n=1), thyroglobulin (n=1), thyroid peroxidase (n=1), CCP (n=1), ds-DNA (n=1). Sarcoidosis patients who were positive for at least one serum autoantibodies had significantly higher percentage of advanced pulmonary radiographic stage (>stageII) compared with those without autoantibodies (67% vs 7%, p<0.005 by Fisher exact test), and had CT findings in the lung consistent with sarcoidosis (78% vs 36%, p<0.05). Age, sex, smoking status, the results of pulmonary function test, serum ACE levels (24.0 U/L vs 21.8 U/L) and number of affected organs (2.11 vs 1.93) were not significantly different between two groups. Results were similar when ANA (>1:160) or rheumatoid factor were included for the definition of autoantibody positive group.

CONCLUSION. Presence of serum autoantibodies was associated with advanced pulmonary lesion in patients with sarcoidosis. Involvement of autoimmune process may affect the pathogenesis and progression of sarcoidosis and response to treatment.

Serious Infections in Sarcoidosis and the Effect of Treatment

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Background Infections resulting in hospitalization (i.e. serious infections) impair quality of life and increase costs, especially if recurrent. Understanding whether sarcoidosis patients have an increased risk and whether it differs by treatment is important for prevention and proper treatment choice.

Objectives Our aim was to compare the serious infection risk
in sarcoidosis compared to the general population and in methotrexate compared to azathioprine initiators as second-line treatments.

**Methods** We identified sarcoidosis cases (22 ICD-coded visits in the Swedish National Patient Register [2003-2012]; n=7820). Treatments were identified from the Prescribed Drug Register (2006-2013). Up to 10 comparators were matched to cases on age, sex, and county of residence (n=77159; mean age 49±17 yrs; 45% female). Serious infections were hospitalizations where infection was the primary discharge diagnosis (Patient Register). Cases and comparators were followed until serious infection, death, emigration, or study end (Dec 2013). We estimated adjusted hazard ratios and 95% confidence intervals (HR; 95% CI) for first or recurrent serious infections using flexible parametric models. We emulated a target trial to compare the 6-month risk for infection in methotrexate vs. azathioprine initiators.

**Results** The HR for first serious infection was 1.9 (95% CI 1.8, 2.0) and 2.2 (95% CI 1.9, 2.5) for pneumonia (the most common serious infection). The HR was highest during the first two years after diagnosis and varied by treatment status (figure). It increased further when recurrent serious infections were modeled. In the methotrexate vs. azathioprine ‘trial’, the risk ratio for infection was 0.5 (95% CI 0.4, 0.7).

**Conclusions** Compared to the general population, sarcoidosis patients have a higher risk for serious infection, especially during the first years after diagnosis. In terms of infection, methotrexate is a safer second-line treatment for sarcoidosis compared to azathioprine.

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**O1-4**

**Recent trends of clinical features of sarcoidosis in Japan**

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**Background:** Sarcoidosis shows variable clinical phenotypes and prognostic diversity in different areas, ethnic groups and time periods throughout the world. It is reported that the frequency of cardiac involvement in Japan is higher than that in western countries (Eur Respir J, 2008). The present study was designed to investigate more recent clinical features of sarcoidosis in Japan.

**Methods:** We conducted a medical record review of 360 sarcoidosis patients in Tohoku University Hospital between January 1, 2000 and December 31, 2018. We classified the patients with cardiac involvement into two groups, a group newly diagnosed as having cardiac involvement during follow-up care for sarcoidosis (A) and a group showing cardiac symptoms preceding the diagnosis of sarcoidosis (B).

**Results:** Among 360 patients, 235 cases (65.2%) were females, and the average ages were 46.1±16.9 in males and 53.1±14.3 in females. The prevalence of the mainly affected organs were eyes (210 cases, 58.3%), lungs (195 cases, 54.1%), skin (73 cases, 20.2%) and heart (60 cases, 16.7%), and the number of patients with treatment using systemic corticosteroids was 51 cases (24.3%), 23 cases (11.8%), 4 cases (5.5%) and 53 cases (88.3%), respectively. Among 60 cases with cardiac lesions, 23 (41.9%) were classified as group A, in which 16 cases (69.6%) were asymptomatic and were detected by regular check-up using electrocardiogram (16 cases, 69.6%), echocardiogram (6 cases, 26.1%) and FDG-PET (1 case, 4.3%). The time interval between the diagnosis of sarcoidosis and the detection of cardiac lesions was 75±107 months. Patients in group A had better left ventricular function and a lower prevalence of serious arrhythmia compared with those in group B.

**Conclusion:** The present study revealed that the patients with sarcoidosis in middle aged and older women have been increasing recently and form a stronger unimodal distribution than in previous surveys. Although the prevalence of patients with cardiac involvement in Japan is still higher than in western countries, their prognosis has not deteriorated. These findings suggest that early detection and early treatment of cardiac involvement in asymptomatic patients with sarcoidosis could contribute to a better prognosis of sarcoidosis in Japan.

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**O1-5**

**Clinical Characteristics and Outcome of Korean Patients with Sarcoidosis**

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**Objectives:** Sarcoidosis is a multi-organ involving systemic disease of unknown etiology, characterized by non-caseating granuloma on biopsy, and its clinical presentation and prognosis vary by race. This study aimed to identify clinical characteristics and outcome of Korean patients with sarcoidosis.

**Methods:** Clinical data were retrospectively analyzed in 367 patients with sarcoidosis (all biopsy proven cases) diagnosed between 2001 and 2017 at Asan Medical Center, Seoul, South Korea.
Korea. Organ involvement was confirmed by multi-disciplinary discussion based on clinico-radiologic-pathologic findings. Treatment responses were classified as improvement, stability or progression based on changes of chest images in patients with lung involvement.

Results: The median follow-period was 42 months. Of 367 patients, the mean age was 47.4 years, 67.3% were female and 69.5% were never-smokers. The highest prevalence was observed in individuals aged 50-59 years (30-39 years in men and 50-59 years in women), and the number of patients diagnosed showed increasing trend. When all patients were classified by using Scadding radiographical staging system, stage 2 (46.9%) was the most common, followed by stage 1 (33.2%), stage 4 (6.3%), stage 3 (5.7%), and stage 0 (7.9%), respectively. Lymph node involvement was the most common (89.1%), followed by lung (71.1%), skin (24.3%), and eye (19.9%), respectively. Among patients with lung involvement (n =261), 32.3% showed abnormal lung function (obstructive pattern in 7.7%, restrictive pattern in 22.3%, mixed pattern in 2.3%) with mild impairment (mean, FEV1, % predicted =86.7±14.5, FVC, % predicted =89.0±13.3).

During follow-up, among patients with lung involvement, 175 patients (67.0%) were treated with systemic steroid. Of them, 59.4% showed improvement, and 20.0% and 18.9% showed stability and progression on chest images. Eleven patients (3.0% of total patients) died during follow-up, and cancer was the most common cause of death (n=4), followed by disease progression (n=3), cardiovascular disease (n=3), respectively.

Conclusions: In this study, Korean patients with sarcoidosis showed similar clinical characteristics to previous reports, but prognosis seemed to be better.

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**O2-1**

**Leicester Cough Questionnaire (LCQ) for Measuring Cough in Sarcoidosis**

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Sarcoidosis is a chronic multisystem granulomatous disease of unknown origin that is most commonly present in the lungs. Probably most disturbing of the respiratory symptoms is cough.

Aim: in this study we analyzed the relation between cough and the parameters of sarcoidosis activity using Leicester Cough Questionnaire (LCQ) for measuring this important symptom.

Methods: 275 biopsy positive sarcoidosis patients were analyzed using this questionnaire. LCQ is a 19-item validated specific QoL measure of cough over the period of previous two weeks. The scores are calculated in 3 domains covering physical (8 items), psychological (7 items), and social (4 items) aspect of chronic cough. It evaluates the impact of cough on patients’ quality of life. Higher scores indicate better quality of life. The group of patients for this analysis were patients with both acute (103pts/37%) and chronic sarcoidosis (172pts/63%). Mean disease duration 15.62±8.56yrs. Female 180 pts and male 95pts. Mean age 50.13±11.07yrs

Results

Physical domain score in this group of patients was: 5.48±1.18 (range 1.88 - 7.00), Psychological domain score 5.64±1.29 (range 1.86 - 7.00) and Social domain score 5.82±1.33 (range 1.75 - 7.00).

Male patients had higher LCQ scores in all domains (physical, physiological and social) and the difference was statistically significant (p<0.05; Pearson correlation). Age of sarcoidosis patients significantly correlate with the severity of cough measured with LCQ. Younger patients had significantly higher LCQ scores in all domains (p<0.01)

At the time of the analysis 68pts had remission on the chest X ray, and the correlation between stage of the lung disease was statistically significant for all LCQ domains, but negative. (p< 0.05 in the domain of social and psychological score) and (p< 0.01 in the domain of physical score). The severity of cough correlates with the disease activity. In a group of patients with high serum ACE values above 65 U/L, reporting sarcoidosis activity all LCQ scores correlates significantly with the disease activity (Pearson correlation p<0.05)

Conclusion

LCQ is a reliable instrument for evaluation of cough in sarcoidosis.

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**O2-2**

**Prevalence of Obstructive Sleep Apnea Syndrome in Sarcoidosis and Impact of CPAP Treatment on Associated Fatigue Status: the SARCOIDOSAS trial**

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**Aims:** Sarcoidosis is a multisystemic granulomatous disease that affects individuals worldwide without known pathogenesis and the role of comorbidities has not been fully assessed. An increased incidence of Obstructive Sleep Apnea Syndrome (OSAS) has been described without clear explanations. Also, a state of physical and mental weariness called fatigue is common in sarcoidosis and OSAS could play a considerable role in such symptom’s evaluation. Moreover, no data are available about Continuous Positive Airway Pressure (CPAP) treatment of OSAS in sarcoidosis. We aim to assess the effect of OSAS in sarcoidosis and to investigate the CPAP treatment effect on fatigue using validated questionnaires.

**Methods:** Prospective analysis of 64 patients enrolled in Sarcoidosis Clinic of Policlinico Gemelli. Baseline polysomnography, Fatigue Assessment Scale (FAS) and Epworth Sleepiness Scale (ESS) questionnaires were performed. When moderate-to-severe OSAS (AHI>5) was diagnosed, CPAP was started and FAS, ESS questionnaires and CPAP compliance analysis were scheduled at 3-month.

**Results:** The baseline polysomnography identified OSAS (AHI>5) in 56 subjects (87.50%) with a mean AHI of 20.20±17.36. In OSAS group, 23 (41.07%) were mild (5<AHI<15) while 33 (58.93%) were moderate-to-severe (AHI>15). CPAP treatment was accepted in 16 moderate-to-severe subjects (48.48%). FAS questionnaire identified fatigue status (FAS>21) in 32 patients, and FAS, ESS questionnaires and CPAP compliance analysis were found. The 3-month follow up of CPAP group showed (Figure 1) both FAS score reduction (∆FAS=-6.18, 95%CI 2.60-9.76, p=0.0022) and ESS score reduction (∆ESS=-3.50, 95% CI 1.74-5.25, p=0.0007). Compliance analysis was “good” (more than 4h per night and 70% nights) in 7 (43.8%) and “poor” (less than 4h per night and 70% nights) in 9 (56.2%). Moreover, Pearson correlation of AHI was significant when compared to BMI (p: 0.40, p=0.0010), FAS (p: -0.30, p=0.0133) and ESS (p: -0.33, p=0.0074). No correlation with Scadding, corticosteroids, immunosuppressors was found.

**Conclusions:** OSAS and fatigue are highly prevalent in sarcoidosis. FAS and ESS scores are negatively correlated with AHI and polysomnography should be considered beyond questionnaires results. Treatment with CPAP demonstrated significant improvement in fatigue and daytime sleepiness in moderate-to-severe OSAS.
cause proximal BVB thickening and TBE. This is followed by upper lobe shrinkage with subpleural thickening, and by formation of honeycombing-like architecture and cysts, leading to respiratory failure with possible complications such as pulmonary hypertension.

O2-4
Experiences with prednisone and methotrexate in a real-world sarcoidosis population

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Background:
There is a major unmet need for better evidence-based treatment in sarcoidosis. Besides organ function, quality of life (QoL) is an important treatment aim. Prednisone is currently the first-choice therapy in pulmonary sarcoidosis. Unfortunately, prednisone often has major side-effects which may lead to impaired QoL. Methotrexate is presently considered second-line therapy, and may have fewer side-effects in clinical practice. We aimed to evaluate the use and presence of side-effects of prednisone and methotrexate in a real-world sarcoidosis population.

Methods:
During a yearly sarcoidosis patient information meeting at the Erasmus University Medical Center in 2019, patients were invited to complete a questionnaire on medication use and experiences with prednisone and methotrexate. Botherliness of side-effects was reported on a scale from 1 (not bothersome at all) to 10 (very bothersome).

Results:
In total, 67 patients completed the questionnaire (response rate + 80-85%). Mean age was 53 (range 31-71) and 60% was female. Average time after diagnosis was 6 years, average time on medication was 40 months for prednisone and 18 months for methotrexate. One-fifth of patients (19%) never used medication for sarcoidosis, 48% reported having used both prednisone and methotrexate, and 18% also used other medication (infliximab, hydroxychloroquine, azathioprine or mycophenolate). Of the 67 responders, 46 (69%) have used prednisone for sarcoidosis (present or former); 78% reported one or more side-effects. Patients reported weight gain (62%), psychological problems/behave change (25%), sleep problems (17%), osteoporosis, hypertension, diabetes and muscle pain. Mean botherliness of side-effects was 6.3 (3-10), and average number of side-effects 2.3 (1-6). Amongst the 38 patients (57%) treated with methotrexate, fewer side-effects were reported: 50% reported one or more side-effects such as nausea or other gastrointestinal complaints (63%), general malaise (21%), headache (n=2) and liver test abnormalities (n=2). Mean botherliness of side-effects was 4.7 (2-7), and average number of side-effects 1.4 (1-3).

Conclusion:
In clinical practice, methotrexate seems to have fewer and less bothersome side-effects than prednisone. A randomized controlled trial comparing effectiveness and side-effects of prednisone vs. methotrexate for (first-line) treatment of sarcoidosis should be performed to confirm these findings.

O2-5
Clinical, Functional, Imaging and Pathological Aspects of Sarcoidosis

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Introduction: sarcoidosis is a granulomatosis which affects most commonly the lungs and lymph nodes. The prognosis of this localization is related to the impairment of respiratory function which may lead to respiratory failure. The purpose of this study is to determine the main aspects of thoracic Sarcoidosis.

Patients and method: it is a retrospective study of 21 cases of sarcoidosis with infiltrative lung disease, admitted in our department during the last 4 years. Results: the group was made of 19 women and 2 men with an average age of 52. All patients suffered from dyspnea and cough. 10 patients experienced arthralgia and 6 had xerostomia. The thoracic tomography had showed an interstitial syndrome made of a reticulo-nodular pattern in 11 cases (52%). It was associated to mediastinal lymphadenopaties in 7 cases (33%). A ground glass pattern was found in 8 cases (38%) and a fibrosis pattern with honeycomb was noted in 2 patients (9, 5%). It was a type II sarcoidosis in 7 cases, 12 patients had a type III sarcoidosis while 2 had a type IV one. The respiratory functional exploration found a restrictive pattern for 5 patients (31, 25%). The bronchoscopy showed thickened inflamed spurs in 8 cases (38%). The Lavage was possible to perform for 18 patients and it found a lymphocytic alveolitis in 11 cases (52, 38%). Bronchial biopsies found non-necrotizing granulomas in 5 cases (23, 8%). A granuloma was found on mediastinal lymph node biopsies by endobronchial ultrasound (EBUS) in 2 cases and by mediastinoscopy in 1 case. The majority of patients were treated with systemic corticosteroids. The follow up was favorable for 19 patients (85, 7%).

Conclusion: despite all the advancement from which the medical field benefited during the last couple of decades, the diagnosis of sarcoidosis still relays on the combination of clinical presentation, imagery and pathology.

O3-1
Macitentan in Sarcoidosis-Associated Pulmonary Hypertension

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Background: Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis and is associated with higher mortality. Underlying pathophysiological mechanisms are unclear and treatment with PH targeted therapies is currently off-label.
**Purpose:** We investigated the use of macitentan as treatment of sarcoidosis-associated pulmonary hypertension (SAPH), including safety and outcomes.

**Methods:** We conducted a single-centre, case-series including all SAPH patients, who were treated with macitentan, with a minimum follow-up of twelve months. Six-minutes walking test (6-MWT), New York Heart Association (NYHA) functional class, NT-proBNP and adverse events were collected.

**Results** Six patients (three men) with a median age of 64 years (range 52-74 years) were identified. At baseline, the median mean PAP was 49 (27-66) mmHg and PVR 10.4 (3.2-13.9) WU. Initial PH-treatment consisted of macitentan (n=4) or sildenafil (n=2). All patients were on dual treatment after a median of two months and continued for a median of 25 months. After twelve months, the 6-MWT distances increased from a median of 352 (145-445) to 367 (244 - 457) meters, the NYHA functional class significantly improved from 3 (3 - 4) to 2.5 (2 - 3) (p=0.046), and NT-pro BNP did not change significantly from 652 to 516 pg/mL. Macitentan was discontinued after one week in one patient due to side-effects.

**Conclusion:** Macitentan is safe and might improve both exercise capacity and functional class in SAPH. Prospective controlled trials are warranted for therapeutic recommendations and patient selection.

**O3-2**

**Serum and BALF Neutrophil Gelatinase-Associated Lipocalin in Patients with Pulmonary Sarcoidosis**

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**Aim:** Sarcoidosis is a systemic granulomatous disorder and its clinical course and prognosis are highly divergent. Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein and regarded as a critical component of the innate immune system. It has a high affinity for siderophores that bind to circulating and intracellular free iron. Elevated expression of NGAL has been detected in various diseases. This study was conducted to examine the expression of NGAL in serum and bronchoalveolar lavage (BAL) fluid in patients with sarcoidosis.

**Methods:** Ninety-six Japanese patients with sarcoidosis were evaluated. Using an enzyme-linked immunosorbent assay, the presence of NGAL in serum and BALF samples collected at the time of diagnosis were examined. In addition, 49 age- and gender-matched healthy subjects without any clinical or radiological evidence of infection, pulmonary, cardiovascular and renal disease, tumor, sarcoidosis, or autoimmune disorders served as a reference population.

**Results:** There were no significant correlations between serum NGAL levels and sex, age, absolute neutrophil counts, estimated glomerular filtration rates or smoking pack-year histories. The median serum NGAL in patients with sarcoidosis was 35.1 ng/mL, which was significantly higher than in healthy controls (17.2 ng/mL, p<0.0001). The median BAL fluid NGAL in sarcoidosis patients was 1.7 ng/mL, which was similar to those in healthy controls (1.5 ng/mL, p=0.7424). Serum and BAL fluid NGAL levels were not correlated with markers for disease activity. 26 patients (27.1%) received systemic corticosteroid therapy during the follow-up period. When we divided patients into two groups according to their corticosteroid therapy, serum NGAL levels (56.5 ng/mL) in corticosteroid-treated group were significantly higher than in those who did not receive corticosteroid therapy (34.3 ng/mL, p=0.0201). Conversely, there was no difference in BAL fluid NGAL between corticosteroid-treated group and non-treated group. Six patients received corticosteroid therapy for the newly appearance of cardiac sarcoidosis and the median serum NGAL level was 22.1 ng/mL. Higher serum NGAL at diagnosis was associated with subsequent use of systemic corticosteroid therapy (hazard ratio, 1.20; 95% confidence interval, 1.09-1.31, p=0.0004).

**Conclusion:** These findings suggest that serum NGAL may predict the disease course of sarcoidosis.

**O3-3**

**Dendritic cells contribute to a T helper 17(1) favoring environment and their cytokine expression correlates with long term prognosis in sarcoidosis**

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**Rationale** Pulmonary sarcoidosis is an idiopathic antigen-driven granulomatous disease. Recently, a dominant T-helper 17 signature was found in bronchoalveolar lavage fluid (BALF), which correlated with disease prognosis. Activation and polarization of T-cells is induced by dendritic cells (DCs), which reside in close proximity to T-cells in sarcoid granulomas. DCs are a heterogeneous population of highly potent antigen presenting cells and can be divided into different subsets. During steady state and inflammation, conventional DCs (cDCs) are potent inducers of T-cell activation. During inflammatory conditions, monocytes are recruited that differentiate into monocyte-derived DCs (moDCs) at the site of inflammation. moDCs control the effector T-cell response through their secretion of pro-inflammatory chemokines. However, the activation status and cytokine expression by DC subsets in sarcoidosis is currently unclear.

**Objectives** To assess the distribution of different DC subsets, activation status, migration capacity and cytokine expression in pulmonary sarcoidosis.

**Methods**
Dendritic cell subset distribution, activation and cytokine expression were determined using 15-color flow cytometry in peripheral blood (PB), BALF and mediastinal lymph node (MLN) from sarcoidosis patients and compared to healthy controls (HC) blood and MLN, and disease control (DC) BALF.

Measurements and Main Results
Conventional DC (cDC) subset distribution was almost similar in blood, MLN and BALF of sarcoidosis and controls. Expression of the migratory molecule CCR7 on sarcoidosis cDCs was decreased in blood and MLN. In sarcoidosis blood, cDCs and monocyte-derived DCs (moDCs) showed increased tumor necrosis factor alpha (TNFα) expression and cDCs harbored enhanced latency-associated peptide/transforming growth factor beta (LAP/TGFβ) expression compared to HC. Interleukin (IL)-6 expression was augmented in both cDCs and moDCs and correlated with Th17.1-cell proportions in sarcoidosis BALF (figure 1a). Strikingly, cDC IL-6 expression in sarcoidosis BALF at time of diagnosis was higher in patients developing chronic disease (figure 1b).

Conclusions
Our study suggests an impaired migration of cDCs from the lung to MLN, resulting in ongoing pulmonary T-cell activation. In sarcoidosis, pulmonary DC cytokine expression favors a Th 17(1.1) response and high IL-6 in pulmonary cDCs appears predictive for chronic disease.

Figure 1

O3-4
Monocytes in lungs of sarcoidosis patients show a hyperinflammatory profile

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Sarcoidosis is characterized by granuloma formation, which is promoted by TNF. In Sweden, one third of sarcoidosis patients present with acute disease onset (often Löfgren’s syndrome (LS)), that have a favorable disease outcome. Detailed analyses on TNF expression in LS and non-LS in response to anti-TNF treatment is incomplete. Dendritic cells (DCs), monocytes and macrophages (mononuclear phagocytes (MNP)s) are major producers of TNF and considered important in sarcoidosis pathogenesis.

The aim is to determine the source and kinetics of TNF in blood and lung of LS and non-LS patients at time of diagnosis, during disease progression and during anti-TNF treatment. In addition, we aim to understand how TNF contributes to disease severity in LS and non-LS patients and whether it predicts response to anti-TNF treatment.

Distribution of MNP subsets from blood and BAL from LS and non-LS patients were compared to healthy controls (HC) by flow cytometry and TNF production assessed by intracellular staining. FACS-sorted MNP were used for RNA sequencing.

Frequencies of inflammatory monocytes (CD14+CD16+) were increased in blood and BAL of LS and non-LS patients compared to HC suggesting local and systemic inflammation. MNP from BAL of non-LS patients were compared to HC indicating a crucial role for monocytes to disease severity. Spontaneous TNF expression in BAL MNP increased over time in a cohort of patients despite overall improved clinical status. BAL MNP from patients with chronic progressive disease treated with anti-TNF (infliximab) showed low spontaneous TNF production prior to treatment, which surprisingly increased after treatment.

MNP from blood and lungs of LS and non-LS patients showed an inflammatory profile with a special role for monocytes, supported by functional and transcriptional data. Linking TNF expression, disease severity and response to anti-TNF treatment will help to early treat non-LS patients with targeted therapy.

O3-5
Trigger Related Phenotypes in Sarcoidosis

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Aim
Sarcoidosis is a heterogeneous, systemic disease characterized by formation of noncaseating granulomas, mostly affecting the lungs, skin, eyes and lymph nodes. Multiple possible antigens have been linked to sarcoidosis pathogenesis, however not simultaneously studied in the same cohort of patients. Correlation between clinical characteristics and immunological response towards different antigens could identify new disease phenotypes.

Methods
A cohort of 203 sarcoidosis patients were included in the study. Patients with Obstructive Sleep Apnea (OSA) were included as control group (n=51). By the use of IFNγ elispot assays, Peripheral Blood Mononuclear Cells (PBMCs) from patients and controls were tested for sensitization towards antigens of P. acnes
WASOG/JSSOG 2019

Abstract

(catalase and heat inactivated whole P. acnes), Mycobacterium tuberculosis (MKA
g, ESAT-6) and vimentin. Furthermore, available clinical data of Interferon gamma release assays
used in the diagnosis of latent or active tuberculosis infection, were analyzed for sensitization to mycobacterial peptides as well.

Results

There was no difference in number of spots between controls subjects and sarcoidosis patients (either with or without immuno-suppressive drugs) after stimulation with anti-CD3 antibody used as positive control (data not shown). Furthermore, no significant differences were observed for ESAT-6, MKA
g, Heat inactivated P. acnes or vimentin sensitization between the sarcoidosis and control group. However, a significantly higher percentage of controls showed sensitization to P. acnes catalase compared to sarcoidosis patients (p=0.003) (fig.1). P. acnes catalase sensitized sarcoidosis patients were younger at time of diagnosis compared to the other sarcoidosis patients (27.94 years versus 43.46 years, p=0.002). Furthermore, a relative high percentage of this group had skin involvement (42.9% compared to 13.3%, p=0.062), while sarcoidosis pa-
tients sensitized to mycobacterial peptides (n=5) were more likely to have cardiac involvement (60% compared to 15%, p= 0.03).

Discussion and conclusion

No strong evidence for involvement of mycobacteria or vimentin in sarcoidosis pathogenesis in Dutch patients was found. Furthermore, our data do not support previous findings of increased P. acnes catalase sensitization among sarcoidosis patients. In contrast, we even found that a smaller percentage of sarcoidosis patients were sensitized to P. acnes catalase compared to controls. Finally, our data suggest a possible link between sensitization for P. acnes catalase and skin involve-
ment in sarcoidosis.

![Graph showing the percentage of positive spots for controls and sarcoidosis patients.](image)

Discussion

No strong evidence for involvement of mycobacteria or vimentin in sarcoidosis pathogenesis in Dutch patients was found. Furthermore, our data do not support previous findings of increased P. acnes catalase sensitization among sarcoidosis patients. In contrast, we even found that a smaller percentage of sarcoidosis patients were sensitized to P. acnes catalase compared to controls. Finally, our data suggest a possible link between sensitization for P. acnes catalase and skin involvement in sarcoidosis.

O3-6

A case of sarcoidosis misdiagnosed as tuberculosis for two years with eosinophilia as the main manifestation

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In our hospital, a case of sarcoidosis with eosinophilia in includ-
ing peripheral blood, sputum, bronchoalveolar lavage fluid (BALF) and bone marrow as the main manifestation was a 47y

patient, male, with lung shadow (Fig.1) was found in physical examination 2 years ago. He was misdiagnosed as tuberculo-
sis with biopsy of epithelioid granuloma, after repeated anti-
tuberculosis treatment for 2 years, with no improvement through CT (Fig.2 & 3). Outpatient: BALF-GM (9.42), after vor-
conazole antifungal therapy, blurred vision was occured to him, causing him to be hospitalized. Auxiliary examinations were done: eosinophilia in peripheral blood and sputum; serum tumor markers 1 ; tuberculosis antibody (4+); FEV1/FVC 72.37%,
FEV1/pre 60.8%; Bronchial provocation test (-), FeNO 79ppb; ophthalmoscopy examination (-); parasite specific antibodies (-); CT (Fig.4): possible Tumor or Lymphoma Splenomegaly; bone marrow: smear (eosinophilia), biopsy (-), mnp-related genes (-), bcr/abl fusion gene (-); 7 lymph node groups EBUS-
TBNA biopsy (Fig.5): Granulomatous inflammation, BALF-GM (-), BALF-GENE-Xpert (-), eosinophilia in BALF; FDG-PET-CT: possible sarcoidosis Color Doppler ultrasound: enlargement of lymph nodes in region IV of neck with biopsy (Fig.6): granulo-
matous inflammation with no obvious necrosis, sarcoidosis, TB-DNA (-); ACE 1 . At last, the patient was diagnosed of pul-
monary sarcoidosis stage III under treatment of methylprednisolone 40mg bid for 3 days, with adjustment of treatment: pred-

nison 40mg qd and discharged. 1 month later, follow-up was done for the patient: EO% return to normal in peripheral blood, chest CT (Fig.7). This case prompted us that biopsy showed granulomatous inflammation, tuberculosis needs to be consid-
ered, but if anti-tuberculosis is ineffective, other diseases mani-
fested as granuloma such as sarcoidosis should be consid-
ered. Peripheral blood eosinophilia in sarcoidosis is about 3% [1][2], but commonly BALF with no greater than 1% eosino-

phils, thus, this case of sarcoidosis with eosinophilia in includ-
ing peripheral blood, sputum, bronchoalveolar lavage fluid (BALF) and bone marrow was exceptional. In addition, BALF-
GM has the possibility of false positive, EBUS-TBNA biopsy could be limited because of the small specimens.

**Abstract**

A case of sarcoidosis misdiagnosed as tuberculosis for two years with eosinophilia as the main manifestation

Haiyun Dai, Yajuan Chen

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In our hospital, a case of sarcoidosis with eosinophilia in includ-
O4-1

Heart Rate Variability in Sarcoidosis and Effect of Obstructive Sleep Apnea Syndrome in Autonomic Dysfunction Analysis

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Aims: The association between sarcoidosis and autonomic dysfunction is demonstrated but poorly known. Heart rate variability (HRV) studies can provide a simple, non-invasive analysis of sympathetic and vagal tone in non-sarcoid cases. Also, comorbidities such as obstructive sleep apnea syndrome (OSAS), may produce effects on autonomic system due to nocturnal apnea or hypopnea events and need to be evaluated. Despite OSAS is highly prevalent in sarcoidosis, HRV has never been assessed taking such condition into account.

Methods: Prospective analysis of 28 patients enrolled in Sarcoidosis Clinic of Policlinico Gemelli hospital. Continuous EKG recording over 24 hours has been performed in patients that have already been recently tested for OSAS with polysomnography. HRV was assessed using time and frequency domain methods.

Results: The analysis of the cohort shows a predominance of female gender (71.4%) and OSAS was diagnosed in 19 (67.9%) patients with moderate-to-severe OSAS. Scadding radiological criteria for sarcoidosis revealed 0/1 stage in 14 (50%) and 2/3/4 stage in 11 (39%). Steroid treatment was on course in 13 patients during medical evaluation. HRV analysis did show mean logarithm of low frequency/high-frequency ratio (Log LF/HF mean) to be correlated with OSAS diagnosis (p = -0.38, p = 0.0443) and an even more strong correlation can be noted in Log LF/HF ratio during daytime (p = -0.49, p = 0.0079). Scadding stage of 0/1 compared to 2/3/4 demonstrated a negative trend of Log LF/HF mean correlation (p = -0.35, p = 0.0646). Treatment with steroids seems to have an effect on autonomic dysfunction due to alterations in both frequency and time domains: LF mean (p = 0.48, p = 0.0089); r-MSSD ms (p = 0.46, p = 0.0118); SDNN (p = 0.43, p = 0.0197); pNN50% (p = 0.37, p = 0.0498). No correlation with CPAP was found.

Conclusions: HRV is an effective tool for autonomic evaluation. Sleep disorders must be considered when HRV is performed in patients affected by sarcoidosis due to the strong correlation between the frequency domain (Log LF/HF mean) and OSAS. Also, treatment with steroids should be taken into account and HRV analysis revealed a correlation in both frequency (LF mean) and time (r-MSSD, SDNN, pNN50%) domains.

O4-2

Gender: an Important Predictor for Cardiac Involvement in Pulmonary Sarcoidosis.

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Introduction: Early detection of cardiac sarcoidosis (CS) is important to prevent life-threatening complications. However, no screening algorithm for detecting CS is validated to date. Advanced imaging techniques (FDG PET and cardiac MRI) can detect CS, but are expensive, require radiation (PET scan) and are not available in all centers.

Purpose: The goal of this study is to identify clinical predictors for the presence of cardiac involvement in patients with extra-cardiac sarcoidosis.

Method: A retrospective, single center cohort study was performed of all the patients discussed in the multidisciplinary CS team (MDT) between January 2014 and January 2019. Patients with extra-cardiac sarcoidosis referred for screening for CS after initial assessment by the pulmonologist were included. Patients already known with CS or in whom (severe) cardiac symptoms were the first manifestation of sarcoidosis (e.g. AV conduction disorders or congestive heart failure) were excluded. All relevant clinical data were collected via chart review. The consensus diagnosis of the MDT classified as ‘probable’, ‘possible’ or ‘no’ CS was considered as gold standard. Only patients with a diagnosis of ‘probable CS’ and ‘no CS’ were included. Univariate and multivariate predictors were calculated.

Results: In total 792 patients were discussed between 2014 and 2019 in the MDT of whom 552 met the inclusion criteria. Currently, data collection was completed in 258 of 552 patients. The mean age is 51.6±11.9 years, 63.6% male. ‘Probable CS’ was diagnosed in 28.7% of patients. The main reasons for CS screening were palpitations (36.8%) or cardiac uptake on FDG PET (23.6%). Cardiac MRI and FDG PET were performed in respectively 96.7% and 96.2%. In multivariate analysis male gender (OR 2.4, p=0.03), complete right bundle branch block (RBBB, OR 4.0, p=0.03) and soluble IL2R level (OR 1.9, p=
0.05) proved to be independent predictors for the presence of CS.

**Conclusion:** Male gender, RBBB and soluble IL2R level are independent predictors for the presence of CS in patients with pulmonary sarcoidosis.

**O4-3**

**Prediction of Clinical Outcomes in Cardiac Sarcoidosis Based on the Japanese 2017 Diagnostic Criteria, the Heart Rhythm Society 2014 Diagnostic Criteria, and LGE CMR in Isolation**

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**Background**

Late gadolinium enhancement (LGE) on cardiovascular magnetic resonance imaging (CMR) has been shown to be more sensitive in the detection of cardiac sarcoidosis than the Japanese Ministry of Health 1993 criteria. Moreover, CMR was recently shown to be the most accurate screening test for cardiac sarcoidosis, using the Heart Rhythm Society (HRS) 2014 criteria as the reference standard.

**Hypothesis**

We hypothesized that LGE CMR in isolation performs as well as the latest Japanese (2017) and the HRS 2014 criteria for the prediction of clinical outcomes in cardiac sarcoidosis.

**Methods**

We studied consecutive patients at the University of Minnesota with biopsy-proven sarcoidosis who underwent CMR for suspected cardiac involvement. Two clinical outcomes were studied - all-cause death, and a composite of major adverse events attributable to cardiac sarcoidosis (CS-MACE): cardiac death, significant ventricular arrhythmia, heart transplantation, or left ventricular assist device implantation. Performance of the Japanese 2017 criteria, the HRS 2014 criteria, and LGE CMR were compared using receiver operating characteristics analyses. Areas under the curve (AUC) were compared using the z test.

**Results**

290 patients were included. At a median of 3.2 years, there were 42 all-cause deaths and 20 CS-MACE (5 cardiac deaths, 17 significant ventricular arrhythmias, 3 heart transplantations, 2 left ventricular assist device implantations). For all-cause death, the HRS criteria (AUC 0.70) performed better than the Japanese criteria (AUC 0.57) but were not significantly different from LGE (AUC 0.69 for LGE presence and 0.66 for LGE extent). For CS-MACE, the Japanese criteria (0.89) were not significantly different from the HRS criteria (0.85), LGE presence (0.80), and LGE extent (0.87). The Table shows the p values for the comparisons.

**Conclusions**

In patients with biopsy-proven sarcoidosis and suspected cardiac involvement, LGE CMR in isolation performs as well as the HRS criteria and is superior to the Japanese criteria for the prediction of all-cause death. LGE CMR is similar to the HRS and the Japanese criteria for the prediction of major adverse events related to cardiac sarcoidosis. LGE CMR in isolation may be used instead of the HRS and the Japanese criteria to guide management in biopsy-proven sarcoidosis patients with suspected cardiac involvement.

| **A. Performance with all-cause mortality as the reference standard:** |
|-----------------|-----------------|---------------|--------|--------|
|                | Sensitivity     | Specificity   | AUC    | PPV   | NPV   |
| Japanese 2017 criteria | 0.57            | 0.65          | 0.67   | 0.57   | 0.69   |
| HRS 2014 criteria    | 0.70            | 0.75          | 0.80   | 0.70   | 0.80   |
| LGE presence         | 0.63            | 0.68          | 0.68   | 0.63   | 0.68   |
| LGE extent           | 0.61            | 0.64          | 0.64   | 0.61   | 0.64   |

| **B. P values for comparisons with all-cause mortality as the reference standard:** |
|---------------------------------|-----------------|---------------|--------|
| Japanese 2017 criteria         | 0.05            | 0.02          | 0.22   |
| HRS 2014 criteria              | 0.02            | 0.04          | 0.22   |
| LGE presence                   | 0.02            | 0.04          | 0.22   |
| LGE extent                     | 0.05            | 0.06          | 0.22   |

| **C. Performance with CS-MACE as the reference standard:** |
|-----------------|-----------------|---------------|--------|--------|
|                | Sensitivity     | Specificity   | AUC    | PPV   | NPV   |
| Japanese 2017 criteria | 0.89            | 0.93          | 0.93   | 0.89   | 0.93   |
| HRS 2014 criteria    | 0.80            | 0.85          | 0.85   | 0.80   | 0.85   |
| LGE presence         | 0.74            | 0.84          | 0.84   | 0.74   | 0.84   |
| LGE extent           | 0.67            | 0.75          | 0.75   | 0.67   | 0.75   |

| **D. P values for comparisons with CS-MACE as the reference standard:** |
|---------------------------------|-----------------|---------------|--------|
| Japanese 2017 criteria         | 0.25            | 0.25          | 0.25   |
| HRS 2014 criteria              | 0.25            | 0.25          | 0.25   |
| LGE presence                   | 0.25            | 0.25          | 0.25   |
| LGE extent                     | 0.25            | 0.25          | 0.25   |
O4-4

Prognosis of Histological and Clinical Cardiac Sarcoidosis from Japanese Nationwide Questionnaire Survey

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Background: Diagnosis of cardiac sarcoidosis (CS) is sometimes difficult because of the low positivity of cardiac biopsy result. To resolve this problem, Japanese guideline has been proposed clinical diagnosis of CS without positive myocardial biopsy findings. This clinical CS diagnosis is Japanese original concept, however the prognosis of clinical CS is still unclear. The purpose of this study was to examine the prognosis of histological and clinical CS using nationwide questionnaire survey in Japan.

Methods and Results: Total 757 patients of 57 hospitals were collected in this study. Patients who had lacked follow-up data, unsatisfied CS criteria of Japanese Cardiac Society (JCS) in 2016, and underwent cardiac transplantation were excluded, and finally 420 patients (287 females, mean age 60 ± 20 years, and median follow-up periods 2208 ± 1703 days) were examined. According to JCS 2016 guideline, histological CS and clinical CS were 76 and 344, respectively. And the number of systemic CS and isolated CS were 386 (92%; pulmonary n=340, eye n=42, nerve/muscle n=5, and others n=39) and 34 (8%), respectively. Left ventricular ejection fraction (LVEF) was taken as the most important prognostic factor.

Conclusions: Both of histological CS and clinical CS according to JCS 2016 can be applied in the clinical setting and low LVEF at the CS diagnosis was the most important prognostic factor and early diagnosis is very important for CS management.

O5-1

SERUM GALECTIN-3 AND TGF-BETA LEVELS IN PATIENTS WITH SARCOIDOSIS

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Background: Sarcoidosis is a chronic granulomatous disease characterized by non-caseating granuloma formation. Galectin-3 is a multifunctional protein involved in many biological processes such as fibrosis, angiogenesis and immune activation. Objectives: To determine the serum galectin-3 and transforming growth factor-beta (TGF-beta) levels in patients with sarcoidosis and to determine a possible correlation with clinical findings.

Methods: Forty-four biopsy proven sarcoidosis patients followed at a single center and age and sex matched 41 healthy volunteers were included in the study. Demographic, clinical, laboratory and radiological data were recorded in all patients. Serum galectin-3 and TGF-beta levels were measured by ELISA method.

Results: Among 44 sarcoidosis patients 13 (29.5%) were male and 31 (70.5%) were female. Average patient age was 47.4 years, mean disease duration was 3.2 years. Twenty-one (47.7%) patients had erythema nodosum, three (6.8%) had uveitis, 40 (90.9%) had arthralgia, 23 (52.3%) had ankle arthritis, 15 (34.1%) had enthesitis. Laboratory evaluation showed increased serum ACE level in 24 (54.5%) patients, increased serum calcium level in 11 (25%) patients, increased serum D3 level in 5 (11.4%) patients, increased ESR and CRP levels in 22 (50%) and 23 (52.3%) patients, respectively. Serum galectin-3 level were similar in the sarcoidosis patients and the control group (p=0.977). No relationship were found between serum galectin-3 level and clinical and laboratory findings (p>0.05). Serum TGF-beta level were higher in patients with sarcoidosis compared with the control group (p=0.005). Serum TGF-beta level was associated only with enthesitis and arthralgia (p=0.006, p=0.02), while no correlation were detected with other disease features (p>0.05).

Conclusions: We found high level of serum TGF-beta, but normal level of galectin-3 in patients with sarcoidosis. These findings suggest that TGF-beta play an important role in the pathogenesis of sarcoidosis. Multicenter prospective studies are needed to illuminate the possible relationship between serum galectin-3 and sarcoidosis.
Assessment of Serum Levels of anti-granulocyte-macrophage colony-stimulating factor Antibodies in Patients with Sarcoidosis

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Aim: Granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies neutralize the GM-CSF activity and cause the disorder by impairing alveolar macrophage-mediated surfactant clearance. Autoimmune pulmonary alveolar proteinosis (APAP) is associated with high levels of GM-CSF autoantibody. Sarcoidosis is a systemic granulomatous disorder involved in macrophage/monocyte-derived cytokines such as GM-CSF. We aimed to clarify the incidence and clinical features of GM-CSF autoantibody-positive patients with sarcoidosis.

Methodology: The current study included 173 consecutive patients diagnosed with sarcoidosis in our hospital between May 2003 and October 2018. Of these, 92 patients whose serum samples were obtained were retrospectively reviewed. Serum GM-CSF autoantibody concentration was measured by ELISA. We determined the cut-off level of GM-CSF autoantibody for diagnosing APAP using receiver operative characteristics curve analysis of consecutive 81 patients with APAP. The incidence and clinical features of serum levels of GM-CSF antibody-positive patients with sarcoidosis were evaluated.

Results: In the 92 sarcoidosis patients, the male to female ratio was 1:1.3, and the median age at diagnosis was 58 years. The area under the curve and the cut-off level of GM-CSF autoantibody were 0.99 and 3.46 pg/ml, respectively. The number of patients who had higher level of GM-CSF autoantibody (≥3.46 pg/ml) were five (5.4%). Of these, two cases were complicated by APAP. In the 90 patients without the complication of APAP, GM-CSF autoantibody levels correlated well with SP-D (ρ = 0.29, p<0.01) and to a lesser extent with %DLco (ρ = 0.34, p<0.01).

Conclusion: The incidence of GM-CSF autoantibody-positive patients with sarcoidosis was 5.4%. In patients with sarcoidosis, GM-CSF autoantibody levels were linked to serum biomarker and pulmonary function. The results of this study support understanding of clinical significance of GM-CSF autoantibody in patients with sarcoidosis.

PET scan and the Correlation with Biomarkers of Sarcoidosis Activity

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Introduction

This study aimed to compare baseline to follow-up 18F-FDG PET/CT findings after treatment of active chronic sarcoidosis and to correlate changes on 18F-FDG PET/CT with changes of two biomarkers, serum chitotriosidase and serum ACE in order to confirm the more reliable one.

Methods

The sample included 90 patients, 59 (65.6%) female, with biopsy positive but chronic form of sarcoidosis and evidence of active inflammation on baseline 18F-FDG PET/CT. Mean age 48.5±11.4 yrs.

The patients were scanned in a 64-slice hybrid PET/CT scanner (Siemens Biograph, Siemens Medical Solutions USA Inc, Hoffman Estates, IL). They fasted for 8 hours before the iv injection of 5.5 MBq/kg of 18F-FDG. PET/CT acquisitions started 60 minutes after the tracer injection.

Before this procedure blood samples for serum chitotriosidase and ACE were taken. Patients with symptoms of disease activity despite the therapy were scheduled for the follow-up 18F-FDG PET/CT at least 6 months after the first 18F-FDG PET/CT. For quantitative analysis of 18F-FDG uptake in the lesion, we derived a SUVmax per focus.

Patients included into this study were not taking medications that interfere with the renin-angiotensin-aldosterone system i.e. ACE inhibitors or angiotensin II receptor antagonists. Chitotriosidase and ACE activity in serum were determined in the Biochemical Laboratory of the Clinical Center of Serbia in Belgrade.

Results

Descriptives: Table 1

Level of chitotriosidase from median 154.3 nmol/mL/h (65.8-224.1) decreased during follow up period significantly (p<0.001) Level of ACE was unchanged (before: 41.2±27.6 U/L, after: 38.4±21.3 U/L, p=0.353).

SUVmax statistically significantly decreased during follow up (before: 7.0 (4.9-9.5) after: 3.5 (0-6.0), p<0.001). There was positive significant correlation between chitotriosidase and SUVmax at first (Spearman rs=0.329, p=0.002) and second measurement (Spearman rs=0.499, p<0.001).

There was no association between SUVmax and ACE level at both measurements.

Conclusion

Analyses of our patients group showed serum chitotriosidase as a reliable biomarker of sarcoidosis activity in symptomatic patients. It correlates significantly with another imaging technique, PET scan, used to assess inflammatory activity in sarcoidosis by detecting and quantifying the degree of inflammatory and granulomatous reactions in the lungs and elsewhere in the body.
O5-4

HLA polymorphisms in Czech patients with sarcoidosis: investigation on the allele level by NGS

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HLA variation has been investigated in sarcoidosis since nineteenth of the 20th century, first on antigenic level using serology and later on the level of allelic groups using different DNA techniques. With expanding knowledge and methodology, recent standard of HLA typing is represented by next generation sequencing (NGS) enabling determination on allele level. Our laboratory has embarked on adoption of this current level into analysing sarcoidosis relationship with HLA [Ref1 in Table]. Here we report the first data from this ongoing research supported from [Ref2].

110 patients with sarcoidosis were diagnosed according to ATS/ERS/WASOG guidelines at the Brno University Hospital. The distribution of chest-X-ray (CXR) stages (I/II/III/IV) was: 36/53/19/2; 23 patients presented with Löfgren syndrome (LS), 33 patients had extrapulmonary sarcoidosis. The HLA was genotyped on seven loci (HLA-A,-B,-C,-DRB1,-DQA1,-DQB1,-DPA1) using Omixon Holotype kit and Twin software. The obtained frequencies of HLA alleles were compared with the distribution of HLA polymorphisms on the same loci using the same typing level, i.e. NGS in 168 healthy unrelated subjects from the Czech population [Ref3].

The HLA alleles most overrepresented in sarcoidosis patients in comparison with our control population were HLA-DRB1*07:01, -DRB1*03:01:01, -DRB1*13:02:01:02, and of the HLA-B locus the alleles -B*08:01:01:01 and -B*18:01:01. By contrast, the alleles HLA-DRB1*07:01:01:01 and HLA-DRB1*01:01:01 occurred more frequently in healthy control population and thus could be of a protective function. The presence of LS correlated with HLA-DRB1*03:01:01. The less favourable course of disease was characterised by presence of the allele HLA-DRB1*15:01:01. Apart from the HLA-DRB1 and HLA-B loci traditionally implicated in sarcoidosis, also loci HLA-C and HLA-DPB1 were characterised by increased polymorphism.

In conclusion, this preliminary analysis of our first patient group by NGS assessment of HLA in sarcoidosis, confirms and extends some previous observations. Next, we will proceed to analysis of haplotypes and its relationship with disease. We will also expand our cohort in order to be able to analyze associations with distinct disease phenotypes in greater detail. We believe that our approach contributes to the knowledge of sarcoidosis associations with HLA and that detailed analyses will bring new findings.

Reference No. Reference text

2 Genoto NLD-00211, IGA PU (JF 2019_009), RVO:56295532, RVO: 00098921

O5-5

Next generation proteomics identifies novel biomarkers from exosomes in Sarcoidosis.

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Background

Sarcoidosis is a complex disease where environmental and genetic factors are important for the disease outcome. It is reasonable to assume that distinct genetic mechanisms and related biological biomarkers will serve to further define sarcoidosis phenotypes and mechanisms. The fields of omics research are widely applied to understand polygenic and phenotypically diverse diseases, such as sarcoidosis. Despite strenuous effort to discover novel biomarkers, there are no specific biomarkers in sarcoidosis. Obstacles to discover biomarkers involve the complexity of samples such as serum as well as immaturity of proteomics. To overcome these hurdles, we focused on proteins of serum exosomes. Of importance, exosomes have key roles in intercellular communication, both locally and systemically, because they transfer their contents such as mRNA, miRNA and proteins between neighboring cells. Given that sarcoidosis is multisystem granulomatous disease, we sought to explore novel biomarkers from exosomes by proteomics.

Method

Serum exosomes were isolated by size exclusion chromatography on drip column. Seven sarcoidosis patients and five healthy controls were included as a discovery cohort. To obtain novel biomarkers for sarcoidosis, we performed a quantitative high throughput proteomics using LC-MS/MS. In addition, these protein signature from exosomes were analyzed by ingenuity pathway analysis (IPA). As a validation cohort, candidate 50 biomarkers were verified by selected reaction monitoring (SRM) in 50 patients and 10 healthy controls.

Results

Isolated exosomes from serum were confirmed by transmission electron microscope, immunoblot, and the Nanoparticle Track-
O6-1

Nintedanib plus Sildenafil Versus Nintedanib Alone in Patients with IPF And Severely Impaired Gas Exchange: Subgroup Analysis in Patients with Pulmonary Hypertension

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Introduction: In the INSTAGE trial in patients with IPF and DLCO ≤35% predicted, nintedanib plus sildenafil was not associated with a significant benefit on St George’s Respiratory Questionnaire (SGRQ) total score (primary endpoint) versus nintedanib alone. However, nintedanib plus sildenafil was associated with stabilisation in brain natriuretic peptide (BNP), a marker of ventricular stress, and reduced decline in FVC.

Aim: To assess whether the presence of pulmonary hypertension at baseline influenced the effects of nintedanib plus sildenafil versus nintedanib alone in the INSTAGE trial.

Methods: Changes from baseline in SGRQ total score and FVC at weeks 12 and 24 and in BNP at week 24; time to absolute decline in FVC ≥5% predicted or death; and time to relative decline in FVC ≥10% predicted or death were assessed in patients with and without pulmonary hypertension. The presence of pulmonary hypertension at baseline was defined based on whether pulmonary hypertension was reported by the investigator as a comorbidity and was not necessarily confirmed by right heart catheterisation.

Results: In total, 41 patients (nintedanib plus sildenafil 14; nintedanib 27) had pulmonary hypertension at baseline and 232 (nintedanib plus sildenafil 123; nintedanib 109) did not. In both subgroups, nintedanib plus sildenafil had a numerically greater effect on change in SGRQ total score at week 24 and all endpoints related to FVC versus nintedanib alone (Table). The benefit of nintedanib plus sildenafil versus nintedanib alone were numerically more pronounced in patients with pulmonary hypertension at baseline, but the treatment-by-subgroup interaction p-values were not significant. The effect of nintedanib plus sildenafil versus nintedanib alone on change in BNP at week 24 was significantly greater in patients with than without pulmonary hypertension at baseline.

Conclusions: In patients with IPF and severely impaired gas exchange, nintedanib plus sildenafil had a numerically greater effect on FVC decline than nintedanib alone both in patients with and without pulmonary hypertension at baseline. The benefit of nintedanib plus sildenafil versus nintedanib alone on reducing BNP was significantly greater in patients with than without pulmonary hypertension.

O6-2

Early treatment with antifibrotic drugs in idiopathic pulmonary fibrosis

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Background: Idiopathic pulmonary fibrosis (IPF) is a chronic, debilitating and progressive fibrotic lung disease. When should treatment with antifibrotic drugs be started for patients with IPF? Actually, “wait and watch” behavior is not rare and is an issue that is still debated.

Aim: The aim of this study was to clarify the efficacy of antifibrotic drugs including pirfenidone and nintedanib for patients with early stage IPF under real world clinical practice in Japan.

Patients and Methods: The medical records of consecutive IPF patients at the Department of Respiratory Medicine of Tsuboi Hospital and Toho University Omori Medical Center from April 2003 to May 2018, were retrospectively analyzed. We examined efficacy of antifibrotic drugs for patients with early stage IPF. In Japan, classification of disease severity of IPF (JRS criteria) comprised from following subjects: stage I (PaO2 ≥ 80 Torr at rest), stage II (80-PaO2 ≥ 70 Torr at rest), stage III (70-PaO2 ≥ 60 Torr at rest), and stage IV (PaO2<80 Torr at rest). If patients with stage II or III have desaturation during 6-minute walk test (6MWT), they are classified into stage III or IV, respectively.

Results: The disease severity of stage I (n=147) by JRS criteria consisted of the following GAP staging criteria: stage I, 88 cases; stage II, 49 cases; stage III, 10 cases. The overall survival was significantly poorer in patients with stage I by JRS criteria with desaturation on 6MWT, increased GAP staging (≥ stage II), or increased mMRC (≥ category II) (Group A) than in...
patients with stage I by JRS criteria without those factors (Group B), respectively. Importantly, the relative decline in FVC% predicted during 6 months was significantly lower in Group A than in Group B, who were treated with antifibrotic drugs, respectively (Group A vs. Group B: -5.7±8.2% vs -0.5±9.9%, P=0.04; -7.7±8.2% vs -2.0±9.5%, P=0.01; -7.4±7.8% vs -2.0±9.5%, P=0.04).

Conclusions: We should start to treat with antifibrotic drugs for elderly patients with IPF aged ≥75 years with an adverse event profile that is manageable for the majority of patients. It is important that adverse events be managed appropriately to help patients to remain on antifibrotic therapy.

**Abstract**

**Efficacy And Safety of Nintedanib in Elderly Patients with Idiopathic Pulmonary Fibrosis**

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**Introduction:** The incidence of idiopathic pulmonary fibrosis (IPF) increases sharply over the age of 65 years. Comorbidities and frailty in elderly patients with IPF are common and may pose a barrier to initiating antifibrotic therapy.

**Aim:** To investigate the efficacy and safety of nintedanib 150 mg bid in elderly patients with IPF.

**Methods:** Post-hoc analyses of efficacy and safety data in patients aged<75 versus ≥75 years at baseline were undertaken using pooled data from the two 52-week randomised placebo-controlled IMPULSIS trials of nintedanib.

**Results:** At baseline, 882 patients (nintedanib 521; placebo 361) were aged<75 years and 179 patients (nintedanib 117; placebo 62) were aged ≥75 years. Mean forced vital capacity (FVC) at baseline was 79.1% and 81.9% predicted in patients aged<75 years and ≥75 years, respectively. Nintedanib reduced the annual rate of decline in FVC versus placebo both in patients aged<75 years and ≥75 years, with no significant difference in the treatment effect between age subgroups (Figure). At baseline, mean St George’s Respiratory Questionnaire (SGRQ) total score at baseline was 38.90 and 42.68 in patients aged<75 years and ≥75 years, respectively. In patients aged<75 years, the changes from baseline in SGRQ total score at week 52 were 4.15 with nintedanib and 5.01 with placebo (difference −0.86 points [95% CI: −3.09, 1.36]) while in patients aged ≥75 years, the changes were 2.04 with nintedanib and 6.62 with placebo (difference −4.59 points [95% CI: −10.11, 0.93]); however, the treatment-by-subgroup interaction was not significant (p=0.94). The adverse event profile of nintedanib was similar in both age subgroups, but a greater proportion of patients aged ≥75 years discontinued treatment due to adverse events (32.5% with nintedanib, 14.5% with placebo) compared to patients aged<75 years (16.3% with nintedanib, 12.7% with placebo).

**Conclusions:** Nintedanib reduces the progression of IPF in patients aged ≥75 years with an adverse event profile that is manageable for the majority of patients. It is important that adverse events be managed appropriately to help patients to remain on antifibrotic therapy.

**Clinical evolution in patients with Idiopathic Pulmonary Fibrosis (IPF) in treatment with Nintedanib in six Spanish hospitals**

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**Objective:** Nintedanib is an antifibrotic drug that reduces the decline of pulmonary function in patients suffering idiopathic pulmonary fibrosis (IPF), trying to slow the progression. Our aim is to identify the baseline qualities of IPF patients receiving Nintedanib, as well as their clinical and lung function evolution, in six Spanish hospitals.

**Material and methods:** Multicenter descriptive study of all patients with IPF in treatment with Nintedanib. It has registered demographic data, comorbidities, other antifibrotic treatment, histopathologic, imaging test and lung function baseline qualities and during their evolution, also clinical evolution and side effects.

**Results:** It was studied 56 patients (85.7% males). The average age was 70 years (from 45 to 81 years-old).

Concerning the comorbidities, 17 patients presented smoking habits (30.3%), 12 (21.4%) had gastroesophageal reflux disease and 11 (19.6%) associated heart disease. The 25% (n=...
Pulmonary lung function is similar to Nintedanib trials. A patient died while they were with active treatment. To suspend treatment. During the follow-up, 14.2% (n=8) of the patients decreased in 26.8% of the patients and in 10.7% was decided side effects were present in the 48.1% (n=26) of the sample, in 32.1% of the patients. Side effects were present in the 48.1% (n=26) of the sample, the most common was diarrhea (29.6%). Nintedanib dose was decreased in 26.8% of the patients and in 10.7% was decided to suspend treatment. During the follow-up, 14.2% (n=8) of the patients died while they were with active treatment.

Conclusions:
- Pulmonary lung function is similar to Nintedanib trials. A higher percentage of patients (39.3%) present combined pulmonary fibrosis and emphysema (CPFE), compared to 23% in INPULSIS trials.
- Side effects were present in 48.1%, but only 10.7% of the patients had to suspend the treatment.
- In an important group of patients (32.1%) there was an improvement of the dyspnoea.

Real world experiences: Pirfenidone 200 mg is effective and well tolerated in patients with idiopathic pulmonary fibrosis

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Introduction: Phase 3 trials showed significant efficacy and acceptable safety profiles for pirfenidone in mild-to-moderate idiopathic pulmonary fibrosis (IPF). There is limited real-life data on pirfenidone 200 mg use.

Aim: In this study we aimed to investigate the effectiveness and safety profile of pirfenidone 200 mg/tablets for the treatment of IPF in a real-life setting.

Methods: Clinical records of patients diagnosed with mild-to-moderate IPF and receiving pirfenidone treatment (pirfenidon 200 mg, total 2400 mg/day) across four centers in Turkey between January 2017 and January 2019 were retrospectively collected. Pulmonary function measurements, including percentage of forced vital capacity (FVC%) and percentage of diffusion capacity (DLCO%) were analyzed in patients who received pirfenidone treatment for at least 6 months. Safety data were included for all follow-up visits.

Results: In the pooled cohort (n=82), 7 of the 82 patients (8.5%) discontinued pirfenidone because of side effects. Patients were mostly men (86.6%) and mean age was 66 years. Average baseline FVC% and DLCO% were 73.7% and 50.3%, respectively. Fifty-five patients (73.3%) had a high-resolution computed tomography scan with a definite usual interstitial pneumonia (UIP) pattern, and 15 patients (20%) had a surgically proven UIP pattern. After 6 months of therapy, 71 patients (94.6%) with IPF remained stable and 4 (5.4%) patients had progressed according to decline in FVC of at least 10% during the therapy course, cough decreased in 61.3% of patients. At least one side effect due to therapy was encountered in 28 (37.3%) IPF patients. Gastrointestinal side effects (20%), weight loss (14%), rash/itching (6.6%), photosensitivity (6.6%) were the most frequent side effects in our cohort. 9 patients (12%) needed dose adjustment. Conclusions: This study showed that pirfenidone 200 mg seems to be an effective treatment for IPF and also had tolerable and relatively acceptable side effects.

Sex specific distinctions in pulmonary fibrosis are mediated by estrogen inhibition of STAT3 signaling

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Abstract: Pulmonary fibrosis is characterized by striking distinctions in mortality according to sex, demonstrating a female predominance and a longer time to death, compared to males. Independent laboratories reported the crucial role of the Programmed Death 1 (PD-1) pathway in pulmonary fibrosis. PD-1+ IL-6+CD4+ T cells induce both profibrotic cytokines, IL-17A and TGF-β1, using distinct signaling pathways.

Methods: In order to more clearly understand the role of PD-1+ CD4+ T cells in the observed sex distinctions and mortality, we investigated IL-6 signaling in PD-1+ CD4+ T cells in humans and murine specimens. Using flow cytometry, ELISA and the Sirol assay to investigate distinctions in pulmonary fibrosis according to sex, we assessed for distinctions among humans with Idiopathic Pulmonary Fibrosis (IPF), Sarcoidosis and Scleroderma, as well as the bleomycin murine model of pulmonary fibrosis.

Results: Despite the male predominance, IPF males possessed higher serum estradiol levels and PD-1+CD4+ T cells, compared to age-matched male controls. We noted significantly higher percentages of PD-1+CD4+ T cells with higher IL-6 production in female sarcoidosis subjects, compared to...
males. While sarcoidosis pulmonary progression was noted in both sexes, males possessed greater percentages of CD4+IL-17A cells compared to females; whereas the female CD4+ T cells expressed significantly higher free TGF-β1. Administration of intranasal bleomycin to male and female mice possessing genetic ablation of the alpha subunit of the Estrogen Receptor (ESRα KO) revealed significant declines in IL-6 but, notably, significant increases in pSTAT3 expression. Surgical removal of ovaries confirmed the observations of significant declines in IL-6 expression from CD4+ T cells and significant increased pSTAT3 and CD4+IL-17A expression. Strikingly, exogenous replacement of estradiol and progesterone in these strains resulted in increased IL-6 expression and reduction of pSTAT3, further confirming the capacity of female hormones to inhibit pSTAT3 expression. PD-1 pathway blockade resulted in reduced collagen production in females compared to males.

Conclusion: This work identifies a crucial, previously unrecognized role of female hormones on pSTAT3 signaling pathways relevant to pulmonary fibrosis, supporting a personalized approach to therapeutic intervention according to sex.
P1-1

Serum propionic acid concentrations in sarcoidosis


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Backgrounds: *Cutibacterium* (formerly *Propionibacterium*) *acnes/granulosum* has long been suspected as one of the leading etiologies of sarcoidosis. Previous studies have shown that large amounts of cutibacterial DNA as well as live bacteria have been detected in sarcoidosis lesions. If eradication of this bacterium is contemplated for treatment of sarcoidosis, a marker reflecting the amount of growth in vivo is required. One of the characteristics of the strain is that it produces propionic acid, as inferred from the species name. In this study, we aimed to evaluate the concentration of propionic acid in the serum of sarcoidosis patients.

Methods: The study subjects were 36 patients with active sarcoidosis (SA, 13 men and 23 women) and 30 healthy volunteers (HV, 13 men and 17 women). Serum propionic acid concentrations were measured by LC-MS/MS. Serum concentrations of cathepsin S (CTSS), a novel serum marker for sarcoidosis that we found were measured by ELISA. The differences between SA and HV were evaluated by the Mann-Whitney U test. Correlation between propionic acid and CTSS was evaluated by the Spearman’s rank correlation coefficient.

Results: Serum concentrations of propionic acid in SA (median, 515 ng/ml; range, 230-1160) were significantly increased compared with those in HV (median, 415 ng/ml; range, 200-730) (p<0.05). Serum concentrations of propionic acid and CTSS were significantly correlated (Spearman’s p=0.41, p<0.0001).

Conclusions: Our results suggest an increased live cutibacterium number in patients with active sarcoidosis and interesting from the viewpoint of causality. Furthermore, this serum biomarker is potentially a marker of responsiveness for antibacterial treatment in sarcoidosis.

P1-2

The High sIL-2R Level Reflects not Cardiac but Thoracic Sarcoidosis Lesion

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Background and purpose: Fluorine-18-fluorodeoxyglucose positron emission computed tomography (18FDG-PET CT) is a sole but time-consuming and expensive examination assessing active inflammatory myocardium noninvasively in patients with cardiac sarcoidosis (CS). In various biomarkers, soluble interleukin-2 receptors (sIL-2R) is known as useful in diagnosis and estimation of severity in pulmonary sarcoidosis, however, it has not yet fully established that sIL-2R could reflect inflammatory degree of thoracic and/or myocardium and therapeutic response in patients with CS. Methods: From Aug 2016, we prospectively enrolled CS patients with FDG accumulated positive. The initial dose of prednisolone was 30mg/day, wherefrom the dose was tapered down 5mg/month until 6 months. After 6 months, follow-up 18FDG-PET was performed. 18FDG-PET were measured semi-quantitative functional parameter such as total lesion glycolysis (TLG) (TLG=SUVmean x metabolic volume) and estimated the relationship between TLG and sIL-2R at pre and post immunosuppression therapy. In therapeutic response, in order to estimate the indexical efficacy of sIL-2R for both cardiac and pulmonary sarcoidosis, cardiac TLG (C-TLG) and thoracic cavity TLG (T-TLG) were separately evaluated. Results: In CS patients, 31 patients had accumulated positive in both cardiac and thoracic cavity and performed serial 18FDG-PET before/after 6 months immunosuppression therapy. 18FDG-PET images were acquired for 7 days carbohydrate limitation and after at least 18-h fasting (mean free fatty acid was 0.96 mEq/L). The mean age and BNP level were 62.7 years old, 165.7 pg/mL at baseline. Because of immunosuppression therapy, both C-TLG and T-TLG value were significantly reduced from 256.1 to 55.1 (p<0.001), and 91.6 to 44.1 (p=0.009) (Figure 1), respectively. Even though sIL-2R level was also reduced from 534.4 to 333.6 (p<0.001), the sIL-2R level reflects not cardiac but thoracic sarcoidosis lesion at pre-immunosuppressive therapy (p=0.002 r²=0.283) (Figure 2). Conclusions: In patients with CS, because sIL-2R level reflect not cardiac lesion but thoracic lesion, sIL-2R is not suitable for therapeutic biomarker at pre-therapy.

P1-3

The use of 12 golden questions - questionnaire versus blood tests in screening for infection before administration of Infliximab in sarcoidosis patients

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Infliximab has been used for many years as an effective treatment in patients with chronic inflammatory diseases such as rheumatoid arthritis and Crohn’s disease. Also, in patients with refractory sarcoidosis treatment with infliximab can be very effective. Prior to administration of infliximab it is important to exclude active infections in light of the strong immunosuppressive
In the Netherlands, patients with Rheumatoid arthritis and Crohn’s disease are screened for active infection using the “12 golden questions”, which is a self-administered questionnaire addressing symptoms of infection (table 1). If all questions are answered with “yes” more tests will follow in order to diagnose a possible infection. However, in sarcoidosis patients screening for infection is performed by blood testing (C-reactive Protein in combination with leucocyte-count) 24-48 hours prior to administration of infliximab instead of the “12 golden questions”. Frequent blood drawing for patients with sarcoidosis treated with infliximab is an extra burden, especially if patients do not have any signs of infection. The aim of the current study is to investigate whether screening for infection using the “12 golden questions” is as safe as using blood testing prior to administration of infliximab in patients with sarcoidosis.

During a 3 month period all sarcoidosis patients currently treated with infliximab are asked to participate in the study. Prior to administration of infliximab both CRP and leucocyte-count will be measured in order to screen for infection (standard of care). Furthermore, patients are also asked to complete the 12 golden questions questionnaire.

The completed questionnaires are sealed and stored without showing the pulmonologist or nurse. After 3 months, the questionnaire results are compared with the blood test results.

During a 3 month period we expect approximately 160 administrations of infliximab and 20 events of cancellation of infliximab administration based on suspicion of infection in a cohort of 60 patients. After 3 months the results of the “12 golden questions” will be correlated with administration or cancellation of infliximab as well as CRP and leucocyte count.

This study is ending in July 2019. We expect to have the results in September 2019.

P1-4

**A case of systemic sarcoidosis**

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**Neurosarcoïdosis following the Long-term Remission of Malignant Lymphoma**

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**Background:** Sarcoïdosis after lymphoma has rarely been reported, although lymphoma after sarcoïdosis is well-known as sarcoïdosis-lymphoma syndrome. While the immune response against lymphoma cells has been speculated as one of the causes of sarcoïdosis, its etiology remains unclear. Herein, we report neurosarcoïdosis after long-term remission of lymphoma.

**Case presentation:** A 57-year-old woman was admitted to our hospital with complaints of subacute progression of paresthesia on her left fourth and fifth fingers and bilateral feet for 8 months as well as subsequent diplopia and right opthalmalgia. Uveitis was detected and treated using corticosteroid eye-drops. Because she had been treated for breast lymphoma 14 years ago, neurosarcoïdosis was suspected due to progressive elevation of serum soluble interleukin-2 receptors (sIL-2R). Neurological examinations revealed abductor impairment of the left eye, weakness and hyperalgesia on her left hand (predominantly in the ulnar nerve innervation), and symmetrical effects of anti-TNF therapy.
sensorimotor deficits of the distal lower extremities. Laboratory studies revealed elevated sIL-2R levels of 1300 U/mL; however, angiotensin-converting enzyme was within the upper normal limit. Analysis of the cerebrospinal fluid revealed slight elevation of protein levels with no other abnormalities. Nerve conduction studies revealed demyelination in the left ulnar and bilateral tibial nerves and axonal involvement in the bilateral tibial, peroneal, and sural nerves. Sural nerve biopsy indicated mild loss of myelinated fibers but the absence of cellular infiltration or granulomas. Positron emission tomography with computed tomography revealed fludeoxyglucose uptake in the mediastinal lymph nodes, left ulnar nerve, and bilateral gastrocnemius muscles. Surgical biopsy of the mediastinal lymph node revealed the presence of non-caseating granulomas. Based on the diagnosis of neurosarcoidosis, she was treated with oral prednisolone 40 mg/day, improving her neurological symptoms. Azathioprine (100 mg/day) was added and the dose of prednisolone was tapered off to 13 mg/day. One year after diagnosis, there was no recurrence of neurological symptoms.

Conclusions: We report neurosarcoidosis after long-term remission of lymphoma. Previous studies have reported the median interval to sarcoidosis is 18 months and is rarely over 10 years. However, sarcoidosis should be considered as a differential diagnosis even after long-term remission of lymphoma.

P1-6

Serum ACE level as a marker for active granulomatous inflammation in leprosy

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Leprosy is caused by a chronic infection of acid-fast bacilli (AFB) Mycobacterium leprae, which invade macrophages and Schwann cells. Diagnosis of leprosy is synthetically given by a combination of clinical and pathological features with skin smear test. Clinically, well-circumscribed infiltrative erythema or vitiligo with impaired sensation is characteristic. Pathologically, non-caseating epithelioid cell granulomas and foam cells are observed and AFB are demonstrated by modified Ziehl-Neelsen or Fite stain. Notably, ordinary Ziehl-Neelsen stain may show false negative. Skin smear test is easy and shows high sensitivity, but it will not be performed unless leprosy is suspected. The incidence of leprosy in Japan is limited in 1 to 2 patients in Okinawa as well as several foreign workers from Brazil and Southeast Asia for recent years. On the other hand, serum ACE level is reportedly elevated in 30 to 40% of leprosy patients because ACE is produced from epithelioid cells and multinucleated giant cells forming granulomas. With these facts in the background, we have recently experienced a case of leprosy in the mainland of Japan, which was initially diagnosed as sarcoidosis because of sarcoidal granuloma formation with negative Ziehl-Neelsen stain and high serum ACE level. We treated the case with prednisolone referring to the serum ACE level, in addition to the multidrug therapy. With a report of the disease course of this case, we propose that the serum ACE level reflecting sarcoidal granuloma formation may indicate active granulomatous inflammation causing skin and neurological manifestations in leprosy.

P2-1

Eye—The Most Common Site of Extra-pulmonary sarcoidosis?

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Eye is the common site of extra pulmonary sarcoidosis reported from 13-80% of sarcoidosis patients. In Sarcoidosis Registry of the Serbian Association of sarcoidosis out of 2286 biopsy positive sarcoidosis patients, the number of 775 patients have extra pulmonary sarcoidosis. Out of the group with extra pulmonary sarcoidosis 173 (22%) were patients with eye involvement. In this study we report ocular manifestations of sarcoidosis in our patients group.

Methods:
Patients with eye symptoms were examined at the uveitis department of the University Clinic for Eye Disease, Clinical Center of Serbia, Belgrade for ocular sarcoidosis. Ophthalmological examination included: dry-eye testing (Srirmer test, tear break-up time and corneal fluorescein staining); intraocular pressure measured, slit-lamp examination; and direct and indirect ophthalmoscopy. Best-corrected visual acuity (BCVA) was measured as well. The diagnosis of ocular sarcoidosis was established according to the International Workshop on Ocular Sarcoidosis criteria (IWOS).

Results:
Ocular symptoms were declared as: decreased vision (42pts (24%)) dryness and itching of the eye (137pts (79%)), red eye (20pts (12%)), painful eye (17pts (10%)), eye protrusion (3pts (2%)), lid ptosis (3pts (2%)), double vision or blurred vision (5pts (3%) ). At ophthalmological examination the most frequent finding was dry eye (57pts (33%) and uveitis (43pts (25%)) anterior uveitis (16%), intermediate uveitis (5%), posterior uveitis (24pts (57%)) and panuveitis (9pts (21%)).

Most frequent complications of sarcoid uveitis were: cataract (10 pts (23%)), glaucoma (9 (20%)), cystoid macular edema in 6 pts (14%), epiretinal membrane thickening 6pts (14%), maculopathy 4pts (10%)

Neuropathological findings in patients with neurosarcoidosis having both eye and neurological manifestations the most frequent finding were present in 17 pts (10%): double visions 4pts (23%) and lid ptosis 4pts (23%). The cranial nerve affection was also detected NIII palsy one patient and N VI palsy one patient. Facial nerve affection was noticed in 5 pts.

Conclusion
Eye was the most frequent site of extra pulmonary sarcoidosis in our patients’ group.
Subcutaneous sarcoidosis: a report of twelve cases from a single institute

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Subcutaneous form sarcoidosis has been considered to be relatively rare. From April 2010 through March 2019, we have experienced 12 cases of subcutaneous sarcoidosis in the Department of Dermatology of Fukushima Medical University. Patients consisted of 3 males and 9 females (M:F=1:3) with a mean age of 57.4 years old (age distribution: 28-74). The involved sites of the subcutaneous lesions were the lower extremity (n=8), upper extremity (4), and trunk (5). Other cutaneous lesions than the subcutaneous nodules included plaques (3), lupus pernio (1), angiolupoid lesion (1), and atypical lesions such as erythema nodosum-like (2) and ichthyosiform (1) lesions. Scar sarcoidosis was observed in 3 cases, in all of which the knee was involved. Lung sarcoidosis was observed in all of the patients, ophthalmological sarcoidosis was observed in 6 patients (50.0%), and cardiac sarcoidosis was observed in 1 patient (8.3%). Other organ involvement included peripheral nerve (1) and lymph node (1). Serum levels of angiotensin converting enzyme were increased in 7 patients, whereas normal levels in 5 patients. Serum soluble IL-2 receptor was measured in 7 patients, among whom elevated levels were observed in 5 patients. In conclusion, subcutaneous sarcoidosis may not be so rare as was previously estimated, in Japanese patients.

Transepidermal elimination in cutaneous sarcoidosis: report of six cases

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Transepidermal elimination is a unique phenomenon observed in several disorders including sarcoidosis. Recently, Ismail et al. reviewed reports on transepithelial elimination in sarcoidosis, and demonstrated that histological feature of transepidermal elimination of sarcoidal granuloma was observed in 18% (J Cutan Pathol 2014). Histological feature of transepidermal elimination of sarcoidal granuloma may not be a rare finding; however, reports are relatively few. To date, we experienced six cases of cutaneous sarcoidosis in which transepidermal elimination was histologically observed. Patients were consisted of 5 female and 1 male, and the age was distributed between 30 and 80 years old. The involved sites were face (n=3) and lower leg (n=3). Five cases were plaque type, and 1 case presented with psoriasiform sarcoidosis. Clinical features assumed scaly erythematous plaques in all cases. In the majority of cases, tranfollicular elimination of sarcoidal granulomas, which strongly expressed CD68, was observed. Subepidermal inflammatory cell infiltration was associated with transepidermal elimination, which may be mediated by the inflammatory process in cutaneous sarcoidal lesions. Lung sarcoidosis was observed in all cases, and ocular sarcoidosis was observed in 4 cases. Cardiac sarcoidosis was not observed in all cases. Among the six cases, one had systemic sclerosis, and granulomatous vasculitis was observed in 1 case.

Case report of sarcoidosis presenting with cutaneous lesions of both lichenoid and plaque type.

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Sarcoidosis is a multisystem disorder of unknown etiology, often resenting with cutaneous involvement. Cutaneous lesions are classified as maculopapular, plaque, scar, subcutaneous nodules or lupus pernio and so on. Lichenoid forms are rare type of cutaneous sarcoidosis. The lichenoid forms manifests with multiple aggregated papules on the extremities or trunk. We report a 70-year-old Japanese man with cutaneous lesions of both a few plaques on the right lower leg and multiple aggregated red-brown papules compatible with lichenoid forms on the extremities and trunk. The cutaneous lesions had been recalcitrant to topical corticosteroids without exact diagnosis in the other dermatological clinic before the first visit on our hospital. He had uveitis treated with eye drops and increased level of soluble IL-2 receptor (sIL-2R) examined in the ophthalmological clinic. Histological examinations of biopsy specimens from the plaque on the leg and papules on the abdomen of cutaneous lesions revealed noncaseating epithelioid granulomas with multinucleated giant cells, respectively. Laboratory investigations showed that the patient had increased level of sIL-2R (1020 U/ml). Levels of serum angiotensin-converting enzyme, calcium and lysozyme were within the normal range. Chest radiography and computed tomography showed no bilateral hilar lymphadenopathy and pulmonary infiltration. Electrocardiography found complete right bundle branch block and cardiac ultrasonography did no abnormal findings. Gallium scintigraphy showed no abnormal uptake. We diagnosed the patient as sarcoidosis with ocular and two different types of cutaneous lesion and treated for cutaneous lesion with minocycline and topical corticosteroid. Four months later, the cutaneous lesions remitted. Lichenoid forms of cutaneous sarcoidosis may be misdiagnosed as common disease such as eczema or prurigo. Intraocular papules should be biopsied, especially with the other types of cutaneous lesions, in consideration of sarcoidosis. The remission of the cutaneous sarcoidosis may demand a long time even if treated.
P2-5

Painful sarcoid myopathy in bilateral quadriceps femoris

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Background: Sarcoid myopathy is rare, and symptomatic patients are reported in only 1% cases. The use of magnetic resonance imaging (MRI) and positron-emission tomography combined with computed tomography (PET-CT) facilitates diagnosis. Herein is presented a case of painful focal sarcoid myopathy in bilateral quadriceps femoris revealed using PET-CT.

Case presentation: A 55-year-old Japanese woman was presented with pain in the bilateral thigh over a period of 2 years. Following administration of oral prednisolone 10 mg/day by the primary care physician, her pain partially resolved. However, there was swelling of the right thigh, and the pre-existing depression worsened; therefore, prednisolone was discontinued. The patient subsequently noticed myodesmia, and vitreous snowballs were detected upon ophthalmologic examination at our hospital. Laboratory examination revealed a mild inflammatory reaction, with elevated angiotensin-converting enzyme and soluble interleukin-2 receptor. Serum creatine kinase level was normal. CT revealed diffuse small granular lesions in the bilateral lungs and bilateral hilar lymphadenopathy. Bronchoscopic biopsy showed small non-caseating granulomas in the lymph nodes and the alveolar tissue. PET-CT evidenced fludeoxyglucose uptake in the diffuse lung lesions, bilateral hilar region, intra pulmonary nodes, bilateral quadriceps femoris muscles, and adjacent fascia and skin. Based on sarcoidosis diagnosis, oral prednisolone 20 mg/day was re-initiated. Although the lung lesions tended to reduce, coexisting diabetes mellitus was extremely exacerbated. Following a gradual decrease in oral prednisolone to 10 mg/day, bilateral myalgia in the patient’s quadriceps femoris relapsed, and she was referred to a rheumatologist. Mild muscle weakness and myalgia were observed in both quadriceps femoris. MRI revealed hypo-intensity and atrophy in the right rectus femoris and bilateral vastus lateralis on T2-weighted image, consistent with sarcoid myopathy. After oral prednisolone increased to 30 mg/day, myalgia and skin changes gradually improved. Azathioprine 50 mg/day was administered and prednisolone was decreased to 8 mg/day; the patient is currently relapse-free for over 18 months.

Conclusion: A case of painful quadriceps myopathy caused by sarcoidosis is described. PET-CT is useful in detecting sarcoid myopathy. Thus, sarcoid myopathy should be considered during the differential diagnosis of painful focal myopathy.

P2-6

Renal sarcoidosis with concomitant perihilar variant of focal segmental glomerulosclerosis

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Renal involvement of sarcoidosis is rare compared with the involvement of other organs. There are some articles that reported various kinds of glomerulonephritis related to sarcoidosis, but the relationship between sarcoidosis and glomerular lesions has not been well understood. We experienced the case of the granulomatous tubulointerstitial nephritis with focal segmental glomerulosclerosis related to sarcoidosis. He was 18-year-old male and had suffered from exertional cough and dyspnea. He also had subnephrotic proteinuria, 3.0g/24hour and subsequent renal dysfunction. He received the oral prednisolone therapy and massive proteinuria disappeared and eGFR recovered from 39.4ml/min to 60.6ml/min. Recurrence didn’t occur to him. The renal pathological finding was characteristic in distinctive granulomatous features. A majority of the granulomas involved arteries and some of these arteries were reduplicated in intimal walls. It suggested the elevation of intravascular pressure and then we thought tubulointerstitial granulomas caused hemodynamic change in renal microvasculature and that it was related with pathogenesis of focal segmental glomerulosclerosis. We discussed the relation between renal sarcoidosis and coincident glomerular lesions.

P2-7

Enlargement of lymph node during the sarcoidosis-case report

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Sarcoidosis as the granulomatous disorde with chronic course, can affect any organ in human body. Enlargement of Lymph nodes are usually during the sarcoidosis. We report the three cases of enlargement lymph nodes due to sarcoidosis. Radiographic and laboratory findings of others organs, obtained normal results. All patients were women of 37 years, 41 years and 52 years. Involvement of lymph nodes were in mediastini, retroperitoneale and regio collii in two patients. In one patient of 52 years, enlargement of lymph node in regio collii were the only finding. In all patients, non other disorders were obtained. Duration of medical treatment along with activity of granulomatous disorders, clinical symptoms and radiographic findings, were 19.4 months. Controls were performed, periodically with no pathological findings, after 2.7 years. Importance of pH verification during the enlargement is huge.

P3-1

MALIGNANCY IN PATIENTS WITH SARCOIDOSIS: A RETROSPECTIVE COHORT STUDY FROM TURKEY

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Objectives: The relationship between sarcoidosis and malig-
The relationship between malignant tumor and sarcoidosis

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[Background] Recently, it has been reported that the use of immune check-point inhibitor initiates the onset of sarcoidosis. However, it has not been established yet that the association between sarcoidosis and malignant tumor. Furthermore, there are few reports regarding the influence of tumor immunity on sarcoidosis.

[Method] In this study, we recruited cases of sarcoidosis diagnosed between 2007 and 2017. We divided cases with or without malignant tumor and analyzed clinical parameters of sarcoidosis.

[Results] Cases of sarcoidosis with a malignant tumor in the past were 34, while cases without malignant tumor were 278. The median period to the onset of sarcoidosis since the past malignant tumor was 2 years. Cases with malignant tumor in the past were older than cases without malignant tumor in the past. Furthermore, oral corticosteroid therapy has been administered more frequently in cases without malignant tumor than cases with malignant tumor in the past.

[Conclusion] There may be an interaction between past history of malignant tumor and the development of sarcoidosis.

The clinical features of malignant diseases in Japanese patients with sarcoidosis

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[Background] It is suggested that sarcoidosis is associated with a significantly increased risk for cancer in affected organs, although results has been still controversial for decades. The aims of this study were to investigate the incidence of malignant diseases associated with sarcoidosis and to evaluate the clinical features of those patients in Japan. [Methods] We conducted the medical record review of 281 sarcoidosis patients in Tohoku University Hospital between January 1, 1981 and May 31, 2017. The clinical records and pathology reports for each sarcoidosis patient with malignancy were screened. We reviewed for clinical information regarding malignancies including origin of malignancies, the onset before or after malignancy and treatment. [Results] A total of 52 (18.5%) patients with malignant diseases were identified in our 281 patients with sarcoidosis. These patients were older, more likely to be female and showed higher levels of serum ACE, compared with the rest of 229 (81.5%) sarcoidosis patients without malignancy. Among 52 patients with malignancy, we identified 62 malignant diseases (17 cases in male and 45 cases in female). The most common malignant disease was breast cancer (14 cases, 22.6%), the second was stomach cancer (8 cases, 12.9%) and the third was cervix uteri cancer (5 cases, 8.1%). Concerning the chronological connection between malignancy and sarcoidosis, 28 cases (45.2%) were diagnosed as having malignant diseases prior to the diagnosis of sarcoidosis, and 34 cases (54.8%) were diagnosed as having sarcoidosis prior to the diagnosis of malignancy. We next focused on the clinical features of patients with both sarcoidosis and breast cancer. Among 14 cases, 8 (57.1%) cases were diagnosed as having breast cancer prior to the diagnosis of sarcoidosis. Notably, all these 8 (100%) cases had undergone surgical resection of the cancer. 4 (50.0%) cases had undergone additional radiotherapy and 4 (50.0%) cases had additional hormone therapy. [Conclusion] There was an occurrence of malignancy among patients with sarcoidosis in Japan. Breast cancer was the most common malignant disease. The surgical resection of breast cancer may be associated with a significantly increased risk for sarcoidosis.
P3-4
Fatigue Assessment Scale Score in Japanese Sarcoidosis Patients
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RATIONAL: Although fatigue is one of the core symptoms of sarcoidosis patients, this symptom has not been enough studied in Japanese sarcoidosis patients.

SETTING: An outpatient clinic in a 358-bed community hospital in Japan

METHODS: Twenty-six Japanese sarcoidosis patients completed the Fatigue Assessment Scale (FAS), Small Fiber Neuropathy Screening List (SFNSL) and Short Form-36 (SF-36) (health-related QOL questionnaire) Japanese version. Simultaneously blood tests including ACE and sIL-2R were done. Clinical parameters were derived from the patients’ medical files.

RESULTS: Study population consisted of 11 men and 15 women with the mean age of 61±15 years. Median duration of disease was 6.9 years (range: 1 to 31 years). Nine patients received systemic corticosteroid (prednisolone 1-25mg/day) and 3 patients received inhalation steroid therapy. Radiographic stages of 0, I, II, III were 9, 5, 6, 6 patients, respectively. Extra-thoracic manifestations included eye (n=13), skin (n=6), nervous system (n=2), and heart, liver, muscle, bone, testes, kidney (n=1, respectively). Mean ACE and sIL-2R value was 17.2 ± 7.7 U/L and 587.5 ± 288.4 U/mL respectively. Median FAS score was 21 (range: 10-39). According to the cutoff point of 22, 12 (46.2%) of the patients were suffering from fatigue. Median SFNSL score was 7.5 (range: 0-54) and according to the cutoff point of 11, 11 (42.3%) of the patients were suffering from small fiber neuropathy. There was a significant relationship between the FAS score and SFNSL score (r=0.718, P<0.0001). With regard to the relationship between FAS score and SF-36, FAS score was significantly related with physical component summary score (r=0.391, P=0.048) and mental component summary score (r=0.526, P=0.006) of SF-36. There was no significant relationship between FAS score and ACE nor sIL-2R value. SFNSL score was significantly related with mental component summary score of SF-36 (r=0.545, P=0.004).

CONCLUSION
Nearly the half of our Japanese sarcoidosis patients were suffering from fatigue. Fatigue degree assessed by FAS was significantly related with health-related QOL, especially for mental domain QOL.

P3-5
General Fatigue in Sarcoidosis in a Municipal General Hospital in Japan
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Background: General fatigue is underestimated symptom in patients of sarcoidosis. Frequency and characteristics of the patients with general fatigue is unknown.

Objective: To clarify the frequency and characteristics of the patients with general fatigue of patients with sarcoidosis, and the difference of frequency of general fatigue in 2019 and 2014.

Method: We analyzed the Fatigue Assessment Scale (FAS) of sarcoidosis patients attending our hospital in 2014 and 2019. Patients with more than 21 FAS score was defined as to have general fatigue. We analyzed correlation to clinical parameters and compared the FAS score between two years.

Result: FAS score was calculated in 51 patients (14 male) in 2014 and 36 patients (14 male) in 2019 and median age were 66 (34-87) and 67 (29-85), respectively. FAS score were 26 (10-47) in 2014 and 24 (10-36) in 2019, respectively. In 2019, FAS score of mental fatigue was higher than those of physical fatigue (p=0.02). Thirteen patients had been given systemic corticosteroids. Chief complaints were dyspnea on effort (7), misty vision (4), cough (4), and twelve patients had no complaints. Involved organs included lymph node (28), lung (26), eye (18), heart (4) and others. Median duration of disease was 3 years (0.1-31 years). In 17 asymptomatic patients, 10 (59%) patients had general fatigue, and the difference of FAS scores between symptomatic and asymptomatic patients was not significant. There was no correlation between FAS score and age, gender, antiotiensin converting enzyme, number of involved organs and duration of disease. There was no difference of FAS score between 2014 and 2019.

Conclusion: FAS should be examined in sarcoidosis patients to find general fatigue, because general fatigue is difficult to find in usual interview. In our patients of sarcoidosis, physical fatigue was predominant.

P3-6
Retrospective analysis of sarcoidosis characteristics and psychological impact between civilian and military populations
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Introduction. Some badly explained symptoms can arise in sarcoidosis. Considering impact of these symptoms on the capacity of our servicemen, we have studied them in military. The aim was to compare sarcoidosis between military and civilian patients.

Methods. Retrospective monocentric study comparing sarcoidosis characteristics, scores of questionnaires validated in sarcoidosis (FAS, HAD), between 3 populations of consecutive patients: military, civilian with histologically proved sarcoidosis and healthy military population.

Results. 126 patients (military and civilian) and 55 healthy military members were included. Military patients were younger. No significantly difference was highlighted concerning sarcoidosis between 2 populations. FEV1 and FVC were significantly better in military population. 23 civilian and 17 military patients answered questionnaires. We compared them to 55 healthy military members. If no difference was detected concerning fatigue, two military populations (healthy and sarcoidosis) were significantly less anxious, less depressive and had better quality of life than civilian population. No significant dif-
ference of these parameters was showed between both military populations.

**Conclusion.** Without difference of sarcoidosis characteristics, the best respiratory parameter of military population could be explained by more physical training. Scores of anxiety, depression and quality of life scales were significantly more altered in the civilian population, not seem to be attributable with sarcoidosis; we can make hypothesis of possible protective effect of social link in military population, in spite of indisputable factors of stress.

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**P4-1**

**Withdraw**

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**P4-2**

**Baricitinib for therapy refractory sarcoidosis**

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A 54-year old male was diagnosed with pulmonary sarcoidosis in 1998 based on compatible clinical features and radiology, the histologic demonstration of noncaseating granulomas in a transbronchial biopsy, and the exclusion of alternative causes of granulomatous diseases, including tuberculosis. He was intermittently treated with prednisone for several years with good clinical response. After cessation of therapy, he was lost to follow up until 2015. His medical history further revealed type 2 diabetes mellitus. He was seen again in 2015 because of a productive cough and worsening shortness of breath. He also complained of arthralgia and fatigue. Forced vital capacity (FVC) was 3.18L (75% predicted value) and diffusion capacity for carbon monoxide, corrected for hemoglobin (DLCOc), 29% predicted value. Soluble interleukin-2 receptor (sIL2R) was 35051 picograms per milliliter (pg/ml, reference value<2500 pg/ml). Chest computed tomography (CT) showed symmetric and calcified mediastinal and hilar lymphadenopathy, nodular abnormalities with a peribronchovascular distribution and signs of fibrosis.

A diagnosis of chronic pulmonary sarcoidosis was made. Pulmonary function declined and Intense uptake persist on 18F-FDG-PET during treatment with prednisone, methotrexate, therapy targeting tumor necrosis factor alpha (TNFø) and methylprednisolone 1000mg daily for three consecutive days. The patient was subsequently treated with baricitinib 4mg once daily. After 3 months, there was an absolute increase of 7% in FVC predicted and 18F-FDG PET showed marked improvement with the maximum standardized uptake value decreasing from 15.6 to 13.1 in the left lung and 17.3 to 12.3 in the right lung (Image 1). There was a 45% decline in serum sIL2R. The Janus kinase (JAK) family consists of four members, which mediate signaling of various cytokines and growth factors. Many cytokines involved in the aberrant immune response and T-cell activation observed in chronic sarcoidosis signal via the JAK pathway. This is the first case describing a profound pulmonary response induced by JAK 1/2 inhibition with baricitinib in a patient with therapy refractory sarcoidosis.

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**P4-3**

**Acute Exacerbation of Pulmonary Sarcoidosis Preceded by Small Fiber Neuropathy of the Torso Presenting as Herpes Zoster Pain: A Case Report**

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Introduction: Pain of unexplainable origin is frequently observed in patients with sarcoidosis, much of which can be diagnosed as pain due to small fiber neuropathy. Diagnosis of small fiber neuropathy is usually made on the basis of clinical features, and can be difficult to treat. Here we describe a case of acute exacerbation of pulmonary sarcoidosis of which the initial symptom was severe pain of the torso mimicking herpes zoster pain.

Case: A 63-year-old woman was referred to our hospital for the evaluation of bilateral hilar lymphadenopathy and hypercalcemia, which were incidentally found when she presented to the pain clinic for a 4-week history of progressively worsening pain of her right torso. The pain was sharp, stabbing, and demonstrated allodynia. She had a past history of herpes zoster of the right torso, and was therefore suspected of recurrence of postherpetic neuralgia, however, the pain did not resolve with pregabalin or paravertebral block. Upon admission to our hospital, the torso pain was accompanied by similar symptoms on her left torso, girdle-like tightening pain and numbness of the upper abdomen, tingling of the left second and third digits, and hypotension. Neurological tests were negative. Oxygenation worsened, and a CT scan revealed progressive opacities in both lungs. On laboratory studies, serum lysozyme and interleukin-2 receptor levels were elevated. Gallium scintigraphy showed uptake in both lungs. Sarcoidosis was confirmed on skin biopsy. The patient was diagnosed with acute exacerbation of pulmonary sarcoidosis, and pain due to small fiber neuropathy. We started her on oral prednisolone 60 mg per day and pulmonary symptoms rapidly resolved. Pain was controlled with opioid intake and topical ketamine, however, after starting prednisolone the pain and autonomic symptoms gradually resolved. Side effects included diabetes mellitus and muscular weakness. After 12 weeks she was discharged home at prednisolone 17.5 mg per day, which continued to be tapered.

Conclusion: Patients presenting with severe pain appearing as a common disease such as herpes zoster may have an underlying condition such as sarcoidosis-induced small fiber neuro-
pathy.

P4-4

A case of pulmonary sarcoidosis: 20-year follow-up without systemic corticosteroid therapy

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Here, we report about a 62-year-old woman who developed uveitis at 15 years of age and was diagnosed as having sarcoidosis. Bilateral lymph node swelling and bronchiectasis developed at 23 years of age. From 30 to 39 years of age, the patient was treated with systemic corticosteroids; however, she discontinued the treatment on her own will. At 40 years of age, chest computed tomography (CT) findings revealed perilymphatic nodules involving the axillbronchovascular interstitium and interlobular septa, focal and patchy consolidation, and cavities. At 44 years of age, perilymphatic nodules decreased, and fibrotic changes progressed. At 47 years of age, the patient was admitted to our hospital because of pneumonitis. At 49 years of age, an intracavitary fungus ball of Aspergillus was found. At 58 years of age, she was admitted to our hospital because of hemoptysis. Moreover, at 62 years of age, she was admitted to our hospital because of pneumonitis. Lung CT findings of sarcoidosis included perilymphatic nodules, focal ground grass opacity, mosaic perfusion, and air trapping on expiratory images. The lung lesions progressed to fibrotic changes, including tronch bronchiectasis and honeycombiing. This case demonstrates the various presentations of sarcoidosis in its natural course.

P4-5

A Deceptive Diagnosis of Sarcoidosis: Diffuse Large B-cell Lymphoma Mimicking Besnier-Boeck-Schaumann Disease

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A 54-year-old never smoking woman presented with a dry cough in November 2017. CT thorax showed subpleural and perilymphatic nodules and her DLCO was slightly decreased (75%). Initial bronchoalveolar lavage fluid (BALF) revealed 81% lymphocytes. sIL2-R was 24,574 U/ml (normal<2500). With sarcoidosis as working diagnosis she started with prednisolone. Initial dose was 20mg once daily, but this was reduced because of muscle complaints and tremor and stopped after 3 months. She was referred to a centre for a second opinion, where a second BALF showed 44% lymphocytes. As the cough had disappeared and DLCO appeared improved (87%), follow-up without treatment was sugested. 11 Months after initial presentation she became dyspneic and DLCO decreased again (66%). CT thorax showed interstitial progression and sIL2-R was 21,184 U/ml. A third bronchoscopy with bronchial biopsies was done, especially because of the unusually high percentage of lymphocytes in the first BALF. Immunologic analysis revealed only 12% T lymphocytes but two populations of mono-clonal B cells (61% B lymphocytes in total and κ/λ<0.1 in both populations). B-cell NHL was supported by biopsies (figure 1a-b). PET scan showed diffuse low uptake in the interstitial pulmonary abnormalities and in one lymph node along the trachea (right N4). Bone marrow analysis showed two populations of monoclonal B cells in 0.5% of the leukocytes. R-CHOP was started in January 2019 and clinically her dyspnea improved dramatically within 1 cycle of R-CHOP. Both CT (figure 1c-d) and DLCO (78%) improved significantly after 3 cycles.

Primary Lymphoma of Lung (PLL) is a rare presentation of Diffuse Large B-cell Lymphoma (DLBCL) but has been described earlier (Neri N et al, Hematology 2011;16:110-112). All described patients (n=82) presented with cough or chest pain. 94% of the cases showed complete response after 6 cycles of CHOP.

This case illustrates that immunologic differentiation between T and B cells in BALF is crucial and that the diagnosis sarcoidosis may be treacherous if not all other diagnoses have been excluded sufficiently. PLL-DLBCL should be included in the differential diagnosis when a patient diagnosed with sarcoidosis shows unexpected signs, such as extremely high lymphocyte counts in BALF.

P4-6

Long-term Results of Methotrexate Monotherapy in Patients with Pulmonary Sarcoidosis

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Methotrexate is the drug, which choices, for treating patients with pulmonary sarcoidosis with contraindications to glucocorticosteroids, and also if the serious adverse events on the background of GCS therapy develops. At the same time, studies on the relapses frequency after the use of methotrexate monotherapy, in patients with pulmonary sarcoidosis have not been conducted previously.

**Aim** - to study the frequency of recurrence of pulmonary sarcoidosis after methotrexate monotherapy.

**Methodology.** Fifteen patients with stage II lung sarcoidosis with respiratory symptoms and/or impaired respiratory function were examined. There were 6 men, women - 9, age - from 31 to 64 years. All patients underwent general clinical examination methods, computed tomography of the chest cavity, spirometry. All patients on the first visit were prescribed methotrexate at a dose of 10 mg/week due to the presence of contraindications to GCS therapy. Duration of treatment was at least one year. Long-term results were evaluated after the end of the treatment period (6, 12 and 24 months).

**Results.** One relapse of the disease was registered at the third dispensary visit (after 24 months): two-sided small-basement dissemination appeared during the CT-examination. At the same time, the patient had no clinical symptoms, impaired lung ventilation function. Thus, the recurrence rate after methotrexate monotherapy was 6.7%.

**Conclusion.** Methotrexate monotherapy is not a risk factor for recurrence of sarcoidosis. At the same time, these results are preliminary and require further investigation.

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**Epigenetic alterations of peripheral Th1 and Th17-lineage cells in pulmonary sarcoidosis**

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**Rationale:** Pulmonary sarcoidosis is characterized by dominant local interferon gamma (IFNγ) expression, whereby it is suggested that IFNγ-producing CD4+ T helper (Th)-cells in BALF positively correlate with a worse disease prognosis. Interestingly, based on chemokine receptor expression, not Th1-cells but IFNγ-producing Th17-cells (Th17.1-cells) are distinctively increased in pulmonary sarcoidosis and correlate with risk of chronic disease. Gene-environment interactions, mediated by epigenetic modifications such as DNA methylation, are proposed to shape clinical heterogeneity. We hypothesize that epigenetic profiling of Th1-cells and Th17-lineage cells in peripheral blood (PB) of sarcoidosis patients may reveal a gene-based signature. Such as signature could yield biomarkers to guide personalized medicine in patients.

**Objective:** To identify differences in epigenetic profiles of isolated PB-derived CD4+ T-cell subsets between sarcoidosis patients and matched healthy controls (HCs).

**Methods:** Using illumina DNA methylation arrays, CpG methylation patterns are determined in genomic DNA of purified Th1-cells (CCR6-CCR4-CXCR3+) and Th17-lineage cells (CCR6+) from 6 sarcoidosis and 6 HC blood samples.

**Main Results:** We identified 2003 and 700 significant epigenetic differences in sarcoidosis Th1-cells and Th17-lineage cells, respectively, compared to HC. Sarcoidosis-specific methylation changes in Th1-cells occurred near genes in pathways involved in cell fate commitment, differentiation, and activation. In sarcoidosis Th17-lineage cells, DNA hypomethylation was observed near genes involved in metabolic processes, such as glycolysis. Comparison of HC Th1-cells and HC Th17-lineage cells showed 341 significant differences, whereas no differences could be detected between sarcoidosis Th1-cells and sarcoidosis Th17-lineage cells.

**Conclusions:** Our study shows that Th1 and Th17-lineage cells in peripheral blood of sarcoidosis patients harbor a distinct DNA methylation pattern as compared to HC. Sarcoidosis Th1-cells show hypomethylated genes involved in cell activation and differentiation, compared to HC Th1-cells. Strikingly, comparing Th1 to Th17-lineage cells in sarcoidosis revealed identical DNA methylation patterns. This could suggest elevated Th1-cell plasticity in sarcoidosis, in line with enhanced conversion of Th1-cells into pathogenic Th17.1-cells. Further insights are needed as this sarcoidosis-specific epigenetic signature in peripheral T cells might identify biomarkers that could aid personalized medicine.

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**Electrocardiographic and Echocardiographic findings in Iranian patients with pulmonary Sarcoidosis**

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**Introduction:** Sarcoidosis is a multisystemic granulomatous disease. Cardiac involvement as one of the most important asymptomatic extra pulmonary manifestations is a common cause of sudden death in sarcoidosis patients. Conduction abnormalities are the most common cardiac findings. The present study assessed the complications in patients with sarcoidosis using their electrocardiographic and echocardiographic reports.

**Materials and Methods:** Current study was performed on 40 patients with proven pul-
Pulmonary arterial hypertension in a patient with sarcoidosis

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Introduction: In sarcoidosis, pulmonary hypertension (PH) might develop as a result of parenchymal lung disease, compression of pulmonary vessels, direct myocardial involvement or granulomatous arteriopathy. Sarcoidosis is classified into group 5 of PH classification. Here we present a rare patient with pulmonary arterial hypertension (PAH).

Case: An 57 years old female presented with dyspnea, cough and sputum. She had diagnosis of asthma and hypertension for five years and progression of complaints last 6 months. She had no smoking history. Physical examination revealed: clubbing, 2-3 cm in size erythematous lesion on the back, bilateral inspiratory fine crackles (+), loud S2 in pulmonary foci. Laboratory findings showed high CRP-18 mg/dL. There was p pulmonale and right heart hypertrophy in ECG. Chest XR showed increase in cardiothoracic index and hilary enlargement. Thoracic CT revealed lymph node, reticular densities and pulmonary artery enlargement. There was no thrombus in pulmonary arteries. Pulmonary hypertension was detected (PASP systolic: 95 mmHg) by transthoracic echocardiography (TTE). Spirometry revealed severe restrictive pattern (FVC: 1.51L, 40%) and DLCO was 65%. Patient was hypoxemic (PaO2: 50 mmHg) in room air. Thyroid function tests, serologic tests were negative (ANA, RF, ANCA, anti-scl 70, anti-ds DNA, anti HIV). Quantiferon was negative. ACE was 92 U/L. Skin and minor salivary gland biopsy showed granulomatous inflammation without significant necrosis foci. Sarcoidosis was diagnosed. Patient could perform 6 minute walk test with oxygen and walking distance was 168m. Functional class was III and Pro-BNP was 669 ng/ml. Methylprednisolone po 32mg/day and long term oxygen (2L/min) were given. During follow up PaO2 increased (PaO2: 64 mmHg), FVC increased (1.75L, 77%) but DLCO decreased (49%). Right heart catheterization performed and mean PAP was 47mmHg, PCWP was 12 mmHg. CO was 3.5 l/min, PVR was 8WU. Bosentan 2x62.5 mg was added to treatment. PAH specific treatment was stopped after 10 months due to clinical progression and patient died after 12 months.

Conclusion: Significant lung parenchymal disease is a highly prevalent condition in patients with sarcoidosis-associated PH. However, other factors which may benefit from PAH specific treatment should be clarified. However, it is difficult to consider PAH specific treatment in these cases.

Key words: Sarcoidosis; Extrapulmonary impact; Cardiac involvement;

P5-3

Long-term outcome of Japanese sarcoidosis patients with pulmonary hypertension

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Backgrounds: Pulmonary hypertension (PH) is an increasingly recognized complication of sarcoidosis. Sarcoidosis-associated PH has been studied almost exclusively for advanced cases, and the long-term clinical significance of PH has not been investigated in a clinic-based cohort.

Methods: Consecutive 242 patients with pathologically diagnosed sarcoidosis were prospectively registered at Kyoto Central Clinic between June 1, 2004 to July 30, 2005. All patients underwent echocardiography to evaluate cardiac function and PH. PH was defined as estimated systolic pulmonary artery pressure (ePAP) ≥ 40mmHg. Clinical features, pulmonary function test values and high-resolution computed tomography of the chest at baseline were reviewed. Echocardiography was performed five and ten years later, and PH at five- and ten-year were consolidated as late PH. The association of baseline data with late PH was analyzed. Outcomes of patients with PH at baseline were also reviewed.

Results: Of 212 patients successfully evaluated for baseline PH, 184 (86.8%) and 105 (50.5%) were available for echocardiographic PH evaluation at five- and ten-year follow-ups. PH was detected in 12 (5.7%), 2 (1.1%) and 3 (2.9%) at baseline, five- and ten-year, respectively. The percent predicted values of forced vital capacity, total lung capacity and diffusion capacity for carbon monoxide (%FVC, %TLC and %DLCO) were associated with late PH (PH at five- or ten-year): %FVC, odds ratio 0.93 (0.87-0.98); %TLC, 0.94 (0.89-0.99) and %DLCO, 0.92, (0.85-0.99). The number of extrapulmonary involved organ systems, pulmonary fibrosis on computed tomography, PH or left ventricular dysfunction (ejection fraction ≤ 50%) at base-
line was not associated with late PH. Of 12 patients with PH at baseline, 3 died during the overall observational period (median 166.5 months): 1 for pulmonary aspergillosis, 1 for pneumonia and one for an unknown reason. Of six patients available for echocardiographic PH evaluation at ten-year, only one had PH.

Conclusions: In a Japanese clinic-based sarcoidosis population, echocardiographic PH is a variable finding throughout the disease course. Although restrictive and diffusion impairments at baseline may be associated with PH five or ten years later, the prediction for late-onset or persistent PH is difficult from baseline findings because of its rare occurrence.

P5-4
Evaluation of Iranian Sarcoidosis Patients Using Six-Minute Walking Test (6MWT)
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Background: The 6-minutes walking test as an important tool has been used for examination of respiratory function in patients with lung diseases. Sarcoidosis is a granulomatous inflammatory disease of unknown etiology that affects multiple organs. The aim of this study is to investigate 6MWT results in Iranian sarcoidosis patients.

Materials and Methods: The current research conducted on 71 patients who were diagnosed with pulmonary sarcoidosis in sarcoidosis clinic of Masih Daneshvari Hospital. They were divided into three groups based on medication therapy including 1) prednisolone 2) prednisolone plus methotrexate 3) prednisolone plus hydroxychloroquine. 6MWD and oxygen desaturation compared among the three mentioned groups as well as four groups according to Scadding criteria. The correlation between 6MWD and spirometric parameters results including FEV1, FEV1/FVC were investigated too.

Results: We studied data from 30 (42%) men and 41 (58%) women. Predicted spirometry indicators did not show considerable difference between men and women. Oxygen desaturation and sarcoidosis severity showed a significant correlation. Oxygen desaturation tended to get higher as the disease got more severe. These results show that patients who received only prednisolone walked significantly further than those who received methotrexate plus prednisone (P=0.003).

Conclusion: Oxygen desaturation during 6MWT should be considered in investigating sarcoidosis severity. 6MWT can be considered not only to help assess sarcoidosis expansion but also help in better medication choose in these patients.

P5-5
Altered distribution and function of respiratory mononuclear phagocytes in sarcoidosis patients

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Sarcoidosis is a T cell-driven inflammatory disease with granuloma formation primarily in the lungs. In Sweden, one third of patients present with acute onset (Löfgren’s syndrome (LS)). LS patients usually resolve symptoms within two years indicative of distinct immunological mechanisms leading to better outcome. Mononuclear phagocytes (MNPs), macrophages, monocytes and dendritic cells (DCs), are likely critical in sarcoidosis as they initiate and maintain T cell activation as well as contribute to granuloma formation by cytokine production.

Our aim is to analyze the distribution, function and transcriptome of MNPs from blood and lung bronchoalveolar lavage (BAL) of non-LS and LS patients over time compared to healthy controls (HC), and identify factors involved in promoting disease resolution or progression in order to allow early identification of patients at risk of developing severe disease.

Blood and BAL from clinically well-characterized patients were analysed by flow cytometry to determine distribution, maturation and function of MNP subsets. In addition, FACS-sorted MNP populations were used for i) RNA sequencing (illumina) or ii) co-culture with T cells.

LS and non-LS patients had higher frequencies of monocytes and lower DC frequencies in BAL and blood compared to HC. Additionally, MNPs from BAL were more mature than in blood and this difference was even more pronounced in LS and non-LS patients than in HC. In non-LS patients, blood MNPs induced higher proliferation of allogeneic T cells and Th1/Th17 related cytokines Interferon gamma and interleukin 17, respectively, compared to BAL MNPs. Blood and BAL DCs were superior to monocytes in inducing T cell proliferation. RNA sequencing showed that DCs of non-LS patients had increased gene expression related to the inflammatory response and antigen presentation compared to HC.

MNPs in the lungs of LS and non-LS patients showed differences in distribution and function supported by RNA sequencing analysis compared to HC. The suppressed T cell activation capacity by MNPs is supportive of an inflammatory lung environment. Understanding the difference in functional capacity of MNPs from LS and non-LS patients may help to link different the outcomes of sarcoidosis patients and to help those at risk of developing severe disease.

P5-6
Usefulness of pulmonary fibrosis markers for pulmonary sarcoidosis

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RATIONALITY:
Although some sarcoidosis patients experience worsening of the disease and develop pulmonary fibrosis, serum markers that reflect the disease status of pulmonary sarcoidosis has yet to be defined. Several markers are reported to be useful for evaluating the disease activity of interstitial pneumonia.

OBJECTIVE & METHOD:
The aim of the study is to evaluate the usefulness of pulmonary fibrosis markers in sarcoidosis. The serum levels of matrix metalloproteinase 7 (MMP-7), chemokine ligand 18 (CCL-18), and periostin were measured in either sarcoidosis patients (n=60) or healthy controls (n=30) using enzyme linked immunosorobent assay. We also analyzed pulmonary fibrosis markers such as Krebs von den Lungen 6 (KL-6) and surfactant protein D in sarcoidosis patients.

RESULT:
Serum MMP-7, CCL-18, and periostin levels were all elevated in sarcoidosis patients compared to healthy controls and significantly correlated with conventional markers of sarcoidosis such as angiotensin converting enzyme and soluble IL-2 receptor. Among these markers, KL-6 and MMP-7 were elevated in the sarcoidosis patients with parenchymal infiltration (stage ≥ 2) in the lungs compared to the patients without parenchymal infiltration (P = 0.02, P = 0.002, respectively). In addition, serum KL-6 and MMP-7 levels were negatively correlated with forced vital capacity (P = 0.02, P = 0.008, respectively).

CONCLUSION:
Our findings indicated that serum KL-6 and MMP-7 might be useful to evaluate the disease status of lung lesion in sarcoidosis.

P5-7
Potential Prognostic Factors for Pulmonary Sarcoidosis in Japanese Patients
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Introduction: Sarcoidosis is a multiorgan granulomatous disease with unknown etiology, heterogeneous clinical presentations, and variable courses and outcomes. Several biomarkers have been suggested to predict the prognosis, however, there are no ideal markers for detecting and monitoring the clinical course of sarcoidosis. The utility of such biomarkers may vary by the target population. In this study, we aimed to find markers which could predict the progression of pulmonary sarcoidosis in Japanese.

Subject/Methods: 94 patients who had not treated with systemic steroids were included for further analyses. Subjects were classified into three groups, “improved”, “stable” and “worsened” according to the change of chest image findings between the first visit and in the end of two years follow up. In addition, we collected the data of potential predictive markers in the clinical, laboratory at the time point of diagnosis: including ages, sex, serum concentrations of ACE, soluble IL-2R and lysozyme, cell fractionation and CD4/CD8 ratio in bronchoalveolar lavage fluid (BALF), respiratory functions, and extrapulmonary involvements.

Results: At diagnosis, median age was 64 years old (range from 26 to 78), and the female to male ratio was 2.4:1 (36 females and 15 males). The numbers of sarcoidosis stage 0, I, II, III and IV were 2 (4.9%), 26 (51%), 21 (41.2%), 1 (2.0%), and 1 (2.0%), respectively. Patients age at diagnosis were younger in improved group than in worsened group (48.9 ± 4.2 vs 62.3 ± 2.9, p = 0.013). The serum concentration of soluble IL-2R tended to be higher in worsened group than in stable group (1284.7 ± 519.6 vs 675.5 ± 673.3 μg/ml, p = 0.07). Lymphocytes in BALF tended to be higher in improved group than in worsened group (42.9 ± 4.1 vs 28.9 ± 5.2 μg/ml, p = 0.26).

Conclusion: Younger age at diagnosis and higher percentage of lymphocytes in BALF may be a good prognostic factor, whereas higher values of soluble IL-2R might be a poor one for pulmonary sarcoidosis in Japanese patients. It would be necessary to verify the trends in larger group if they were prognostic factors of pulmonary sarcoidosis.

P6-1
Nationwide survey on the organspecific prevalence and its interaction with sarcoidosis in Japan
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Background:
Previous studies attempted to characterize the subjects with sarcoidosis according to differences in sex, age, and the presence of specific organ involvement. However, significant interactions among these factors precluded a clear conclusion based on simple comparison. This study aimed to clarify the age and sex-stratified prevalence of specific organ involvement and the heterogenous nature of sarcoidosis.

Methods:
Using the data of 9,965 patients who were newly registered into a database at the Ministry of Health, Labour and Welfare, Japan between 2002 and 2011, we evaluated the age- and sex-specific prevalence of the eye, lung, and skin involvement of sarcoidosis.
sarcoidosis. We also attempted corresponding analysis considering multiple factors.

Results:
As compared with several decades ago, the monophasic age distribution in men became biphasic, and the biphasic distribution in women, monophasic. The prevalence of pulmonary and cutaneous lesions was significantly associated with age, whereas the prevalence of ocular involvement showed a biphasic pattern. The prevalence of bilateral hilar lymphadenopathy was significantly higher, whereas the prevalence of diffuse lung shadow was significantly lower, in subjects with ocular involvement than those without ocular involvement. Corresponding analysis visually clarified the complex interactions among factors.

Conclusion:
Our results contribute to a better understanding of the heterogeneous features of sarcoidosis. Sarcoidosis is heterogeneous multisystem disorder, and epidemiological study has reported the demographics of patients with sarcoidosis. However, the clinical phenotype is still insufficiently understood.

P6-2
Background and Characteristics of Lung Granuloma Detected in Surgically Resected Specimens

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Background
Granulomatous lung diseases are caused by wide varies of etiologies including infection and non-infectious inflammation.

Patients and Methods
Patients who underwent diagnostic open lung biopsies or who underwent partial resection, segmentectomy, lobectomy or pneumonectomy or who underwent lung transplantation as recipients in Kyoto University Hospital from 2005 to 2019 were included in this study. Autopsy cases were excluded.

We retrospectively reviewed medical records of cases in which granulomas had been reported in surgical lung specimens. We also overviewed the final diagnosis in each case and tried to organize the etiologies of lung granulomas.

Results
Using the database on histopathology diagnosis, 4359 specimens were identified as those which were obtained from lung, bronchi, or pleura by surgical resections. Among those, 410 specimens were extracted by searching any words of ‘granuloma’, ‘granulomatous’, or equivalent Japanese words of those in the pathology reports. A hundred and fifty-eight specimens were excluded because the reports negated the existence of granulomas, and, as a result, 252 specimens obtained from 246 patients were thought appropriate for the analysis. Five specimens from 4 patients had been excluded because they would have caused the redundant results. A patient who underwent bilateral lung transplantation had two counts of pathological specimens, thus, 247 specimens from 246 patients were analyzed.

Two hundred and forty-seven specimens were categorized into 120 necrotizing granulomas, 50 epithelioid cell granulomas, 14 foreign body granulomas, 5 cholesterol granulomas, 2 hyalinizing granulomas, 1 xanthogranuloma, 1 necrotizing-and-cholesterol granuloma, 1 epithelioid-and-hyalinizing granuloma, and 42 granulomas not otherwise specified (NOS).

In 120 necrotizing granulomas were included 69 mycobacteriosis, 12 fungal infections, 2 rheumatoid nodules, one granulomatosis with polyangiitis (GPA), and one necrotizing sarcoïd granulomatosis (NSG), while in 60 epithelioid cell granulomas were included 21 sarcoidosis, 9 sarcoïdoidal reactions, and 3 chronic hypersensitivity pneumonitis (CHP). Both epithelioid cell granuloma and hyalinizing granuloma were observed around the amyloid deposition in a specimen obtained from a patient with Sjogren’s syndrome. Forty-two cases with granulomas diagnosed as NOS included 11 malignant cases, 4 CHP, 4 unclassifiable interstitial pneumonias, 4 Graft-versus-host diseases (GVHD), 2 apical caps, and one granulomatosis with polyangiitis (GPA).

Summary
Majorities of necrotizing granulomas were caused by infection, but not limited to it. Epithelioid cell granulomas were observed in non-infectious causes such as sarcoidosis and CHP. Granulomas diagnosed as NOS showed various backgrounds.

P6-3
Withdraw

P6-4
Epidemiological approaches for identification of host susceptibility factors for sarcoidosis in Japan

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Sarcoidosis is an amplified and persistent granulomatous reaction to inhaled antigens. There is insufficient evidence of the involvement of host susceptibility factors for disease onset. Genetic factors associated with immune responses, such as T-helper type 1 (Th1), Th17, and regulatory T cells have been reported in previous studies. To identify additional host susceptibility factors, we conducted the epidemiological survey to evaluate age-related differences and historical changes in clinical characteristics. We also performed a case-control study.

**AIM:**
Sarcoidosis is an amplified and persistent granulomatous reaction to inhaled antigens. There is insufficient evidence of the involvement of host susceptibility factors for disease onset. Genetic factors associated with immune responses, such as T-helper type 1 (Th1), Th17, and regulatory T cells have been reported in previous studies. To identify additional host susceptibility factors, we conducted the epidemiological survey to evaluate age-related differences and historical changes in clinical characteristics. We also performed a case-control study.

**METHODOLOGY:**
We reviewed 588 consecutive Japanese patients newly diagnosed as sarcoidosis between 1974 and 2012 at our department. We compared organ involvement between subgroups classified by sex and age (<45 years; n=275; ≥45 years; n=313) at diagnosis and evaluated historical changes in age-specific distribution at 10-year intervals. In case control study, we enrolled 222 sarcoidosis patients (78 male, 144 female) admitted to our department between 1984 and 2012. We also enrolled 529 control subjects (251 male, 278 female), matched for sex, age at admission, and year of admission. Surgical, family, and smoking history were compared.

**RESULTS:**
Most patients had lung involvement. Intrathoracic/extrathoracic lymph node involvement was more prevalent in young patients; extrathoracic involvement of non-lymphatic organs and hypercalcemia was more prevalent in older patients. Most patients in their 20s presented with bilateral hilar lymphadenopathy, which was consistently less common among older patients. Over time, age at diagnosis had shifted toward the older group. Incidence rate had decreased among young patients, but a second peak among postmenopausal women had been observed throughout the period. In case-control study, multivariate analysis revealed that a history of appendectomy (OR, 1.55; 95% CI, 1.05-2.29) and tonsillectomy (OR, 2.79; 95% CI, 0.91-8.56) were significantly associated with the occurrence of sarcoidosis.

**CONCLUSIONS:**
A historical upward shift in age at diagnosis suggests a role for host susceptibility factors, especially environmental factors in disease onset. Candidates include exposure to diverse microorganisms, age, ovarian insufficiency, appendectomy, and tonsillectomy, all of which may cause disequilibrium between Th1 and Th17 responses and regulatory mechanisms in immune-mediated inflammatory diseases. A likely pathology of sarcoidosis is the breakdown of immune tolerance to inhaled antigens.

**P6-5**
Characteristics of patients with a diagnosis of sarcoidosis: Comparison of the 2006 and 2015 versions of diagnostic criteria for sarcoidosis in Japan

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**AIM:**
Histological verification of epithelioid cell granuloma is important in diagnosing sarcoidosis, and tissue sampling is a diagnostic requirement worldwide. To lower medical expenses and avoid invasive procedures, the Japanese government previously allowed use of clinical diagnostic criteria without histological verification (Diagnostic Standard and Guideline for Sarcoidosis - 2006, Japan Society of Sarcoidosis and Other Granulomatous Disorders).

In 2015, the Japanese Ministry of Health, Labour and Welfare proposed new diagnostic criteria allowing clinical diagnosis based on evaluation of respiratory, ocular, and cardiac involvement and requiring involvement of at least two of these systems. This has increased the need to sample tissue from possibly involved organs that are clinically unevaluateable in patients with suspected sarcoidosis. The study aimed to compare the characteristics of patients diagnosed as having sarcoidosis using the 2006 and 2015 criteria.

**METHODOLOGY:**
Using the 2015 version, we re-evaluated the characteristics of 264 patients with diagnosed or suspected sarcoidosis at Jichi Medical University Hospital during 2004-2012 (84 with clinical diagnosis, 117 with histological diagnosis, and 63 with suspected sarcoidosis) based on the 2006 criteria, and we compared differences between the two versions.

**RESULTS:**
Re-evaluation revealed diagnoses consistent with clinical diagnosis in 43 patients, histological diagnosis in 123 patients, and suspected sarcoidosis in 98 patients. Thirty-nine patients moved from the clinical diagnosis group to the suspected sarcoidosis group due to absence of at least two-system involvement; 2 patients had insufficient laboratory data suggestive of sarcoidosis. Six patients moved from the suspected sarcoidosis group to the histological diagnosis group due to greater leniency of criteria for supportive findings (clinical, laboratory, and clinical findings strongly suggestive of organ involvement).

Most clinically unevaulable lesions under the 2015 criteria did not require treatment; 3 patients with renal involvement/hypercalcemia and 1 patient with neurological involvement were treated with systemic steroids. The latter had an intradural extramedullary tumor, revealed to be schwannoma on biopsy following no response to steroid treatment.

**CONCLUSIONS:**

The 2015 version may be more suitable for detecting suspected sarcoidosis without histological specimens. These new criteria provide useful guidance for follow-up and evaluation of indications for systemic treatment, when pathological specimens are unavailable.

**P6-6**

ELDERLY—ONSET SARCOIDOSIS: A SINGLE CENTER COMPARATIVE STUDY

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**Objectives:** Sarcoidosis is a chronic granulomatous inflammatory disease characterized with non-caseified granuloma formation. It is rarely affects patients older than 65 years old. The purpose of this study is to compare and evaluate the demographic, clinical and laboratory features of elderly-onset (EOS) and young-onset sarcoidosis (YOS) patients. **Methods:** One hundred and thirty-one patients diagnosed with sarcoidosis according to clinical, radiologic and histopathological evaluation were included in this study. The patients with initial symptoms started after age 65 were accepted as EOS. Demographic, clinic, radiologic, and laboratory data and the medication which the patients received were recorded and retrospectively evaluated.

**Results:** Twenty (15.3%) of 131 patients were diagnosed as EOS, and 111 (84.7%) patients were evaluated as YOS. Fifteen of 20 EOS patients were female and 5 of them were male. Average duration of the disease was determined as 38.4 months for YOS and 22.5 months for EOS (p=0.556). Delay of the diagnosis was 12 months for YOS while it was 3 months for EOS (p=0.001). Higher rates of fatigue, comorbid diseases and more Hydroxychloroquine (HQ) use were detected in EOS patients comparing to YOS (p=0.010, p=0.003 and p=0.039 respectively). There was obviously more disease modifying anti-rheumatic drugs (DMARDs) use by YOS group but statistical difference wasn’t significant. The 3-year survival rate after diagnosis of sarcoidosis was %95 in the EOS group, compared with %100 in the YOS group.

**Conclusions:** In this study we showed that YOS and EOS patients may be presented with different clinical, and laboratory features. EOS patients are characterized with higher rates of fatigue and comorbid diseases, less inflammatory sign and delayed diagnosis, and less DMARDs usage.

**P7-1**

Subepicardial Involvement and Chest Pain in Patients with Cardiac Sarcoidosis

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**Introduction:** Chest pain is one of the symptoms of cardiac sarcoidosis. However, its prevalence and causes remains unknown. Our aim was to determine the incidence of chest pain and its association to clinical manifestations.

**Methods:** We retrospectively studied 51 cardiac sarcoidosis patients with normal coronary arteries. All patients underwent cardiac magnetic resonance Imaging (CMR), echocardiography, positron emission tomography/computed tomography (PET/CT), and 24-h ambulatory Holter monitoring. Serum angiotensin converting enzyme (ACE) and B-type natriuretic peptide (BNP) levels were also evaluated.

**Results:** Of the studied population, 16 patients (31.4%) had experienced chest pain. Pulmonary involvement was found in 40 patients, and ventricular tachycardia in 13 patients. PET-CT demonstrated positive findings in 43 patients, and CMR revealed subepicardial late gadolinium enhancement (LGE) in 19 patients. Multivariate analysis revealed a significant association between chest pain and ventricular tachycardia (odds ratio [OR]: 5.02; 95% confidence interval [CI]: 1.02-24.70, P=0.047), and subepicardial LGE (OR: 4.80; 95% CI: 1.08-21.30, P=0.039). Meanwhile, age, gender, pulmonary involvements, serum ACE and BNP levels, positive PET-CT findings, and echocardiographic parameters (left ventricular ejection fraction, A/E ratio) were not associated with chest pain.

**Conclusions:** Chest pain was common in patients with cardiac sarcoidosis. Ventricular tachycardia and subepicardial involvement may account for the symptom in certain subset of patients.

**P7-2**

Outcome of Cardiac Sarcoidosis Patients with Atrioventricular Block and Moderately Reduced Left Ventricular Ejection Fraction

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**Background:** Atrioventricular block (AVB) is the most common initial manifestation of cardiac sarcoidosis (CS); on the other hand, the incidence of sustained ventricular tachycardia (VT) and sudden cardiac death (SCD) is not low among CS patients.
Implantable cardioverter defibrillator (ICD) implantation is recommended in CS patients with AVB but even without left ventricular ejection fraction (LVEF) ≤35% or prior VT history in Japan. However, few reports are available on this issue.

Objective: The aim of this study is to identify predictors for VT or SCD in CS patients with AVB and without LVEF ≤35% or prior VT history.

Methods: We examined the prognosis of CS patients with AVB performing a nationwide questionnaire survey in Japan. Total 57 of 359 hospitals (16%) responded to this survey and 757 patients were collected. Patients unsatisfying the criteria for CS in Japanese Circulation Society Guidelines and lacking follow-up data were excluded. The number of CS patients with AVB and without LVEF ≤35% or the history of VT is 125.

Results: 97 patients had normal LVEF (LVEF ≥50%) and 28 patients had moderately reduced LVEF (35%<LVEF<50%). Kaplan-Meier analysis revealed that the incidence of VT or SCD was higher in CS patients with moderately reduced LVEF than in those with normal LVEF (Log-rank p=0.001). Cox proportional hazard model revealed that moderately reduced LVEF and non-sustained ventricular tachycardia (NSVT) were the independent predictors for VT or SCD. The frequency of VT or SCD within 2 years was 50% in CS patients with moderately reduced LVEF and NSVT.

Conclusions: In CS patients with AVB and LVEF ≥35%, moderately reduced LVEF and NSVT were the predictors for VT or SCD. ICD implantation might be useful in CS patients with AVB, moderately reduced LVEF and NSVT.

P7-3
Withdraw

P7-4
Efficacy and risk of hypoglycemia in strict pretest preparation of 18F-FDG PET for assessment of cardiac sarcoidosis

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Introduction
18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) is an important diagnostic tool in the assessment of cardiac sarcoidosis (CS). Optimal pretest preparation is important since the physiological myocardial 18F-FDG uptake precludes the accurate image interpretation. The combination of prolonged fasting (12-18h), dietary modification and adjunctive heparin administration are proposed in the latest joint SNM/ASNC expert consensus published in 2017. However, few studies are available to investigate the efficacy and adverse events of strict preparation.

Purpose
To elucidate the efficacy of the suppression of physiological glucose uptake and the risk of hypoglycemia.

Methods
We studied consecutive patients who were referred for assessment of CS and compare two protocols 18h fast with three low-carbohydrate meals (each diet includes <5g carbohydrate) (strict protocol) and 18h fast with one low-carbohydrate meal as a dinner and intravenous unfractionated heparin (UFH) (50 IU/kg) (permissive protocol) regarding the efficacy of the suppression of physiological myocardial 18F-FDG uptake and the risk of hypoglycemia (defined plasma glucose level <70mg/dL). 18F-FDG PET images were interpreted according to a predefined standard operating procedure.

Results
Two hundred thirty-five scans were included from 98 patients. Of the 85 scans in the strict protocol group, no scans (0%) showed physiological myocardial 18F-FDG uptake. In contrast, 21 of the 150 scans in the permissive protocol (14%) showed physiological myocardial 18F-FDG uptake. There were 9 hypoglycemic events (6%) in the 150 scans of the permissive protocol and 25 hypoglycemic events (29%) in the 85 scans of the strict protocol. Patients with hypoglycemia had lower BMI than those without hypoglycemia (20.2 vs 22.9, p<0.01).

Conclusions
The strict protocol was effective in inhibiting physiological myocardial 18F-FDG uptake; however, it could lead to hypoglycemia in patients with sarcoidosis, especially in lean patients.

P7-5
Effectiveness and Safety of Infliximab in Refractory Cardiac Sarcoidosis

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Introduction: Active cardiac sarcoidosis (CS) is an indication for immunosuppressive therapy to prevent potential life-threatening complications. Infliximab is an anti-tumor necrosis factor-α agent proven to be effective as 3rd line immunosuppressive therapy in refractory sarcoidosis. However, it is hardly used in CS. In the last years we used infliximab treatment in refractory CS.

Abstract
Purpose: The goal of this study is to assess the effectiveness and safety of infliximab in CS.

Method: A retrospective, single center cohort study was performed of 19 patients treated with infliximab because of refractory CS between January 2016 and December 2018. They received infliximab intravenously at a dose of 5 mg/kg at week 0, 2, 6, 10, 14 and 18. Response to treatment was evaluated after 6 months in the multidisciplinary team (MDT) after FDG-PET, measurement of serum soluble interleukin-2 receptor (sIL2R) and echocardiography. All relevant clinical data were collected via chart review.

Results: The mean age is 51.3 ± 7.1 years, 63.1% male. Metabolic response on FDG-PET was seen in 85% of patients: a complete response in 32% and a partial response in 53%. One patient showed progressive disease. Overall, the mean LVEF changed from 44 ± 14% to 48 ± 12%. The LVEF increased >10% in 3 patients (16%) and was stable in 15 patients (79%). Three patients (16%) received appropriate ICD therapy due to new onset of ventricular tachycardia, despite complete or partial metabolic response on FDG-PET. In 1 patient with stable disease, therapy was changed to adalimumab due to anti-infliximab antibody formation. Infliximab was well tolerated in all other patients; in particular, no clinical worsening due heart failure was reported.

Conclusion: This is the largest cohort of patients with active cardiac sarcoidosis treated with infliximab to date. Treatment of CS with infliximab was safe and effective in reducing disease activity and preserving LV function.

Background: We demonstrate clinical course and histopathology of the autopsied heart of a fifty-something man with cardiac sarcoidosis with refractory heart failure over a long duration of about 20 years. In spite of multidisciplinary treatment including the cardiac resynchronization therapy with defibrillator (CRTD), he died of multiple organ failure and an autopsy was accepted only for the heart. Methods and Results: At autopsy, the heart was huge with increased weight of more than 1000g. The left ventricle was markedly dilated. Severe and diffuse interstitial fibrosis was observed particularly at the lesion of interventricular septum. No sarcoid granuloma was found. On the other hand, diffuse infiltration of macrophages was observed. The immunohistochemical (IHC) study revealed that most macrophages were M2 macrophages. In addition, the IHC staining using the anti-transforming growth factor beta 1 (TGFβ1) antibody revealed that infiltrating large mononuclear cells (probably monocytes/macrophages) are strongly positive for TGFβ1. Conclusion: Although this is preliminary data, it may suggest a significant role of TGFβ1 producing M2 macrophages in the development of severe cardiac fibrosis observed in this cardiac sarcoidosis case with refractory heart failure.

P8-1

Significance of Macrophages Observed in the Heart of a Patient with Cardiac Sarcoidosis with Refractory Heart Failure

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Background: Early diagnosis of cardiac sarcoidosis is difficult because it requires special tests for diagnosis. FDG-PET and myocardial biopsy are high examinations in terms of patient burden and cost, and are often not performed in LGE negative cases.

Case: A 36-year-old male with pulmonary sarcoidosis was referred to our department due to the electrocardiogram change during the clinical course. The electrocardiogram showed Complete Right Bundle Branch Block. Any morphological and functional abnormalities were not detected in the echocardiography. LGE was not detected in cardiac magnetic resonance (CMR). However, FDG-PET/CT showed FDG uptake in the myocardium. Therefore, right ventricular endomyocardial biopsy was performed. The biopsy specimen exhibited noncaseating granulomas, confirming the diagnosis of cardiac sarcoidosis. Steroid treatment was initiated and FDG uptake in the myocardium disappeared after 1 month.

Conclusion: CMR alone cannot detect myocardial inflammation in all cases of sarcoidosis. Without FDG-PET/CT and/or myocardial biopsy, it is difficult to detect early cardiac lesions. Steroid treatment was initiated and FDG uptake in the myocardium disappeared after 1 month. Even in LGE negative cases, FDG-PET/CT should be performed without hesitation.
P8-3

Clinical significance of interventricular septal thinning in Japanese sarcoidosis patients

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Backgrounds: Interventricular septal thinning has been recognized as a diagnostic echocardiographic feature of cardiac involvement in sarcoidosis patients. Interventricular septal thinning has been studied almost exclusively in cardiac sarcoidosis, and the long-term clinical significance of interventricular septal thinning has not been investigated in a large cohort of sarcoidosis patients with and without cardiac involvement.

Methods: Consecutive 1,013 patients with pathologically or clinically diagnosed sarcoidosis and undergoing echocardiography at Kyoto Central Clinic between January 1, 2008 to December 31, 2013 were retrospectively investigated. Interventricular septal thinning was defined as the base of interventricular septum ≤ 4 mm or the ratio of base thickness to one-third point nearby the annulus in the interventricular septum ≤ 0.6. The associations of interventricular septal thinning at baseline with left ventricular ejection fraction (LVEF) at five-year follow-up and LV dysfunction-free survival time were analyzed.

Results: Of 1,013 Japanese sarcoidosis patients, 23 (2.3%) had interventricular septal thinning by echocardiography at baseline. Interventricular septal thinning was associated with less LVEF and older ages. Of 530 patients available for echocardiography at five-year follow-up, 18 had LV dysfunction (LVEF<50%) at follow-up visits. Interventricular septal thinning and LVEF<60% at baseline were independently associated with LV dysfunction at five-year: interventricular septal thinning: odds ratio, 8.26 (1.79-40.1); LVEF<60%: odds ratio, 29.8 (5.59-154.5). None of five patients with interventricular septal thinning and LVEF ≥ 60% had LV dysfunction at five-year. Of 775 patients without LV dysfunction at baseline and available for longitudinal echocardiographic evaluation, 38 developed LV dysfunction during the median observational period of 89.0 months. Interventricular septal thinning and Interventricular septal thinning and LVEF<60% at baseline were independently associated with LV dysfunction-free survival time: interventricular septal thinning: hazard ratio, 5.15 (1.81-12.8); LVEF<60%: odds ratio, 17.3 (8.41-34.5).

Conclusions: In a large cohort of Japanese sarcoidosis patients, echocardiographic interventricular septal thinning was observed in 2.3% and a significant predictor for LV dysfunction at five-year follow-up and late-onset LV dysfunction even after adjustment for LVEF at baseline.

P8-4

Mycobacteria: A Possible Trigger of Cardiac Sarcoidosis

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Aim

Sarcoidosis is a heterogeneous, systemic disease characterized by formation of noncaseating granulomas, mostly affecting the lungs, skin and lymph nodes. Multiple possible antigens have been linked to sarcoidosis pathogenesis. The relation between clinical characteristics, like organ involvement, and certain antigens have not been described before but could identify new disease phenotypes.

Methods

In a previous study of 201 sarcoidosis patients who were tested for all possible antigens related to sarcoidosis pathogenesis including metals, propionibacteria and mycobacteria, we found a high prevalence of latent tuberculosis infection (LTBI) in 5 patients; 3 of these patients had cardiac sarcoidosis (CS). To investigate this possible relation between LTBI and CS, available clinical data of Interferon release assays (IGRAs) or tuberculin skin tests (TST) were analyzed in a cohort of CS patients (n=225) and compared to an extra-cardiac sarcoidosis (ECS) group (n=177).

Results

Retrospective data of IGRAs or TST were available from 151 CS patients and 153 ECS patients. Of the CS group, 10 patients were diagnosed with LTBI (6.6%) compared to only one patient of the ECS group (0.7%), p=0.005. In none of the patients with a positive IGRA or TST were signs an active tuberculosis infection.

Discussion and conclusion

Our data suggest a possible link between a latent tuberculosis infection and cardiac involvement in patients already diagnosed with sarcoidosis. The mechanism behind this correlation is unclear. Presence of Propionibacterium acnes antigens however, another microorganism related to sarcoidosis pathogenesis, was already demonstrated in granulomas in myocardial tissue of some patients with CS. Future studies should determine if mycobacterial antigens can be found as well in myocardial tissue of patients with CS in order to unravel this possible association.

P8-5

Isolated Cardiac Sarcoidosis Based on New Guidelines in the Era of FDG-PET

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Introduction: Sarcoidosis is a systemic inflammatory disease which can involve any organs. The reported prevalence of isolated cardiac sarcoidosis (CS) varies widely because of the lack of an agreed definition of isolated CS (iCS). iCS was newly defined in the new guidelines for CS by Japanese Circulation Society.

Purpose: We aimed to examine the diagnostic accuracy of FDG PET/CT and the ratio of iCS in the whole CS by reviewing the patients with suspected CS undergoing the whole-body and cardiac FDG PET/CT scans.

Methods: We retrospectively reviewed 74 consecutive patients undergoing FDG PET/CT from 2013 to 2018 (mean age 60 ± 14 years, 37 male) without the initiation of corticosteroid. Myocardial FDG uptake in CS was defined as a "focal" or "focal on diffuse" pattern. Systemic sarcoidosis with CS (sCS) and iCS were diagnosed according to guidelines for the diagnosis and treatment of CS by Japanese Circulation Society. In short, iCS was diagnosed clinically when no clinical findings of sarcoidosis in any other organs and FDG uptake in heart were shown in addition to the following three of four criteria: high-grade atrioventricular block or fatal ventricular arrhythmia, structural abnormality, left ventricular contractile dysfunction, and delayed Gadoinium enhancement of myocardium on MRI.

Results: Of 31 patients with extra-cardiac sarcoidosis, 10 already met the diagnostic criteria of sCS before undergoing FDG PET/CT and 11 was newly diagnosed as sCS after FDG PET/CT. Of the remaining 43 without extra-cardiac sarcoidosis, 18 had FDG uptake in heart. Of 18 with FDG uptake in heart, iCS was diagnosed in 7, and CS in 3 with extra-cardiac uptake of FDG as well as myocardium. Finally, 24 and 7 patients met the criteria of sCS and iCS based on the guideline, respectively. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of FDG PET/CT for CS including sCS and iCS were 90, 87, 88, 85, and 92%, respectively.

Conclusion: The ratio of iCS on the basis of new guidelines for diagnosis and treatment of CS was 22% of the whole CS.

P9-1

Change in real-world clinical practice in IPF according to new guidelines and its impact on survival: Results from two consecutive nationwide registries

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Background: The Korean interstitial lung disease study group carried out two nationwide, multicenter consecutive registries on idiopathic pulmonary fibrosis (IPF). Comparing two registries, we evaluated the clinical features, diagnostic modalities, and prognostic factors in real clinical practice according to the change in diagnosis and pharmacological therapy.

Methods: 1839 patients were enrolled from the 1st registry (2008 group, from January 1, 2002, to September 2008) and 1345 patients were enrolled from the 2nd registry (2018 group, from January 1, 2012, to August 31, 2018). Survival curves were estimated using the Kaplan-Meier method. To evaluate the risk factor for the mortality, a Cox regression model was used, and the interaction p-value was checked to evaluate the difference of hazards ratio of respective independent variable in 2008 group and 2018 group.

Results: 2018 group were younger (p=0.025), had fewer symptoms (p<0.001), had longer follow-up months (p<0.001), had performed lung function testing more regularly (p<0.001), had less honeycombing (p<0.001), and was less frequently diagnosed with surgical biopsy (p<0.001). In 2018 group, the use of steroid, conservative care declined and the use of N-acetylcysteine (p<0.001) increased. Pirfenidone and nintedanib were only used in 2018 group. The 2018 group showed a better survival. In the evaluation of the risk factor for mortality, no variable showed heterogeneity of hazard ratios between two groups.

Conclusions: Our showed that the actual clinical practice in the diagnosis and treatment of IPF patients had changed in adherence to guidelines, that the survival of IPF patients improved over the decades. Our study also showed how the changes in baseline characteristics, diagnostic test result, and treatment medication effected mortality.

P9-2

Impact of Smoking on the Development of Idiopathic Pulmonary Fibrosis: Results from a Nationwide Population-Based Cohort Study

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Background: The reported effect of smoking on the development of idiopathic pulmonary fibrosis (IPF) in previous studies has been inconsistent. Therefore, we investigated the effect of...
smoking on the development of IPF using data from a large population-based cohort.

**Methods:** We searched the National Health Information Database (NHID) for citizens who had participated in the health check-up service between 2009 and 2012. We excluded individuals who were diagnosed with IPF before their health check-up service. We screened the insurance claim of the included citizens through 2016 using the NHID to identify all cases of newly-diagnosed IPF. Newly-diagnosed IPF was defined as an international code of disease 10 (ICD-10) of IPF with medical claims for chest computed tomography and pulmonary function tests. Detailed smoking history was surveyed by a questionnaire completed at the time of the health check-up.

**Results:** A total of 23,242,836 citizens were registered in the Health Check-up database, and 25,113 were identified with incident IPF; a total of 17,314 (70%) were male. The mean age of patients with incident IPF was 64.1±11.3 years. The number of patients with incident IPF, who were current smokers, former smokers, and non-smokers, was 6,842 (27.2%), 5,826 (23.2%), and 12,445 (49.6%), respectively. The risk of IPF development was higher in current and former smokers than non-smokers, with adjusted hazard ratios (HRs) of 1.66 (95% confidence interval [CI]: 1.605-1.724) and 1.42 (95% CI: 1.371-1.475), respectively (Table 1). The adjusted HR increased as the amount and duration of smoking increased. The effect of smoking was greater in women than in men (adjusted HR values for smoking pack-years<10, 10 to<20, 20 to<30, and ≥30 in women were 1.459, 2.250, 2.625, and 2.279, respectively, and in men were 1.13, 1.304, 1.507, and 1.953, respectively).

**Conclusion:** The risk of IPF is higher in current and former smokers than non-smokers, and current smokers have a higher risk than former smokers. A dose-response relationship exists between smoking and development of IPF, and this effect was greater in women than men.

### Table 1: Data of development of IPF among existing cases

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>n</th>
<th>%</th>
<th>Incident IPF</th>
<th>%</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>14,657,557</td>
<td>63.2</td>
<td>1,369 (0.01%)</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2,505,063</td>
<td>10.5</td>
<td>422 (1.7%)</td>
<td>1.40 (1.25-1.55)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>6,438,494</td>
<td>27.3</td>
<td>1,680 (2.6%)</td>
<td>1.32 (1.20-1.46)</td>
<td></td>
</tr>
</tbody>
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### P9-4

**Prognostic differences in patients with acute exacerbation of idiopathic interstitial pneumonias across several etiologies**

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**Background and aim**

Acute exacerbation of progressive fibrotic idiopathic interstitial pneumonias (AE-IIPs) is associated with short survival times and a high mortality rate. An international working group proposed revised diagnostic criteria for AE-IIPs, suggesting in 2016 that they be classified as idiopathic, or triggered. Many factors are known to trigger AE-IIPs, including surgery, infection, and drugs. However, it is not known which of these triggers dictates a worse prognosis. The purpose of this study was to evaluate the prognosis of patients with various types of AE-IIPs, particularly infection-triggered, non-infection triggered, and idiopathic AE-IIPs.

**Methods**

In this study, we retrospectively collected the records of 156 patients who were hospitalized with respiratory failure between April 2009 and March 2019. Among these patients, 79 who had developed AE-IIPs were enrolled into this study. We classified these patients into three groups: idiopathic, infection-triggered, and non-infection-triggered AE-IIPs. We analyzed differences in patient characteristics, radiological findings at the onset of AE-IIPs, pre-existing radiological findings before the development of AE-IIPs, prior treatment for baseline IIPs, treatment for AE-IIPs, and prognosis. Then, we evaluated the risk factor for early death (death within 30 days from the onset of AE-IIPs) associated with AE-IIPs.

**Results**

Among the patients who developed AE-IIPs, 34 were characterized as having idiopathic, 25 were characterized as having
Abstract

Diffuse Alveolar Hemorrhage Mimicking Acute Exacerbation of Idiopathic Pulmonary Fibrosis Treated with Pirfenidone

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Acute exacerbation (AE) of idiopathic pulmonary fibrosis (AE-IPF) is frequent complications of IPF with high mortality. So earlier detection and management are important to improve outcome. Diffuse alveolar hemorrhage (DAH) is the bleeding into the alveolar space and associated with several immune and non-immune disorders. Although rare, if DAH develop in IPF, it is very difficult to differentiate between DAH and IPF-AE. We present a case of patient with IPF, whose worsening clinical conditions were caused by DAH. An 67-year-old male with IPF presented at emergency department with acute worsening of dyspnea, cough with blood tingled sputum developed 3 days ago. He did not have fever or purulent sputum. White cell count was minimally increased and C-reactive protein was 16.5 mg/dL but procalcitonin was within normal limit. He was diagnosed of IPF 3 years ago and took Pirfenidone 600mg three times a day 2 years ago without adverse events. His dyspnea scale (mMRC) and pulmonary function were stable during pirfenidone treatment (FVC 58% and DLCO 53% of predicted 2months before admission). On admission, his chest CT showed newly developed diffuse bilateral ground glass opacity (GGO) (Figure) with underlying IPF. These findings were suggestive of AE-IPF. Fifty percent oxygen was delivered by high flow nasal cannula to maintain oxygen saturation above 90%. Echocardiography did not show left heart failure. Although worsening respiratory failure by bronchoalveolar lavage (BAL) could happen, BAL was done on 2nd day of admission to rule out infectious or potential causes of diffuse GGO. Unexpectedly, DAH was highly suggestive (Figure) and hemosiderin laden macrophage was confirmed later. To find the cause of DAH, detailed medication history and lab tests were done but unremarkable except recent herb medications. DAH without immune-mediated cause usually treated with supportive care. But because AE-IPF caused or triggered by DAH cannot be completely excluded, 1mg/kg methylprednisolone was administered and tapered gradually. Oxygen requirement decreased gradually and he was discharged home with 25mg of prednisolone and 3L/min of home oxygen on 19th hospital day. We can suggest the usefulness of early BAL to guide the treatment of patient with suspected AE-IPF.

Diffuse Alveolar Hemorrhage Mimicking Acute Exacerbation of Idiopathic Pulmonary Fibrosis Treated with Pirfenidone

The Predictive Factors for Lung Cancer Occurrence in Patients with IPF

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Introduction: Idiopathic pulmonary fibrosis (IPF) is known as a risk factor for lung cancer (LC) by several previous studies, and that the presence of LC shortens survival in patients with IPF. However, the risk factors for the development of LC after the diagnosis of IPF have not been fully evaluated. We investigated the predictive factors for LC by longitudinal cohort analysis.

Patients and methods: This was a retrospective study of a single center interstitial lung disease cohort. Study patients were consecutively enrolled to the cohort between March 2006 and December 2018 at Bucheon ST. Mary’s Hospital, The Catholic University of Korea. This cohort study consists of 102 patients with IPF, and the incidence of LC and the outcomes were investigated.

Results: During the mean follow-up periods of 62.7 months, 27 patients (26%) developed LC. The most frequent cell type was Squamous cell carcinoma, and the proportion of male was higher in IPF-LC group (92.6% vs 70.7%, p=0.021). In univariate cox regression analysis, low forced vital capacity (FVC) < 75% (p<0.001), and low diffusion capacity of the lungs for carbon monoxide (DLco) <55% (p<0.001) was associated with LC development. In Cox proportional hazards model, low FVC (hazard ratio [HR]: 5.65; 95% confidence interval [CI]: 1.78-
17.84, p=0.003) and low DLco (HR: 27.5; 95% CI: 1.97-386.6, p=0.014) were independent predictive factors for LC in stepwise multivariate analysis.

**Conclusion:** Low FVC and Low DLco, which are pulmonary function parameters reflecting their severity of IPF, are suggested as independent risk factors for LC development in IPF patients.

**P9-7**

**Lung Cancer Related Interstitial Lung Disease: Serial Case Report**

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**Background:** Risk of lung cancer increased in Interstitial lung disease (ILD). Idiopathic pulmonary fibrosis (IPF) is one of ILD form. Lung cancer prevalence on IPF is 2.7% - 48%. The most type lung cancer in IPF is squamous cell carcinoma and adenocarcinoma after that. Lung cancer with ILD have poor prognosis.

**Case Presentation:**

There were two patients admitted to our centre, with breathlessness as their chief complaint. They had different sex. Their age around 60 years old. They had exposed to fogging and firewood smoke more than five year. Chest High Resolution Computed Tomography (HRCT) demonstrated a ground glass appearance with honey comb appearance with infiltrates. One of them with small solitary tumor with irregular shape on right lung. Both of them underwent bronchoscopy and bronchoalveolar lavage (BAL). There were no abnormality on the first patient from bronchoscopy. Meanwhile the other only with hyperemic mucosa. We found squamous cell carcinoma from BAL.

**Discussion:**

There is a connection between ILD and lung cancer. Risk factor for lung cancer are smoking, exposed to hazard material and also idiopathic pulmonary fibrosis. In this case they were exposed to fogging and firewood smoke. Physiopathology IPF similar with lung cancer that is epithelial damage, abnormal repair of epithelial cells, mesenchymal epithelial transition because of inflammation and immunosupression. Male, age over 60 years old and smoking is the risk factor for both lung cancer and ILD. The clinical manifestation for lung cancer and ILD is similar, so we need to diagnostic it with chest X-Ray, HRCT and bronchoscopy with BAL. Predilection for lung cancer in ILD mostly in peripheral zone and lower lobe. Non small lung cancer is often seen in IPF especially squamous cell carcinoma like in our serial case.

**Conclusion:**

Patient with respiratory problem that have risk factor for lung cancer and ILD should underwent chest X-ray, HRCT and bronchoscopy with BAL.

**P10-1**

**The Occurrence of a TERT founder Mutation in Pulmonary Fibrosis Patients in the Netherlands**

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Germline mutations in Telomerase Reverse Transcriptase (TERT) cause telomere syndromes such as dyskeratosis congenita, bone marrow failure, liver cirrhosis or pulmonary fibrosis. Our familial pulmonary fibrosis (FPF) cohort (n=217) was screened for mutations in TERT. The TERT c.2005C>T (NM_198253.2) mutation, resulting in the amino acid substitution p.(Arg669Trp), was found in 6 families of our FFP cohort of which 1 proband was homozygous. Remarkably, all families lived in the same region in the eastern part of the Netherlands. Therefore, we investigated if the variant is a neutral regional founder mutation or if it is associated with pulmonary fibrosis in the Netherlands. Genealogical research was performed to reveal family connections.

A custom designed taqman genotyping assay on a Quantstudio 5 analyser was used to genotype the TERT c.2005C>T polymorphism. In total 1031 pulmonary fibrosis (PF) patients, 327 non-pulmonary fibrosis (non-PF) patients and 529 Dutch healthy control subjects of the ILD-biobank at St Antonius ILD center of Excellence were genotyped. A medical genealogist was consulted to reveal family connections.

To investigate whether the variant is a neutral regional founder mutation, 327 non-PF patients, who were living in the eastern part of the Netherlands were tested for c.2005C>T carriership. None of the non-PF patients were carrier of the c.2005C>T mutation. Additionally, to examine whether this TERT mutation is associated with PF in the Netherlands, 205 regional and 826 non-regional PF patients were genotyped. Seven of the PF patients were carrier of the c. 2005C>T mutation, 5 regional and 2 non-regional. None of the 529 healthy controls were carrier of the c.2005C>T. In total, the TERT c. 2005C>T mutation was found in 13 families. Genealogical research revealed that 4 families had a common ancestor 7 generations back.

We showed that TERT c. 2005C>T is a pathogenic founder mutation that originated in the eastern part of the Netherlands. The mutation was only found in patients with pulmonary fibrosis. Genealogical research revealed that the mutation probably originated at least 7 generations back. Many generations have passed before manifestation of disease in these families, suggesting that disease anticipation with associated telomere attrition is slow for TERT c. 2005C>T.

**Table 1 TERT c.2005C>T genotype distribution and odds ratio for disease in FFP, PF, non-PF and healthy control subjects.**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Lung Fibrosis</th>
<th>Healthy Control</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TERT c.2005C&gt;T</td>
<td>FFP (n=1031)</td>
<td>Healthy Control (n=529)</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Wild-type (WT)</td>
<td>327/704</td>
<td>529/529</td>
<td>1.00</td>
</tr>
<tr>
<td>Homozygous (H/H)</td>
<td>0/1</td>
<td>0/1</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* *probebands*

**FFP:** familial pulmonary fibrosis; **PF:** pulmonary fibrosis; **non-PF:** ILD subjects with and without FFP; **NL:** Netherlands; **OR:** Odds ratio for a pulmonary fibrosis; **95% CI:** 95% confidence interval.
Abstract

**P10-2**

Human Telomerase Reverse Transcriptase Mutation In Idiopathic Pulmonary Fibrosis

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Aim: To the best of our knowledge, there is no declared study about IPF and telomere biology in our country. Thus, the aim of the study is to determine the frequency of hTERT mutation in IPF and to investigate the relationship between clinical characteristics of IPF and hTERT mutation. Material and method: 48 IPF patients and 49 healthy subjects who admitted to Cukurova University Faculty of Medicine, Department of Chest Diseases between 2019 enrolled in the study after assignment of written informed consent form. The IPF patients are diagnosed due to clinical-radiological and/or histopathological evaluation compatible with IPF. DNA isolation from blood samples was performed using Roche, High Pure Polymerase Chain Reaction (PCR) Preparation Kit. Isolated DNAs were examined using the Light Cycler Fast Start DNA Master HybProbe for the rs2853669 TERT polymorphism. The C>T single nucleotide polymorphism was referenced in the DNA chain. Results: The frequency of hTERT mutation in IPF patients was 76.5% and 75.7% in the control group respectively (p = 0.05). There was no statistically significant difference between IPF patients and control group in terms of hTERT mutation, the mean forced vital capacity (FVC) of IPF patients with hTERT mutation was 63.8 ± 17.6%, whereas it was 70.2 ± 23.1% in IPF patients without hTERT mutation, and the difference was statistically significant (p = 0.019). Conclusion: As FVC is a good indicator of pulmonary functional impairment in IPF patients, these results may be a caution for clinicians to keep in mind that IPF patients with hTERT mutation carriers may progress more rapidly in clinical follow-up.

**P10-3**

TGF β POLYMORPHISM IN SERBIAN PATIENT WITH IDIOPATHIC PULMONARY FIBROSIS

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Transforming growth factor beta (TGF β) plays a significant role in pathogenesis of idiopathic pulmonary fibrosis. Significance of TGF β-509 C/T polymorphism in susceptibility to IPF and clinical course of the disease is still controversial. The aim of this study was to investigate the roles of TGF β-509 C/T gene polymorphisms and the clinical course in Serbian IPF patients. Material and method: 26 IPF patients and 30 control subjects were genotyped for TGF β-509 polymorphism. Instances of polymorphism were examined by PCR-RFLP (polymorphism detection based on the restriction fragment length) on the DNA isolated from the blood by the commercial kit (Qiagen). Results: Compared to healthy control subjects, IPF patients showed no deviation in genotype and allele frequency distribution. Higher FVC values (% predicted) were observed in CC (69.2±28.71) compared to CT (71.95±14.91) and TT (64.90±22.62) carriers. Patients with TT genotype had the lowest DLCo values (% predicted) (32±19.13), compared to carriers of CC (46.13±13.07) and CT (43.7±6.84) genotypes. There were no differences in SpO2 values, 6 minutes walking test distance, 6MWT desaturation and mean pulmonary artery pressure. Conclusion: We found no association between TGF beta gene polymorphism and susceptibility to IPF in our study, but this polymorphism may play a role in predicting the clinical course.

**P10-4**

Effects of Diesel Exhaust Particle in Human Bronchial Epithelial Cell Migration and the Intracellular Signaling Pathway

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Diesel exhaust particle (DEP) is the major components of PM 2.5. We recently reported that diesel exhaust (DE) was an important factor in bleomycin-induced lung injury and fibrosis in mice due to its induction of oxidative stress. Cell migration plays a fundamental role in many biological processes, such as tissue remodeling. The current study was designed to elucidate the effect of DEP and the intracellular signaling pathway of DEP in the cell migration on HBEC.

We used human bronchial epithelial cell line BET-1A. The cells were plated into 24-well plates in the culture medium (LHC-9). When 90% confluent, in the first experiment, DEP (Standard Reference Material 2975) was treated culture cells with various concentrations for 24hs; in the second experiment, DEP was treated with 25μg/ml and Gi Protein inhibitor (pertussis toxin solution, PT) or ROCK inhibitor (Y-27632) treated with various concentrations for 24hs. The cell layers were wounded using a pipette tip. Cultures were then incubated in basal medium (LHC-D) with 30% LHC-9 for 24hs, after which the cell layers were fixed and stained with May-Gimza. Photomicrographs were taken and then examined cells migration in each group. We also examined N-cadherin and α-SMA expression in HBEC after DEP exposure. It was found that DEP stimulated HBEC migration, and this stimulation on HBEC migration were inhibited by a pretreatment of the cells with the antioxidant N-acetylcysteine (NAC). DEP stimulation on HBEC migration was also blocked by a Gi protein inhibitor. DEP slightly induced the gain of N-cadherin and α-SMA expression in HBEC.

These results suggested that oxidative stress caused by DEP promote HBEC migration was involved in tissue remodeling, and might be through modulating epithelial-mesenchymal transition (EMT) process in respiratory diseases, such as lung fibrosis.
P10-5

Fibrosis patterns of pulmonary sarcoidosis in comparison with idiopathic pulmonary fibrosis

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Aim
It has been acknowledged that fibrosis is mainly derived from granulomata in pulmonary sarcoidosis. However, some cases in fibrotic stage of pulmonary sarcoidosis must be differentiated from the cases with idiopathic pulmonary fibrosis (IPF). This study is aimed to clarify the fibrosis pattern of pulmonary sarcoidosis in comparison with those of IPF in autopsy cases.

Study population
Twenty one autopsy cases with pulmonary sarcoidosis between 1980 and 2017 were examined. They were 14 women and 7 men with 62 years of mean age and 15.5 years of duration of illness. 11 autopsy cases with IPF (10 men and 1 woman) were also examined.

Results
The upper lobe contraction was the characteristic gross finding (67%) in pulmonary sarcoidosis. Bronchovascular bundle (BVB) fibrosis was remarkably observed in the contracted upper lobe (80%), continuously involving from the proximal segmental bronchus to the bronchioles. The dense collagen deposition of BVB fibrosis involving peribronchiolar alveoli was considered to be consequent to scarred granulomata. Bronchocentric lesion was frequent (67%), corresponding to the BVB fibrosis. In the lobules, fibrosis pattern from granulomata revealed stellate (95%) and band-like fibrosis (87%), which were located at the bronchioles, interlobular septa and along the blood vessels. Enlarged hyalinized hilar lymph nodes compressed the proximal arteries, veins and bronchi. Only one case revealed pulmonary hypertension. In the upper lobe, cystic bullous change (52%) and cavitation (43%) were observed. These structural distortions of the lung were important for the occurrence of aspergilloma, which became a direct cause of death in long-standing pulmonary sarcoidosis in 8 patients (38%). Honeycomb-like lesions can be observed in long-standing pulmonary sarcoidosis, not only in the lower lobe, but also in the upper lobe. The important histological distinction between honeycomb-like lesion of pulmonary sarcoidosis and honeycombing of IPF/UIP reveal prominent intra-lobular ectatic bronchioles and less perilobular atelectasis in the former. However, sarcoidosis and IPF may coexist in some cases.

CONCLUSIONS
Dense bronchovascular bundle fibrosis in the upper lobe is the important prognostic factor in pulmonary sarcoidosis and is considered to be a target for adequate treatment.

P10-6

Morbidity and Mortality of Surgical Lung Biopsy in The Diagnosis of Usual Interstitial Pneumonia

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The aim:
The aim of this study was to evaluate morbidity and mortality of surgical lung biopsy (SLB) in diagnosing usual interstitial pneumonia (UIP).

Methodology:
Patients undergoing surgical lung biopsy over a 5-year period from January 2013–October 2018 with the ultimate diagnosis of UIP/idiopathic pulmonary fibrosis (IPF) were studied. Clinical data concerning medical history, histology, pulmonary functions, radiology, length of hospital stay (LOS), morbidity and mortality status were retrospectively recruited from 4 hospitals.

Results:
The study included consecutive 93 patients with a SLB diagnosis of UIP. Mean age was 61 ± 8 years, with one third of the patients were ≥65 years. Most of the patients (62.4%) were male. In 58 cases (62.4%), the biopsy was performed by video-assisted thoracoscopic surgery (VATS), in 35 (37.7%) by limited thoracotomy. Eighty patients (86%) had possible usual interstitial pneumonia, 12 (12.9%) had inconsistent with UIP and 1 patient (1.1%) had usual interstitial pneumonia pattern on high-resolution computed tomography. The mean LOS was 5.47 ± 3.16 days. LOS was associated with smoking status (p = 0.024), type of biopsy (p=0.00), 6-minute walk test (p=0.00) and number of biopsy (p=0.00). There was no in-hospital and 30-day mortality in our cohort, and 90-day mortality rate was 1.1%. There were no intraoperative morbidity. On the other hand, in 7 patients (7.5%) we observed postoperative morbidities, predominantly prolonged air leakage (7.5% of all cases). Postoperative morbidity was only associated with the type of SLB. Patients with limited thoracotomy showed greater morbidity rates (17.1% vs 1.7%, p=0.011).

Conclusion:
SLB is a relatively safe procedure in the diagnosis of UIP and can be performed in suitable patients with suspected UIP/IPF.

P10-7

Are there differences between ANCA positive and negative cases of lung fibrosis in the absence of vasculitis?

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Aim:
Patients with interstitial lung disease of UIP pattern who are ANCA-positive (Anti-neutrophil cytoplasmic antibody, MPO subtype) but without signs of vasculitis are not well described. The aim of this study was to compare this subgroup with our
Pleuroparenchymal Fibroelastosis in Korean: Clinico-radiologic-pathologic Features and Outcome

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Background: Pleuroparenchymal fibroelastosis (PPFE) is one of the rare idiopathic interstitial pneumonias (IIP) and characterized by predominantly upper lobe involvement with pleural fibrosis and subjacent parenchymal fibrosis. The aim of this study was to evaluate the clinico-radiologic-pathologic features and prognosis of Korean patients with PPFE.

Method: A total of 26 patients, who were confirmed by lung biopsy (surgical lung biopsy: 15, transbronchial lung biopsy: 11) from 2010 to 2017 at Asan Medical Center, Seoul, Korea, were included and clinical data and radiologic-pathologic findings were retrospectively analyzed. The Reddy’s criteria was used for diagnosis of PPFE.

Results: Median follow-up period was 23.8 months. Mean age was 62.5 years, 61.5% were men and 50% were smokers. Cough and dyspnea were the most frequent presenting symptoms, and restrictive pattern (73.1%) was the most common in the lung function. In 88.5% of the subjects, other interstitial lung disease (ILD) was found in their lower lobes on chest computed tomography (CT) scan, and PPFE pattern was the most common (76.9%), followed by usual interstitial pneumonia (11.5%). Among patients whose lower lobe was biopsied (n=13), UIP pattern was the most common (46.2%) and fibroelastosis was found in 38.5%. Subjects with lower-lobe involvement showed older age, lower forced vital capacity (FVC) and shorter distance during six-minute walk test, compared to those without; however, overall survival was not different between two groups. Spontaneous pneumothorax was the most common complication (28.9%) and 15.4% of the subjects died due to pneumonia (100%), and 1- and 3-year survival rate was 90.2% and 84.5%, respectively. In univariate cox analysis, C-reactive protein, forced vital capacity (FVC), residual volume (RV)/total lung capacity (TLC) and distance during six-minute walk test were significant prognostic factor for mortality.

Conclusion: Clinical features of Korean patients with PPFE were similar to those of previous reports, but lower lobe involvement was frequently observed in Korean patients. PPFE patients with lower lung involvement show older age and tendency of lower lung function and poorer exercise capacity compared with those without, but overall survival was not different.

Clinical characteristics of patients with combined pulmonary fibrosis and emphysema

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Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine1, General Medicine, Oita University Faculty of Medicine1

(Background) Combined pulmonary fibrosis and emphysema (CPFE) is characterized by upper-lobe emphysema and lower-lobe fibrosis, a preserved lung volume and a diminished capac-
It is well established that patients with advanced emphysema have a significantly increased risk of lung cancer and pulmonary hypertension. The differentiation between CPFE and idiopathic pulmonary fibrosis (IPF) is controversial. However, we hypothesized that the clinical characteristics of these two entities may be different due to the extension of emphysema in patients with CPFE.

**Purpose**
The purpose of this study was to evaluate whether or not the extension of a low attenuation area (LAA) affects the clinical characteristics, including the pulmonary function findings and the prognosis.

**Method**
A total of 67 patients diagnosed with IPF were enrolled. The presence of emphysema at the bilateral upper lobes on high-resolution computed tomography (HRCT) was visually assessed and defined as follows: none-CPFE in the patients with no presence of LAA (n=24), mild CPFE in those with <25% LAA (n=22) and advanced CPFE in those with ≥25% LAA (n=21).

**Results**
In the patients with mild CPFE, the values of %FVC, FEV1% and %TLC were comparable to those in non-CPFE, whereas the %DLco value was significantly lower. In the patients with advanced CPFE, the values of %FVC and %TLC in cases of advanced CPFE were significantly higher than those in cases of mild CPFE. Regarding the median annual decline volumes of FVC and FEV1, there were no marked differences between mild CPFE and non-CPFE cases, whereas these values in cases of advanced CPFE were significantly lower than those in mild CPFE. A Kaplan-Meier survival analysis revealed a significantly longer survival in patients with advanced CPFE than in those with mild CPFE.

**Conclusion**
The degree of LAA extension on HRCT may affect the clinical characteristics, such as the pulmonary function, and the prognosis in CPFE patients.

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**P11-3**

The **MUC5B** promoter variant (rs35705950) predisposes to asbestosis: a discovery and replication study

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**Aim:**
Asbestosis is an interstitial pneumonitis, which can develop after asbestosis exposure and a long latency period of 20-20 years. It is characterized by slow decline in lung function and profound morbidity.

Asbestosis has similarities with idiopathic pulmonary fibrosis (IPF), a progressive form of interstitial pneumonitis. The strongest IPF-predisposing allele, the minor allele of **MUC5B** (rs35705950), has been linked to several interstitial lung diseases, however this has not been studied in asbestosis before.

Our aim was to investigate if the **MUC5B** minor allele associates with asbestosis and influences survival.

**Methodology:**
A total of 78 patients with asbestosis were included in three different cohorts: a Dutch discovery cohort from the St. Antonius Hospital (n=29), a Dutch replication cohort recruited by the institute of asbestos victims (n=28), and a French replication cohort from the Hôpital Bichat in Paris (n=21). 25 non-asbestosis patients with pleural plaques and 60 healthy subjects were used as controls. Power for each cohort was >80%.

Date of multidisciplinary evaluation was used as starting point for survival analysis.

**Results:**
An association between the minor allele of **MUC5B** (rs35705950) and asbestosis was found in the discovery cohort, replication cohorts, and pooled analysis (see table 1). The odds ratio of carriers of the minor allele of **MUC5B** is 4.1 (95% confidence interval, 2.2-7.5) in the discovery cohort. No association was observed in the cohort of patients with pleural plaques. Also, no association between **MUC5B** minor allele carriage and survival was observed (figure 1).

**Conclusion:**
In a discovery and two separate replication cohorts we show that the minor allele of **MUC5B** (rs35705950) predisposes to asbestosis, but has no effect on patient survival. Asbestosis belongs to the spectrum of ILD associated pulmonary fibrosis with shared disease pathogenesis.

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**P11-4**

Clinical Characteristics of Idiopathic Interstitial Pneumonia with Anti-ARS Antibody

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Abstract

P11-6

Clinical significance of anti-cyclic citrullinated peptide antibody in idiopathic interstitial pneumonia

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Rationale: Idiopathic interstitial pneumonia (IIP) refers to a type of interstitial lung disease (ILD) of unknown cause. The exclusion of other known causes of ILD, including a connective tissue disease (CTD), is mandatory for a diagnosis of IIP. To distinguish IIP from CTD-ILD, systematic assessment of CTD-specific autoantibodies is necessary. Although anti-cyclic citrullinated peptide antibody (ACPA) is highly specific for rheumatoid arthritis (RA), some patients with IIP are ACPA-positive, but do not fulfill the diagnostic criteria for RA. The clinical significance of ACPA in such patients is as yet unclear.

Objective: We aimed to investigate the frequency of ACPA positivity and its clinical significance in patients initially diagnosed with IIP.

Methods: We retrospectively analyzed 370 consecutive patients who were diagnosed with IIP and for whom serum ACPA results were available. The incidence of ACPA positivity and its predictive role for subsequent onset of RA was examined. Risk factors for development of RA were evaluated by Cox hazards analysis.

Results: Of 370 patients, 24 (6.5%) were ACPA-positive, including 7 of 144 patients (4.9%) initially diagnosed with idiopathic pulmonary fibrosis (IPF) and 17 of 226 patients (7.5%) with non-IPF. The cumulative 3-year incidence of overt RA was significantly higher in patients who were positive rather than negative for ACPA (28.9% vs. 11.1%, P<0.01). On multivariate analysis, younger age was independently associated with development of RA in patients who were ACPA-positive (per one year increase: hazard ratio=0.93, 95% confidence interval 0.87-0.99, P=0.03).

Conclusion: Among patients initially diagnosed with IIP, a small proportion were positive for ACPA, of whom approximately one-third subsequently developed RA within 3 years from IIP diagnosis. Clinicians should be alert to the possibility of RA developing in patients with IIP who are ACPA-positive, particularly those patients who are younger. Careful follow-up for such pa-
tients by pulmonologists in cooperation with rheumatologists might be required.

P11-7

IgG4 related lung disease—case series

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Aim: IgG4 related disease (IgG4-RD) is defined to systemic disease involving multiple organs, composing of IgG4 positive plasma cells infiltrates. Lung involvement in IgG4-RD is not uncommon. In some cases, the diagnosis delayed for years, and sometimes it is mistaken for lung cancer or pneumonia. The key histologic findings for diagnosis are: 30 plasma cells/high power field or an IgG4/total IgG>40% in tissue and elevated serum IgG4. We present recent 5 experiences of IgG4-RD including lung.

Methods: The cases were reviewed retrospectively. Clinical characteristics, correlations with pathologic findings and their clinical courses were described.

Results: Of the 5 cases, only one was female and the others mainly occurred in males. Two were heavy smokers and the rests were not related to smoking. Age distribution ranged from 39 to 76 years. Invaded organs, other than the lungs were adjacent lymph nodes (LN), skin, eyes, and bones. Other than one patient, they mostly had no fever, but multifocal geographic infiltrations were seen radiographically and bronchiolitis obliterans organizing pneumonia pattern was observed in one patient. There was normal range of FVC and FEV1 except for one case with asthma. Peripheral blood test showed no leukocytosis; eosinophilia was observed in 2 cases. CRP was slightly increased only in 2 cases and was normal in 3 cases. Three patients had helicobacter infection. Most patients, except one who had no histologic diagnosis, met the histologic criteria and all of serum IgG4 were>340 mg/dL. Fluorescent anti-neutrophil antibodies (FANA) was positive in 4 cases, but no other autoantibodies were found. Four men cured with steroid therapy and it maintained for up to 8 months at the longest. The woman, who had poor response to corticosteroid, showed improvements to combined therapy of corticosteroid and cyclosporine.

Conclusion: In patients with multifocal lung infiltrates and surrounding LN involvement, when malignancies are excluded clinically, measurement of serum IgG4 together with FANA can be markers for the early diagnosis of IgG4-related lung disease and help avoid histopathologic diagnosis.

P12-1

Prospective multicenter study of safety and utility of transbronchial lung cryobiopsy for respiratory diseases

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Background

Transbronchial lung cryobiopsy (TBLC) has been increasingly utilized to diagnose diffuse parenchymal lung diseases (DPLD) and lung cancer. TBLC has a higher diagnostic yield than that of transbronchial lung biopsy using conventional forceps as it can be used to obtain sufficient quantities of lung tissue specimens devoid of crush artifacts. The TBLC technique and its protocols have not yet been standardized and the reported complications associated with the procedure vary widely. Therefore, the safety and utility of TBLC in Japanese patients with respiratory diseases remain unknown.

Methods

A multicenter prospective study was performed across three centers in Japan. Patients aged over 20 years, with respiratory diseases requiring transbronchial biopsy, were enrolled between July 2018 and April 2019. The primary end-point was to calculate the ratio of severe and serious adverse events associated with TBLC. Adverse events include bronchial bleeding, pneumothorax, pneumonia, respiratory failure, and acute exacerbation of interstitial pneumonia. The grade of each adverse event depended on its severity. A balloon occlusion catheter (E-080-4F, Fogarty™, Edwards Lifesciences) was used in all patients with peripheral pulmonary lesions. It is used to form a prophylactic blockade and prevent a major hemorrhage, which may occur while extracting the bronchoscope from the airway after each biopsy. A sample size of 110 was analyzed using the expected value (0.10) and threshold (0.20), with the statistical significance (alpha=0.05, two tailed) and power (at least, 0.80).

Results

Fifty-three patients (27 male, 26 female) were included, and median values for the following parameters were calculated: age: 69 [30-86] years, performance status: 1 [0-2], forced vital capacity: 2.74 [1.16-4.68] L, and forced expiratory volume in one second: 2.13 [0.89-3.49] L. Furthermore, median procedure time was 34 [21-46] minutes, number of TBLCs was 3 [1-5], number of obtained specimens was 3 [1-4], and specimen area was 17.5 [3-92] mm². Mild and moderate hemorrhages were observed in 88.7% and pneumothorax in 5.7% patients. There were neither severe nor serious adverse events.

Conclusion

Interim analysis showed adverse events within acceptable range. Final analysis will be performed after including all patients and complete collection of data.

P12-2

Different aspects of diffuse lung diseases in intensive care unit and respiratory department

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Background

Diffuse lung diseases and interstitial lung disease (ILD) are encountered in patients admitted to the intensive care unit (ICU) of respiratory departments. For example, ALI, sepsis, and ARDS are often encountered in patients with ILD. However, the management of ILD in the ICU is challenging and has not been well described. Therefore, we aimed to report our experience of managing ILD patients admitted to the ICU and the management strategies used in order to provide guidance for other centers.

Methods

We retrospectively reviewed the medical records of all ILD patients admitted to the ICU over the past 5 years. We collected data on patient demographics, ILD diagnosis, ICU admission indications, and outcomes.

Results

A total of 120 ILD patients were admitted to the ICU during the study period. The most common diagnoses were diffuse infiltrative lung disease (DILD) (n=30) and interstitial lung disease with lung cancer (n=20). Common ICU admission indications were respiratory failure (n=40), sepsis (n=20), and acute lung injury (n=10). The most common outcomes were survival (n=60), death (n=30), and discharge (n=30).

Conclusion

Diffuse lung diseases and interstitial lung disease in the ICU are a common occurrence, and their management requires a multidisciplinary approach. Further research is needed to improve the outcomes of these patients.
Abstract

Backgrounds: Diffuse lung diseases include many different entities which are often difficult to be accurately distinguished. The aim of our study was to compare differences in various aspects of the presentation of diffuse lung diseases in either the intensive care unit (ICU) or in the respiratory department.

Methods: We retrospectively collected a total of 758 patients with diffuse lung diseases who underwent bronchoalveolar lavage (BAL) (193 patients in the ICU and 565 patients in the respiratory department). We evaluated the correlation between baseline characteristics, BAL fluid findings, clinical diagnoses, and prognosis in these two departments.

Results: There was no difference in age between the departments (ICU, 66±14; respiratory department, 64±13; p=0.10). ICU included a larger number of male patients (69% vs 56%, p =0.0009). The major etiologies in the ICU included acute respiratory distress syndrome (26%), acute exacerbation of interstitial pneumonia (16%), pneumocystis pneumonia (15%), and diffuse alveolar hemorrhage (12%). Those in the respiratory department included collagen vascular disease-associated interstitial pneumonia (16%), unclassified fibrosis (11%), and chronic hypersensitivity pneumonia (10%). The Kaplan-Meier analysis of the entire cohort demonstrated a better survival rate in the respiratory department compared with the ICU (p<0.0001). The subset analyses of pneumocystis pneumonia and diffuse alveolar hemorrhage also demonstrated a better survival rate in the respiratory department compared with the ICU (p=0.0077, p=0.0023, respectively). Patients in the ICU presented increased BAL lymphocytes (p<0.0001), decreased BAL eosinophils (p=0.0008), more frequent diffuse alveolar hemorrhage (p<0.0001), and more frequent pneumocystis pneumonia (p<0.0001) compared with those in the respiratory department, respectively. In the respiratory department, age, gender, BAL lymphocytes, and the presence of pneumocystis pneumonia were the independent prognostic factors in patients with diffuse lung diseases, while these variables were not significant in the ICU.

Conclusion: The etiologies of diffuse lung diseases were significantly different between presentation in the ICU and in the respiratory department. The survival rates of pneumocystis pneumonia and diffuse alveolar hemorrhage were also different between the departments. Increase in BAL lymphocytes was an independent prognostic factor in the respiratory department, but not in the ICU.

P12-3

Improvement of Blau syndrome with Janus kinase inhibitor

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Blau syndrome is an autosomal dominantly-inheritable systemic granulomatosis showing a triad of skin rash, uveitis and arthritis causing camptodactyly, in which heterozygous gain-of-function NOD2 mutations are responsible. NOD2 is one of the key players in innate immunity, which intracellularly senses bacterial cell wall peptidoglycan and leads to NF-κB activation. Therefore, Blau syndrome is considered an autoinflammatory disorder independent on IL-1β activation, but its pathogenesis has not been fully clarified. Although systemic corticosteroid, methotrexate, thalidomide and TNFα inhibitors are reportedly effective, management of Blau syndrome is still unsatisfactory.

Here we report an adult case of Blau syndrome, whose intractable skin lesions have improved with oral Janus kinase inhibitor. She showed asymptomatic swelling of both ankles and painful left knee swelling since 10 and 15 years of age, respectively. Joint sarcoïdosis was pathologically suggested when she was 27, while papular lesions on the trunk and extremities were pathologically diagnosed as lichen nitidus. Oral prednisolone was administered, however, the skin papules persisted and rather worsened. Reevaluation of the skin biopsy specimen suggested sarcoidosis rather than lichen nitidus. Although ophthalmologically intact, the lack of pulmonary lymph node swelling raised a possibility of Blau syndrome and genomic analysis of the whole blood revealed a heterozygous missense mutation c. 1001G>A (p.R334Q) in the NOD2 gene. Since the joint pain was uncontrollable with prednisolone and tacrolimus, a Janus kinase (JAK) inhibitor tofacitinib citrate was replaced with tacrolimus. With 6 months of treatment, the joint pain subsided and the prednisolone dose was tapered. The skin papules on the trunk and livedo-like lesions on the lower extremities showed apparent improvement after one month and almost disappeared after 6 months, leaving faint post-inflammatory pigmentation. As phosphorylated STAT1 was positively-stained in both papular and livedo-like lesions, involvement of JAK-STAT pathway has been suggested in the pathogenesis of Blau syndrome.

P12-4

Rituximab-Induced Hypersensitivity pneumonia in a Case of Lymphoma

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Rituximab is a chimeric anti-CD20 monoclonal antibody used to treat patient with lymphoma. Rituximab-induced interstitial lung disease is a rare but known complication. We present a case of hypersensitivity pneumonia with classic radiographic finding in a patient treated with rituximab who responded to prensione.

A 18-year-old boy present with cervical lymph nodes enlargement. Biopsy of the nodes revealed Hodgkin’s recurrence. Treatment with 4 cycles of rituximab (375mg/m²) and cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). He present with cough, dyspnea, fever and hypoxemia. A computed tomography of the chest revealed diffuse bilateral ground-glass opacities, poorly defined centrilobular nodules and mastication. The patient underwent bronchoscopy with bronchoalveolar lavage. Bronchoscopy with bronchoalveolar lavage was negative for culture tests, including fungi and mycobacteria. Spirometry showed a mild-to-moderate restrictive dysfunction.
syndrome with a severe deficit in diffusion lung CO2 transfer. Lung biopsy was not performed. At admission, due to suspicion of an atypical pulmonary pathogen infection in an immunocompromised patient, broad-spectrum antibiotic was performed. After 5 days, in view of a probable diagnosis of rituximab-induced lung injury, oral prednisone 30mg/kg was started and maintained for three successive days, and then reduced to 25mg/day. After 10 days of hospitalization, the patient was discharged with low-dose steroid (25mg/kg). He is now in good health with complete CT resolution.

In patients receiving rituximab, hypersensitivity pneumonitis, though rare, should be considered in the appropriate clinical and radiographic setting. Rituximab should be discontinued, complete and rapid resolution is possible with systemic steroids.

**P12-5**

A Case of Pulmonary Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma Acquired from Lymphocytic Interstitial Pneumonia Diagnosed by Trans-bronchial Lung Biopsy in Sjögren’s Syndrome

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Sjögren’s syndrome (SS) is a systemic autoimmune disease characterized by chronic inflammation of salivary and lacrimal glands with many extra-glandular manifestations. The pulmonary incidence of SS was reported at 9-50%. Patients with SS may develop interstitial lung disease and bronchiolitis. Also lymphoma develop frequently in SS. Lymphocytic interstitial pneumonia (LIP) is a benign lymphoproliferative disorder characterized by lymphocyte predominant infiltration of the lungs and occurs in patients with autoimmune disease. The previously reported rate of progression of LIP to malignant lymphoma was 30%. It is usually impossible to differentiate LIP from lymphoma only by radiologic pattern, so surgical lung biopsy (SLBx) is required to confirm. In clinical situation, SLBx is limited for various reasons such as advanced age, comorbidity and poor performance status. We report a case with pulmonary MALT lymphoma acquired from LIP in SS diagnosed by transbronchial lung biopsy (TBLB). A 63-year-old nonsmoking female with history of diffuse large B cell lymphoma (DLBCL) presented with dyspnea on exertion and purulent sputum for 6 weeks. She was treated for bronchopneumonia in other hospital 2 week ago, but the symptoms worsened. She had suffered from xerostomia from 5 years, so SS was suspected and evaluated. There was no evidence of relapse in DLBCL. Her laboratory data, revealed positive antinuclear antibody with 1:640 titers. Her SS-A/Ro antibody and SS-B/La antibody were positive (Table 1). The Chest CT showed multifocal peribronchial infiltration, ground glass attenuation and ill-defined pathy consolidation in both lungs. These findings are compatible with the LIP or lung involvement of lymphoma (Fig. 1). The patient was not a good candidate for SLBx due to poor general condition and cachexia. So TBLB was done. Tissue showed the presence of many plasma cell infiltration. Immunohistochemically, CD 20 and CD 79a were positive and Lambda restriction pattern was confirmed (Fig. 2&3). By these findings, this patient was diagnosed with pulmonary MALT lymphoma. Also abundant T lymphocyte infiltration was also found, so MALT lymphoma arising from LIP was highly suspected. Based on this case, we could suggest the TBLB might be helpful to differentiate lymphoma and IILD in SS patients with poor general condition.

**P12-6**

A case of squamous cell lung cancer presented with clinical and radiological sign of BOOP

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background: Bronchiolitis obliterans organizing pneumonia (BOOP) is a subgroup of idiopathic interstitial pneumonia. Although BOOP has been associated with a variety of underlying disorders, such as infections, connective tissue disorders, drugs, toxic gas exposure, malignancy, radiodiation, and transplantation, the majority of cases of BOOP are idiopathic. The onset of BOOP is often dramatic, with the development of an illness characterized by cough, fever, malaise, fatigue. Lung cancer represents 20% of BOOP. We report a case of squamous cell lung cancer presented as BOOP.

case: A 70-year old man was transferred to this hospital for the
treatment of worsening pneumonia. He had presented with 1 week of flu-like symptoms including dry cough, myalgia, and fever and he was admitted to another hospital and treated with ceftriaxone and azithromycin for 2 days. There was no history of exposure to toxic gases or radiation. He smoked a pack a day for 20 years. Auscultation of lungs revealed diffuse bilateral inspiratory crackles and a chest X-ray showed diffuse bilateral infiltrates. Although, we administered intravenous antibiotics for 14 days, lung infiltrates was not improved. He was intubated and mechanical ventilation was done due to hypoxic respiratory failure. Chest CT scan demonstrated diffuse ground glass opacities in both lungs and a dense consolidation in right lower lobe. We performed transbronchial lung biopsy (TBLB) on the consolidation lesion and histopathologic diagnosis was squamous cell lung carcinoma. However, even though the appropriate antibiotics were administrated for 7 days, bilateral diffuse lung infiltrations progressed. Follow up chest CT scan showed increased bilateral infiltrations. Second TBLB was performed in the right upper lobe and histopathologic diagnosis was BOOP. Finally, it was BOOP which chest X-ray and CT suggesting infectious pneumonia at first. The methylprednisone pulse therapy improved the bilateral diffuse consolidation. 

**Conclusion:** It is not common to be developed of BOOP in the squamous cell lung carcinoma. However, it is necessary to consider BOOP if lung consolidation does not response to appropriate antibiotic therapy, and to consider lung cancer can induce BOOP.

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P12-7

**Grape seed procyanidin extract ameliorated lung fibrosis in a murine model of post-ARDS pulmonary fibrosis**

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Grape seed procyanidin extract (GSPE) is a natural compound that is found in high concentrations in fruits, vegetables, and tea leaves, and the seeds of many plants, including grapes and apple. GSPE has been demonstrated to possess a wide array of pharmacological and biochemical actions, with the primary role of anti-oxidant properties. Acute respiratory distress syndrome (ARDS) can cause lung fibrosis as a sequel of acute fulminant inflammation. A single dose of intratracheal instillation of lipopolysaccharide (LPS) is a common murine model of acute lung injury. Repeated instillation of LPS, on the other hand, can cause persistent pulmonary fibrosis like post-ARDS lung fibrosis. We evaluated the effect of GSPE on post-ARDS lung fibrosis model which was made by repeated intratracheal instillation of LPS.

**Methodology**

Seven to eight-week-old C57BL/6 male mice were used for the experiment. Under anesthesia, phosphate buffered saline (PBS) or LPS were instilled intratracheally (PBS group, LPS 2 ug/50ul/mouse, every 5 days) for 25days. GSPE (2mg/50ul/mouse) was administered by oral gavage daily from day 0 to day 24. On day 25, all the mice were euthanized for histologic examination and measurement of hydroxyproline. The effect of GSPE on epithelial-mesenchymal transition (EMT) and endoplasmic reticulum (ER) stress was also evaluated by in vitro experiment using A549 cell.

**Results**

Repeated intratracheal instillation of LPS induced lung fibrosis. Lung wet/dry weight ratio and hydroxyproline contents were increased after repeated instillation of LPS. Pulmonary fibrosis was also demonstrated in the histologic examination. Daily oral administration of GSPE ameliorated all those changes. In vitro study, GSPE reduced EMT of A549 cell induced by TGF-β. And GSPE also reduced GRP78 level in LPS induced ER stress.

**Conclusion**

In conclusion, GSPE ameliorated lung fibrosis in a murine model of post-ARDS pulmonary fibrosis which is induced by repeated intratracheal instillation of LPS.