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VASCULITIS AND DIFFUSE LUNG DISEASES

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Serum Amyloid A in lung transplantation

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Abstract. *Background:* Serum Amyloid A (SAA) is an acute phase protein and we analyzed its concentrations in lung transplantated patients (LTX). *Methods:* 26 LTX patients (58.6 ± 11 years) and 11 healthy controls (55 ± 11.3 years). Three groups of LTX patients: acute rejection (AR, 7) bronchiolitis obliterans syndrome (BOS, 3), acute infection (INF, 9) and stable patients (NEG, 7). *Results:* In LTX patients SAA concentrations were significantly increased, particularly in AR and INF. In LTX-AR patients were observed a correlation between SAA levels and peripheral CD4+ lymphocyte percentage (r=0.9, p<0.01) and a reverse correlation with FVC percentages (r -0.94, p=0.01). *Conclusions:* SAA may represent a potential biomarker of LTX acute complications, with a prognostic value in AR. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 2-7)*

Key words: serum amyloid A, serum biomarkers, lung transplantation

Abbreviations: serum amyloid A (SAA), lung transplantation (LTX), acute rejection (AR), acute infection (INF), stable patients (NEG)

Introduction

Lung transplantation (LTX) is an option for end-stage lung disease patients no longer responsive to optimal medical therapy or for which no effective medical or surgical treatment is available (1,2). Complications of LTX include Acute Rejection (AR), a complex manifestation of vascular and parenchymal damage due to the action of T lymphocytes, macrophages and other inflammatory mediators. AR commonly occurs at least one week after LTX, time necessary for the differentiation of the effector T lymphocytes and for the production of specific antibodies (3). T lymphocytes play a decisive role in AR by responding to alloantigens, including MHC molecules, expressed on endothelial and parenchymal transplant cells. Once activated, T lymphocytes induce direct lysis of transplanted cells and cytokine production facilitating the recruitment and activation of inflammatory cells leading to tissue necrosis (3). The gold standard for AR diagnosis is transbronchial biopsy. There are various degrees of rejection: in most advanced stages, there is also a widespread commitment to alveolar and interstitial space (3). AR is clinically associated with nonspecific signs, consisting of cough, dyspnoea, and fever, associated with a functional reduction of FEV1 and FVC >10%. High-resolution CT scan (HRCT) cannot differentiate this condition from other complications such as

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reperfusion injury and infections. Chronic lung graft dysfunction (CLAD) constitutes the first cause of death after the first year from the transplant and is characterized by a histological pattern of obliterative bronchiolitis (BOS) (4). BOS is a syndrome caused by an irreversible obstruction of the distal airways associated with progressive dyspnea and coughing; HRCT can reveal hyperinsufflation and bronchiectasis. The initial pathological process of BOS is characterized by a lymphocyte infiltration of the submucosa and the airway epithelium, a condition known as lymphocytic bronchiolitis (3, 4).

Infections of the respiratory tract are associated with infiltrates at chest X-ray scan and with reduction of pulmonary function. For this reason, it is commonly difficult to differentiate, in LTX patients, infections from rejection on the basis of clinical and radiological evaluations (5, 8) and it is generally necessary to perform bronchoscopy with BAL and transbronchial biopsy. After the first month of transplantation, in fact the reactivation of latent infections from viruses (Herpes and Cytomegalovirus), or fungi (such as Pneumocystis Jirovecii) is a common event that is necessary to recognize and differentiate from AR (8, 9).

Serum amyloid A (SAA) is an acute phase protein with multiple immunological functions involved in lipid metabolism and inflammatory reactions. Four genes on chromosome 11 responsible for the synthesis of SAA1, SAA2, SAA3 and SAA4 have been identified in the human genome (10, 11). A-SAA is a single polypeptide of 104 amino acid residues; although its exact tertiary structure is unknown, the critical role of the 10 amino-terminal residues is recognized in the formation of amyloid fibrils that bind high density lipoprotein (HDL) (10). Proteins SAA1 and SAA2 act as acute phase reactants in plasma and are also plasma precursors of amyloid A fibrils (12-15). SAA has been studied in many biological fluids from patients with different lung diseases, including lung cancer and obstructive/restrictive lung diseases (10,12). Most plasma A-SAA is synthesized by the liver, although extrahepatic synthesis by macrophages, endothelial cells, smooth muscle fibrocells, adipocytes and cancer cells has been described (13, 15). Its role as a potential prognostic biomarker has been suggested in carcinogenesis process (16), granulomatous interstitial lung diseases (17) and obstructive lung disorders (18-20).

This pleiotropic protein with various immunological functions has never been evaluated in patients undergoing LTX: this study aims to evaluate SAA behavior in different conditions of LTX patients and its prognostic value.

Materials and Methods

Study population and design of the study

SAA levels were evaluated in a population of 26 patients undergoing LTX at Siena Regional Referral Center for Sarcoidosis and other Interstitial Lung Diseases, Lung Transplantation Unit. The indication and timing of the LTX were set according to international guidelines (25). These 26 patients (13 males, 58.6 ± 11 years) included: 16–single and 10 bilateral transplants. As a control group, SAA were measured in a population of 11 healthy controls (3 males, 55 ± 11.3 years). LTX group was affected by: Idiopathic Pulmonary Fibrosis (IPF) (n = 12), Cystic Fibrosis (n = 5), Bronchiectasis (n = 1), Pulmonary emphysema (n = 5). Patients undergoing LTX were further subdivided, based on clinical, radiological and histological data, in different groups: AR (7 patients, 3 males, 51.4 ± 5.9 years); BOS (3 patients, 2 males, 64.6 ± 5.7 years); infection (INF) (9 patients, 7 males, 60.1 ± 7.5 years); Stable patients (NEG; 7 patients, 3 males, 48.4 ± 16.1 years). Clinical, functional and radiological data were collected from all these patients in a specific database. In particular, the following parameters were taken into consideration:

- *Serum evaluations*: blood count, ESR, CRP, PT%, APTT sec, fibrinogen, D-dimer, LDH, creatinine, urea, total bilirubin, direct bilirubin, GOT, GPT, ferritin, transferrin, C3 - C4, IgA, IgG, IgM, total cholesterol, cholesterol HDL, LDL cholesterol, triglycerides, albumin (% and absolute value of the predicted), alpha1- alpha2-β1- β2- γ globulins (%).

- *Lymphocytic typing of peripheral venous blood*: Cell differential count was performed on cytocentrifuge preparations. Peripheral lymphocyte phenotype was characterized using flow cytometry (FacsCantoII; Becton&Dickinson) and monoclonal antibodies (anti-CD3, CD4, CD8, CD19, NK and CD4/CD8; Becton&Dickinson).

- *Bronchoalveolar lavage (BAL)*: Bronchoscopy with BAL was performed in all patients for diagnostic reasons. Bronchoalveolar lavage cell popula-

tion were reported as percentages of macrophages, lymphocytes, neutrophils and eosinophils. Lymphocyte phenotype was analyzed by flow cytometry (FacsCantoII; Becton Dickinson) using anti -CD3, -CD4, -CD8 monoclonal antibodies.

- *Pulmonary function tests (PFR)*: The following lung function measurements were recorded, using a Jaeger Body Plethysmograph with corrections for temperature and barometric pressure: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity (TLC), residual volume (RV), carbon monoxide lung transfer factor (TLCO) and capacity carbon monoxide lung transfer factor/alveolar volume (TLCO/VA). TLCO measurement could not be collected in 10 patients unable to perform properly single-breath maneuver. PFTs were performed after at least 2 hours from exhaled NO measurements.

SAA assay

Serum sampling was performed in all patients after 10 hours of fasting. The assay of the SAA was carried out according to the enzyme immuno-enzymatic method (Enzyme Linked-Immuno-Sorbent Assay) kit Invitrogen (Invitrogen Corporation). The wells of the microplates were coated with a highly purified and specific human monoclonal antibody SAA. During the first incubation, the standards with known SAA contents, controls and samples were pipetted into the coated wells, followed by the addition of a second biotinylated monoclonal antibody. After washing, the enzyme Streptavidin-peroxidase was added; the latter by binding to the biotinylated antibody, has completed the characteristic sandwich of the ELISA method. After a second incubation and a second washing (necessary to remove the unbound enzyme) a solution was added, in order to be accepted by the bound enzyme to produce color. The intensity of the resulting coloring was considered directly proportional to the concentration of Human SAA present in the samples analyzed.

Statistics

Statistical analysis was conducted with GraphPad Prism v 6.0 software for Windows, using non-parametric tests; the differences between groups of two variables were studied with the Mann-Whitney test, while the variance analysis was conducted with the Kruskal-Wallis test. As regards the correlations between the clinical-functional parameters and the values of the SAA, the Spearman correlation index "r" was used. Kaplan Meier curves with log-rank test for curve comparison were conducted for survival analysis. Differences with $p < 0.05$ were considered significant. All data were expressed as mean ± standard deviation, unless otherwise indicated.

Results

The clinical characteristics of the population were reported in Table 1 revealing that the different populations, included in the study, were sex and age matched. Serum levels of SAA in LTX subgroups were listed in Table 2 and they resulted significantly increased in LTX patients compared to healthy controls ($p < 0.001$) (Fig. 1). LTX patients with AR or INF showed significantly higher SAA levels than healthy controls ($p = 0.01$) and stable LTX patients (NEG) ($p < 0.05$).

In LTX patients statistically significant correlations were found between SAA levels and the following parameters: C reactive protein (CRP) (r 0.46, $p = 0.02$); ferritin (r 0.58, $p = 0.008$); α1-globulins (alpha1%) (r 0.56, $p = 0.02$); C3 (r 0.56, $p = 0.04$) and LDL cholesterol (r 0.42, $p = 0.06$) (Figs. 2 and 3). In AR group, statistically significant correlations were found between SAA serum levels and peripheral CD4+ T-lymphocyte percentages (r 0.9, $p = 0.01$) and FVC percentages (r -0.94, $p = 0.01$) (Figs. 4 and 5). Regarding survival analysis, we choose the 75° percentile of SAA levels (8267 ng/ml) as the cut-off value to stratify the population. In our population, patients with SAA concentrations above 75° percentile showed a worse prognosis than those with lower levels, even not significantly (log rank test, $p=0.0694$; HR 3.68, 95% CI 0.9 to 15.06) (Fig. 6).

Discussion

SAA is a pleiotrophic protein involved in the regulation of inflammatory processes as well as in lipid metabolism (21, 22). Its concentrations is increased in serum of patients with chronic inflammatory lung diseases, sarcoidosis for example. Its role as a potential biomarker of different lung diseases has been established, although no data is available on LTX patients

Table 1. Patient demographics, respiratory function tests (PFR) and bronchoalveolar lavage (BAL) cellular composition in patients of the present study with Idiopathic Pulmonary Fibrosis (IPF) and undergoing Pulmonary Transplantation (LTX AR = transplanted with acute rejection, LTX CLAD = transplanted with chronic rejection, LTX INF = transplanted with acute infection, LTX NEG = stable transplanted, CONTROLS=healthy controls); (* n.d = data not available)

Data	LTX AR	LTX CLAD	LTX INF	LTX NEG	Controls
N° pt	7	3	9	7	11
Age (years)	51,4 ± 5,9	64,6 ± 5,7	60,1 ± 7,5	48,4 ± 16,1	55 ± 11.3
Sex (male)	3 (42,8%)	2 (66,6%)	7 (77,7%)	3 (42,8%)	3 (27.2%)
PFR					
FEV1 % pred	66,6 ± 11,2	n.d*	61,7 ± 19,9	52,6 ± 21,6	n.d
FVC % pred	72,0 ± 7,6	n.d	71,8 ± 8,7	63,4 ± 13,2	n.d
ITGV % pred	109,8 ± 24,1	n.d	125,1 ± 71,7	139,7 ± 43,4	n.d
TLC % pred	92,2 ± 13,0	n.d	93,8 ± 42,4	106,1 ± 27,0	n.d
RV % pred	138,6 ± 36,5	n.d	147,3 ± 98,5	196,0 ± 89,4	n.d
DLCO % pred	45,8 ± 11,3	n.d	62,7 ± 9,2	57,9 ± 14,8	n.d
KCO % pred	71,3 ± 10,0	n.d	94,2 ± 14,7	80,0 ± 25,0	n.d
BAL					
Cell tot (106)	6,5 ± 3,8	n.d	6,4 ± 4,9	9,5 ± 4,7	n.d
Cell 103/ml	178 ± 50,3	n.d	165,2 ± 56,5	337 ± 182,4	n.d
Macrophages %	61,1 ± 31,8	n.d	56,3 ± 30,8	54,6 ± 36,0	n.d
Lymphocytes %	15,6 ± 11,2	n.d	24,5 ± 29,9	22,3 ± 12,8	n.d
Neutrophils %	16,5 ± 17,4	n.d	18,6 ± 15,3	23 ± 28,3	n.d
Eosinophils %	10 ± 17,3	n.d	5,6 ± 9,0	0	n.d
RCD4/CD8	0,6 ± 0,5	n.d	0,4 ± 0,3	0,3 ± 0,1	n.d

Table 2. Serum levels of SAA in LTX patients (* = groups of patients in the study where the high levels of SAA are statistically significant)

LTX AR*	115.60 ± 38.04 μg/ml
LTX CLAD	109.37 ± 56.04 μg/ml
LTX INF*	127.89 ± 38.88 μg/ml
LTX NEG	76.84 ± 39.06 μg/ml
CONTROLS	43.02 ± 25.18 μg/ml

(26-28). In our study SAA concentrations were evaluated in LTX to contribute to the definition of novel biomarkers of clinical utility in this field. Serum levels of SAA, as expected, correlated with other acute phase proteins such as CRP, C3, alpha1-globulin and ferritin concentrations, bio-indicators already demonstrated to interfere with inflammatory and infective mechanisms occurring in LTX patients.

Although the small sample size and monocentric design of the study could influence the poten-

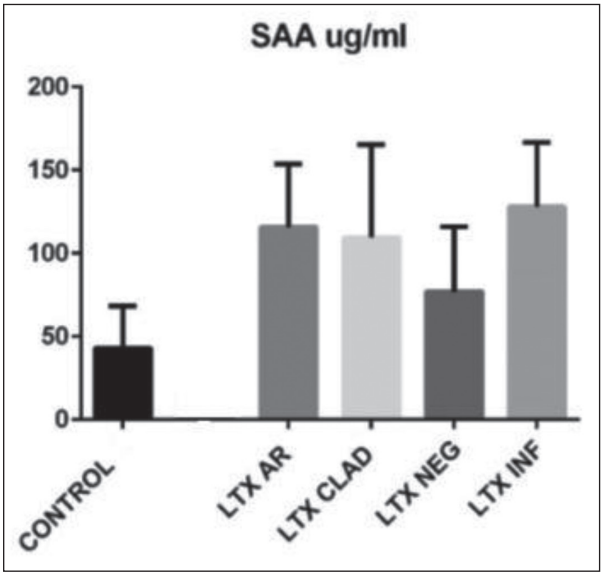

Fig. 1. Statistically significant differences found between serum levels of SAA in controls and in LTX patients with acute rejection (LTX AR) (p = 0.01), in patients with acute infection (LTX INF) (p = 0.01). No significant differences were found between the levels of SAA in LTX patients with CLAD and stable transplant patients (NEG) compared to healthy controls

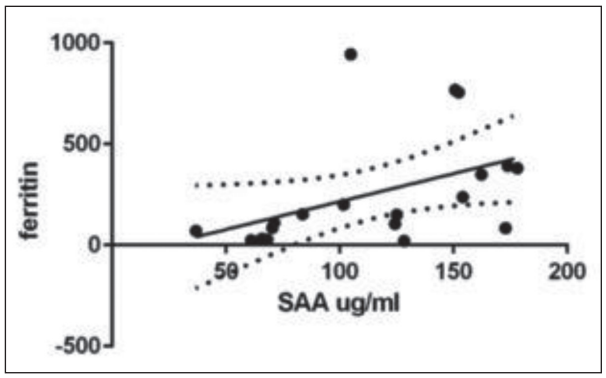

Fig. 2. Positive statistical correlation between SAA and Ferritin values in LTX patients (r 0.58, p = 0.008).

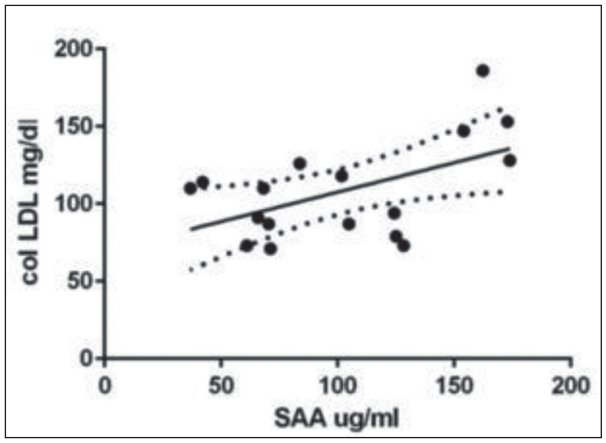

Fig. 3. Positive correlation between SAA and LDL cholesterol (with LDL) in LTX patients (r 0.42, p = 0.06).

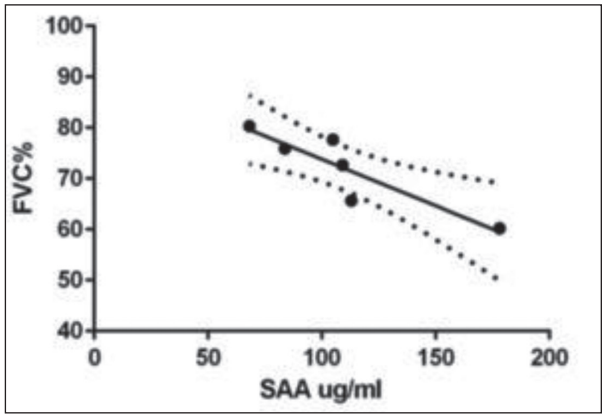

Fig. 4. Negative statistical correlation between SAA and FVC (% of predicted) values in LTX patients with acute rejection (r -0.94, p = 0.01).

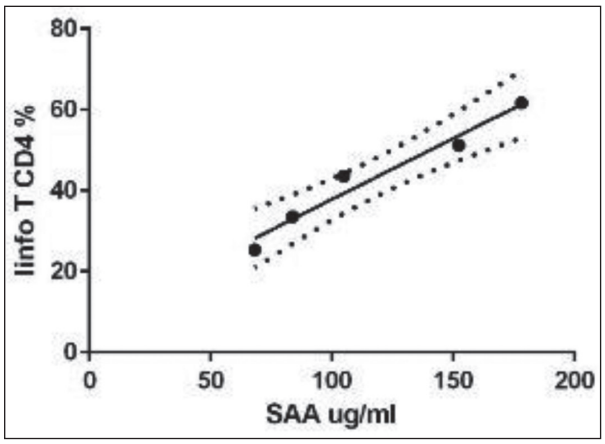

Fig. 5. Graphical representation of the statistical correlation between SAA and CD4 + T lymphocytes of peripheral venous blood (lymphoid T CD4%) in lung transplanted patients with acute rejection (r 0.9, p = 0.01).

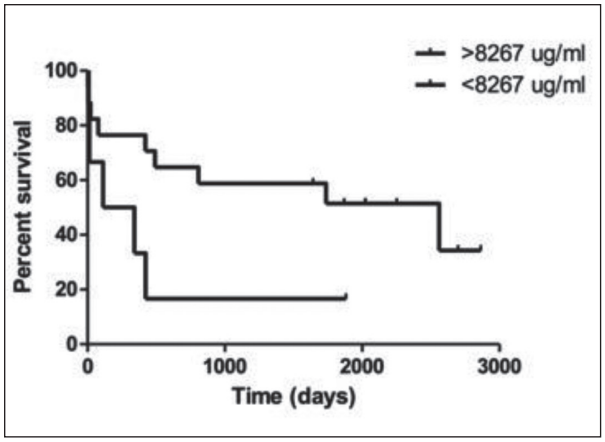

Fig. 6. Kaplan-Meier curves for the comparison of survival time in a population of LTX patients, stratified according the 75° percentile of SAA levels.

tial interpretation of the results about the role of SAA in predicting post-transplant complications, our results showed SAA concentrations higher in AR and INF subgroups than in stable LTX patients and controls. This bioindicator was overexpressed in patients with acute complications as a consequence of proinflammatory events, occurring in particular during AR (23). AR patients presented the highest SAA values, that were also correlated with peripheral CD4+ lymphocyte percentages. This data supported the crucial role of CD4+ T cells in AR pathogenesis through a potential SAA signaling that may activate macrophages and overproduction of different acute phase proteins (24). It can be hypothesized that in-

creased SAA levels induce proinflammatory CD4+ cells functions promoting AR. Despite small sample size of our study, outcome analysis was performed and showed a trend between elevated SAA levels and mortality. This data, event if not significant, is interesting and may be driven by the increase of SAA in AR or ongoing infections in LTX, that are both associated with a worse outcome (7). To clarify this point, our data needs to be validated in a larger cohort of patients with a prospective multicenter study focused on a single type of lung transplant complication such as acute rejection.

Moreover, an inverse correlation was observed between SAA levels and FVC percentages in AR patients, suggesting a prognostic role of SAA in acute complications of LTX, rather than a diagnostic biomarker.

In conclusion, SAA resulted an intriguing molecule with a potential prognostic value in patients with AR or infections after lung transplantation.

L.V. and E.B. conceived of the presented idea, D.B. and A.F. developed the theory, P.C., M.d. and L.B. performed the computations, P.P and L.L discussed the result and contributed to the final manuscript, F.G. and M.M. performed the radiological evaluations and designed the study, D.S. and P.S. planned the study and the analysis, P.R. encouraged the authors contributed to the final version.

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Serum soluble interleukin-2 receptor level is a predictive marker for EBUS-TBNA-based diagnosis of sarcoidosis

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Abstract. *Background:* Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a widely available diagnostic tool for suspected stage I/II sarcoidosis. Combination of EBUS-TBNA and transbronchial lung biopsy (TBLB) has been proposed as diagnostic procedure in clinical settings. *Objectives:* The aim of this study was to assess the diagnostic yield of combined EBUS-TBNA and TBLB and identify the markers correlated with a high diagnostic rate. *Methods:* We retrospectively analyzed the data of 37 patients with suspected stage I/II sarcoidosis with enlarged hilar or mediastinal lymph nodes on computed tomography (CT) images. These patients had been scheduled to undergo EBUS-TBNA and TBLB. Serum levels of sarcoidosis markers (angiotensin-converting enzyme [ACE], soluble interleukin-2 receptor [sIL-2R], and lysozyme), CT findings, and examination techniques were evaluated as predictive markers for diagnosis. *Results:* Of the 37 patients, 32 had undergone both EBUS-TBNA and TBLB, while the remaining 5 patients had only undergone EBUS-TBNA. The diagnosis was confirmed by TBLB in 16 of the 32 patients (50.0%), EBUS-TBNA in 31 of the 37 patients (83.8%), and combined TBLB and EBUS-TBNA in all patients (100.0%). The serum level of sIL-2R, but not that of ACE or lysozyme, was correlated with successful diagnosis by EBUS-TBNA. *Conclusion:* In patients with stage I/II sarcoidosis, the serum level of sIL-2R is a promising and useful marker for predicting the diagnosis by EBUS-TBNA and reducing the burden of additional TBLB and its possible complications. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 8-16)*

Key words: Sarcoidosis, EBUS-TBNA, TBLB, Soluble interleukin-2 receptor

Introduction

Sarcoidosis is characterized by bilateral hilar and mediastinal lymphadenopathy concomitant with lesions in multiple organs, including the lungs, heart, eyes, and skin. Although its pathophysiology has yet to be fully understood, previous reports have indicated the possibility of abnormalities in immunological regulation (1-3). In many cases, patients with sarcoidosis present with a stable condition with no symptoms. However, some patients often develop progressively worsening pulmonary conditions that could lead to interstitial lung disease with respiratory failure. There is also a possibility that, in addition to pulmonary disorders, other cardiac or neurological lesions might be fatal. Thus, early diagnosis and optimal treatment is essential in such cases.

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Detection of non-caseous granuloma is critical for diagnosis of sarcoidosis. Endoscopic approaches are used for collecting histological samples from the lungs or hilar and mediastinal lymph nodes (4-6). Transbronchial lung biopsy (TBLB) has conventionally been employed as a diagnostic method for sarcoidosis. However, it yields a diagnosis rate of about 50% and is, therefore, not adequate as a definitive diagnostic examination (7-10). In addition, TBLB entails the possibility of complications, including bleeding and pneumothorax. Therefore, further methodological improvement of this approach is an urgent necessity. Recently, a clinical and universally available method that uses endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for diagnosis of sarcoidosis has been developed. This examination has improved the diagnostic rate of sarcoidosis to 80-90% (11-14). Although EBUS-TBNA entails the risk of mediastinitis as a rare complication, it is usually safe for most patients who are qualified for bronchoscopic examination. These characteristics support its high practicality, although there is room for improvement in some points, including the limited size of tissues and longer examination time (8, 15-17). It has been proposed that EBUS-TBNA and TBLB can be performed during the same examination in order to increase the diagnostic rate. However, this combined approach might require a longer examination time and involve a higher incidence of concomitant complications. Therefore, there is a controversy about whether both methods should be simultaneously applied for patients with suspected sarcoidosis (7, 18-20).

In clinical settings, several biomarkers are used for diagnosing sarcoidosis, including angiotensin-converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R), and lysozyme (21-24). High serum levels of these markers indicate a definite diagnosis of sarcoidosis. Although ACE is the most commonly used biomarker for diagnosing sarcoidosis, it is not well correlated with active sarcoidosis or the progressive stage of the disease. In fact, lysozyme and sIL-2R are more sensitive markers than ACE (22). Furthermore, sIL-2R is related to the presence of pulmonary manifestations or extrapulmonary organ lesions, which suggests its importance for predicting progressive and complicated disease states. However, a specific marker that is correlated to a high diagnostic rate with combined TBLB and EBUS-TBNA has yet to be identified.

In this study, we analyzed the detection rates of non-caseous granulomas and their relationship with clinical characteristics in patients with suspected stage I/II sarcoidosis scheduled to undergo simultaneous EBUS-TBNA and TBLB. In addition, we investigated which serum marker of sarcoidosis can help improve the diagnostic rate of TBLB and EBUS-TBNA. We also analyzed the relationship of the selected biomarker to disease status on the basis of patient characteristics.

Methods

Subjects

Using a digital data system in our hospital to retrieve patient records for the period of January 2012 to December 2017, we retrospectively identified 37 patients with suspected stage I/II sarcoidosis with enlarged (>10 mm) hilar or mediastinal lymph nodes on computed tomography (CT) images. These patients had been scheduled to undergo combined EBUS-TBNA and TBLB for diagnosis of sarcoidosis. Patients with suspected malignancies or prior established diagnosis of sarcoidosis were excluded on the basis of imaging and serological data. For safety concerns, the patients were managed on an inpatient basis after bronchoscopy. Written informed consent for the examination was obtained from all patients included in this study. For further evaluation, the electronic records of these patients were retrospectively obtained.

Examination procedures

All patients were scheduled to be examined by three diagnostic modalities – EBUS-TBNA, TBLB, and analysis of bronchoalveolar lavage fluid [BALF] – during the same examination. All bronchoscopic procedures were performed under local and systemic anesthesia to keep the patients conscious. Briefly, anesthesia was achieved by nebulization, topical application of lidocaine spray, and intravenous administration of midazolam and pethidine. During the procedure, the patients were monitored for electrocardiogram, pulse oximetry, and blood pressure readings.

First, EBUS-TBNA was performed by using a convex-probe endobronchial ultrasound bronchoscope (BF-UC260F-OL8; Olympus, Tokyo, Japan). Images were acquired by directly contacting the probe or by attaching an inflated saline-filled balloon to its tip, which kept the probe in contact during sampling. A dedicated 22-gauge needle (NA-201SX-4022; Olympus) was used for TBNA. The status of lymph nodes was determined in accordance with the International Staging System (25). The retrieved histological specimens were fixed in formalin and subsequently examined for the presence of non-caseating granuloma in the pathology department.

After EBUS-TBNA, BALF was collected by using a standardized method (50 mL x 3 times; total volume: 150 mL). Then, biopsy specimens were randomly collected from the upper to lower lobes (in order) by TBLB. If CT findings showed any evidence of pulmonary parenchymal involvement, biopsy specimens were collected mainly from the targeted lesion.

Processing of BALF cells

BALF cells were processed for analysis in accordance with standard guidelines as previously described (26). BAL data were available for 36 of the 37 patients included in this study.

Analysis of serum parameters

The serum levels of sIL-2R, ACE, and lysozyme were routinely analyzed during the initial hospital visit, by using commercially available assay kits. For each assay, the normal range was defined on the basis of the manufacturer's recommendations. Normal values of these markers are: 145-519 U/mL for sIL-2R, 8.3-21.4 U/L for ACE, and 5.0-10.2 μg/mL for lysozyme. We only considered the data from patients with suspected sarcoidosis who did not receive any immunosuppressive therapy. The data on sIL-2R, ACE, and lysozyme levels were available for 31, 37, and 29 patients, respectively.

Statistical analysis

Diagnostic accuracy was calculated by using standard definitions. Data were compared by the Mann-Whitney U test. For categorical data, inter-group differences were evaluated by the chi-square test. Correlations between different parameters were determined using Spearman's rank correlation coefficient. P values < 0.05 were regarded as significant.

Ethics committee approval

This study was approved by the ethical committee of Sano Kosei General Hospital (No. 3029).

Results

Combination of EBUS-TBNA and TBLB for detecting granulomas

Table 1 presents the demographic and clinical data of the 37 patients included in this study. To investigate the usefulness of combined EBUS-TBNA and TBLB, we compared the detection rates of non-caseous granuloma among patients who underwent EBUS-TBNA, TBLB, and both. While the detection rates of EBUS-TBNA and TBLB were 83.8% and 50.0%, respectively, the combined examination yielded a higher detection rate of 100.0%. Patients with pathological findings indicating the presence of granulomas were diagnosed as having sarcoidosis. There was an exception in one case, where liver biopsy was needed to confirm the diagnosis in a patient who had concomitant pneumoconiosis with suspected secondary granulomatous changes in the lungs. In addition, 5 patients underwent only EBUS-TBNA; they did not undergo TBLB because of the long examination time and/or a persistent cough, which made it difficult to ensure their safety during the examination.

Relationship between patient characteristics and detection of granuloma by TBLB

To identify a specific marker related to the detection of granulomas by TBLB, we compared patient information, serum levels of sarcoidosis markers, pulmonary or extrapulmonary sarcoidosis lesions, and examination procedures between patients with and without granulomas identified by TBLB (Table 2). There were no statistically significant differences in demographic data between the two groups. The number of patients with pulmonary lesions in the granuloma-positive group was greater than that in

Table 1. Characteristics of the whole study population

Characteristics	
Demographic data	
Men, %	45.9 (17/37)
Age, years	58.5 ± 15.9
Pulmonary involvement, %	59.5 (22/37)
Extrapulmonary involvement, %	27.0 (10/37)
Eye involvement, %	18.9 (7/37)
Skin involvement, %	2.7 (1/37)
Stage of sarcoidosis (I/II), n	15/22
Laboratory data	
ACE concentration, U/L	21.3 ± 7.9
sIL-2R concentration, U/mL	1,155.8 ± 834.3
Lysozyme concentration, μg/mL	12.7 ± 8.8
Bronchoscopic findings	
Implementation of EBUS-TBNA, %	100.0 (37/37)
Lymph-node count targeted in EBUS-TBNA	1:19 2:18
Detection of granuloma in EBUS-TBNA samples, %	83.8 (31/37)
Implementation of BAL, %	97.3 (36/37)
%lymphocytes in BALF, %	32.1 ± 15.5
CD4/CD8 ratio of lymphocytes in BALF	8.6 ± 6.1
Implementation of TBLB, %	86.5 (32/37)
Detection of granuloma in TBLB samples, %	50.0 (16/32)

Abbreviations: ACE=angiotensin-converting enzyme, BAL=bronchial alveolar lavage, BALF=bronchial alveolar lavage fluid, EBUS-TBNA=endobronchial ultrasound-guided transbronchial needle aspiration, sIL-2R=soluble interleukin-2 receptor, TBLB=transbronchial lung biopsy. Values are the proportion of patients in the study group (mean ± standard deviation).

the granuloma-negative group, although the difference was not statistically significant. The serum levels of all three sarcoidosis markers (ACE, sIL-2R, and lysozyme) were higher in the granuloma-positive group than in the granuloma-negative group; however, these differences did not reach statistical significance. The findings of BALF analysis (i.e., percentage of lymphocytes in the total cell population and CD4:CD8 ratio of lymphocytes) were not correlated with the detection rate of granulomas by TBLB. Thus, no marker was identified as being predictive of successful diagnosis by TBLB.

Relationship between patient characteristics and detection of granuloma by EBUS-TBNA

Next, to identify a specific marker for predicting the detection of granulomas by EBUS-TBNA, we compared patient information, serum levels of sarcoidosis markers, pulmonary or extrapulmonary sarcoidosis lesions, and examination procedures between patients who did and did not have granulomas sampled by EBUS-TBNA (Table 3). There were no statistically significant differences in demographic data between the two groups. The number of punctures

Table 2. Comparative analysis of patients with sarcoidosis with and without granulomas detected by TBLB

Characteristics	Granuloma		*P*
	Not detected (n = 16)	Detected (n = 16)	
Demographic data			
Men, %	43.8 (7/16)	50.0 (8/16)	1.00*
Age, years	59.8 ± 15.4	53.1 ± 16.6	.25†
Pulmonary involvement, %	50.0 (8/16)	68.8 (11/16)	.28*
Extrapulmonary involvement, %	31.3 (5/16)	31.3 (5/16)	1.00*
Eye involvement, %	25.0 (4/16)	18.8 (3/16)	.67*
Skin involvement, %	0.0 (0/16)	6.3 (1/16)	.31*
Stage of sarcoidosis (I/II), n	8/8	5/11	.28*
Laboratory data			
ACE concentration, U/L	19.0 ± 6.6	22.6 ± 8.3	.18†
sIL-2R concentration, U/mL	1,018.3 ± 501.8	1,354.0 ± 1,120.8	.33†
Lysozyme concentration, μg/mL	11.3 ± 7.0	15.5 ± 10.7	.25†
Bronchoscopic findings			
Implementation of BAL, %	100.0 (16/16)	100.0 (16/16)	
%lymphocytes in BALF, %	27.5 ± 15.5	36.2 ± 16.1	.13†
CD4/CD8 ratio of lymphocytes in BALF	9.1 ± 7.4	7.7 ± 5.1	.56†

Abbreviations: ACE=angiotensin-converting enzyme, BAL=bronchial alveolar lavage, BALF=bronchial alveolar lavage fluid, sIL-2R=soluble interleukin-2 receptor, TBLB=transbronchial lung biopsy
Values are the proportion of patients in each study group (mean ± standard deviation)
*chi-square test
†Mann-Whitney test

(1 or 2) was not correlated with successful sampling of granulomas. Among the evaluated serum markers of sarcoidosis, sIL-2R (but not ACE or lysozyme) showed higher concentrations in the granuloma-positive group than in the granuloma-negative group (Figure 1A), which suggested its greater sensitivity for predicting successful diagnosis. Thus, this study identified a useful predictive marker for the positive detection of granuloma by EBUS-TBNA.

Characterization of patients with sarcoidosis with high serum levels of soluble IL-2R

To characterize the predictive ability of serum sIL-2R as a marker for choosing EBUS-TBNA as the preferred diagnostic tool for sarcoidosis, we performed receiver operating characteristic curve analysis (Figure 1B). The cutoff index was set at 841 U/mL (area under the curve: 0.7615; Youden index: 0.4538). With this cutoff point, 94.4% of patients with high serum levels of sIL-2R were successfully diagnosed with granulomas by EBUS-TBNA. In contrast, the detection rate of granulomas by EBUS-TBNA in the low-sIL-2R group was only 69.2%.

To investigate the role of sIL-2R in stage I/II sarcoidosis, we compared patient information between those with high and low levels of serum sIL-2R by using the cutoff index (Table 4). Notably, the serum concentrations of the other two markers, ACE and lysozyme, were also higher in the high-sIL-2R group than in the low-sIL-2R group. Furthermore,

Table 3. Comparative analysis of patients with sarcoidosis with and without granulomas detected by EBUS-TBNA

Characteristics	Granuloma		*P*
	Not detected (n = 6)	Detected (n = 31)	
Demographic data			
Men, %	66.7 (4/6)	41.9 (13/31)	.27*
Age, years	47.8 ± 16.9	60.6 ± 15.2	.13†
Pulmonary involvement, %	66.7 (4/6)	58.1 (18/31)	.69*
Extrapulmonary involvement, %	33.3 (2/6)	25.8 (8/31)	.70*
Eye involvement, %	0.0 (0/6)	19.4 (6/31)	.24*
Skin involvement, %	0.0 (0/6)	3.2 (1/31)	.66*
Stage of sarcoidosis (I/II), n	2/4	13/18	.69*
Laboratory data			
ACE concentration, U/L	19.0 ± 8.7	21.8 ± 7.8	.50†
sIL-2R concentration, U/mL	666.2 ± 402.4	1,249.9 ± 867.3	.035†
Lysozyme concentration, μg/mL	11.5 ± 5.4	12.9 ± 9.3	.68†
Bronchoscopic findings			
Lymph-node count targeted in EBUS-TBNA	1:4 2:2	1:15 2:16	.41*
Implementation of BAL, %	100.0 (6/6)	96.8 (30/31)	
%lymphocytes in BALF, %	33.5 ± 14.2	31.8 ± 16.0	.80†
CD4/CD8 ratio of lymphocytes in BALF	6.1 ± 3.3	9.1 ± 6.4	.12†

Abbreviations: ACE=angiotensin-converting enzyme, BAL=bronchial alveolar lavage, BALF=bronchial alveolar lavage fluid, EBUS-TBNA=endobronchial ultrasound-guided transbronchial needle aspiration, sIL-2R=soluble interleukin-2 receptor
Values are the proportion of patients in each study group (mean ± standard deviation)
*chi-square test
†Mann-Whitney test

the serum levels of all three markers were mutually and significantly correlated with each other (Supplementary Figure 1), with the serum levels of sIL-2R and lysozyme being most strongly correlated with each other (r = 0.94; $P < 0.001$). The percentages of patients with values above normal values of these markers were 69.2% and 100.0% for sIL-2R, 7.7% and 66.7% for ACE, and 0% and 61.5% for lysozyme in the low-sIL-2R group and the high-sIL-2R group, respectively. The incidence of pulmonary involvement or stage II sarcoidosis and ratio of CD4:CD8 cells were higher in the high-sIL-2R group than in the low-sIL-2R group; however, these differences did not reach statistical significance.

Discussion

The findings of this study revealed that simultaneous EBUS-TBNA and TBLB is safe, does not involve serious complications, and helps improve the diagnosis rate of sarcoidosis. In addition, our results demonstrated that high serum sIL-2R concentration indicates a better diagnostic rate of sarcoidosis by EBUS-TBNA. The serum levels of ACE and lysozyme – although not associated with successful diagnosis by EBUS-TBNA – were correlated with those of sIL-2R, suggesting a possible additional benefit for sarcoidosis diagnosis.

sIL-2R is closely related to disease activity in

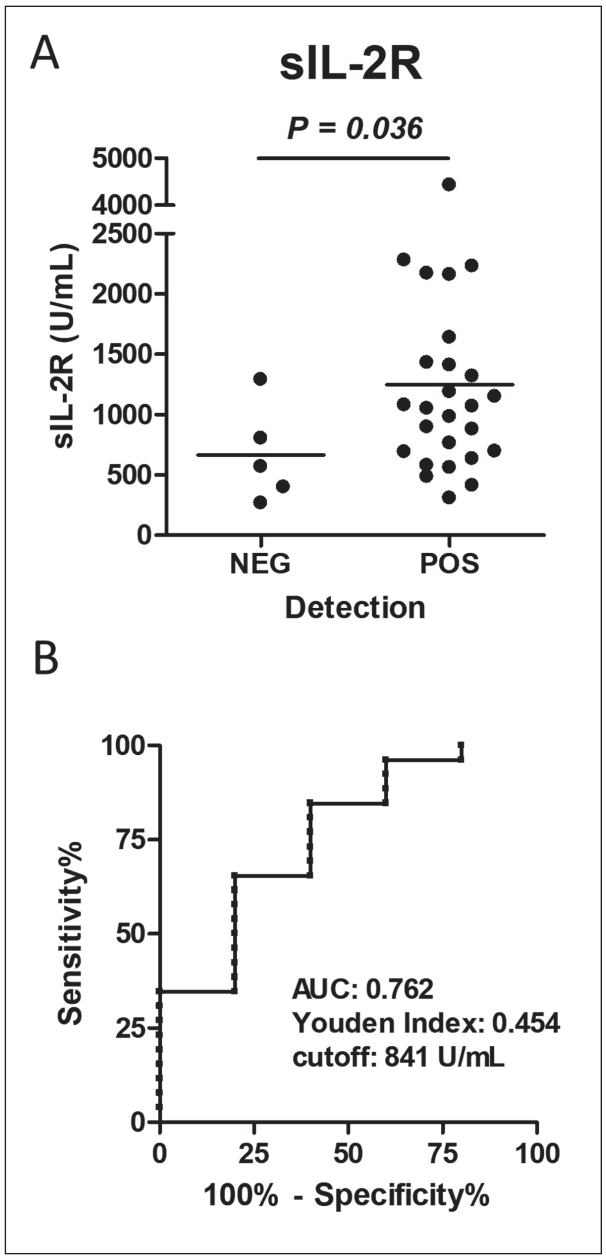

Fig. 1. Relationship between serum sIL-2R level and detection of granuloma by EBUS-TBNA. A) Comparison of serum sIL-2R levels between the granuloma-positive and -negative groups on the basis of EBUS-TBNA findings. B) Findings of receiver operating characteristic curve analysis of the ability of serum sIL-2R level to predict the detection of granulomas in patients with suspected sarcoidosis by EBUS-TBNA. AUC=area under the curve, EBUS-TBNA=endobronchial ultrasound-guided transbronchial needle aspiration, NEG=negative, POS=positive, sIL-2R=soluble interleukin-2 receptor

sarcoidosis (23, 27-33). Previous studies have shown that a high serum concentration of sIL-2R indicates more severe sarcoidosis. Extrapulmonary lesions are also related to elevated levels of serum sIL-2R. These results indicate that many cases of stage I/II sarcoidosis with high serum levels of sIL-2R can progress to stage III/IV. The relationship between lymph-node lesions and serum sIL-2R levels remains unknown. However, this marker is correlated with disease activity in lymphoma, which indicates that it is closely related with other lymphadenopathic diseases, including sarcoidosis. Thus, in patients with stage I/II sarcoidosis, elevated sIL-2R levels suggest the progression of active formation of non-caseous granulomas in lymph nodes.

In addition to sIL-2R, ACE and lysozyme are also employed as serum markers of sarcoidosis. Previous studies have reported that high serum ACE and lysozyme levels might indicate severe disease state in sarcoidosis (23, 34-36). However, our results showed that these markers are not significantly correlated with the detection rate of non-caseous granuloma in lymph nodes by EBUS-TBNA. In fact, our results demonstrated a positive relationship between sIL-2R and ACE/lysozyme levels, suggesting that sIL-2R is a more sensitive serum marker than the other two.

Although EBUS-TBNA is a useful diagnostic method for sarcoidosis, there is room for further improvement. For example, the puncture method has been modified for collecting larger samples for detecting non-caseous granuloma. Changes in needle size and puncture time and the use of rapid cytological analysis are thought to increase the detection rate of non-caseous granulomas (13, 15, 16, 37). It is necessary to improve the diagnostic approach for patients with suspected sarcoidosis who are scheduled for EBUS-TBNA diagnosis. However, knowledge regarding useful serological biomarkers for predicting a higher rate of successful diagnosis by EBUS-TBNA might encourage clinicians to choose this method, which increases the importance of sIL-2R as a biomarker.

In the present study, patient information and clinical data were retrospectively analyzed, which might have led to bias in the findings. Second, there were missing values in the laboratory data, including sIL-2R and lysozyme levels, which might have decreased the statistical power of the markers for

Table 4. Comparative analysis of patients with sarcoidosis with high and low serum sIL-2R levels

Characteristics	Serum sIL-2R level (U/mL)		*P*
	< 841 (U/mL) (n = 13)	≥ 841 (U/mL) (n = 18)	
Demographic data			
Men, %	53.8 (7/13)	38.9 (7/18)	.41*
Age, years	54.7 ± 17.3	59.8 ± 17.2	.43†
Pulmonary involvement, %	46.2 (6/13)	72.2 (13/18)	.14*
Extrapulmonary involvement, %	30.8 (4/13)	22.2 (4/18)	.59*
Eye involvement, %	23.1 (3/13)	11.1 (2/18)	.37*
Skin involvement, %	0.0 (0/13)	5.6 (1/18)	.39*
Stage of sarcoidosis (I/II), n	7/6	5/13	.14*
Laboratory data			
ACE concentration, U/L	16.9 ± 5.4	24.9 ± 8.3	.003†
sIL-2R concentration, U/mL	551.6 ± 169.4	1,592.1 ± 852.9	<.001†
Lysozyme concentration, μg/mL	6.2 ± 1.6	16.6 ± 9.8	.001†
Bronchoscopic analysis			
Implementation of BAL, %	92.3 (12/13)	100.0 (18/18)	
%lymphocytes in BALF, %	35.7 ± 16.0	34.6 ± 15.1	.85†
CD4/CD8 ratio of lymphocytes in BALF	6.6 ± 4.3	9.2 ± 5.2	.16†

Abbreviations: ACE=angiotensin-converting enzyme, BAL=bronchial alveolar lavage, BALF=bronchial alveolar lavage fluid, sIL-2R=soluble interleukin-2 receptor
Values are the proportion of patients in each study group (mean ± standard deviation)
*chi-square test
†Mann-Whitney test

predicting significant differences in diagnosis of sarcoidosis. Third, the laboratory data of healthy controls without sarcoidosis were not collected, which might have caused an improper setting of the cut-off index. Fourth, in some cases, EBUS-TBNA and TBLB were not performed simultaneously, which led to incomplete assessment of the usefulness of the combined examination. Fourth, the number of patients enrolled in this study was small. Therefore, we might have missed some clinically important relationship between the diagnosis rate of sarcoidosis by EBUS-TBNA and the evaluated markers.

In conclusion, this study demonstrated the diagnostic utility of combined EBUS-TBNA and TBLB in enhancing the detection rate of non-caseous granuloma in patients with suspected sarcoidosis. Our findings indicated that serum levels of sIL-2R might predict a higher diagnostic rate by EBUS-TBNA but not TBLB. These findings might help avoid unnecessary examination and possible complications and improve the diagnostic strategy for early-stage sarcoidosis.

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Factors associated with implantable cardioverter defibrillators appropriate therapy in cardiac sarcoidosis: a meta-analysis

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Abstract. *Background:* Patients with cardiac sarcoidosis (CS) are at increased risk of atrioventricular blocks, ventricular arrhythmias, and sudden cardiac death. Objectives We aimed to investigate the characteristics associated with appropriate therapy in implantable cardiac defibrillator (ICD) -implanted CS patients. *Methods:* We performed a PubMed and Web of Science search for studies reporting patients with CS who underwent an ICD implantation. The primary criterion was an appropriate therapy. *Results:* We screened 705 studies, of which 5 were included in the final analysis. We conducted a meta-analysis including 464 patients (mean age 55 years, 282 males (60%)). The mean follow-up was 3.5 years. Among the 464 patients, 180 received an appropriate therapy (39%). Patients who received an appropriate therapy were younger (-3.33, 95% confidence interval (CI) -6.42 to -0.23, p=0.004), were more likely to be male (OR 2.06, 95% CI 1.37-3.09, p=0.0005), had a lower left ventricular ejection fraction (LVEF) (-10.5, 95% CI -18.23 to -2.78, p=0.008), had a higher rate of complete heart block (OR 2.19, 95% CI 1.20 to 3.99, p=0.01), and more frequently had ventricular pacing (OR 6.44 95% CI 2.57 to 16.16, p<0.0001). *Conclusions:* Appropriate ICD therapy during CS is associated with young age, male sex, low LVEF, history of complete heart block, and ventricular pacing. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 000-000)*

Key words: cardiac sarcoidosis, sudden death, implantable cardioverter defibrillator, complete heart block, meta-analysis

Sarcoidosis is a multisystemic granulomatous disease of unknown cause that occurs in young adults (1). Clinical cardiac involvement occurs in 5% of patients with sarcoidosis (2). However, autopsy studies suggest that cardiac involvement might concern more than 25% of patients with sarcoidosis (3-5). Patients with cardiac sarcoidosis (CS) are at increased risk for atrioventricular blocks, ventricular arrhythmias, and sudden cardiac death (6-8). Implantable cardioverter defibrillator (ICD) implantation is a high cost procedure and may lead to severe complications, especially in young patients who have been exposed to immunosuppressive drugs (9). Recent guidelines suggest that ICD implantation is recommended for patients with spontaneous sustained ventricular arrhythmias or left ventricular ejection fraction (LVEF) <35% (class I); can be useful for patients with an indication for permanent pacemaker implantation, unexplained syncope or inducible sustained ventricular arrhythmias (class IIa recommendation); and may be con-

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sidered for patients with LVEF 36% to 40%, right ventricular ejection fraction <49%, or both (class IIb recommendation).

However, the efficacy and safety of ICDs in CS is debated. The subpopulation that benefits the most from an ICD implantation remains unknown. Appropriate ICD therapies refer to shock or antitachycardia pacing for ventricular tachycardia (VT) or ventricular fibrillation (VF). Appropriate therapy has been investigated in nonischemic cardiomyopathy and is a reliable surrogate criterion for sudden cardiac death (10).

We conducted a meta-analysis to identify the factors associated with appropriate ICD therapy in patients with CS.

Methods

Literature search

Two main investigators (L.-D.A. and F.C.-A.) searched MEDLINE (1966-July 2018) and Web of Science (1900-2018) for original articles without language restrictions. The search strategy combined free text search, advanced research, exploded MESH/EMTREE terms, and all synonyms of the following Medical Subject Headings terms: *sarcoidosis, CS, ICD, cardiac sudden death, VT, VF, and cardiac arrhythmias.* (The search strategy is detailed in Supplemental Table S1.) We also searched for additional articles from the reference lists of relevant papers obtained from the electronic search.

Selection criteria were determined before data collection. Inclusion criteria were as follows: (1) studies reporting on ICD (2) in patients with definite or suspected CS as defined in the Heart Rhythm Society (HRS) consensus statement in 2014 or the Japanese Ministry of Health and Welfare criteria (11) (3), in which patients who received an appropriate therapy were compared with patients who did not. Studies reporting reviews, case reports, editorials and guidelines were excluded. Studies reporting on CS patients with insufficient available information or nonextractable data were excluded. Whenever disagreement occurred, it was resolved by discussion between the 2 investigators and the advice of a third one (Z.A.) until a consensus was reached. A flow chart of reasons for rejection of citations identified from the searches was performed and is shown in Figure 1.

Data extraction

The data were simultaneously and independently extracted by 2 investigators (L.-D.A. and F.C.-A.). For each study, the recorded information included the number of patients, inclusion criteria, CS diagnosis criteria, definition of appropriate therapy, number of patients in the appropriate therapy group, age, sex, LVEF, history of syncope or complete heart block (CHB), left or right bundle branch block (LBBB or RBBB), ventricular pacing, cardiac magnetic resonance imaging (MRI) results, and mean follow-up.

Risk of bias assessment

A subjective assessment of the methodological quality of the observational studies was evaluated by two investigators using the Newcastle-Ottawa Scale (NOS) (12), which is a quality assessment tool for nonrandomized studies. NOS uses a "star system" based on three major perspectives: the selection of the study groups (0 to 4 stars), the comparability of the groups by controlling for important and additional relevant factors (0 to 2 stars), and the ascertainment of outcome of interest or exposure (0 to 3 stars). A total score of 3 or less indicates poor quality, 4-6 indicates moderate quality, and 7-9 indicates high quality. We also used the thresholds for converting the NOS to the Agency for Healthcare Research and Quality (AHRQ) standards. Discrepant opinions between the investigators were resolved by consensus.

Data analysis

As previously indicated, appropriate therapy referred to shock or antitachycardia pacing for VT or VF. Percentages were assessed for dichotomous variables; means and standard deviations were assessed for continuous variables. We compared the characteristics of the patients in the "appropriate therapy" group versus the "no appropriate therapy" group. All included articles were analyzed using Cochrane Collaboration Review Manager statistical software (version 5.3; Cochrane Collaboration, Oxford, UK). The I^2 statistic was used to measure consistency. The

fixed-model effect was used, and a random-effects model was used whenever I^2 exceeded 0% (suggesting a mild, moderate or important heterogeneity). A $p<0.05$ was considered significant. A Mantel-Haenszel test was used for dichotomous variables, and an inverse variance test was used for continuous variables. Odds ratio were estimated for dichotomous variables comparisons. The PRISMA checklist is detailed in Supplemental Figure S1.

Results

We extracted 705 articles. According to the selection criteria, 68 articles were assessed for eligibility (Figure 1). The main reason that studies were excluded was the type of articles; many of them were case reports. Five retrospective cohorts, published between 2011 and 2018, were included in the final analysis (13-17). The main results of these studies are detailed in Table 1. These 5 studies were categorized as poor or fair quality studies, according to the NOS or AHRQ tools, respectively.

A total of 464 participants were included. Across the 5 studies, the mean age was 55 years (11.6). Among these 464 patients, 282 (60%) were male. The estimated mean follow-up was 3.5 years. One hundred and eighty patients (39%) received an appropriate therapy.

Five factors were significantly associated with receiving an appropriate therapy among the cardiac sarcoidosis patients who were implanted with an ICD: age, sex, LVEF, CHB, and ventricular pacing. These results are shown in Figure 2.

Patients who received an appropriate therapy were younger (- 3.33, 95% Confidence interval (CI) -6.42 to -0.23, p=0.004, I^2=41%), more frequently male (OR 2.06, 95% CI 1.37 to 3.09, p=0.0005, I^2=0%), and had a lower LVEF (-10.5, 95% CI -18.23 to -2.78, p=0.008, I^2=85%). For LVEF, patients of the appropriate therapy group had a mean LVEF of 36.1% (14.8) versus 47.5% (14.4) in the no appropriate therapy group. Mean age in the appropriate therapy group was 53.9 years (11.8) versus 56 years (11.0) in the no appropriate therapy group.

For age: AT group 53.9 years (11.8); NAT group 56 years (11.0)

Three studies mentioned the presence of CHB, and the patients who received an appropriate therapy had a significant higher rate of CHB (OR 2.19, 95% CI 1.2 to 3.99, p=0.01, I^2=0%) (13-15). Two studies mentioned the presence of ventricular pacing (14, 15). Patients who received an appropriate therapy were significantly more frequently paced (OR 6.44 95% CI 2.57 to 16.16, p<0.0001, I^2=0%).

Conversely, LBBB, RBBB, positive CMR, syncope were not associated with receiving an appropriate therapy. The data included in such analyses were

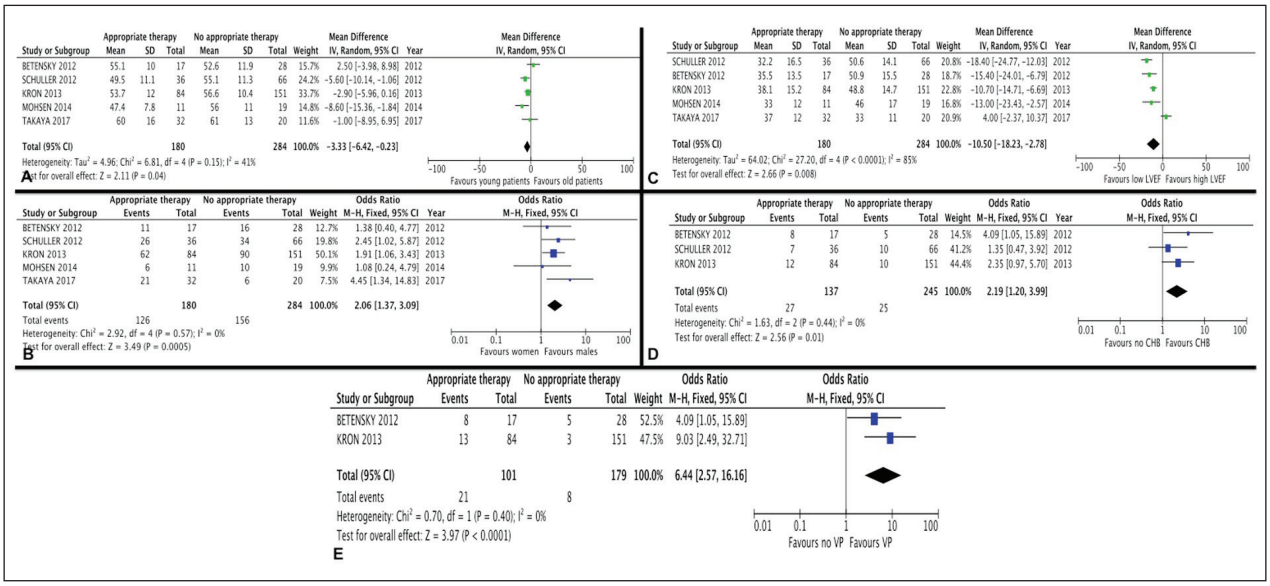

Fig. 1. Flow diagram of the assessment of studies identified in the meta-analysis

Table 1. Characteristics of the design and population in the 5 studies included in the meta-analysis

Ref	Schuller (2012)	Betensky (2012)	Kron (2013)	Mohsen (2014)	Takaya (2017)
n*	102	45	235	30	52 (27 definite CS, 25 suspected CS)
Design	Single-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort
Inclusion criteria	CS receiving an ICD	CS receiving an ICD	CS receiving an ICD	CS receiving an ICD	CS receiving an ICD
Exclusion criteria	-	Coronary heart disease More plausible explanation for their heart disease	-	-	-
Cardiac sarcoidosis definition	Modification of the JMHW	JMHW or extracardiac sarcoidosis associated with a positive CMR, PET imaging, heart biopsy or explant pathology	Biopsy-proven CS or suggestive CMR or extracardiac sarcoidosis and a presumptive cardiac involvement	Biopsy proven CS or biopsy proven extracardiac sarcoidosis associated with 2 or more of the following criteria: clinical abnormality, low LVEF, suggestive CMR, suggestive ECG or EPS, suggestive PET scan	Definite CS or suspected CS according to the JMHW
Age (years) mean (SD)	53.1 (11.2)	53.5 (11.2)	55.6 (11.1)	53 (11)	60.1 (15.1) Definite CS 63 (13) Suspected CS 57 (17)
Male, n (%)	60 (59%)	27 (60%)	152 (65%)	16 (53%)	27 (52%)
LVEF (%) mean (SD)	44.1 (15)	45.4 (16.4)	45 (15.7)	41 (18)	36 (12) Definite CS 35 (14) Suspected CS 37 (10)
Syncope, n (%)	NA	NA	68 (29%)	16 (53%)	NA
RBBB, n (%)	30 (29%)	6 (13%)	63 (28%)	NA	NA
LBBB, n (%)	NA	3 (7%)	NA	NA	NA
Ventricular pacing	NA	13 (29%)	16 (7%)	NA	NA
Positive CMR definition	-	Focal or diffuse areas of delayed gadolinium enhancement occurrence in a distribution inconsistent with scar due to prior infarction	Delayed contrast enhancement, wall motion abnormalities, LV dysfunction, chamber dilation	Patchy late gadolinium enhancement of the mid- myocardium and/or epicardium	-
Positive CMR	NA	4 (9%)	99 (86%)	8 (27%)	NA
Primary prevention	NA	29 (64%)	147 (63%)	11 (37%)	27 (52%)
Follow-up from ICD implantation (years) mean (SD)	2.4	2.6 (2.7)	4.2 (4.0)	3.8 (4.0)	NA (Median: 2)

(continued on next page)

Table 1. Characteristics of the design and population in the 5 studies included in the meta-analysis

Appropriate therapy definition	ATP or shocks for VT or VF	1 or more ATP or shock for sustained monomorphic or polymorphic VT or VF; electrical storms were tabulated as a single "event"	ATP or shocks (for VT or VF)	ATP or shocks	ATP or shocks for ventricular tachyarrhythmias
Appropriate therapy					
Yes No	36 (35%) 66 (65%)	17 (38%) 28 (62%)	84 (36%) 151 (64%)	11 (37%) 19 (63%)	32 (61%) 20 (39%)
NOS (stars)	Selection: 3 Comparability: Outcome: 2	Selection: 3 Comparability: 0 Outcome: 2	Selection: 3 Comparability: 0 Outcome: 2	Selection: 3 Comparability: 0 Outcome: 2	Selection: 3 Comparability: 0 Outcome: 2
Quality assessment	Fair quality	Fair quality	Fair quality	Fair quality	Fair quality
AHRQ standards	Poor quality	Poor quality	Poor quality	Poor quality	Poor quality

* number of patients included in the study
CS cardiac sarcoidosis; EPS electrophysiologic study; JMHW Japanese Ministry of Health and Welfare; ATP Antitachycardia pacing; VT Ventricular tachycardia; VF Ventricular fibrillation; AHRQ Agency for Healthcare Research and Quality; CMR Cardiac magnetic resonance; LVEF Left ventricular ejection fraction
NA Not available; ECG Electrocardiogram; RBBB Right bundle branch block; LBBB Left bundle branch block; ICD Implantable cardioverter-defibrillator; PET Positron emission tomography; NOS Newcastle-Ottawa Scale

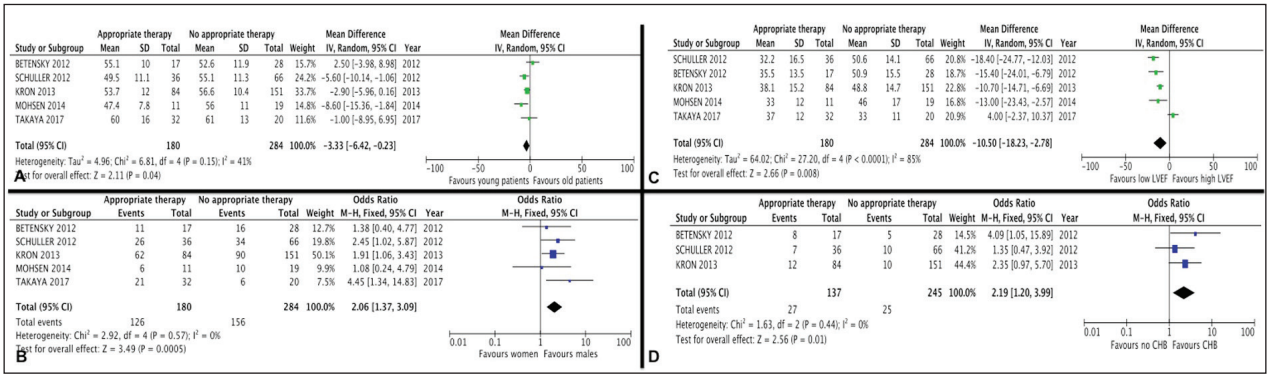

Fig. 2. Forest plot of trials that analyzed appropriate versus no appropriate therapy in patients with cardiac sarcoidosis and an implantable cardioverter defibrillator. Impact of age (A), sex (B), left ventricular ejection fraction (LVEF) (C), complete heart block (CHB) (D), and ventricular pacing (E)

obtained from 2 or 3 articles (Supplemental Figure 2).

Finally, receiving an appropriate therapy was not associated with being implanted with an ICD for secondary prevention. Four studies were included in this analysis (14-17). This result is probably explained by a marked heterogeneity (I^2=80%).

Discussion

Based on the results of 5 retrospective cohorts, this meta-analysis suggests that patients with cardiac sarcoidosis who were implanted with an ICD and received an appropriate therapy are more likely to be young males with a low LVEF, ventricular pacing, and a history of CHB.

In our meta-analysis, we found a higher rate (39%) of appropriate therapy than in previous studies reporting on other heart disease, such as ischemic heart disease or dilated cardiomyopathy, suggesting that patients with cardiac sarcoidosis are at high risk for arrhythmias. For example, 13.4% of patients received appropriate therapy after 1.9 years of follow up in a cohort of patients with ischemic heart disease and low LVEF (18). In a cohort of patients with low LVEF who had been implanted for primary prevention of cardiac sudden death, 18% had appropriate therapy during a 35-month follow up (19).

In this meta-analysis, we used appropriate therapy as the primary criterion. Appropriate shock has been investigated as a surrogate marker for sudden cardiac death in nonischemic cardiomyopathy in a randomized controlled trial including 458 patients. This study suggested that a 2:1 ratio was relevant for defining appropriate therapy as a surrogate for sudden cardiac death (10).

In addition to a LVEF <35% and spontaneous sustained ventricular arrhythmias, specific indications for ICD implantation in CS are not supported with a high level of evidence. HRS guidelines suggest an ICD implantation in patients with LVEF <35% (class I recommendation) or an LVEF between 36 and 49% or right ventricular ejection fraction (RVEF) <40% (class IIb recommendation). The impact of LVEF on the incidence of ventricular arrhythmias was recently investigated in CS (20). In this study, echocardiography recorded a LVEF <40% in 30 of 62 patients (48.4%); in the univariate analysis, these patients experienced worse survival compared with those patients with LVEF ≥40% (p=0.017). No patient with an LVEF between 41 and 50% died or had a transplant. All the studies included in our meta-analysis reported a mean LVEF lower than 40% (32-38%) in the "appropriate therapy" group, whereas all of the LVEF means in the "no appropriate therapy" group were 46-51% (except the series by Takaya, which reports a mean LVEF of 33% in the "no appropriate therapy" group), supporting the finding that LVEF is a main determinant of arrhythmia occurrence.

Cardiac sarcoidosis is a class IIa (level of evidence C) recommendation for an ICD when a pacemaker implantation is required (high-degree atrioventricular block). We found that patients who received an appropriate therapy were more likely to have CHB. These results are consistent with recent data: in a recent study, a high rate of ventricular arrhythmias and sudden cardiac death was found in patients with CS presenting with Mobitz II or CHB (21). The 5-year incidence of sudden cardiac death was 9% in the high atrioventricular block group (no VT and LVEF >50%), 14% if atrioventricular block was associated with an altered LVEF (between 35 and 50%), and up to 34% in the subgroup with VT or severe left ventricular dysfunction (<35%).

Our study has several limitations. First, the quality of all selected studies was poor to fair according to the NOS. All five were retrospective studies. Some patients were included in several studies: we could not determine which patients were included twice because it was not possible to obtain individual data. Thus, this could represent a substantial bias. However, cardiac sarcoidosis is rare and evidence level is low for its management. Thus, despite this bias, the results of this meta-analysis could help supporting low-grade recommendations (11). In this meta-analysis, we did not use data from randomized or controlled trials, because they were not available. Only retrospective studies were available. The primary endpoint was a surrogate marker of sudden cardiac death. Finally, 17 studies were excluded because the data could not be properly extracted.

Patients with CS are at high risk for sudden cardiac death, and ICD implantation should be considered in selected patients. In this meta-analysis, we identified 5 factors associated with appropriate ICD therapy in CS: age, male sex, LVEF, CHB, and ventricular pacing. These results suggest that in CS patients, low LVEF and a history of CHB should indicate ICD implantation, especially in young male patients. Ventricular pacing in a patient who was previously implanted with a pacemaker might be an indication for an ICD upgrade or subcutaneous ICD implantation.

Authors contributions
L.-D.A., X.W., and F.C.-A. designed the study; L.-D.A., X.W., and F.C.-A. collected the data; L.D.-A. and F.C.A. conducted the statistical analysis; L.-D.A., X.W., J.H., Z.A., and F.C.-A. analyzed and interpreted the data; L.-D.A. and F.C.-A. wrote the manuscript.

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The incidence, comorbidity and mortality of sarcoidosis in Korea, 2008-2015: a nationwide population-based study

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Abstract. *Background:* Few national level, population-based studies are present on the epidemiology of sarcoidosis and it is unclear whether these patients have higher mortality than the general population. The objective of this study was to investigate the nationwide epidemiology, comorbidity and mortality in sarcoidosis in Korea. *Material and Methods:* For the period between 2008 to 2015, we used the national population-based database operated by Rare Intractable Disease registration program in which patients' diagnosis are based on uniform criteria. All sarcoidosis patients were identified and followed-up using the National Health Insurance database to determine their incidence, comorbidity, mortality, causes of death and standardised mortality ratio (SMR). *Results:* During the study period, we identified 3,259 new sarcoidosis patients. The average annual incidence was 0.81 per 100,000. The annual mortality rate was 9.26 per 1,000 person-years. The mortality rate were significantly higher than those of the general population (SMR 1.91, 95% confidence interval 1.62-2.25). The major comorbidities of sarcoidosis patients were the diseases of the respiratory system (17.64%), heart (5.43%), eyes (4.27%) and cancer (2.3%). Mortality was higher in patients with lung involvement. Of the 84 deaths identified in this study from 2008-2013, the most common cause of death was cancer (41.7%), followed by respiratory disease (13.1%), sarcoidosis (13.1%) and heart disease (8.3%). *Conclusions:* We reported a nationwide incidence of sarcoidosis as 0.81 per 100,000 in Korea. The mortality of sarcoidosis patients was higher compared to the general population and the major causes of death were cancer, respiratory disease and sarcoidosis. Sarcoidosis patients with comorbid diseases showed increased mortality. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 24-36)*

Key words: sarcoidosis, incidence, comorbidity, mortality, cause of death

Abbreviation list:
ICD-10 = International Classification of Diseases, 10th revision,
RID = Rare Intractable Disease,
NHI = The National Health Insurance
CI = confidential interval
SMR = Standardised Mortality Ratio

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Introduction

Sarcoidosis is an inflammatory disease characterized by non-caseating granuloma that generally affects the lungs, but can also involve various organs such as the liver, skin, eyes, heart and nervous system (1).

The incidence of sarcoidosis is known to vary according to race and region (2, 3). It is observed to be higher among African Americans compared to Caucasians (4, 5), and higher in northern European countries than southern countries. Although lower incidence has been reported in Asia (6-8), these studies were conducted based on a small population.

The morbidity of sarcoidosis is associated with the extent of organ involvement and the diseases resulting from them (9-13). These comorbid conditions effect the prognosis of sarcoidosis in patients (14, 15), however the relationship between comorbidity of sarcoidosis and mortality has been poorly studied. Previous studies (14, 16, 17) that have investigated comorbidities in sarcoidosis were mostly hospital based where limited number of patients were available. The effect of comorbidity on mortality has rarely been researched specially in Asian countries where the incidence is relatively low.

Although sarcoidosis is usually a self-limited disease (18), it can be fatal when accompanied by organ failure, especially in the lungs, heart and nervous system (19, 20). However, it remains controversial whether sarcoidosis patients have a higher risk of mortality than the general population and only a few studies have investigated the causes of death (21-24). Also, though it reported that patients of Asian ethnicity have less severe symtoms (6), there is insufficient evidence if the severity and mortality of sarcoidosis differs according to race or region (9,19).

Previous epidemiological studies on sarcoidosis included only a small number of patients from a specific geographical areas (8, 22). In particular, the majority of mortality studies were cross-sectional in nature by using routinely collected administrative data rather than following-up patients, and were hospital-based instead of population-based (7, 25). Since few comorbidity and mortality studies followed-up sarcoidosis patients (23, 24), data from large-scale population-based nationwide studies are needed.

This study investigated the epidemiology, comorbidity, mortality and cause of death of sarcoidosis patients in Korea using Rare Intractable Diseases (RID) database linked with National Health Insurance (NHI) database which covers entire Korean population. To be registered in the RID program, which is run by the Korean government, patients must receive a physician-certified diagnosis based on uniform criteria. In this study, all sarcoidosis patients identified from the RID database were followed from 2008-2015 to determine their incidence, comorbidity and mortality.

Materials and methods

Data source

This study used claims data from the NHI database and registration data from the RID database. The Korean government implemented a national health insurance program for all citizens, which covers more than 50 million individuals. Each medical institution submits an electronic form including the diagnosis and treatments of all inpatients and outpatients to the NHI for claims of reimbursement. These data recorded in the NHI database contain information from the time of patients' diagnosis and thereafter, including the diagnosis, demographics, prescription history, surgical records and screening history. Patients' diagnostic information was recorded according to the International Classification of Diseases, 10th Revision (ICD-10).

Within this system, the NHI has established a registration program for rare intractable diseases (RIDs), including sarcoidosis, that provides copayment reduction to patients. To be registered in this RID program, specific diagnostic criteria need to be met and certified by a physician. Thus, the RID database allowed the current study to analyze reliable epidemiological features of sarcoidosis. We used this database to investigate the national incidence, mortality and causes of death of sarcoidosis in Korea.

Identification of sarcoidosis patients

Our study was based on data of all sarcoidosis patients registered in the RID program extracted from the NHI-RID database from January 2008 to December 2015.

All patients registered in the RID were identified and followed-up until 2015. Patients identified using the RID registration code (V111) combined with the ICD-10 codes (D860-D863, D868, D869) were included. The NHI diagnostic criteria for sarcoidosis(26) include noncaseating epithelioid cell granulomas detected microscopically from a histologic biopsy of pulmonary or suspected organ and a compatible clinical presentation as well as the finding from chest radiography. In making the diagnosis, other granulomatous diseases, such as silicosis, berylliosis, hypersensitivity pneumonitis etc., should be excluded.

Identification of comorbidity

In order to identify the comorbidity, we followed up the sarcoidosis patients using the NHI-RID database. From previous studies (6, 22, 23, 25, 27-30) we employed commonly related organ systems affected by sarcoidosis (neoplasm, respiratory disease, heart disease, renal disease, liver disease et al) as comorbidities for sarcoidosis, a list of which is provided in the supplementary material (Supplementary 1). We defined the comorbid disease as diagnosed code based on the ICD-10 codes for inpatient hospitalization and the comorbidities before diagnosis of sarcoidosis were excluded.

Identification of mortality and causes of death

To determine the mortality and causes of death, we linked patients' data to Statistics Korea. Statistics Korea is a government operated database established in 1981 that includes death certificates of all deceased persons in Korea. By law, death certificates must contain the cause of death issued by the attending physician at the time of death and recorded according to the ICD-10. Statistics Korea is supplemented by the NHI and the National Police Agency information to ascertain the cause of death when the diagnosis was uncertain. A 91% agreement rate has been reported (31) between the causes of death recorded in Statistics Korea and those confirmed through medical chart review. By using this database, we followed-up all sarcoidosis patients from 2008 to the end of 2013 to determine the causes of death.

The personal information of patients was protected and kept anonymous. Anonymous data linkage was processed by a third party organization. This study was approved by the Korea University.

Statistical Analysis

In this study, we calculated and stratified into different age bands sarcoidosis incidence, annual mortality and the standardised mortality ratio (SMR) from 2008-2015 and causes of death from 2008-2013.

We defined an incident case as a newly diagnosed sarcoidosis patient registered in the RID program in the same year. Only patients identified as an incident patient during the study period were included in the numerator of this study. Annual incidence was calculated by dividing the number of total incident cases by the total population number as of July in the corresponding year. As prevalent cases may confound incident cases, we applied a 3-year washout period to exclude patients who had been diagnosed before they were registered in the RID program. The average age- and sex-specific incidences were calculated by dividing the number of cases in each age and sex group by the age- and sex-specific population and averaging these data from 2008-2015. We used the Poisson regression and Cochran-Armitage Trend Test to investigate the annual incidence trends. Incidence and mortality were calculated for each involved organ. As the RID program does not include diagnostic criteria for specific types of sarcoidosis, organ involvement type was determined by using ICD-10 codes. We classified organ involvement as lung, lymph nodes, skin and other organ (eyes, heart and nerves), based on the ICD-10 codes. When one person had multiple organ involvement, they were counted as separate cases.

All individuals with sarcoidosis were followed up till they were diagnosed with comorbidity, and then all individuals with each of the comorbidities were tracked till 2016 and at that point they were assessed for their vital status and the mortality was calculated. The comorbidity was presented as frequency (as a percentage), defined as the number of patients with specific comorbidity divided by the total number of sarcoidosis patients and it was also presented as an organ system. The mortality with each comorbidity was presented as the percentage of death among the sarcoidosis with comorbidity.

From the mortality data including causes of death obtained from Statistics Korea, the annual mortality rate was calculated by dividing the number of sarcoidosis patients who had died in the year by the person-years of sarcoidosis patients registered in RID. Person-years for patients were accumulated at the time of entry in this study until death. Mortality was compared to the general Korean population using SMR with 95% confidence interval (CI). The SMR is the ratio of observed deaths over expected deaths derived from the mortality of the total Korean population obtained from Statistics Korea data.

Survival data from Statistics Korea linked to the NHI-RID database were used in our survival analysis. We evaluated survival curves according to the Kaplan-Meier method. The date of initial registration in the database was considered the date of diagnosis. Patients were censored when a patient was alive at the time of last follow-up. A log-rank test was used to compare the cumulative survival of sarcoidosis patients by gender.

For all mortality cases, the causes of death were analyzed and presented by major disease classification. Causes of death were investigated for all sarcoidosis mortality cases using the Statistics Korea database between 2008 and 2013. We calculated the SMR by cause of death to compare cause-specific mortality between sarcoidosis patients and the general population.

Results

Incidence

Table 1 shows the annual incidence of all sarcoidosis patients from 2008 to 2015. A total of 3,259 sarcoidosis patients were diagnosed. The incidence rate averaged during the study period at 0.81 per 100,000. The annual incidence showed a statistically significant increasing trend, with an increase of 1.03 cases per year on average. The male incidence rate was 0.64 per 100,000 and female incidence was 0.98 per 100,000 with a male:female ratio of 1:1.5. The age- and sex-specific incidence of sarcoidosis is displayed in Figure 1. Male patients exhibited a bimodal distribution, peaking at 30-39 years and again at 60-69 years, whereas females had a single peak at 50-59 years.

Our analysis of the distribution of organ involvement showed that lung involvement accounted for at most 60% (1,955 cases). 35.4% of patients (1,154 cases) exhibited involvement of the lymph nodes, 10.2% (332 cases) had skin involvement and 12.9% (421cases) had other involvements, including eyes, heart and nervous system (Table 2).

Comorbidity and Mortality

The major comorbidities of sarcoidosis patients were the diseases of lungs (575 cases, 17.64%), heart (177 cases, 5.43%), eyes (139 cases, 4.27%) and cancer (75 cases, 2.3%). Interstitial lung disease, chronic obstructive pulmonary disease, lung cancer and pneumonia were common comorbid respiratory disorders, while cardiomyopathy, ischemic heart disease and heart failure were common cardiac comorbidities. Iridocyclitis was the most common eye disease identified as comorbidity and colon and rectum cancer among malignancies, while chronic kidney disease and acute renal failure among renal disease. Among them, higher mortality was observed with pneumonia (63 deaths), chronic obstructive pulmonary disease (30 deaths), interstitial pulmonary disease (24 deaths), chronic kidney disease (13 deaths), acute renal failure (11 deaths), and lung cancer (7 deaths). Among patients with cardiac involvement, we identified mortality as 34.5% (25 deaths/ 73 patients) for patients with heart failure, 17.95% (7 deaths/ 39 patients) for patients with cardiomyopathy and 14.58% (7 deaths/ 48 patients) for patients with chronic ischemic heart disease.

The post-diagnosis survival of sarcoidosis patients is shown in Figure 2. We tracked 3,259 incident cases of sarcoidosis from diagnosis during a mean follow-up of 4.4 years, amounting to 15,119 person-years of observation. Women exhibited a slightly higher survival rate of 96.8%, while male survival was 93.4%.

The annual mortality rates are shown in Table 3. From 2008 to 2015, 140 of 3,259 patients with sarcoidosis died (78 males and 62 females). The annual mortality rate was 9.26 per 1,000 person-years, with a male and female annual mortality rate of 13.69 per 1,000 person-years and 6.58 per 1,000 person-years, respectively. The male: female ratio was 2.1:1. A high mortality rate of 38.43 per 1,000 person-years was observed among patients aged 0-19 years, after which mortality increased with increasing age, from 2.63 in the 20-39 year age group to 21.90 in the 60-79 year age group.

The age- and sex-specific SMRs for sarcoidosis are shown in Table 3. The mortality of sarcoidosis patients was significantly higher than the general population. The SMR was 1.91 (95% CI 1.62, 2.25), with a male SMR of 2.17 (95% CI 1.74, 2.71) and female SMR of 1.66 (95% CI 1.29, 2.12), indicating a higher mortality among males. Compared to the general population, the younger age groups of 0-19 years and 20-39 years exhibited significantly higher

Table 1. Incidence of sarcoidosis in Korea, 2008-2015

Year	Number of population	Incident cases			Incidence per 100,000/year		
	Total	Male	Female	Total	Male	Female	Total
2008	49,404,648	143	237	380	0.58	0.96	0.77
2009	49,656,756	132	230	362	0.53	0.93	0.73
2010	49,879,812	123	228	351	0.49	0.92	0.70
2011	50,111,476	148	242	390	0.59	0.97	0.78
2012	50,345,325	158	246	404	0.63	0.98	0.80
2013	50,558,952	182	253	435	0.72	1.00	0.86
2014	50,763,158	202	282	484	0.80	1.11	0.95
2015	50,951,719	195	258	453	0.77	1.01	0.89
Total		1,283	1,976	3,259	0.64	0.98	0.81

$$\text{incidence} = \frac{\text{incident cases}}{\text{total Korean populations}} \times 100{,}000$$

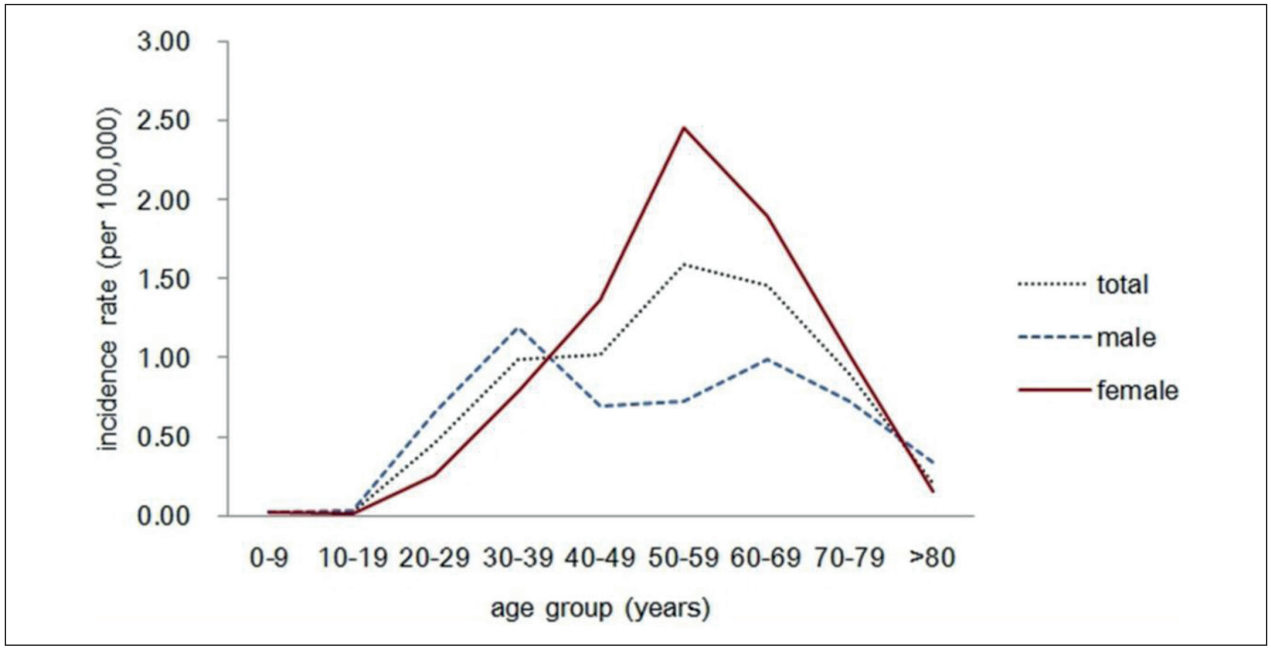

Fig. 1. Incidence of sarcoidosis by sex and age in Korea, 2008-2015. The vertical axis shows incidence rates by 100,000 people; the horizontal axis shows age in 10-year increments until the age of 80 years

SMRs of 240.83 and 3.74, respectively, while patients aged over 40 years had an SMR of 2.69.

According to organ involvement, mortality was higher in sarcoidosis patients with lung involvement, at 8.30 per 1,000 person-years than in patients with other involvement including lymph nodes (6.91 per 1,000 person-years) and skin (3.12 per 1,000 person-years) (Table 2).

Cause of Death

Of the 84 deaths identified in this study from 2008-2013, the most common cause of death was neoplasms (35 deaths, 41.7%), followed by diseases of the respiratory system (11 deaths, 13.1%), sarcoidosis (11 deaths, 13.1%), and cardiac disease (7 deaths, 8.3%) (Table 4). Among the respiratory

Table 2. Incidence and mortality by distribution of organ involvement at the time of diagnosis among patients with sarcoidosis in Korea, 2008-2015

Site of lesion	Incidence		Mortality	
	No of patients(%)	Person-years	No of observed deaths(%)	Mortality rate (per 1000 person-years)
lung	1,955(60.0)	9,160	76(54.2)	8.30
lymph nodes	1,154(35.4)	5,356	37(26.4)	6.91
skin	332(10.2)	1,602	5(3.6)	3.12
eye, heart and nervous system	421(12.9)	2,314	16(11.4)	6.90
total	3,259		140	

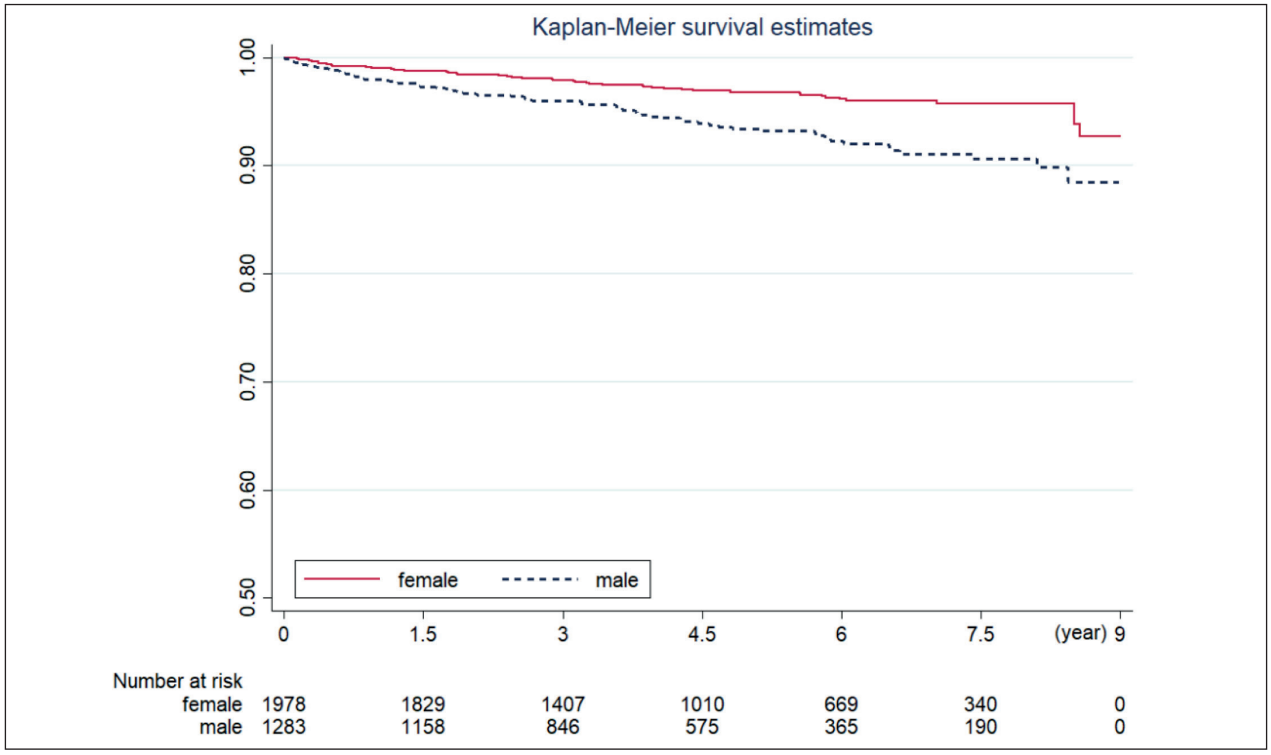

Fig. 2. Survival curve of patients with sarcoidosis by gender. The vertical axis represents survival rate ; the horizontal axis represents years after diagnosis

diseases, 54.5% (6 cases) of patients had interstitial pulmonary disease.

Discussion

In this nationwide population-based study, we identified 3,259 incident cases of sarcoidosis from

Table 3. The annual mortality and age-and sex-specific standardised mortality ratios (SMR) of sarcoidosis in Korea, 2008-2015

Age group	No of deaths/No of person			Annual mortality per 1000 person-years (95% confidence interval)			SMR (95% confidence interval)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0-19	2/12	2/8	4/20	31.35 (7.84, 125.35)	49.64 (12.41, 198.48)	38.43 (14.42, 102.39)	160.74 (40.20, 642.70)	480.03 (120.06, 1900.00)	240.83 (90.39, 641.68)
20-39	6/580	5/317	11/897	2.31 (1.04, 5.15)	3.15 (1.31, 7.58)	2.63 (1.46, 4.75)	3.01 (1.35, 6.70)	5.91 (2.22, 15.74)	3.74 (2.01, 6.96)
40-59	30/456	22/1,174	52/1630	14.46 (10.11, 20.68)	3.90 (2.57, 5.92)	6.73 (5.13, 8.84)	3.02 (2.06, 4.44)	2.36 (1.54, 3.62)	2.69 (2.02, 3.58)
60-79	36/227	31/468	67/695	38.09 (27.47, 52.80)	14.66 (10.31, 20.85)	21.90 17.23, 27.82)	1.72 (1.25, 2.38)	1.34 (0.93, 1.92)	1.53 (1.20, 1.94)
≥80	4/8	2/9	6/17	187.96 (70.54, 500.80)	57.11 (14.28, 228.37)	106.57 (47.88, 237.22)	1.85 (0.88, 3.89)	0.97 (0.44, 2.16)	1.31 (0.76, 2.25)
overall	**78/1,283**	**62/1,976**	**140/3,259**	**13.69 (10.96, 17.09)**	**6.58 (5.13, 8.44)**	**9.26 (7.85, 10.93)**	**2.17 (1.74, 2.71)**	**1.66 (1.29, 2.12)**	**1.91 (1.62, 2.25)**

$$\text{Annual mortality} = \frac{\text{total deaths with sarcoidosis}}{\text{The person-years of total sarcoidosis}} \times 100{,}000$$

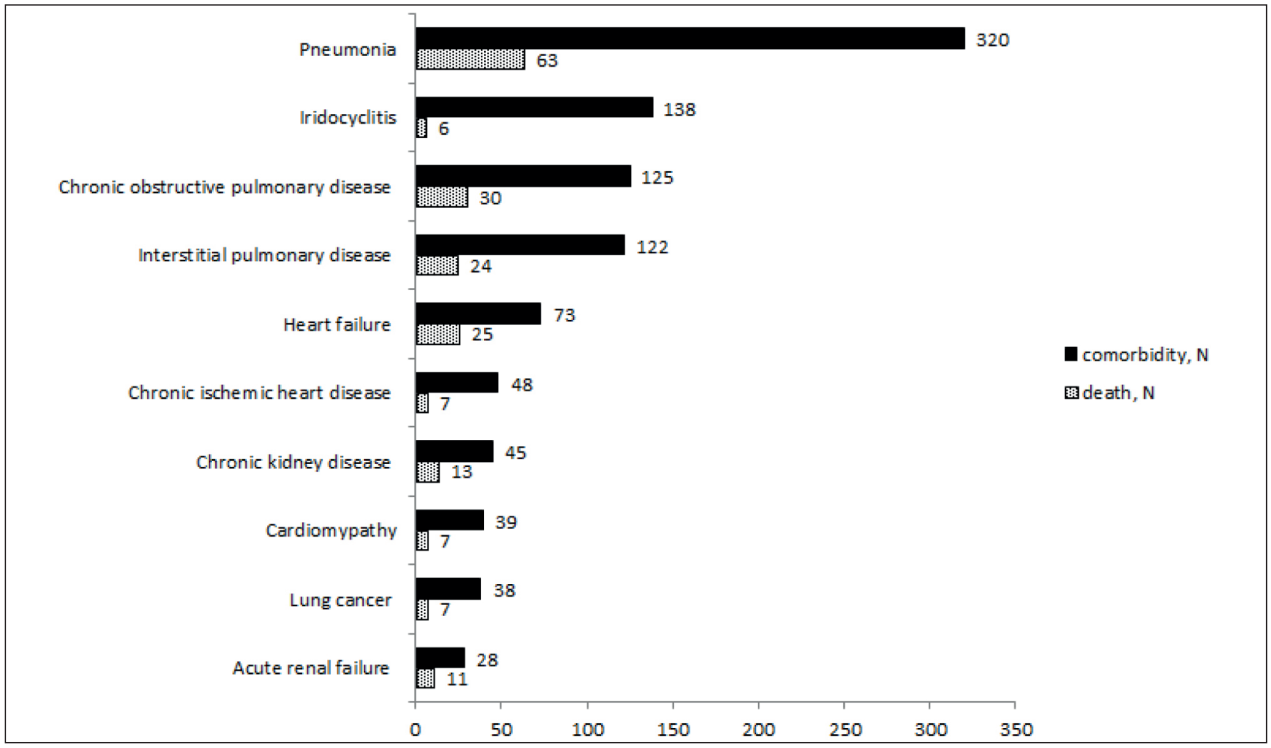

Fig. 3. Mortality associated with comorbidities in sarcoidosis in Korea, 2008-2015. The vertical axis represents comorbidities in sarcoidosis; the horizontal axis represents the number of comorbidity and death in sarcoidosis

Table 4. The cause of death among patients with sarcoidosis in Korea, 2008-2013

Condition (ICD-10 code)	No of observed deaths (%)		
	Male	Female	Total
Neoplasms (C00-D48)	**16 (19.0)**	**19 (22.6)**	**35 (41.7)**
Malignant neoplasms of colon (C18)	4 (4.8)	2 (2.4)	6 (7.1)
Malignant neoplasm of bronchus and lung (C34)	4 (4.8)	0 (0.0)	4 (4.8)
Malignant neoplasm of connective tissue of breast (C50)	0 (0.0)	4 (4.8)	4 (4.8)
Malignant neoplasm of bone and articular cartilage of other and unspecified sites (C41)	2 (2.4)	1 (1.2)	3 (3.6)
others	6 (7.1)	12 (14.3)	18 (21.4)
Disease of the respiratory system (J00-J99)	**8 (9.5)**	**3 (3.6)**	**11 (13.1)**
Pneumonia, organism unspecified (J18)	1 (1.2)	1 (1.2)	2 (2.4)
Other chronic obstructive pulmonary disease (J44)	2 (2.4)	0 (0.0)	2 (2.4)
Status asthmaticus (J46)	0 (0.0)	1 (1.2)	1 (1.2)
interstitial pulmonary disease (J84)	5 (6.0)	1 (1.2)	6 (7.1)
Sarcoidosis(D86)	**5 (6.0)**	**6 (7.1)**	**11 (13.1)**
Diseases of the circulatory system(I00-I99)	**6 (7.1)**	**1 (1.2)**	**7 (8.3)**
Acute myocardial infarction (I21)	1 (1.2)	0 (0.0)	1 (1.2)
Chronic ischemic heart disease (I25)	2 (2.4)	0 (0.0)	2 (2.4)
Acute myocarditis (I40)	1 (1.2)	0 (0.0)	1 (1.2)
Heart failure (I50)	1 (1.2)	1 (1.2)	2 (2.4)
Intracerebral hemorrhage (I61)	1 (1.2)	0 (0.0)	1 (1.2)
Diseases of the nervous system (G00-G99)	**1 (1.2)**	**2 (2.4)**	**3 (3.6)**
Encephalitis, myelitis and encephalomyelitis (G04)	0 (0.0)	1 (1.2)	1 (1.2)
Spinal muscular atrophy and related syndromes (G12)	1 (1.2)	0 (0.0)	1 (1.2)
Multiple sclerosis (G35)	0 (0.0)	1 (1.2)	1 (1.2)

2008-2015. The average annual incidence of sarcoidosis was 0.81 per 100,000. The average annual mortality rate was 9.26 per 1,000 person-years and the 5-year survival rate was 95.5%. Commonly associated comorbidities in sarcoidosis patients were the disease of lungs (575 cases, 17.64%), heart (177 cases, 5.43%), eyes (139 cases, 4.27%) and cancer (75 cases, 2.3%). It was also observed that the patients with these comorbidities show higher mortality.

Our study based on population-based data covering the entire population is less at risk of selection bias compared to surveys or hospital-based studies. Also, incidence, mortality and survival rates were investigated in the same cohort during an 8-year follow-up period and so the entire mortality pattern and natural course of sarcoidosis could be understood. Similar with many existing reports (6, 32), the NHI diagnostic criteria for sarcoidosis used in our study required the identification of granulomas through histological findings, thus our findings are more comparable.

The incidence reported in this study is markedly lower than findings from the United States and Europe. The incidence of sarcoidosis in the United

Table 5. Comorbidities associated with sarcoidosis in Korea, 2008-2015

Disease Condition (ICD-10 code)	The number of comorbidity(%)		
	Male	Female	Total
Neoplasms			
Malignant neoplasm of bronchus, trachea and lung (C33~34)	19(0.58)	19(0.58)	38(1.17)
Malignant neoplasms of colon, rectosigmoid junction and rectum (C18~C20)	9(0.28)	15(0.46)	24(0.74)
Malignant neoplasm of connective tissue of breast (C50)	0(0)	9(0.28)	9(0.28)
Malignant melanoma of skin (C43)	1(0.03)	1(0.03)	2(0.06)
Disease of the respiratory system			
Pneumonia(J17, J18)	149(4.57)	171(5.25)	320(9.82)
Chronic obstructive pulmonary disease (J44)	64(1.96)	61(1.87)	125(3.84)
Interstitial pulmonary disease (J84)	61(1.87)	61(1.87)	122(3.74)
Pulmonary hypertension(I27.0, I27.2)	3(0.09)	5(0.15)	8(0.25)
Diseases of the circulatory system			
Heart failure (I50)	27(0.83)	46(1.41)	73(2.24)
Ischemic heart disease (I25)	20(0.61)	28(0.86)	48(1.47)
cardiomyopathy (I42)	18(0.55)	21(0.64)	39(1.20)
Acute myocardial infarction (I21)	11(0.34)	3(0.09)	14(0.43)
Stroke (I64)	7(0.21)	7(0.21)	14(0.43)
Intracerebral hemorrhage (I61)	4(0.12)	6(0.18)	10(0.31)
myocarditis (I40, I41.8)	2(0.06)	1(0.03)	3(0.09)
Diseases of the renal system			
Chronic kidney disease (N18)	25(0.77)	20(0.61)	45(1.38)
Acute renal failure (N17)	21(0.64)	7(0.21)	28(0.86)
Diseases of the Liver			
Hepatic failure(K72)	3(0.09)	6(0.18)	9(0.28)
Diseases of the nervous system			
Multiple cranial nerve palsies in sarcoidosis (G53.2)	3(0.09)	3(0.09)	6(0.18)
Encephalitis, myelitis and encephalomyelitis (G04)	3(0.09)	2(0.06)	5(0.15)
Spinal muscular atrophy and related syndromes (G12)	1(0.03)	0(0)	1(0.03)
Diseases of the musculoskeletal system			
Myositis in sarcoidosis (M63.3)	1(0.03)	3(0.09)	4(0.12)
Diseases of the eye and adnexa			
Iridocyclitis (H20, H22.1)	45(1.38)	93(2.85)	138(4.23)
Diseases of the skin			
erythema nodosum(L52)	0(0)	5(0.15)	5(0.15)

States is about 10.00 - 39.10 per 100,000(5, 22, 33), and that in Europe is 3.80 - 7.00 per 100,000 (24, 34, 35). Our findings are analogous with a Japanese study that reported an incidence of 1.01 per 100,000(6). In Asia, incidences have been reported ranging from 0.56-4.00 per 100,000(29, 36, 37), and the incidence of this study falls within this range. However, a direct comparison with these studies

may be difficult considering differences in methodology.

The incidence of sarcoidosis was 1.5 times higher in women. The female dominance observed in our study is comparable to other reports, in which incidence ranged from 1.22-2.08 times higher among women(6, 38). In males, the pattern of the age-specific incidence of sarcoidosis was biphasic, peaking twice at 30-39 and at 60-69 years of age, and monophasic in females, peaking at 50-59 years of age. Due to the preventive effect of female hormones, the peak of sarcoidosis among women is over fifty years of age (39).

In our study, lung and respiratory diseases were common comorbid disease with higher mortality. These findings are in line with previous studies that report common comorbidity as chronic pulmonary disease and obstructive pulmonary disease (14, 16, 17) and common cause of death as pneumonia, pulmonary fibrosis and obstructive airway disease (23, 25, 30) in sarcoidosis patients.

This study found the that 5-year survival rate after sarcoidosis diagnosis was 95.5%, which is comparable to the survival rate of 93.0% reported in a study of sarcoidosis in the UK (24). The annual mortality rate for patients with sarcoidosis was 9.26 per 1,000 person-years, which is similar to two previous studies that reported mortality rates of 9.40 per 1,000 person-years and 14.00 per 1,000 person-years (23, 24). Even though the incidence of sarcoidosis in Asia is much lower, our mortality and survival findings are similar to western countries.

Notably, the mortality of younger patients aged 20 years and under (38.43 per 1,000 person-years) was higher than adult patients aged 20 to 60 years (5.29 per 1,000 person-years). The main cause of deaths under 20 years of age were, systemic involvement of connective tissues, followed by breast cancer and heart failure. While skin melanoma accounted for all deaths under the age of 10 years. Though published data on the long-term prognosis of sarcoidosis in children are scarce, previous studies have found a poorer prognosis among young children with sarcoidosis (40, 41) associated with sequelae and progressive disease (42, 43). Our findings reflect the need for further detailed studies on the prognosis of sarcoidosis.

The SMR of sarcoidosis patients in this study was higher than the general population. There is a debate surrounding whether the mortality of sarcoidosis is higher than the general population. Earlier (21, 22) no difference in mortality rates between sarcoidosis patients and the general population was reported, while some studies(23, 24) found a higher hazard ratio among sarcoidosis patients compared to the general population, which is similar to our results. In interpreting results, it should be taken into consideration that previous studies used hospital-based design which only included sarcoidosis patients followed up at hospitals, while our study used a population-based design in which all Korean sarcoidosis patients were followed with reliable SMR estimates.

Among organ involvement, lungs accounted for 60.0% of cases in our study (1,955 cases), which is consonant with previous studies from other countries (6, 28). Mortality was higher in lung involvement than with any other organ. This coincides with a previous study where pulmonary disease and upper respiratory mucosal involvement had unfavourable clinical courses compared to acute arthritis and bilateral hilar lymphadenopathy(19).

We found that cancer, respiratory disease and sarcoidosis were the main causes of death and these showed higher cause-specific SMRs compared to the general population. This finding is in line with several studies (10) that reported higher incidence of cancer among sarcoidosis patients. We reported that among the different types of cancer, colon and lung cancer were the most common causes of death. Our study also found that respiratory disease was also significant cause of death in sarcoidosis, with interstitial pulmonary disease in particular showing higher mortality. Consistent with our findings, one report (44) found interstitial lung involvement with pulmonary fibrosis and pulmonary hypertension were associated with increased mortality and another study reported that pulmonary fibrosis accounted for 9.0% of deaths (30).

In this study although cardiac involvement was relatively common among sarcoidosis patients, the deaths due to cardiovascular disease were low. In interpreting the cause of death in our study we should take into account the cause of death registration system in Korea, where the National Statistics Office registers the cause of death for each deceased patient as one single underlying disease. In this system, the cause of death of patients with underlying cardiovascular disease may be registered as immediate cause such as pulmonary embolism or as primary disease

such as sarcoidosis. In this case, cardiovascular diseases may not be recorded as underlying cause of death.

In order to identify the type of treatment for sarcoidosis patients, we searched the KoreaMed, domestic medical research database with the keyword "sarcoidosis" and identified 103 studies (3 case series and 100 case reports (supplementary 2). Of the 260 patients with sarcoidosis, 162 (62.3%) were treated with steroids. In some of the patients in these studies, methotrexate (45-49), hydroxychloroquine (50, 51), and azathioprine (45, 52) were combined with steroids when multiorgan involvement was present such as lungs, eyes, muscles, liver, joints, and gastrointestinal tract and these results were similar to the standard treatment of sarcoidosis (53). In several cases, it has been reported that corticosteroids are effective in sarcoidosis treatment, but some studies report recurrences or steroid related complications due to long term use (54-57). In the literature, the effect of steroids for sarcoidosis still remains unclear.

The limitations of this study are as follows. First, because we used registration data, we were unable to identify detailed clinical features of sarcoidosis including clinical and radiological results. Second, ICD-10 code does not include information on specific organ involvement and therefore we could not determine the organ involvement separately for eye, heart and nervous system involved. Rather the patients invaded in eye, heart and nervous system were confirmed through comorbidity disease followed up in NHI database. Third, because we relied on government administrative cause of death data which includes one underlying cause, we could not investigate in detail the causes of death specifically designed for sarcoidosis patients. Therefore, sometimes it is difficult to distinguish whether designated cause of death was immediate cause or underlying disease. Finally, the use of ICD code registration data as diagnosis may raise questions concerning the diagnostic accuracy. However, the NHI provides uniform diagnostic criteria that must be followed in order to be registered in the RID and each diagnosis is reviewed at the healthcare institution before submission to the NHI to assure it meets the criteria. Through this process, we assumed that we maintained a high diagnostic reliability in this study.

Conclusion

This nationwide population-based study investigated the incidence, comorbidity, mortality and causes of death of sarcoidosis in Korea. The incidence of sarcoidosis was 0.81 per 100,000, which is lower than the United States and Europe, but similar with Japan. The annual mortality rate of 9.26 per 1,000 person-years and the survival rate of 95.5% were similar with previous studies. The mortality was significantly higher than the general population (SMR 1.91, 95% CI 1.62, 2.25) and was particularly high in younger age groups. The most common causes of death were cancer, sarcoidosis itself and respiratory diseases. Increased mortality was observed in sarcoidosis patients with comorbid diseases.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (1); 37-42 DOI: 10.36141/svdld.v37i1.7980

Interstitial lung disease and microscopic polyangiitis in chilean patients

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Abstract. *Objective:* To describe the clinical and serological patients characteristics with Microscopic Polyangiitis (MPA) and Interstitial lung disease (ILD). *Methods:* Of all the patients with AAV diagnosed between 2007-2017 at the Hospital Clinico Universidad de Chile, those with MPA and ILD were selected and studied retrospectively. *Results:* All patients were Hispanic; median age at diagnosis 65 years (32-84). 59% were female. All were positive for p-ANCA, 16 patients for MPO. Most common manifestations were constitutional symptoms, weight loss and fever. CT-Scans patterns were Usual Interstitial Pneumonia (UIP) in 10 patients, Nonspecific Interstitial Pneumonia (NSIP) in 6 and fibrosis not UIP or NSIP pattern in 1. In 6 cases, ILD was diagnosed 0.5-14 years before MPA and concomitantly in 11. *Conclusions:* Although infrequent, Microscopic Polyangiitis should be suspected in patients with ILD particularly if extra-pulmonary manifestations that rise the possibility of a systemic illness are present, regardless of the time elapsed between the latter and the diagnosis of this type of lung involvement. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 37-42)*

Key words: microscopic polyangiitis, interstitial lung disease, ANCA vasculitis

Introduction

Microscopic Polyangiitis is a systemic necrotizing vasculitis that predominantly affects small vessels in the absence of granulomas. It is associated to antineutrophil cytoplasmic antibodies (ANCA), with p-ANCA (perinuclear) fluorescence pattern and anti-myeloperoxidase (MPO) specificity. Immune deposits are scarce or absent (1). Without treatment, the mortality rate in the first year of disease is approximately 80 %. With adequate therapy, survival rates are between 82-92% (2).

The clinical onset of MPA can be acute or protracted. Clinical manifestations vary in scope and severity. Besides musculoskeletal and constitutional symptoms, the most commonly involved systems are: kidney (80-100%), peripheral nervous system and skin (30%) (1).

Pulmonary involvement has been observed in 25-55% of patients. Its most frequent expression is alveolar hemorrhage, showing patchy ground-glass attenuation on high resolution CT scan in 90% of cases (3,4). More recently it has been recognized that interstitial lung disease (ILD) is a significant although infrequent clinical manifestation of MPA (5,6,7). A limited number of ILD associated with

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MPA has been reported in the literature, two of them in Hispanic population (8,9). Therefore, the clinical and serologic characteristics and the prognosis of these patients is not completely known. Neither is clear if the clinical manifestations are different in patients of different genetic ancestry.

The aim of our study is to report the clinical and serological characteristics of 17 MPA Chilean patients with associated ILD and to compare them with other foreign series.

Patients and methods

All patients with ANCA associated vasculitis (AAV) diagnosed by a Rheumatologist, that fulfill ACR or Chapell Hill (10,11) classification criteria, between 2007-2017 at the Hospital Clínico Universidad de Chile were studied. Patients with ILD, defined as diffuse parenchymal lung disease on CT scan with UIP or NSIP pattern were selected and followed. All patients had at least two High Resolution Lung CT scan, one at the moment of diagnosis and one after at least 3 months of therapy. The CT scans were re-analyzed by a pulmonary radiologist, who was aware of the diagnosis of vasculitis. Patients with other rheumatic diseases, drugs or toxic exposure that could explain the pulmonary involvement were excluded. Blood cell counts, ESR, blood chemistry and urinalysis were performed monthly in all our patients. Indirect immunofluorescence for ANCA, ELISA assay for MPO-ANCA and PR3-ANCA, detection of rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), Antinuclear antibodies, antibodies to extractable antigens, complement and C-reactive protein (CRP), were performed according to the manufacturer's Instructions, at some point to every patient. None of our patients underwent lung biopsy. The Birmingham Vasculitis Activity Score (BVAS) was calculated at diagnosis.

Although this report is a retrospective study, all patients were studied and treated according to an institutional protocol for patients with severe vasculitis. Data are presented as percentages, medians and ranges.

Review of the clinical charts was performed and data were extracted on standardized forms, with the approval of the local Ethics Committee.

Results

101 Patients with AAV were diagnosed between 2007-2017 at the Hospital Clinico Universidad de Chile. 38 (37.6%) were MPA and 28 of them (73,6%) had pulmonary involvement. 17 had ILD. All patients were Hispanic; median age at diagnosis was 65 years (32-84). 59% were female. Clinical findings are summarized in Table 1. Most common manifestations at diagnosis were constitutional symptoms, weight loss and intermittent fever (> 38°C) in 100%, 70% and 70%, respectively. All patients had normocytic, normochromic anemia, high ESR (mean 83 mm/hr., range 33 - 120) and CRP (8-15 times above upper normal limit). All were positive for p-ANCA, 16 patients for MPO (titers between 23 and 100 IU; Normal <5). The median BVAS score at diagnosis calculated in 16 patients was 15.18 (range= 13–28).

In 10 cases, ILD was diagnosed concomitantly with MPA. In the other 7 patients idiopathic pulmonary fibrosis was diagnosed 0.5 to 14 years before AAV. In these patients vasculitis associated-ILD was suspected when additional non-respiratory symptoms appeared leading to further study. 5 patient developed signs of pulmonary hemorrhage.

The patterns described at CT Scans were Usual Interstitial Pneumonia (UIP) in 10 patients and Nonspecific Interstitial Pneumonia (NSIP) in 6 patients. One patient did not meet the complete criteria of UIP or NSIP. Non specific radiographic finding that might suggest vasculitis etiology was found.

All except 3 patient received 6 monthly iv cyclophosphamide (CF) as induction therapy. One patient died soon after the diagnosis, in two patient CF was suspended due to severe infections. All patients started with prednisone [1 mg/kg/day]. In 5 patients with associated alveolar hemorrhage, mononeuritis multiplex or optic neuropathy, methylprednisolone pulses [1gram/day per 3 days] were administered prior to oral therapy. Maintenance therapy was carried out with Azathioprine [1.5-2 mg/kg/day], and corticosteroids in low doses [5-10 mg/day]. 2 patients with progressive lung involvement received Rituximab one with stabilization of the disease, the other without success, died 17 months after diagnosis. One patient received rituximab due to relapse with alveolar hemorrhage with good response.

All patients with neurological involvement remained with some degree of sequelae. Arthritis, cu-

Table 1. Clinical features in 17 MPA with ILD patients

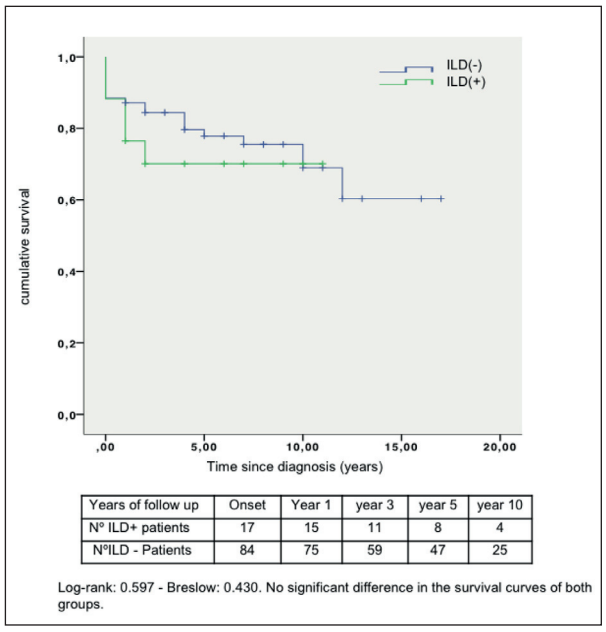
Age	Sex	BVAS (Initial)	CT	Chronolgy ILD-MPA (month)	RN	MC	NS	MS	Treatment	Moratlity
55	M	20	UIP	C	NO	NO	MM	M/S	CS/CF/AZ	NO
68	F	17	UIP/DAH	B (10)	NO	LR	PNP	M/A	CS/CF/AZ	NO
79	M	15	UIP	B (5)	NO	LR	PNP	M/S	CS/CF/AZ	NO
69	F	15	UIP	C	NO	LR	PNP	S	CS/CF/AZ	NO
77	F	19	UIP	C	GN	LR/CV	MM/SNHL	S	CS/CF/AZ	SÍ
64	F	13	UIP	C	GN	LR	NO	M/A	CS/CF/AZ	NO
81	M	19	UIP	C	GN	NO	NO	NO	CS/CF/AZ	NO
84	F	22	UIP/DAH	C	RPGN	Oral Ulcers	NO	NO	CS/CF	SÍ
63	F	22	UIP	B (168)	GN	NO	CNS/ SNHL	NO	CS/CF/AZ	NO
63	M	24	NSIP	B (24)	NO	NO	MM	S	CS/CF/AZ	Sí
53	F	23	NSIP	C	GN	LR	NO	A	CS/CF/RX/ AZ	SÍ
68	F	13	NSIP/DAH	B (50)	NO	NO	PNP	M	CS/CF/PX/ AZ	SÍ
57	M	25	NSIP/DAH	C	RPGN	NO	PNP	NO	CS/CF/AZ	NO
78	M	19	Not UIP/Not NSIP	B(60)	NO	NO	SNHL	M/S	CS/CF/AZ	NO
54	F	16	NSIP	C	NO	LR	PNP	A	CS/CF/AZ	NO
32	F	28	UIP/DAH	B(84)	NO	CV	NO	NO	CS/CF/AZ	NO
54	M	NA	NSIP	C	GN	NO	NO	M	CS/CF/RX	NO

M: Male F: Female; Y: Yes N: No ;B: Before C: Concomitant ;ILD: Interstitial Lung Disease MPA: Microscopic Polyangiitis CT: Computed Tomography UIP: Usual Interstitial Pneumonia NSIP: Non Specific Instertitial Pneumoniae DAH: Difusse alveolar hemorrhage; RN: renal GN: Glomerulonephritis RPGN: Rapidly progressive glomerulonephritis MC: Mucocutaneus LR: Livedo CV: Cutaneus vasculitis; NS: Nervous system MM: Multiple Mononeuritis PNP: Polyneuropathy SNHL: Sensorineural hearing loss CNS: Central nervous system ; MS: Musculosqueletal M: Myalgia S: Synovitis A: Arthralgia ;CS: Corticosteoids CF: Cyclophosphamide AZ: Azathioprine RX: Rituximab PX: Plasmapheresis

taneous manifestations and constitutional symptoms remitted with treatment without relapse.

5 of 17 patients analyzed, died. 3/5 (60%) with NSIP and 2 (40%) with UIP; 2 because of pulmonary infection, one from stroke, 1 from catastrophic respiratory failure due to disease progression and 1 died from unknown cause.

Survival analysis - Kaplan-Meier curve comparison of patients with AAV with and without ILD was performed. No statistically significant difference was found between two groups. (Figure 1)



Years of follow up	Onset	Year 1	year 3	year 5	year 10
N° ILD+ patients	17	15	11	8	4
N°ILD - Patients	84	75	59	47	25

Log-rank: 0.597 - Breslow: 0.430. No significant difference in the survival curves of both groups.

Fig. 1.

Discussion

Classically, MPA was described as a kidney-lung syndrome; however, during the last few years new forms of presentation, such as ILD, have been reported (5,12). To date, the clinical and pathological characteristics of ANCA associated ILD do not allow differentiate from idiopathic pulmonary fibrosis (IPF) (13). The prevalence of ANCA antibodies in patients with isolated IPF is estimated to be 8 to 36% (13,14,15). However, ILD associated to ANCA is not enough to diagnose AAV. The diagnosis also requires another clinical features that demonstrate vasculitis.

There is some data that suggests that the clinical phenotype of MPA differs with ethnicity so it is relevant to study clinical manifestations and outcomes of the disease in different populations (14,16). To our knowledge, there are only few cases of ILD associated to MPA reported in Hispanic population and our report has the biggest number of patients from South America (12)

The prevalence of ILD as a manifestation of MPA is thought to be low. However, different series report that among all MPA patients, ILD prevalence range from 2,7 to as high as 45%, with slight predominance in men, and 65 years as median age of presentation (14). We are reporting 17 cases of MPA with ILD in Chilean patients. In our cohort, 44,7% of MPA patients had ILD, the median age at presentation was 64,6 years (32-84), and 59% were female. Demographic data are similar to Asiatic patients and slightly older than in the other two Latin American series (Table 2).

As described in the literature, ILD can precede or occur concomitantly with other vasculitic manifestations in 14-85% and 36-67% respectively (6,12,14,15). In our cohort 41,2% preceded and 58.8% appeared simultaneously with MPA. No patient developed new ILD after the MPA diagnosis. As shown on table 2 we found a higher percentage of NSIP (35%) on CT scan than other patterns.

In many of our patients, the association of fever, polyarthritis, cutaneous manifestations and peripheral neuropathy were the findings that led us to suspect systemic vasculitis, and the interpretation of lung involvement as a manifestation of MPA occurred afterwards. In all of our patients, nonspecific findings, such as anemia, high ESR and CRP, rather than ILD, contributed to raise the suspicion of systemic illness. It is important to point out that most of our patients had high titers of rheumatoid factor with negative ACPA. This lead to an initial misdiagnose of rheumatoid arthritis in two of our patients.

It has been reported that between 80 and 100% of MPA patients have some degree of kidney involvement (1). Similar rates have been previously described in the series of ILD associated to AAV (5,6,14,15). Interestingly only 47% of our patients had clinical or laboratory expression of glomerular injury, and all of them had favourable outcome after treatment (Table 1).

The presence of ILD has been associated with poor prognosis and mortality in MPA (16,17). Reported mortality in ILD associated to AAV reaches 80 % (5,6,14,15). Factors associated with death in this patients are age at diagnosis of AAV, age at diagnosis of ILD, weight loss, eosinophil count and respiratory insufficiency. (17). In our series the mortality rate was 30 %. The higher percentage of NSIP pattern (35%) in our patients could explain the lower mortality rate compared with the predominance UIP pattern reported worldwide. In our cohort, we found no significant difference in mortality between groups with AAV with and without ILD, however this could be related to the sample size (Figure 1).

The age at diagnosis of our patients is similar

Table 2. Clinical and tomographic findings in worldwide series

Country	CHI	ARG	MEX	CHIN	JAP	USA	CAN	FRA	UK
Nº patients	17	9	19	19	19	3	6	49	14
Age (mean)	64.6	58.4	54.2	63.6	66.2	72.3	69.8	68	67.3
Sex % (Female)	59	54.5	47.1	58	48	76.7	50	39	28.5
Chronology ILD-MPA %									
• **Before**	41.2	55,5	82,3	68,4	52,6	33,3	50	45	14.4
• **Concomitant**	58.8	54.5	17.7	31.5	47.3	76.7	33.3	21	64.2
• **After**	0	0	0	0	0	0	16.7	12	21.4
CT %.									
• **UIP**	59	88.8	100	100	100	0	100	57	57.1
• **NSIP**	35	0	0	0	0	0	0	7	7.1
• **non UIP-NSIP**	6	11.2	0	0	0	100	0	26	35.8
Mortality %	30	44.4	41.2	31	47	33.3	83.3	61	71

CHI: Chile ARG: Argentina MEX: México CHIN: China JAP: Japan USA: United States CAN: Canada FRA: Francia UK: United Kingdon. ILD: Interstitial Lung Disease MPA: Microscopic polyangiitis CT: Computed Tomography UIP: Usual Insterstitial Pneumoniae NSIP: Non Specific Interstitial Pneumoniae.(7,14)

to what has been described in other series. However, in contrast with our results (female 59%), in European series a male predominance has been reported, 66,3% (5,13,16). The time of onset of pulmonary involvement is highly variable and could precede, be concomitant with or develop after other vasculitic manifestation. (Table 2)

ILD has been progressively described as a manifestation of MPA. Our reports suggest that the presence of constitutional symptoms, other parenchymal involvement, anemia, high ESR or CRP should raise the suspicion of AAV. In these patients testing for ANCA is of especial interest.

ILD associated to ANCA vasculitis might be a potentially treatable cause of ILD. Here we report the first series of ILD associated to MPA in Chilean patients. Further studies are warranted to determine specific clinical characteristics and best therapeutic approach in this newly described subset of MPA patients in different populations.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (1); 43-52 DOI: 10.36141/svdld.v37i1.8144

Incidence and economic burden of sarcoidosis in years 2011–2015 in Silesian voivodeship, Poland

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Abstract. *Background:* Sarcoidosis is a rare, chronic systemic disease. Earlier data (2006-2010) suggest that the incidence of pulmonary sarcoidosis in Silesian voivodeship increased, however there is no current data on other clinical forms of the disease. *Objectives:* The aim of presented study was an analysis of the actual epidemiological situation of sarcoidosis with simultaneous estimation of treatment cost financed from public funds. *Methods:* Epidemiological descriptive study concerned registered cases of sarcoidosis diagnosed in adult inhabitants of the Silesian voivodeship in years 2011-2015. Secondary epidemiological data on the main diagnosis and comorbidity were obtained from the National Health Fund (NFZ) database in Katowice. Territorial and temporal variability of standardized incidence rates were analysed with simultaneous estimation of treatment costs reimbursed from the state budget. *Results:* Pulmonary sarcoidosis was the most frequently registered clinical form of such disease in the Silesian voivodeship (65% of total cases). The highest number of cases was diagnosed in the age 35–54 years, frequently in men than in women. Significantly decrease of the standardized incidence of sarcoidosis noticed between 2011 and 2015 is related with observed lower number of total cases of pulmonary disease. Observed territorial variability of the sarcoidosis incidence requires future, well-planned studies. The annual average direct cost of sarcoidosis treatment is high and exceed 538 EUR per patient. *Conclusions:* It was confirmed that sarcoidosis in the Silesian Voivodeship is a rare disease, however reimbursed direct costs of treatment remains very high. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 43-52)*

Key words: sarcoidosis, incidence, economic burden, descriptive study

Introduction

Sarcoidosis is a chronic disease manifested by the presence of granulomas in many tissues or organs, mainly in lungs, but also in lymph nodes, heart, organs of sight, liver or heart (1-3, 8, 9). The aetiology of the disease remains unexplained (4) although there are reports on genetic determinants appropriate for specific ethnic groups (5-7, 9, 12, 13), and also indicating an abnormal immune response due to exposure (6, 9, 12, 13). The factors include: fungi, mycobacteria, bacteria, parasites (1, 6, 13) and pollen, metals, chemicals, or medicines (1, 9, 13).

The incidence of sarcoidosis substantially differs between regions, the highest values were reported in the African-American population of the United States (35.5/100,000), as well as in the populations of Northern European countries (Sweden 24/100,000, Norway 14-15/100,000, Finland 11.4/100,000) (6, 10). The lowest incidence was recorded in Southern European countries (Spain 0.42/100,000, Greece 1.07/100,000) and also in Japan (0.56-1.01/100,000 population) (10). The incidence of pulmonary sar-

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coidosis in Poland, estimated in years 2006-2010 was at the level of 3.8-4.5/100,000 population (11).

There is no separate registry of particular form of sarcoidosis hospitalization cases in Poland, current registry include the number of entire cases of certain disorders involving the immune mechanism (D86) with pulmonary sarcoidosis and other allergic lung diseases, as well as autoimmune and granulomas (14). In the period 2011-2015, the number of hospitalizations due to total cases of diseases in this group was constantly increasing and ranged from 6,589 to 8,113 per year.

The cost of sarcoidosis treatment is high, eg. total annual direct cost of treatment in the United States is about 1.3-8.7 billion USD, and the average annual cost is at the level USD 19,714 per patient (15). Moreover, it is documented that the largest annual average cost of treatment of a patient with sarcoidosis (80-100th percentile of total costs) reached USD 7,345 (EUR 59,719.76) (16). The average cost of total granuloma treatment in the period 2011-2015, in Poland are stable and ranged PLN 4,850.18 (EUR 1,149.99) per patient and PLN 4,943.76 (EUR 1,172.17), in 2011 and 2013 year respectively (14).

Observed progressive aging of population causes increase the number of chronic diseases, including number of patients hospitalized due to sarcoidosis (11, 14). Those observation justify needs of epidemiological study in the aim of current situation assessment in one of the biggest Polish agglomeration (Silesian Voivodeship), including incidence, hospitalization and total cost of treatment granted from the government funds.

Methods

This paper presents results of descriptive epidemiological study conducted in the Silesian voivodeship and based on secondary epidemiological data registered by National Health Fund (NHF) in Katowice, in years 2011-2015. Obtained data on sarcoidosis (D86; ICD-10 version) include addresses of services providers, type of service (outpatient, stationary), admission mode, mode of discharge and cost of benefits. Moreover, anonymous patient data were collected, age, gender and place of residence, and the major diagnosis code according to ICD-10 along with three comorbidities. The including criterion was ever diagnosed sarcoidosis recognized as the main diagnosis and/or as one of the comorbidities. The following forms of the disease were included in final database: sarcoidosis of the lung (D86.0) and sarcoidosis of the lung with sarcoidosis of lymph nodes (D86.2), sarcoidosis of lymph nodes (D86.1), sarcoidosis of skin (D86.3), sarcoidosis of other sites (D86.8) and unspecified sarcoidosis (D86.9).

The number and percentage of patients with sarcoidosis, separately women and men in the following age groups: 19-34, 35-54, 55-64 and 65+, were determined. Crude and standardized incidences of sarcoidosis in particular years of the study period (2011-2015) were presented as a rate per 100,000 population of 19+ years. The average number of inhabitants in 2011-2015 was 3,722,496 (3,712,784÷3,728,366). Their temporal variability in the Silesian Voivodeship was shown in separated local administrative units according to NTS-4 (Nomenclature of Territorial Units for Statistics), for which detailed description of procedure was presented in the earlier publication (11). The assessment of sarcoidosis territorial variability was presented on contour maps of the Silesian Voivodeship as an averaged value of incidence rates in 2011-2015. For this purpose, the geographical information system ArcGIS 9.2 was used. Moreover, the direct costs of sarcoidosis treatment, in both outpatient visits and hospitalization, incurred in 2011-2015 were estimated. On the basis of data on the services number in particular reported years, the average unit costs of disease treatment in PLN were calculated. The structure of these expenses was presented based on the following rounded quantile values: $k_{0.25}$=50, $k_{0.5}$=500, $k_{0.75}$=5,000. The study wasn't any medical experiment, and the secondary character of data didn't need Bioethics Committee permission.

Statistical analysis of data was based on MS Excel 2013 (Microsoft Office 2013) software and the 2.11.1 R package (GNU GPL license).

Results

According to the assumed aim of the study, appropriate crude and standardized incidence rates were calculated, detailed results are presented in Table 1. As it was expected, the standardized values were almost two times smaller than the crude val-

ues: 7.08-13.08/100,000 vs 12.04-22.09/100,000 population 19+ years. The highest standardized incidence rate was obtained for pulmonary sarcoidosis with values ranging from 9.55/100,000 in 2011 to

Table 1. Crude and standardized incidence rates of sarcoidosis (D86; ICD-10 version) in adults aged 19 and over (n/100,000), Silesian Voivodeship

Year	Main diagnosis				Main or co-existing diagnosis			
	Crude ratio	Standardized ratio			Crude ratio	Standardized ratio		
	Total	Total	Women	Men	Total	Total	Women	Men
Sarcoidosis D86								
2011	22.09	**13.08**	11.31	14.71	25.65	**15.02**	12.93	17.00
2012	18.27	**10.86**	11.01	10.45	21.32	**12.57**	12.73	12.13
2013	13.80	**8.39**	7.40	9.31	16.22	**9.80**	8.64	10.85
2014	12.28	**7.71**	6.16	9.20	14.41	**8.91**	7.16	10.60
2015	12.04	**7.08**	5.61	8.52	14.44	**8.40**	6.61	10.13
Sarcoidosis of lung D86.0, D86.2								
2011	16.07	**9.55**	7.69	11.32	18.36	**10.78**	8.56	12.93
2012	12.77	**7.62**	7.48	7.57	14.32	**8.49**	8.38	8.42
2013	8.86	**5.33**	4.69	5.94	10.34	**6.18**	5.39	6.92
2014	6.96	**4.35**	3.23	5.45	8.09	**4.97**	3.71	6.20
2015	7.35	**4.32**	3.47	5.16	8.65	**5.05**	3.89	6.18
Sarcoidosis of lymph nodes D86.1								
2011	2.68	**1.57**	1.51	1.61	2.90	**1.69**	1.61	1.77
2012	2.90	**1.72**	1.82	1.60	3.25	**1.91**	2.00	1.77
2013	2.26	**1.43**	1.29	1.55	2.52	**1.60**	1.41	1.76
2014	2.82	**1.81**	1.59	2.00	3.20	**2.05**	1.75	2.35
2015	2.50	**1.56**	1.16	1.95	2.91	**1.76**	1.35	2.16
Sarcoidosis of skin D86.3								
2011	0.27	**0.15**	0.30	0.00	0.35	**0.20**	0.39	0.00
2012	0.24	**0.15**	0.21	0.07	0.32	**0.20**	0.29	0.11
2013	0.35	**0.19**	0.16	0.22	0.43	**0.24**	0.22	0.26
2014	0.32	**0.18**	0.26	0.11	0.35	**0.19**	0.27	0.11
2015	0.13	**0.05**	0.07	0.02	0.16	**0.07**	0.12	0.02
Sarcoidosis of other sites D86.8								
2011	1.18	**0.71**	0.77	0.64	1.40	**0.85**	0.91	0.78
2012	0.67	**0.37**	0.51	0.23	0.83	**0.45**	0.56	0.34
2013	0.67	**0.41**	0.51	0.29	0.89	**0.53**	0.64	0.42
2014	0.51	**0.33**	0.34	0.32	0.56	**0.36**	0.39	0.32
2015	0.27	**0.15**	0.19	0.11	0.30	**0.16**	0.19	0.14
Unspecified sarcoidosis D86.9								
2011	1.88	**1.09**	1.03	1.14	2.66	**1.50**	1.46	1.52
2012	1.69	**1.00**	0.99	0.98	2.60	**1.52**	1.50	1.49
2013	1.66	**1.04**	0.75	1.31	2.04	**1.25**	0.99	1.49
2014	1.67	**1.03**	0.74	1.33	2.20	**1.34**	1.04	1.63
2015	1.78	**1.00**	0.72	1.28	2.42	**1.36**	1.07	1.64

4.32/100,000 in 2015 year. Moreover, the value was higher in men than in women (5.16-11.32/100,000 vs 3.23-7.69/100,000 respectively).

Figure 1 illustrates the territorial variability of sarcoidosis incidence rates (values averaged in the study period 2011-2015). The highest values were observed in the following cities: Siemianowice Slaskie, Gliwice, Ruda Slaska, Dabrowa Gornicza and Tychy and districts: gliwicki, lubliniecki, bierunsko-ledzinski. The lowest values concerned cities: Bytom, Zory and districts: wodzislawski, rybnicki, cieszynski.

It is worth noting that most frequently sarcoidosis was detected in people aged 35-54 years (Figure 2). Patients with sarcoidosis as the major diagnosis were somewhat younger (46.6±13.3 years) than those with sarcoidosis as a co-occurring disease (47.3±13.5 years).

Sarcoidosis mostly affected men than women (52.0% vs. 48%), both total and particular forms of the disease (Figure 3).

Detailed data on the number of new outpatient visits or hospitalization due to sarcoidosis was shown in Table 2. It was noted, that a total number of cases and a number of outpatient visits significantly decreased in subsequent reporting years with a relatively stable number of hospitalizations in the entire study period 2011-2015. The highest number of patients was observed in the beginning year of the study.

Most frequently diagnosed form of sarcoidosis was the pulmonary form of the disease (D86.0, D86.2; ICD-10 version) and contained about 65% of all cases (N=3427) recognized in the study period (2012-2015) and over 70% of cases in the beginning year (N=956; 2011). Sarcoidosis of lymph nodes (D86.1) occurred in about 16% of patients, lower percentages were related to diagnoses of unspecified sarcoidosis (D86.9) - 10% of cases, sarcoidosis of other sites (D86.8) - 4% of cases, as well as sarcoidosis of skin (D86.3) - 2% of cases, in 2012-2015 (N=3427).

Table 3 presents a history of treating patients with sarcoidosis. In the case of over 80% of people, treatment started in a planned mode, based on a referral. Over half of patients with sarcoidosis (60%)

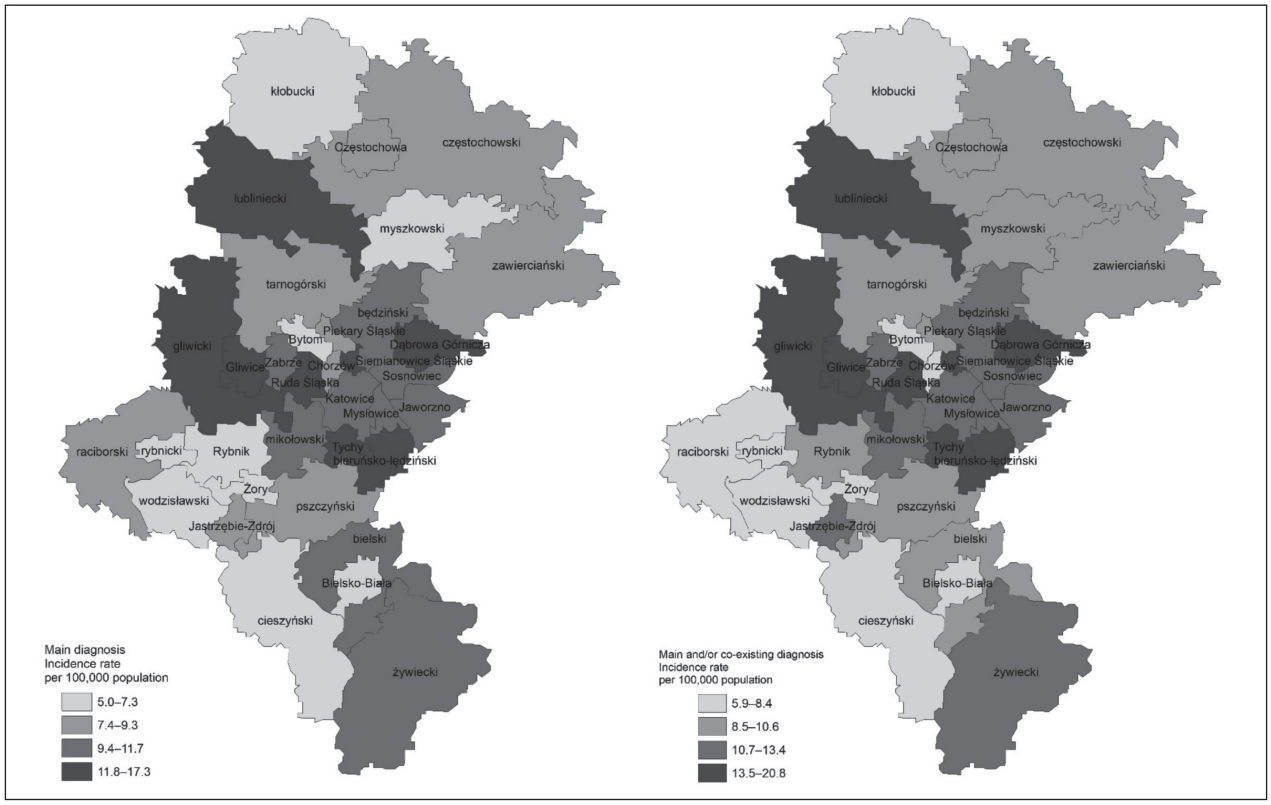

Fig. 1. Standardized incidence rates of sarcoidosis in adults inhabitants of Silesian voivodeship, values averaged for the period 2011-2015 (n/100,000)

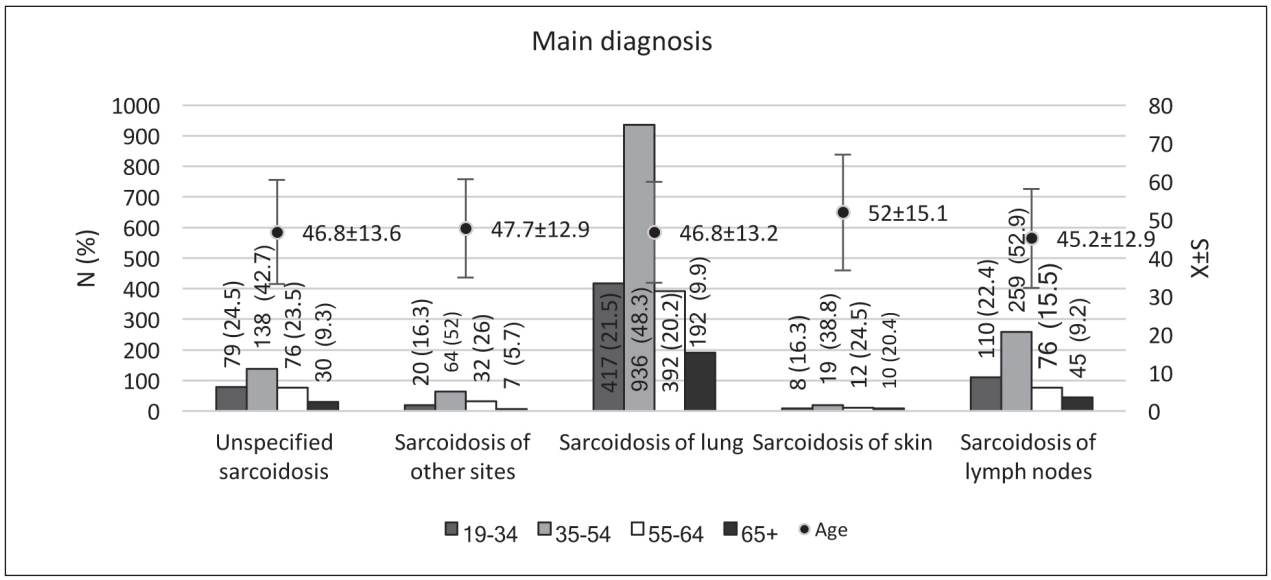

Fig. 2. Numbers and % of first-time diagnosed sarcoidosis (D86; ICD-10 version) in the entire period (2011-2015) by age of patients, Silesian Voivodeship

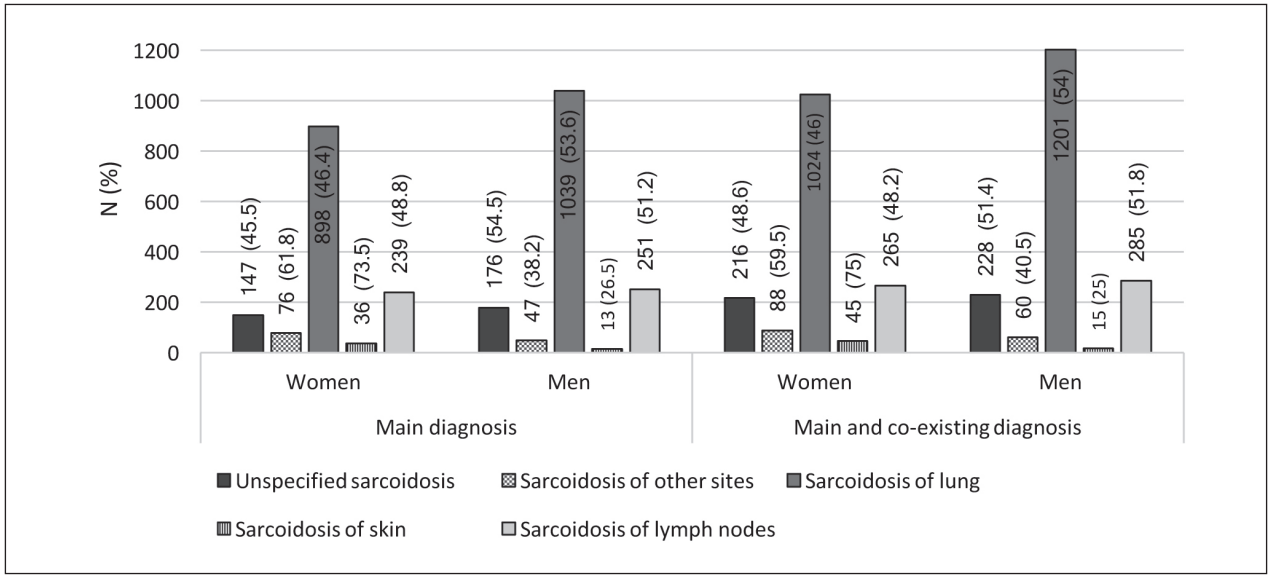

Fig. 3. Total number and percentage of first-time diagnosed sarcoidosis (D86; ICD-10 version) in the entire study period (2011-2015), Silesian Voivodeship

were referred for further treatment, after discharge from the hospital. In the study period, none patient died due to sarcoidosis as the major diagnosis.

The average costs of hospitalization patients with sarcoidosis as a major diagnosis (funds granted from the budget) were PLN 5,115.17 (EUR 1,177.80) per patient and were similar to those refunded in patients with sarcoidosis as a co-morbid disease (PLN 4,684.03 - EUR 1 078.52). Detailed data are presented in Table 4.

It is worth noting that in the case of nearly 30% of unit services, the annual cost did not exceed PLN 50 per patient. The percentage of patients for which the funds spent were greater than PLN 5,000 did not exceed 13.8% (patients with the main diagnosis) and 12.5% (patients with comorbid sarcoidosis).

Table 2. The number of first-time outpatient visits or hospitalizations due to particular form of sarcoidosis in adults 19+ years, Silesian Voivodeship

Year	Total number of sarcoidosis D86			Sarcoidosis of lung D86.0, D86.2			Sarcoidosis of lymph nodes D86.1			Sarcoidosis of skin D86.3			Sarcoidosis of other sites D86.8			Unspecified sarcoidosis D86.9			Number of total death
	O	H	Total N (%)	O	H	Total N (%)	O	H	Total N (%)	O	H	Total N (%)	O	H	Total N (%)	O	H	Total N (%)	Total N (%)
Main diagnosis																			
2011	425	398	**823 (100)**	305	294	599 (72.8)	51	49	100 (12.2)	8	2	10 (1.2)	25	19	44 (5.3)	36	34	70 (8.5)	5 (0.6)
2012	464	217	**681 (100)**	349	127	476 (69.9)	52	56	108 (15.9)	7	2	9 (1.3)	14	11	25 (3.7)	42	21	63 (9.3)	6 (0.9)
2013	298	216	**514 (100)**	210	120	330 (64.2)	34	50	84 (16.3)	7	6	13 (2.5)	10	15	25 (4.9)	37	25	62 (12.1)	16 (3.1)
2014	221	236	**457 (100)**	137	122	259 (56.7)	42	63	105 (23)	5	7	12 (2.6)	9	10	19 (4.2)	28	34	62 (13.6)	11 (2.4)
2015	201	246	**447 (100)**	132	141	273 (61.1)	36	57	93 (20.8)	2	3	5 (1.1)	3	7	10 (2.2)	28	38	66 (14.8)	27 (6)
Total N (%)	**1609 (55.1)**	**1313 (44.9)**	**2922 (100)**	**1133 (58.5)**	**804 (41.5)**	**1937 (66.3)**	**215 (43.9)**	**275 (56.1)**	**490 (16.8)**	**29 (59.2)**	**20 (40.8)**	**49 (1.7)**	**61 (49.6)**	**62 (50.4)**	**123 (4.2)**	**171 (52.9)**	**152 (47.1)**	**323 (11.1)**	**65 (2.2)**
Sarcoidosis as a main or co-existing diagnosis																			
2011	451	505	**956 (100)**	327	357	684 (71.5)	52	56	108 (11.3)	8	5	13 (1.4)	27	25	52 (5.4)	37	62	99 (10.4)	12 (1.3)
2012	491	304	**795 (100)**	369	165	534 (67.2)	54	67	121 (15.2)	8	4	12 (1.5)	15	16	31 (3.9)	45	52	97 (12.2)	12 (1.5)
2013	325	279	**604 (100)**	227	158	385 (63.7)	35	59	94 (15.6)	9	7	16 (2.6)	12	21	33 (5.5)	42	34	76 (12.6)	27 (4.5)
2014	246	290	**536 (100)**	149	152	301 (56.2)	49	70	119 (22.2)	5	8	13 (2.4)	10	11	21 (3.9)	33	49	82 (15.3)	22 (4.1)
2015	237	299	**536 (100)**	154	167	321 (59.9)	40	68	108 (20.1)	2	4	6 (1.1)	4	7	11 (2.1)	37	53	90 (16.8)	37 (6.9)
Total N (%)	**1750 (51.1)**	**1677 (48.9)**	**3427 (100)**	**1226 (55.1)**	**999 (44.9)**	**2225 (64.9)**	**230 (41.8)**	**320 (58.2)**	**550 (16)**	**32 (53.3)**	**28 (46.7)**	**60 (1.8)**	**68 (45.9)**	**80 (54.1)**	**148 (4.3)**	**194 (43.7)**	**250 (56.3)**	**444 (13)**	**110 (3.2)**

O - outpatient treatment visits; H - hospitalization, stationary treatment

Table 3. History of treatment patients with sarcoidosis in Silesian voivodeship (D86; ICD-10 version) entire study period (2011-2015)

Admission	Sarcoidosis as a major diagnosis N (%)	Sarcoidosis as a major or coexisting diagnosis N (%)
Outpatient treatment		
Emergency admission	157 (9.8)	171 (9.8)
Planned admission based on referral	1405 (87.3)	1498 (85.6)
No data	47 (2.9)	81 (4.6)
Total	**1609 (100)**	**1750 (100)**
Hospitalization (stationary treatment)		
Emergency admission	239 (18.2)	418 (24.9)
Planned admission based on a referral	1074 (81.8)	1259 (75.1)
Total	**1313 (100)**	**1677 (100)**
Discharge		
Referral for further treatment	799 (60.9)	1080 (64.4)
Discharge against medical advice (AMA)	7 (0.5)	10 (0.6)
The end of the therapeutic or diagnostic process	507 (38.6)	579 (34.5)
Death of the patient	0 (0)	8 (0.5)
Total	**1313 (100)**	**1677 (100)**

Discussion

Obtained results confirmed that the current epidemiological situation of sarcoidosis (2011-2015) in the Silesian Voivodeship is satisfactory. First, we observed a decrease of new cases of disease which was basically related to decreasing the number of dominant clinical forms of the disease - pulmonary sarcoidosis (about 65% of cases). Similarly, lung sarcoidosis is the most common form of the disease in the USA, data of the Foundation for Sarcoidosis Research (FSR) suggests that this form of disease affected even up to 90% of patients (17). Extrapulmonary sarcoidosis includes the following forms: peripheral lymph nodes, heart, eyeballs, nervous system, skin, liver and/or spleen, the osteoarticular system (1, 12, 17). Own data confirmed that 16% of patients had sarcoidosis of lymph nodes, sarcoidosis of other sites occurred in 4% of patients, sarcoidosis of skin was diagnosed in 2%, and unspecified sarcoidosis in more than 10%. A similar structure of disease was observed in the Netherlands where pulmonary form concerned 82% of patients, ocular sarcoidosis 3.8%, neurosarcoidosis 3.3%, cardiac sarcoidosis 1.6%, hypercalcemia 2.2% and sarcoidosis of skin and other symptoms occurred in 7.1% of patients (18). The Case-Control Etiologic of Sarcoidosis Study (ACCESS) indicated, that the dominant form was the pulmonary sarcoidosis (51.9% of patients), next sarcoidosis of skin (12.7%), sarcoidosis of other sites (6.3%) and unspecified sarcoidosis (15.9%) (25).

Treatment of sarcoidosis has an individual character without unambiguous standards methods (19). The Polish NHF registry indicated that more than half of patients (55.1%) in the Silesian Voivodeship were treated in out-patient visits immediately after the first-time diagnosis, whereas 1313 (44.9%) of patients were hospitalized. Most people with pulmonary sarcoidosis and sarcoidosis of skin were patients of outpatient treatment, while people with sarcoidosis of lymph node and sarcoidosis of other sites rather required hospitalization. The observed difference was most likely a consequence of better availability of detailed diagnostic methods and appropriate therapy in hospitals only (2). The results of other studies in the United States revealed that the rate of hospitalization due to sarcoidosis was significantly higher than the rates of hospitalization of patients without sarcoidosis (17.3/100 vs 12.6/100 person-years, respectively) (22). We observed, that 60% of patients hospitalized due to first-time diagnosed sarcoidosis in the Silesian voivodeship were referred for further treatment.

Table 4. Total and unit cost of health services granted from the budget (PLN) in particular form of sarcoidosis. (PLN to EUR according to the NBP exchange rate from 2018-06-28: EUR/PLN = 0.2303)

Diagnosis		Actual direct costs of treatment patients with sarcoidosis PLN / EUR					Total cost 2011-2015 PLN / EUR	Average unit cost 2011-2015 PLN / EUR	Total cost 2011-2015 PLN / EUR		Average unit cost 2011-2015 PLN / EUR	
		2011	2012	2013	2014	2015			O	H	O	H
Main diagnosis	Unspecified sarcoidosis	152,188.50 35,042.25	101,237.10 23,310.41	123,520.85 28,441.36	172,780.65 39,783.71	171,454.25 39,478.30	721,181.35 166,056.02	**2,232.76** **514.11**	11,960.35 2,753.94	709,221.00 163,302.09	**69.94** **16.10**	**4,665.93** **1,074.36**
	Sarcoidosis of other sites	93,654.75 21,564.53	58,557.00 13,483.08	81,037.00 18,659.22	49,249.50 11,339.97	30,469.00 7,015.66	312,967.25 72,062.45	**2,544.45** **585.87**	3,173.75 730.77	309,793.50 71,331.68	**52.03** **11.98**	**4,996.67** **1,150.51**
	Sarcoidosis of lung	1,615,996.55 372,092.21	708,757.16 163,195.28	635,279.51 146,276.65	665,461.36 153,226.19	666,388.90 153,439.76	4,291,883.48 988,230.08	**2,215.74** **510.19**	82,581.95 19,014.95	4,209,301.53 969,215.13	**72.89** **16.78**	**5,235.45** **1,205.49**
	Sarcoidosis of skin	3,648.53 840.09	3,620.90 833.73	11,348.15 2,612.97	14,137.90 3,255.33	5,248.45 1,208.48	38,003.93 8,750.62	**775.59** **178.58**	1,064.93 245.21	36,939.00 8,505.41	**36.73** **8.46**	**1,846.95** **425.27**
	Sarcoidosis of lymph nodes	257,533.65 59,298.56	329,574.10 75,886.27	288,272.20 66,376.28	332,850.22 76,640.62	257,750.79 59,348.56	1,465,980.96 337,550.28	**2,991.80** **688.88**	15,012.89 3,456.80	1,450,968.07 334,093.48	**69.83** **16.08**	**5,276.25** **1,214.89**
	Total	2,123,021.98 488,837.64	1,201,746.26 276,708.77	1,139,457.71 262,366.49	1,234,479.63 284,245.81	1,131,311.39 260,490.75	6,830,016.97 1,572,649.46	**2,337.45** **538.21**	113,793.87 26,201.67	6,716,223.10 1,546,447.79	**70.72** **16.28**	**5,115.17** **1,177.80**
	The average unit cost per patient	**2,579.61** **593.97**	**1,764.68** **406.33**	**2,216.84** **510.44**	**2,701.27** **621.98**	**2,530.90** **582.75**	**2,337.45** **538.21**	-	**70.72** **16.28**	**5,115.17** **1,177.80**	-	-
Main or co-existing diagnosis	Unspecified sarcoidosis	243,287.95 56,018.41	190,041.31 43,758.07	145,769.45 33,564.23	243,701.19 56,113.56	234,680.25 54,036.44	1,057,480.15 243,490.70	**2,381.71** **548.40**	12,871.55 2,963.75	1,044,608.60 240,526.95	**66.35** **15.28**	**4,178.43** **962.11**
	Sarcoidosis of other sites	103,873.95 23,917.56	67,100.60 15,450.29	109,878.74 25,300.19	51,186.60 11,786.00	30,507.80 7,024.59	362,547.69 83,478.63	**2,449.65** **564.05**	3,547.59 816.85	359,000.10 82,661.77	**52.17** **12.01**	**4,487.50** **1,033.27**
	Sarcoidosis of lung	1,786,760.77 411,411.62	823,568.31 189,631.19	759,642.43 174,911.90	746,828.05 171,961.32	749,027.59 172,467.78	4,865,827.14 1,120,383.81	**2,186.89** **503.54**	86,678.28 19,958.16	4,779,148.87 1,100,425.65	**70.70** **16.28**	**4,783.93** **1,101.53**
	Sarcoidosis of skin	8,426.53 1,940.26	6,457.60 1,486.90	12,779.45 2,942.54	15,820.90 3,642.85	8,368.45 1,926.88	51,852.93 11,939.43	**864.22** **198.99**	1,120.93 258.10	50,732.00 11,681.33	**35.03** **8.07**	**1,811.86** **417.19**
	Sarcoidosis of lymph nodes	286,728.45 66,020.82	384,184.30 88,460.58	327,536.67 75,417.14	350,402.22 80,682.06	288,338.94 66,391.65	1,637,190.58 376,972.25	**2,976.71** **685.40**	15,554.24 3,581.45	1,621,636.34 373,390.80	**67.63** **15.57**	**5,067.61** **1,166.85**
	Total	2,429,077.65 559,308.66	1,471,352.12 338,787.02	1,355,606.74 312,136.00	1,407,938.96 324,185.79	1,310,923.03 301,847.33	7,974,898.49 1,836,264.81	**2,327.08** **535.62**	119,772.59 27,578.31	7,855,125.90 1,808,686.50	**68.44** **15.76**	**4,684.03** **1,078.52**
	The average unit cost per patient	**2,540.88** **585.05**	**1,850.76** **426.15**	**2,244.38** **516.78**	**2,626.75** **604.82**	**2,445.75** **563.15**	**2,327.08** **535.82**	-	**68.44** **15.76**	**4,684.03** **1,078.52**	-	-

O - outpatient treatment; H - hospitalization, stationary treatment

The demographic structure of patients with pulmonary sarcoidosis in the present study was similar to those observed in earlier research period 2006-2010 (11). The frequency of disease was the highest in people aged 35-54 years. Polish and USA studies confirmed that sex is a serious determinant of the diagnosed form of the disease, sarcoidosis of lymph node and unspecified sarcoidosis were dominant forms in Polish males while in female sarcoidosis of skin and sarcoidosis of other sites were the major forms (11, 20). In the USA neurosarcoidosis, ocular sarcoidosis and erythema nodular were significantly more frequently recognized in women than in men (20).

Obtained results confirmed significant temporal variability of sarcoidosis incidence in the Silesian voivodeship. During an earlier period (years 2006-2010) an increase of the standardized incidence rate was observed from the value of 3.8/100,000 to 4.3/100,000. Next in 2011 was noted a double increase of incidence to the value 9.55/100,000 population. Current data confirmed a significant decrease in incidence rate in years 2012-2015 to the values 7.62-4.32/100,000 population respectively. Such observation is difficult to explaining in the case of descriptive study thus, it cannot be ruled out that an unstable register is responsible for this variability, and we have to project future research in which confounder and modifying factors will be taken into account. However, contrary to our observations, the epidemiological situation of sarcoidosis in the United States was quite stable, the incidence in the years 2010-2013 was at the level 7.6-8.8/100,000 population. Similarly, stable values of crude incidence in the years 1991-2003 was recorded in Great Britain, the incidence of sarcoidosis was in the range of 4.45-5.59/100,000 population (23). Concluding, the current incidence of sarcoidosis in Silesian Voivodeship is consistent with some other cited studies. Significantly higher values apply to Northern European countries with values 24/100,000 in Sweden, 11.4/100,000 in Finland, 14-15/100,000 in Norway and 7.2/100,000 in Denmark. On the other hand, Southern European countries have a lower incidence, respectively: 0.42/100,000 in Spain and 1.07/100,000 in Greece (10).

Observed in own study significant territorial variability of incidence is consistent with those reported in the United States. The highest value (9.45-11.83/100 000 population) concerned north USA regions, while slightly lower was registered in southern and western US states (7.84-9.43/100,000 population and 4.31-4.93/100,000 population respectively) (21). It is worth referring to the earlier publication, in which authors conclude that observed territorial variability of lung sarcoidosis is related to potentially higher exposure to pesticides and wood dust of people living in districts with a predominance of arable and/or forest land (11). The observations of Italians are also interesting, they pointed to the possible connection between the place of residence in the peripheral areas of cities and rural areas and the increased incidence of lung sarcoidosis (24). However, such hypothesis requires future research in which we have to control exposure.

The average annual cost of sarcoidosis treatment in the Silesian Voivodeship was PLN 2,337.45 (EUR 538.21) per patient. It should be noted a significant disproportion of costs in particular clinical forms of the disease. The lowest cost, on average PLN 775.59 (EUR 178.58) per patient was related to sarcoidosis of skin treatment, while the highest (on average PLN 2,999.80, EUR 688) are related to the lymph nodes sarcoidosis treatment. The cost of hospitalization of sarcoidosis of lung was one of the highest (on average PLN 5,235.45, EUR 1,205.49), and it is worth to notice that in Poland hospitalization of granulomas, allergic and autoimmune pulmonary disease is related with the highest cost of hospitalization in comparison to the most frequent diseases (25). Additionally, the cost of hospitalization was much higher than the cost of outpatient treatment, which is basically associated with the need to finance the simultaneous treatment of co-morbidities and specialist treatment (16). Really, 1/3 of patients with pulmonary sarcoidosis visit a first-time medical doctor with a significant delay (usually half-yearly) in relation to early respiratory symptoms, which causes an increasing cost of treating patients with advanced disease (26). In the end, we should refer to existing problems of health services financing in Poland which are a consequence of insufficient access to guaranteed services. According to the Watch Health Care (WHC) report, the average waiting time in 2017 was dependent on the medical specialization (eg. dermatology needs 2.2 months, internal medicine about 3.1 months, cardiology 5.0 months, and ophthalmology 5.6 months) (27). This situation usually leads to transferring significant costs of diagnosis and treatment to the house budget. It happens that patients ignore symptoms, which ultimately results

in the prolonged diagnostic process and increases the cost of treatment. The matter seems to be important to public health because the last EHCI rankings point to the need for expected reforms in Poland in a range of improvement in the availability and quality of health services provided (28).

Conclusions

Obtained results confirmed, that sarcoidosis in the Silesian Voivodeship is rather a rare disease with pulmonary sarcoidosis as a dominant clinical form of the disease. The highest number of patients was registered in adults aged 35-54 years, the frequency is higher in men than woman. Significantly decrease of the standardized incidence of sarcoidosis noticed between 2011 and 2015 is related to the observed lower number of total cases of pulmonary disease, and the picture is different than the previous observation registered in years 2006-2010. The average annual unit cost of sarcoidosis hospitalization was significantly higher than the cost of outpatient treatment.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (1); 53-65 DOI: 10.36141/svdld.v37i1.7837

Miliary Sarcoidosis: does it exist? A case series and systematic review of literature

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Abstract. *Background and Objectives:* Sarcoidosis typically presents with peribronchovascular and perilymphatic nodules on high-resolution computed tomography (HRCT); a miliary pattern is reported but not well described. *Design, setting:* We describe four patients with miliary sarcoidosis and results of a systematic review of all previously reported cases from 1985 onwards. *Results:* We identified only 27 cases of "miliary" sarcoidosis in the HRCT era. These patients were older (85.2% older than 40 years), had more co-morbidities (72.7%) and were symptomatic compared to "typical" sarcoidosis. Respiratory symptoms were present in 61.9% at diagnosis. Hypercalcemia was seen in 28.5%. On review of HRCT images, only 34.6% (9/26) had a "true miliary" pattern without fissural nodules. In our series, prominent perivascular granulomas were seen on histopathology in all. 44.4% (12/27) had tuberculosis preceding or concurrent to miliary sarcoidosis. Of the eight true associations, tuberculosis preceded sarcoidosis by 52 (median, IQR 36) weeks in six and occurred concurrently in another two. The diagnosis of tuberculosis was clinical in all with concurrent diagnosis of tuberculosis and sarcoidosis. Treatment with steroids had 100% response and 14.2% relapse. *Conclusions:* A true miliary pattern in the HRCT era is very rare in sarcoidosis and subtle perilymphatic pattern is nearly always seen; this should be labeled "pseudo-miliary". Prominent perivascular granulomas are associated with true miliary pattern. Miliary sarcoidosis patients are older and symptomatic, needing treatment at diagnosis. "Miliary" sarcoidosis may follow treatment for tuberculosis; concurrent cases possibly indicate the difficulty in differentiating both or a "tuberculo-sarcoid" presentation. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 53-65)*

Key words: sarcoidosis, miliary, micronodules, miliary tuberculosis

Introduction

Miliary sarcoidosis has been described as a rare presentation of sarcoidosis and was reported in <1% of all cases in the pre-computed tomography (CT) era on chest radiography (1). With the advent of high-resolution-CT (HRCT), peribronchovascular and perilymphatic nodules in relation to the secondary pulmonary lobule are recognized as classic of sarcoidosis (2). However, random micronodules (miliary pattern) have been described and sarcoidosis is included in the differential diagnosis of a "miliary" pattern on HRCT (3, 4). There are no well-described series or systematic reviews of "miliary" sarcoidosis in the high-resolution CT (HRCT) era. On the other hand, tuberculosis continues to be a global pandemic with an estimated 10 million cases worldwide in 2016 (5). Miliary tuberculosis accounts for 1-2%

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of all cases of new cases of tuberculosis and 8% of all extra-pulmonary tuberculosis (6). The relationship between tuberculosis and sarcoidosis continues to be enigmatic; tuberculosis can precede, follow or present concurrently with sarcoidosis (7). In patients with miliary tuberculosis, the clinical symptoms of night sweats, weight loss and fatigue are non-specific and overlap markedly with sarcoidosis. Respiratory symptoms are often minimal in either forms of miliary disease and microbiological evidence of *M.tuberculosis* is only present in 20-30% of miliary tuberculosis (8). Sarcoidosis has a characteristic perilymphatic pattern on histopathology and radiology (2); the co-relation of random nodules seen on radiology with pathology in "miliary" sarcoidosis is unclear. We describe a series of patients with miliary sarcoidosis and the results of our systematic review on miliary sarcoidosis in the HRCT era.

Materials and methods

We describe four patients with miliary nodules and proven sarcoidosis that was managed in the authors' institution over three years and performed a systematic search of literature for miliary sarcoidosis.

Systematic search of literature

Two of the authors (R.S and R.K) conducted a systematic search of literature in PUBMED independently using the MeSH term "miliary" *AND* "sarcoidosis" limited to title/abstract and restricted the search from the year 1985 onwards (9). The choice of the year was defined by the first description of the current HRCT protocols and detailed description. This was further supplemented by search of IndMed using the same terms, the references of retrieved articles, our personal records and the Internet search engine GOOGLE. These articles were screened without blinding, by title and abstract review to identify relevant studies. Any discrepancy was resolved by consensus. Full texts or abstracts were then retrieved to identify the type of lung involvement in reported cases with miliary sarcoidosis. Only those articles that included patients with HRCT according to established protocols (9), included representative images or detailed descriptions and had a histological diagnosis compatible with sarcoidosis (10) were included for analysis. For the purpose of this systematic review, we included all descriptions that were accepted as "miliary" in published cases but reanalyzed the images independently. The diagnosis of sarcoidosis was according to previous published guidelines (10).

Data extraction

Data was abstracted from selected cases in a predefined data extraction form (Supplementary Table).

Statistical analysis

Continuous data are presented as mean (standard deviation (SD), median [range or Interquartile Range (IQR)] and categorical data as percentages and proportions. All statistical analysis was done using the Statistical software SPSS Version 14.

Ethics

The Human Ethics Committee of PSG IMS&R, Coimbatore, approved the study. All data was anonymized to maintain patient confidentiality.

Case reports

Case 1

A 65-year-old lady presented with cough, night sweats and exertional breathlessness of two months' duration. There was no history of weight loss or fever. Her past history was significant for hypertension and non-productive cough two years before that was evaluated at another center. CT had shown right paratracheal and bilateral hilar lymphadenopathy along with upper lobe-predominant micronodules. Tuberculin skin testing was negative and endobronchial ultrasound-guided needle aspiration (EBUS-FNA) and transbronchial lung biopsy (TBLB) were performed. EBUS-FNA showed few non-caseating granulomas and TBLB was non-contributory. A presumptive diagnosis of tuberculosis was made and four-drug anti-tuberculosis treatment (ATT) was administered for six months with improvement in cough. Examination was unremarkable during current evaluation. There was no exposure to pets, drugs

or occupational dusts. Chest radiography was normal. Spirometry was normal and diffusion capacity showed mild reduction. HRCT showed profuse random micronodules without lymphadenopathy and an upper-lobe and peripheral predominance that was visualized better with maximum intensity projection (MIP, Figure 1). Renal function tests, serum calcium and angiotensin-converting enzyme (ACE) levels were normal. Fibreoptic bronchoscopy (FOB) was done with bronchoalveolar lavage (BAL) and TBLB; BAL Fluid was negative for acid-fast bacilli and Xpert MTB/RIF and TBLB showed interstitial inflammation only. Surgical lung biopsy was performed and showed extensive perivascular non-caseating granulomas (Figure 2). BAL mycobacterial cultures were subsequently reported as negative. She was started on steroids with resolution in cough and breathlessness by second month of treatment. She remains asymptomatic and off steroids after one year of treatment.

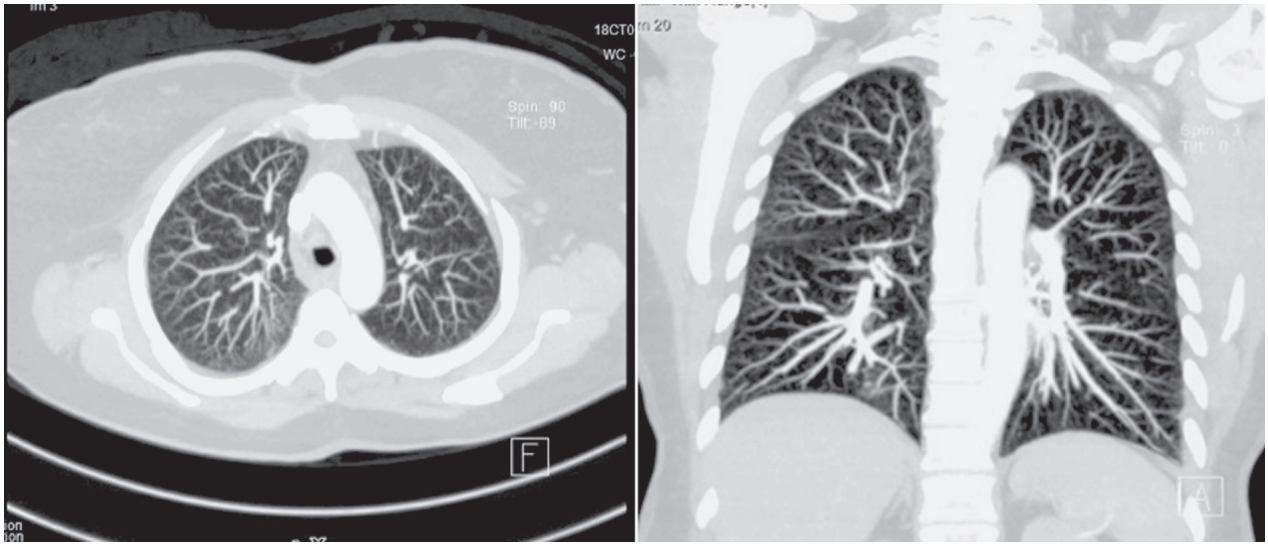

Fig. 1. Composite image of Maximal Intensity Projection images of high-resolution computed tomography (HRCT) of the thorax from patient 1 showing upper-lobe and peripheral-predominant miliary micronodules

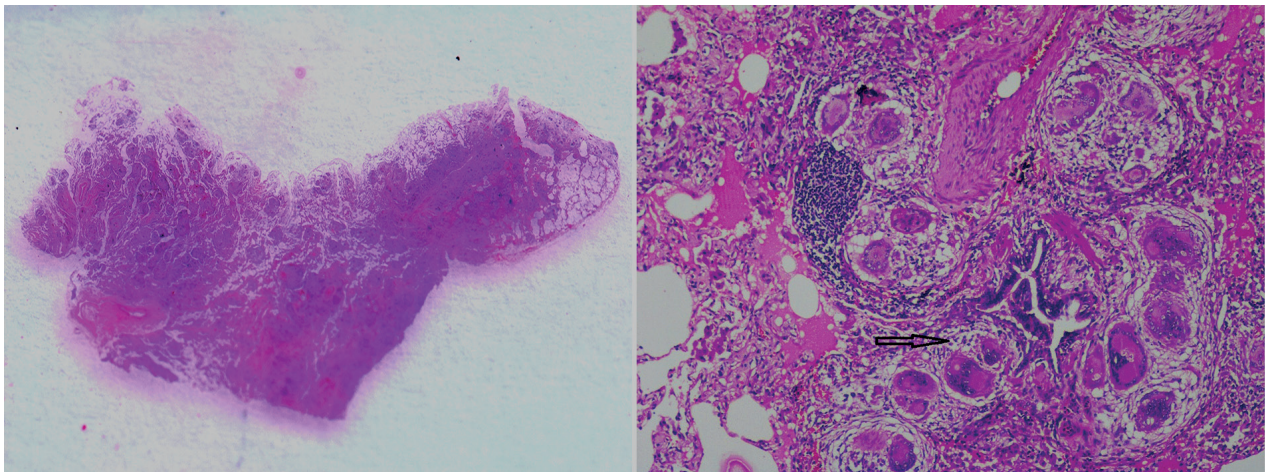

Fig. 2. Composite image of photomicrographs of surgical lung biopsy specimen of Patient 1 with left [Gross Pathological specimen, transverse plane] showing subpleural sparing and (right, Hematoxylin and Eosin stain (H & E), x 4) showing peribronchial and perivascular granulomas (arrow)

Case 2

A 40-year old gentleman presented with polyuria, fatigue and nausea of 20 days duration. There was also history of unquantified weight loss and exertional dyspnea. He did not smoke and did not raise pets, abuse drugs or have exposure to occupational dusts. Physical examination showed raised papulonodular skin lesions over hands and legs. Renal function tests showed serum creatinine of 2.65 mg/dL (normal <0.8 mg/dL); Urine microscopy showed 2+ albumin with bland sediments. Hemoglobin was 10.9 g/dL with normal leukocyte and platelet counts. Ultrasound showed normal kidney size with preserved corticomedullary distinction. Chest radiographs showed miliary nodules. Serum ionized calcium was 1.8 mg/dL (normal 1.1-1.3 mg/dL) with suppressed parathyroid hormone (1.9 pg/mL, normal 15-65) and normal vitamin D levels (23.6 ng/mL). ACE levels were elevated (98 U/mL, normal 8-53). Tuberculin skin testing was negative. CT-Chest showed random micronodules without zonal preponderance and bilateral hilar lymphadenopathy (Figure 3, left). FOB was done with BAL and TBLB; BAL was negative for acid-fast bacilli and Xpert MTB/RIF. TBLB showed perivascular non-caseating granulomas with Schaumann and asteroid bodies (Figure 4). Punch biopsy of the skin also showed non-caseating granulomas in the dermis**.** He was started on steroids with resolution of hypercalcemia and normalization of renal function. His subsequent course was complicated by steroid-aggravated diabetes presenting with hyperosmolar coma; methotrexate was added and steroids were tapered. He remained asymptomatic with near-complete radiologic clearing (Figure 3, right) after one year of stopping methotrexate but relapsed by 18 months and remains on methotrexate.

Case 3

A 55-year old gentleman with moderately controlled diabetes mellitus presented with exertional breathlessness, cough, right-sided shoulder pain and weight loss of one month's duration. There was no anorexia or expectoration. He was a farmer by occupation and did not have exposure to poultry or occupational dusts and chemicals. Physical examination showed fine bilateral crepitations without clubbing. Renal function tests, serum calcium, urine microscopy, ACE levels and hemogram were normal. Chest radiographs showed miliary nodules (Figure 5, left). Human Immunodeficiency virus was negative by enzyme-linked sorbent assay. Tuberculin skin testing was strongly positive (18 mm, 1 TU). CT-Chest showed random micronodules without lymphadenopathy (Figure 6, left). FOB was done with BAL

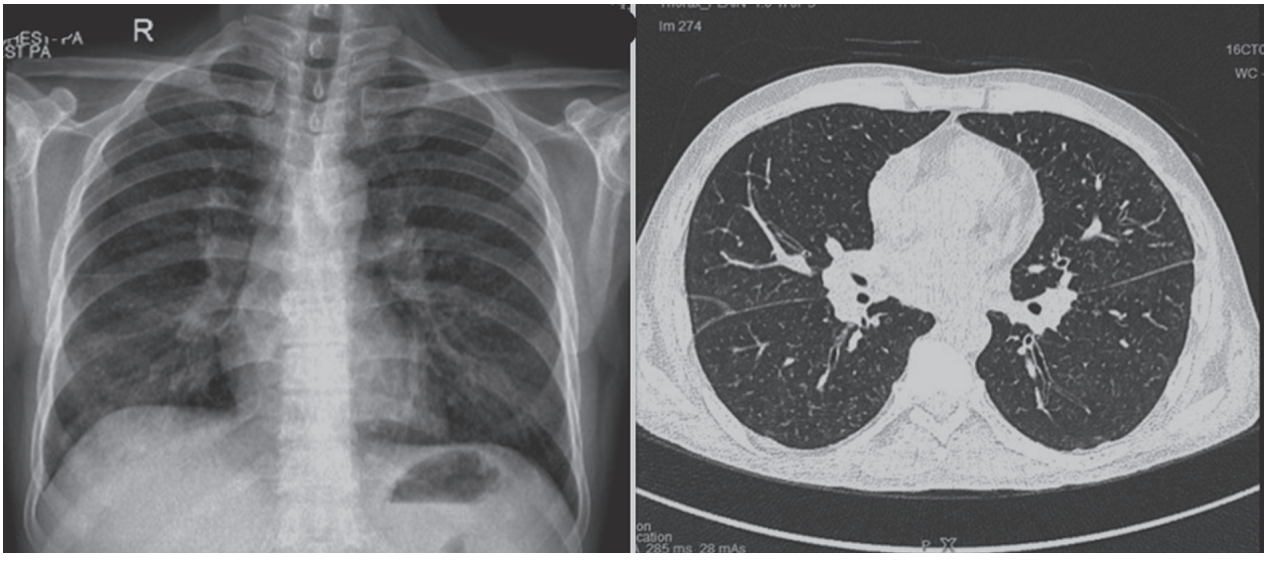

Fig. 3. Composite images of chest radiography of patient 2 showing miliary nodules (left) and HRCT images (major fissure level) showing upper lobe-predominant random nodules. No involvement of the fissure or "beading" of the fissure is seen

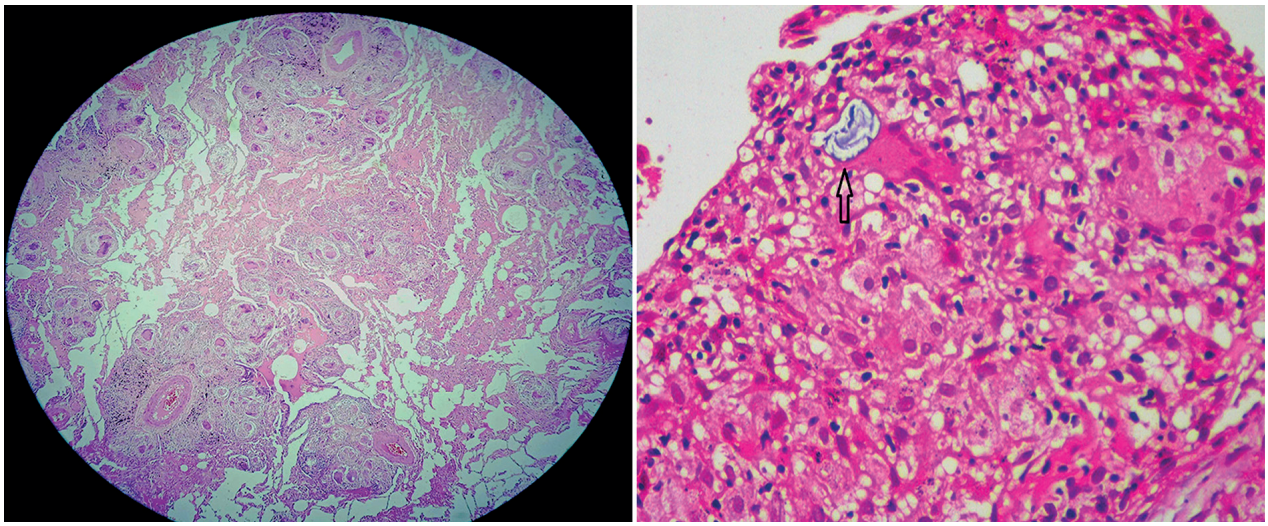

Fig. 4. Composite image of Photomicrographs of lung biopsy sample of Patient 2 with left, [Hematoxylin and Eosin stain (H & E), x scanner power] showing multiple non-necrotizing perivascular granulomas, and right, [H & E stain, x 40) showing a Schaumann body within a giant cell (arrow)

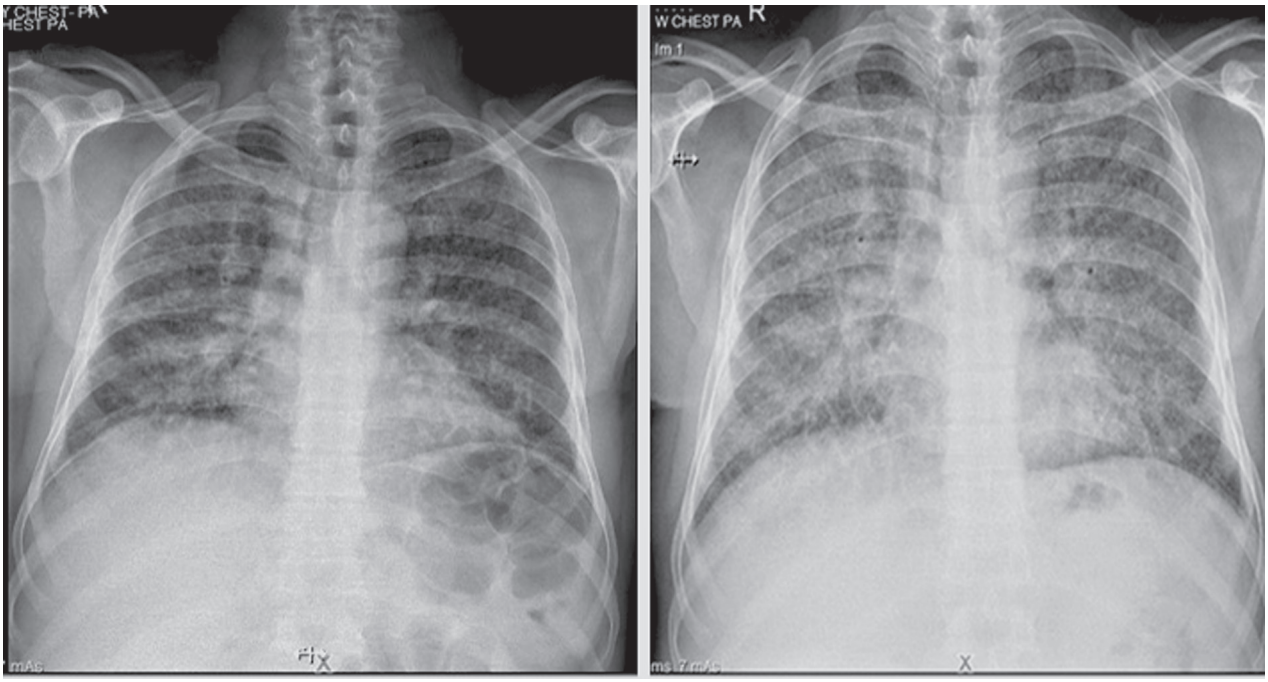

Fig. 5. Composite image of the Chest Radiographs of Patient 3 at initial evaluation (left) showing extensive miliary nodules. Subsequent Chest radiograph (right) after six weeks of anti-tuberculosis treatment alone show profusion of nodules with diffuse ground-glass opacification. Worsening hypoxemia was clinically noted

and TBLB; BAL was negative for acid-fast bacilli and Xpert MTB/RIF. TBLB showed well-formed perivascular granulomas with Langhans' giant cells, occasional fibrinoid necrosis and lymphocytes rimming (Figure 6, right). A diagnosis of miliary tuberculosis was made and four-drug weight-based ATT was started. However, his symptoms continued to worsen with worsening nodules and development

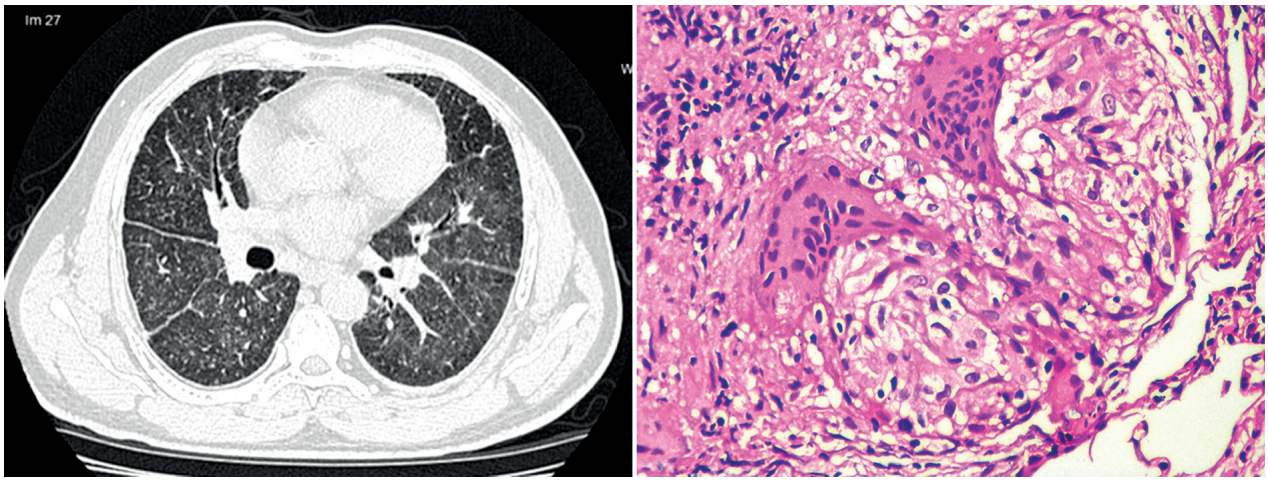

Fig. 6. Composite image of the HRCT image of Patient 3 at the level of major fissure during worsening hypoxemia corresponding to right-side of Figure 5 (left), showing random nodules with fissural prominence, with beading in both oblique fissures; some interlobular septal thickening and diffuse ground glass opacity can be seen and right, (Hematoxylin and Eosin stain, x 40) showing a non-necrotizing granuloma with peripheral lymphocyte cuffing

of hypoxemia needing oxygen at four weeks (Figure 5, right). BAL mycobacterial cultures were negative in the meantime. Steroids were added with a presumptive diagnosis of immune reconstitution syndrome, with resolution of hypoxemia and symptoms. Symptoms recurred after stopping steroids at four weeks; right-sided vision loss due to uveitis occurred. After a clinico-pathological review, a possibility of concurrent miliary tuberculosis with sarcoidosis was considered. ATT was continued and low-dose tapering steroids and methotrexate (in view of poorly controlled diabetes) were added, with complete resolution of symptoms by eight weeks. He remains asymptomatic after two years of cessation of ATT and methotrexate.

Case 4

A 48-year-old gentleman presented with fatigue for two weeks. There was no history of night sweats, weight loss or fever. He did not smoke, did not raise pets, abuse alcohol or drugs and did not report exposure to occupational dusts. Physical examination was normal. Renal function tests, urine microscopy and hemogram were normal. Serum calcium was elevated (1.43 mg/dL, normal 1.1-1.3). Chest radiographs showed miliary nodules (Figure 7, left). ACE levels were elevated (76 U/mL, normal 8-53). Tuberculin skin testing was negative. CT-Chest showed upper lobe predominant random micronodules and lower-lobe interlobular septal thickening (Figure 8, left & right). FOB was done with BAL and TBLB; BAL was negative for mycobacterial cultures and Xpert MTB/RIF. TBLB showed prominent perivascular non-necrotizing epitheloid granulomas with asteroid bodies (Figure 7, right). A diagnosis of miliary sarcoidosis was made and steroids were initiated. His symptoms and hypercalcemia resolved by four weeks and steroids were tapered over the next nine months. He remains asymptomatic on follow-up.

Results of the systematic search

Our systematic search identified 27 reports of miliary sarcoidosis in 21 reports (3, 11-30); this included 16 men and 9 women (Table 1, supplementary Table). This cohort of "miliary sarcoidosis" was older, was mostly symptomatic and had high co-morbidity burden. The mean age of the included patients was 47.5±13.2 years; 85.2% were older than 40 years. 72.7% reported at least one associated co-morbidity (11, 12, 16, 18, 21, 27, 30).

The median time to presentation was 8 (IQR 12) weeks. The majority had symptoms at the time of presentation (90.9%, 20/22); only two patients recognized by surveillance transbronchial lung biopsies post-lung transplantation were asymptomatic

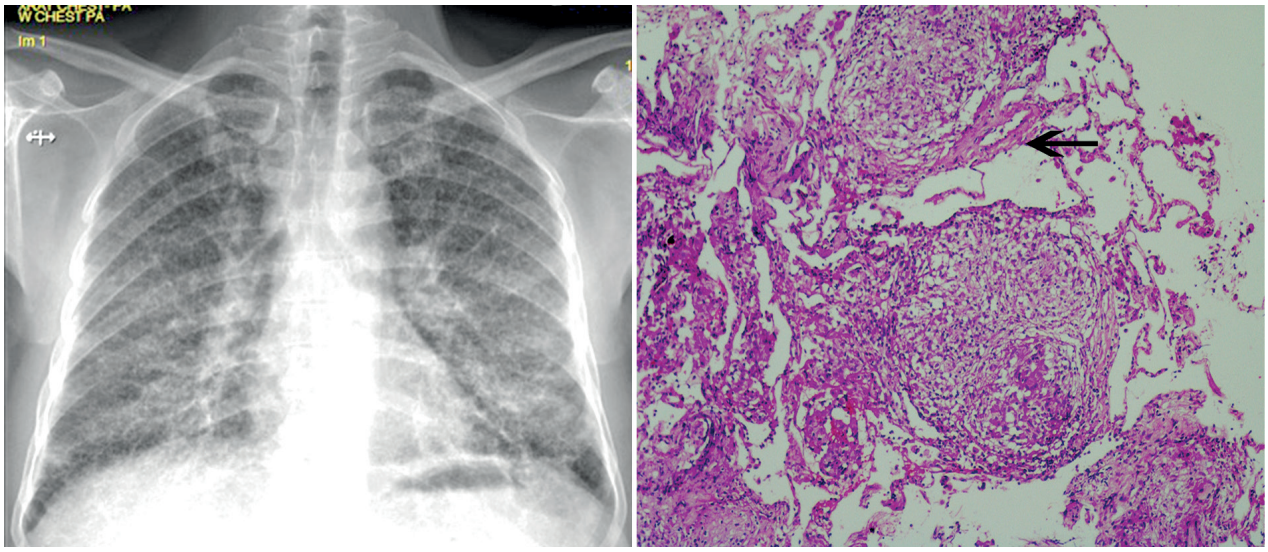

Fig. 7. Composite image of chest radiography images (left) of Patient 4 showing miliary nodules at diagnosis and photomicrographs of the lung biopsy specimen [right, Hematoxylin and Eosin stain (H & E) x 4] showing multiple perivascular granulomas (arrow)

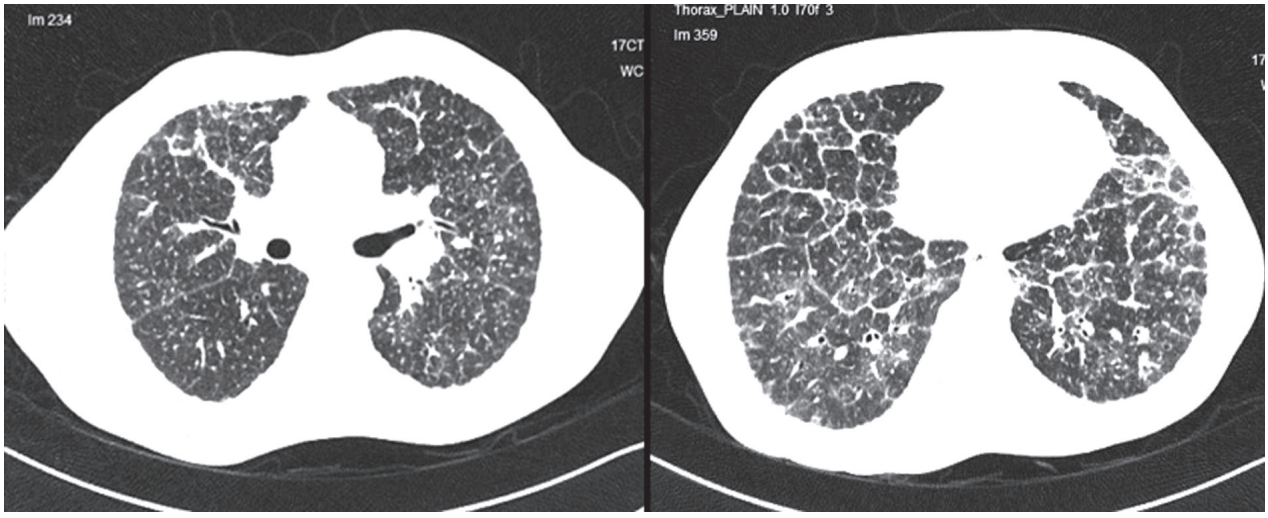

Fig. 8. Composite image of the HRCT image of Patient 4 showing (left, upper lobes) random nodules with perilymphatic predominance, beading of the right oblique fissure and perivascular nodules and (right, lower lobes) marked interlobular septal thickening in the lower lobes associated with random nodules

at diagnosis (11, 12). Respiratory symptoms, however, were present in 63.6% only at diagnosis (13, 14, 16, 20, 21, 23-25, 28-30). In those with respiratory symptoms, breathlessness and cough were present in less than 50% (45.4%). Fever (27.3%) (13, 21-23, 29), night sweats (11.1%) (22, 27) and weight loss (22.7%)(18, 22, 27) were all seen in a significant percentage at diagnosis.

Symptomatic multi-systemic disease in association with miliary sarcoidosis was seen in 36.4%.(17, 19, 20, 23, 30) Hypercalcemia was seen in 27.3% (19, 20, 23, 27) and acute kidney injury was seen in 9.1% (19) at diagnosis. None needed dialysis but chronic kidney disease occurred in association with nephrocalcinosis (19). Ocular (13.6%, 3/22) involvement (25), bone (4.5%, 1/22) disease (17), sicca syndrome

Table 1. Summary of clinical features of all reported cases of thoracic sarcoidosis with miliary nodules on High-resolution Computed Tomography (N=27) [$]

Characteristic	Description
Age, Mean ± S.D, N=24	47.5±13.2 years; Age >40 years 85.2%
Gender (Male: Female), N=25	16:9
	In those >40 years, Male: Females O.R 0.26, p=1.00 (61.9% vs 75%)
Country of description	India (10/26), United States (7/26), Greece (5/26), Japan (3/26), Germany (1/26)
Symptoms at presentation	
Any symptoms, N=22	None, asymptomatic (9.1%, 2/22)
Symptom duration prior to presentation, Median, IQR N=19	8, (12) weeks
Symptoms	Any respiratory symptom (63.6%, 14/22)
	Dyspnea (45.4%, 10/22), cough (45.4%, 10/22)
	Fatigue (30.4%, 7/23), fever (27.3%, 6/22), weight loss (22.7%, 5/22), night sweats (11.1%, 3/22)
Acute kidney injury	9.1%, 2/22
Hypercalcemia	27.3%, 6/22
Co-morbidities, N=22	Any 72.7% (16/22)
	Smoking (18.2%, 4/22), diabetes (13.6%, 3/22), hypertension (18.2%, 4/22), lung transplantation (9.1%, 2/22), dust exposure (13.6%, 3/22)
Symptomatic disseminated sarcoidosis	8/22 (36.4%)
Other site involvement	Ocular (13.6%, 3/22), pleural effusion (9.1%, 2/22), bone (4.5%, 1/22), sicca syndrome (4.5%, 1/22), pancreas (4.5%, 1/22)
Radiological findings (N=26)	
True miliary pattern on HRCT	17/26 (65.4%) only
Perilymphatic nodules on HRCT in miliary CT	8/17 (47.1%); Truly random nodules total 9/26 (34.6%)
Zonal predominance seen	Upper & middle (7/26, 26.9%), central (7.7%, 2/26), peripheral (19.2%, 5/26)
Fissural nodules	65.4% (17/26)
Peripheral subpleural predominance	69.2% (18/26)
Interlobular septal thickening	23.1% (6/26)
Intralobular septal thickening	11.5% (3/26)
Ground glass opacity	11.5% (3/26)
Mediastinal adenopathy	Yes (50%, 13/26); Right paratracheal (23.1%, 6/23), bilateral hilar (23.1%, 9/23), others (8.7%, 2/23)
Generalized lymphadenopathy	8.7% (2/23)
Steroid treatment	Yes 21/22 (95.2%), Response 100% (21/21)
Relapse	14.2% (3/21)
Tuberculosis and miliary sarcoidosis	
Both tuberculosis and sarcoidosis	Both tuberculosis and sarcoidosis 44.4% (12/27)
	Definite or probable tuberculosis followed by sarcoidosis 29.7% (8/27)
	Probable misdiagnosis of tuberculosis 33.3%, (4/12)
	Microbiologically proven 37.5% (3/8) of all cases only
	Sequential (87.5%, 7/8), concurrent (25%, 2/8)[@@]

(continued on next page)

Characteristic	Description
Time to sequential miliary sarcoidosis in those with tuberculosis preceding sarcoidosis, (Median, IQR) N=7	52 (36) weeks
Site of tuberculosis	Pulmonary 87.5% (7/8), spinal 12.5% (1/8)
Yield of TBLB, N=21	85.7% (18/21)
Miliary tuberculosis preceding or concurrent with miliary sarcoidosis	5/8 (62.5%), 2/5 with miliary TB preceding miliary sarcoidosis
ATT-induced hepatitis	2/8 (25%)

Abbreviations: S.D standard deviation, IQR Inter-quartile range, HRCT High-resolution Computed Tomography, TBLB transbronchial lung biopsy, ATT Anti-tuberculosis treatment
[@@]One patient had both sequential and concurrent diagnosis of tuberculosis and sarcoidosis

(4.5%, 1/22) (20) and pancreatic mass (4.5%, 1/22) (28) were the other manifestations seen. Pleural effusion was seen in association in 9.1% (2/22) (24, 28).

On review of the HRCT images, a "true miliary" pattern was seen in 65.4% (17/26) of the reported cases only. In these cases, fissural nodules and prominence could still be seen in 47.1% (8/17); only 34.6% (9/26) of reported cases could be classified as random micronodules on radiologic review (12-14, 17, 18, 24, 26, 28, 30). An upper and middle lobe distribution of nodules (11-13, 15, 16, 25-27) was seen in 26.9% (7/26) and a peripheral distribution was seen in 69.2% (11, 12, 15, 24, 28). Perilymphatic clustering of nodules (3, 11-18, 22, 24-26, 28) or a perivascular dominance (3, 13, 15, 19, 22, 26-28) of nodules was seen in 65.4% and 42.3% respectively. Interlobular septal thickening, often lower-lobe in distribution, was seen in 23.1% (Table 1) (12, 14, 15, 18). Mediastinal adenopathy was observed in 50% in association with micronodules and generalized systemic lymphadenopathy was seen in 8.7% of patients (19, 20).

44.4% (12/26) of the reported patients had tuberculosis preceding or concurrent to the diagnosis of miliary sarcoidosis (13-17, 20-22, 29). In four of these patients, this was likely a misdiagnosis (13, 14, 30). In eight patients, tuberculosis occurred preceding (15-17, 21, 22) sarcoidosis in six (62.5%), concurrently in one (37.5%) (29) and both in one (23). In those with tuberculosis preceding sarcoidosis, a microbiological confirmation was made in 42.9% (15-17, 22); Others were diagnosed based on pathology and clinical response (21). In patients with concurrent diagnosis of tuberculosis and sarcoidosis, the diagnosis of tuberculosis was clinical in all; in all these patients, clinical and pathological findings, including caseous necrosis, were consistent with tuberculosis but clinical resolution occurred on initiation of steroids only (23, 29). The time to subsequent diagnosis of miliary sarcoidosis after treatment for tuberculosis was a median of 52 (IQR, 36) weeks. Miliary tuberculosis followed or concurrent with miliary sarcoidosis was reported in four patients (Table 2) (15, 16, 23, 29).

TBLB was the most common modality used for diagnosis and was reported as diagnostic in 85.7%. As most patients were symptomatic, treatment with steroids was offered in 95.2%, with 100% response. Methotrexate was administered in two patients for steroid-related severe adverse effects, with good response in both. Three patients (14.2%) relapsed after steroid taper; prompt response was noted on re-institution without further relapse.(21)

Discussion

The description of "miliary" refers to small, well-defined, 1 to 3 mm nodules on chest radiography and is derived from Latin miliarius, meaning millet seed (8). This pattern implies hematogenous dissemination of disease and is classically associated with hematogenous spread of tuberculosis, fungal infections and malignancy (31). However, more than 40 diseases have been associated with this pattern on chest radiography (Table 2). The importance of quickly establishing the diagnosis, especially in high prevalence areas of tuberculosis, is that miliary tuberculo-

Table 2. Reported causes of miliary nodules on High-resolution Computed Tomography

Classification	Cause of miliary Nodules	Site of micronodules in SPL
Infectious	Mycobacterium tuberculosis	Random
	Disseminated Bacillus-Calmette-Guerin infection	Random
	Bacterial: Mycoplasma pneumoniae, Hemophilus influenzae	Centrilobular
	Fungal: Histoplasmosis, Coccidioidomycosis, hematogenous Candida infection	Random
	Viral: Varicella-zoster, cytomegalovirus	Centrilobular
	Parasitic: Tropical pulmonary eosinophilia	Centrilobular
Immunologic	Pneumoconiosis: Silicosis	Perilymphatic
	Pneumoconiosis: Coal worker's pneumoconiosis	Perilymphatic
	Hypersensitivity pneumonitis	Centrilobular
	Sarcoidosis	Perilymphatic
	Idiopathic pulmonary hemosiderosis	Centrilobular
	Pulmonary alveolar microlithiasis	Centrilobular
	Diffuse panbronchiolitis	Centrilobular
	Allergic bronchopulmonary aspergillosis	Centrilobular
Malignancy	Secondaries from bronchogenic carcinoma	Perilymphatic
	Others: melanoma, papillary thyroid carcinoma, renal, breast, Trophoblastic tumor, osteosarcoma	Random
	Pulmonary Langerhans' cell histiocytosis	Random
	Metastasizing leimyoma	Random
	Lymphoma	Perilymphatic
Substance abuse	Excipient lung disease	Centrilobular

Abbreviations: SPL secondary pulmonary lobule

Table 3. High-resolution computed tomography findings in Thoracic Sarcoidosis (Modified from Criado et al)

Typical features	
Lymphadenopathy	Site (hilar, right paratracheal), bilateral, symmetrical, well defined. May show "cluster of black pearls" sign. If calcified, patchy or egg-shell
Nodules	Micronodules 2-4 mm, bilateral, well-defined, upper and middle zone and peri-hilar predominant. Peri-bronchovascular, subpleural, interlobular septal (peri-lymphangitic pattern)
Fibrotic changes	Interlobular septal thickening, Reticular opacities, architectural distortion, traction bronchiectasis
Atypical features	
Lymphadenopathy	Unilateral, isolated, anterior or posterior mediastinal
Nodules	Miliary
	Lower-lobe predominant, unilateral, "Halo" sign or "Atoll" sign
Consolidation	Mass-like opacities, conglomerate masses, solitary pulmonary nodules, confluent alveolar opacities and ground-glass opacities
Linear opacities	Intra-lobular septal thickening
Airway	Mosaic attenuation, trachea-bronchial abnormalities, atelectasis
Pleural	Effusion, chylothorax, pneumothorax, pleural thickening, calcification, plaque-like lesions

sis is the most common cause, has 25-30% mortality in adults and is invariably fatal if untreated (8).

The finding of a miliary pattern on chest radiographs was noted in early roentgenologic series of thoracic sarcoidosis; 1.3% (2/150) had "miliary" disease (1). Thoracic sarcoidosis has been reported to have several typical and atypical findings on HRCT; miliary is classified as an atypical finding (Table 3) (3). The description of micronodules by their distribution in relation to the "secondary pulmonary lobule" on HRCT along with the clarity of margins and attenuation further helps in narrowing the differential diagnosis of diffuse pulmonary micronodules. Micronodules can be accurately classified as having a centrilobular, perilymphatic or random distribution with their characteristic disease associations (Table 2) (4). Miliary nodules have a random distribution and can be seen in relation to pleural surfaces, small vessels and interlobular septa but do not have a consistent or predominant relationship to any of these (31). Given the reported prevalence of sarcoidosis varies from 4.5-36 per 100,000, the very small number of cases of "miliary" sarcoidosis reported in literature in the HRCT era (Table 1) suggests that this is a very rare occurrence. Most series of computed tomographic findings in sarcoidosis and a review on atypical findings in thoracic sarcoidosis did not report "miliary" sarcoidosis (32, 33).

Our systematic review suggests that this small reported number is an overestimate as a true miliary pattern was seen only in 34.6% (9/26) of the published cases of "miliary" sarcoidosis; and subtle perilymphatic pattern is nearly always seen and the term "pseudo-miliary" may be more appropriate. Distinct perilymphatic clustering of nodules or a perivascular dominance of nodules was seen in 65.4% and 42.3%; fissural nodules leading to the "beaded fissure sign" was prominent and seen in 65.4% of cases. Further, unlike true miliary nodules that lack any zonal predominance, an upper lobe and peripheral clustering was seen in 30.8% and 19.2% respectively. In all our patients with random micronodules, we observed a prominent perivascular distribution of micronodules on histopathology (Figures 2, 4, 6 and 8); two of these had associated "beaded fissure sign" on HRCT. Pathologically, sarcoidosis causes perilymphatic clustering of granulomas; hematogenous or airway spread has not been postulated (34). Profuse clustering of micronodules along the centrilobular and perilymphatic compartments gives rise to an appearance of random nodules in the majority with a "pseudo-miliary" appearance. In the few patients with a true random pattern, prominent perivascular granulomas or drainage into the pulmonary lymphatics and subsequent dissemination by hematogenous route could be postulated.

The link between mycobacteria and sarcoidosis continues to be an enigma (7, 35). In the original descriptions, about 5% of sarcoidosis had tuberculosis preceding them. Polymerase chain reaction analyses of lung biopsies of sarcoidosis have shown mycobacterial DNA in 26.4%.(35) Tuberculosis may present concurrently and confound the diagnosis and management of these patients (23, 36, 37). It has been hypothesized that the immunological responses in sarcoidosis are analogous to "tuberculoid" or "pauci-bacillary" leprosy (38); persisting immunological responses to mycobacterial antigen can explain the extraordinarily high rates of tuberculosis preceding the diagnosis of pseudo-miliary sarcoidosis in the present systematic review.

The diagnosis of sarcoidosis rests on a constellation of clinical, radiological, histopathological and laboratory findings (39). Constitutional features including significant weight loss can occur in up to 25% of patients (Table 2). Fibrinoid necrosis and rarely, caseation can occur in sarcoidosis on histopathology (40, 41). Caseation may sometimes be absent in tuberculosis (41). Radiology can help in the differentiation of sarcoidosis from tuberculosis (26). The presence of hypercalcemia, skin involvement, negative tuberculin skin-testing, upper and middle-lobe distribution of nodules, a peripheral distribution of nodules when present and interlobular septal thickening all point to the diagnosis of "pseudo-miliary" sarcoidosis alone (42). However, sarcoidosis can precede, occur concurrent with or follow tuberculosis and differentiating tuberculosis from sarcoidosis remains a major challenge, especially in high prevalence areas of tuberculosis (43, 44). When the constellation of findings are non-conclusive, a trial of anti-tuberculosis treatment is appropriate in high prevalence areas given the very small number of true miliary sarcoidosis reported in literature. Steroids could be added when there is no clear response at 4-6 weeks (39, 43).

Conclusion

A true miliary pattern in the HRCT era is very rare in sarcoidosis and subtle perilymphatic pattern is nearly always seen; this pattern should be labeled "pseudo-miliary". Prominent perivascular granulomas are associated with true miliary pattern. Miliary sarcoidosis patients are older and symptomatic and mostly need treatment at diagnosis. "Miliary" sarcoidosis may follow treatment for tuberculosis; concurrent cases possibly indicate difficulty in diagnosis or a "tuberculo-sarcoid" presentation. Transbronchial lung biopsy had a good yield for diagnosis. Most patients were symptomatic and treated with steroids, with 100% response and 14.4% relapse.

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Dr. R.S, Dr. RM.PL and Dr. R.K were responsible for patient care and initiated the manuscript preparation and performed the systematic review. Dr. S.S reported the histopathologic findings of these patients and provided valuable inputs to the manuscript. Dr.B.D reviewed all the radiology images and the images retrieved from the systematic review for re-reporting.

Drs. R.S and Dr. S.S take responsibility for the content of the manuscript, including the data and analysis

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The effect of global longitudinal strain on impaired six-minute walk test performance in patients with sarcoidosis

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Abstract. *Background:* Sarcoidosis is a multisystem and granulomatous disease associated with impaired functional capacity as a result of pulmonary and cardiac involvement. Factors adversely effecting functional capacity in patients with sarcoidosis have not been systematically assessed including myocardial strain imaging on echocardiography which enable to diagnose subclinical cardiac dysfunction. We aimed to evaluate the effect of left and right ventricular global longitudinal strain (GLS) on submaximal exercise capacity in patients with sarcoidosis who do not have clinically manifest cardiac involvement. *Methods:* Extracardiac biopsy proven 56 patients with sarcoidosis and 26 controls were included consecutively. Submaximal exercise capacity of the subjects was assessed with six-minute walk test (6 MWT). Pulmonary function tests and standard transthoracic and two-dimensional speckle tracking echocardiography were performed to the all subjects. Linear regression analysis was performed to find independent predictors of 6 MWT. *Results:* Fifty-six patients (18% male) with a mean age of 52.5 ± 10.7 years were included. Patients with sarcoidosis had low 6 MWT performance and higher New York Heart Association classes and NT-proBNP levels. There were no significant differences between controls and patients with sarcoidosis in parameters of pulmonary function test. Biventricular GLS levels and biatrial reservoir and conduit function values were lower and systolic pulmonary artery pressure (SPAP) was significantly higher in patients with sarcoidosis as compared with controls. Older age and higher SPAP were found as independent predictors of poor 6 MWT performance. *Conclusion:* Although biventricular GLS levels were lower in the patients with sarcoidosis, only age and SPAP elevations were independent predictors of the submaximal exercise capacity. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 63-73)*

Key words: global longitudinal strain, sarcoidosis, six-minute walk test, two-dimensional speckle tracking echocardiography, pulmonary hypertension

Introduction

Sarcoidosis is a multisystem and granulomatous disease primarily effecting the lungs and lymph nodes. Despite the unknown etiology, sarcoidosis stems from interaction of genetic and environmental factors (1-3). Although sarcoidosis often has good prognosis, coexistence of pulmonary and cardiac involvement and pulmonary hypertension (PHT) can deteriorate the clinical course. Cardiac manifestations of sarcoidosis are silent disease, heart block, ventricular tachycardia and dilated or hypertrophic cardiomyopathy. Clinically overt cardiac involvement occurs in 5% of patients in sarcoidosis. In addition, 25-30% of patients with sarcoidosis have asympto-

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matic cardiac involvement shown in autopsy series and newer imaging studies (4, 5). Several studies have used the myocardial strain imaging to detect asymptomatic cardiac involvement earlier (6-10). However, their prognostic roles need to be further clarified.

The six-minute walk test (6 MWT) is a simple, inexpensive and reproducible test to quantify the submaximal exercise capacity (11-14). Recent studies have shown that several factors are associated with poor 6 MWT performance including gender, forced vital capacity (FVC) or forced expiratory volume in 1 second (FEV1) and systolic pulmonary artery pressure (SPAP) (15-18). However, no previous study has examined the relationship between subclinical cardiac dysfunction determined by two-dimensional (2D) speckle tracking echocardiography (STE) and 6 MWT performance in patients with sarcoidosis.

The aim of this study is to evaluate whether biventricular functions determined by 2D STE contribute to impaired submaximal exercise capacity quantified by six-minute walk distance (6 MWD) in patients with sarcoidosis.

Materials and Methods

Study population

60 patients with biopsy proven extracardiac sarcoidosis were enrolled into the study. A comprehensive transthoracic echocardiography was performed to all study patients for evaluation cardiac functions. Patients who have impaired left ventricular (LV) function (ejection fraction < 50%), poor echogenicity, moderate to severe valvular pathology, history of coronary artery disease, diagnosis of malignancy, administration of chemotherapy, musculoskeletal disorders effecting 6 MWT performance were excluded from the study. One patient had impaired LV function, one patient had poor echogenicity, one patient had aortic valve prosthesis and one patient had history of coronary artery disease. Moreover, demographically similar 26 subjects were included as control group.

Measurements

Clinical data including history of systemic hypertension or diabetes, organs involvement, duration of illness, steroid usage, New York Heart Association (NYHA) functional class, radiological stages (according to chest radiography) and results of pulmonary function testing, were recorded for all patients. Pulmonary function parameters were measured according to American Thoracic Society (ATS) and European Respiratory Society recommendations (19). The 6 MWT was conducted in accordance with ATS guidelines (20). Pulse oximetry saturations were recorded at the beginning and the end of the test. The total walking distances were recorded at the end of the test.

Standard and 2D Speckle Tracking Echocardiography

A detailed transthoracic examination was performed using a commercially available system (Epiq 7, Philips Healthcare, Andover, MA, USA) equipped with a 3.5 mHz (S5-1) transducer. Images which have three cardiac cycles were digitally stored for offline analysis (Xcelera, Philips). Conventional left and right ventricular echocardiographic parameters were measured according to the standard recommendations (21). LV ejection fraction (EF) was calculated using the modified Simpson's biplane method (21). The LV mass was calculated by the formula recommended by the guidelines (21). Tricuspid annular plane systolic excursion (TAPSE), right ventricular (RV) fractional area change (FAC) and the lateral side tricuspid annular peak systolic velocity (S') were measured. RV free wall thickness was also measured according to guideline recommendations (21). Systolic pulmonary artery pressure (SPAP) was calculated using tricuspid valve regurgitation jet and estimated right atrial pressure by inferior vena cava size and collapsibility (21). LV diastolic function was assessed by transmitral inflow pulse-wave Doppler velocities and the lateral side of the mitral annular tissue Doppler velocities (22).

Myocardial strain analysis was performed to the all subjects as described previously (23-24). Apical (four-chamber, three-chamber and two-chamber views) and parasternal short-axis (the level of the base, papillary muscles, and apex) views were used to measure LV longitudinal and circumferential strain. End-systole has been accepted as aortic valve closure. End-diastolic regions of interest were traced on the endocardial cavity and the software tracked the border automatically. RV-focused apical four-chamber view were used for RV strain analyses. Longitudi-

nal strain values of basal, mid, and apical segments of RV free wall were measured. The average of RV free wall longitudinal strain values was accepted as RV global longitudinal strain (RV GLS). For the left atrial (LA) and right atrial (RA) strain analyses, apical four-chamber view were used. The value of peak early and late diastolic longitudinal strain was determined as LA and RA reservoir and conduit function. For interobserver and intraobserver variability, 10 patients were selected at random, measurements were reanalyzed by the same and another operator. The interobserver and intraobserver variabilities were 5.4 and 5.8 %, respectively in our study.

Statistical Analysis

Data were analyzed using SPSS for Windows (Version 16.0; SPSS, Chicago, IL). One-sample Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Normal distributed data were presented as mean ± SD, whereas variables not displaying normal distribution were presented as median with interquartile range. Categorical variables were summarized as percentages. For continuous variables, normal distributed parameters were compared by T-test, otherwise comparison was done by Mann-Whitney U-test. Categorical variables were compared by x^2 test. Linear regression analyses were then performed to assess the independent correlates 6 MWD in the patient population. To estimate the significant correlated parameters Pearson correlation test were used. Then LV GLS, RV GLS, body mass index (BMI), E/e' ratio, age, SPAP, FVC and TAPSE were added into the multivariate analysis. P values < 0.05 were accepted significant.

Results

Data from 56 patients with sarcoidosis and 26 demographically similar controls were used in the analysis. Radiological stage, organ involvement, NYHA class of the patients with sarcoidosis were shown in Table 1. The median duration of the illness of patients with sarcoidosis was 4.0 (4.75) years and 22 (39.3%) of all patients were receiving steroid therapy. There were no differences between patients and controls regarding the prevalence of major comorbidities including diabetes, hypertension and smoking (Table 2). There were also no differences between patients and controls in terms of pulmonary function test parameters (Table 2). The submaximal exercise capacity quantified by 6 MWD was significantly lower in patients with sarcoidosis. Although before and after test oxygen saturation levels were lower in patients, there were no significant differences for oxygen demand between patients and controls (Table 2). Patients with sarcoidosis had high NT-proBNP and uric acid levels (Table 2).

Table 1. Baseline characteristics of the patients with sarcoidosis*

Radiological stage	**n (%)**
0	2 (3.5%)
1	19 (33.9%)
2	24 (42.9%)
3	6 (10.7%)
4	3 (5.4%)
Organ involvement	
Pulmonary	54 (96.4%)
Skin	10 (17.8%)
Eye	5 (8.9%)
Neurologic	1 (1.8%)
NYHA functional class	
1	38 (67.8%)
2	10 (17.8%)
3	5 (8.9%)
4	3 (5.3%)

NYHA: *New York Heart Association Functional Classification*
* Numerical variables are displayed as mean ± standard deviation and categorical variables are displayed as percentages

Between patients with sarcoidosis and controls, there were no differences regarding LV systolic functions (Table 3). However, LV diastolic function parameters such as mitral E/A ratio and transmitral E-wave DT were impaired in patients with sarcoidosis (Table 3). As shown, patients with sarcoidosis had significantly higher SPAP values, RV free wall thicknesses and lower TAPSE and RV FAC values (Table 3).

Table 4 shows the comparison of speckle tracking parameters between the two groups. Biventricular strain values were significantly lower in patients with sarcoidosis than in controls. LA and RA both reservoir and conduit functions were also significantly lower in sarcoidosis patients than controls.

Table 2. Demographic characteristics, cardiovascular risk factors and laboratory findings of the patients with sarcoidosis and controls*

	Patients with sarcoidosis n = 56	**Controls n = 26**	**P value**
Age (years)	52.5 ± 10.7	48.8 ± 7.1	0.114
Gender male (n) (%)	10 (17.9)	6 (23.1)	0.565
BMI (kg/m2)	30.2 ± 5.2	28.2 ± 4.4	0.095
Hypertension (n) (%)	11 (19.6)	2 (7.7)	0.209
Diabetes (n) (%)	12 (19.6)	2 (7.7)	0.206
Smokers (n) (%)	6 (10.7)	7 (26.9)	0.101
NT-proBNP (pg/ml)	80.1 (223)	27.3 (49.8)	< **0.001**
Uric acid (mg/dl)	5.3 ± 1.6	4.2 ± 1.2	**0.003**
Creatinine (mg/dl)	0.75 ± 0.3	0.7 ± 0.1	0.317
Hemoglobin (gr/dl)	13.2 ± 1.7	13.3 ± 1.2	0.681
6 MWD (m)	425 ± 88.6	501.9 ± 48.9	< **0.001**
Before test O^2 saturation (%)	96.8 ± 3.3	98.6 ± 0.6	**0.009**
After test O^2 saturation (%)	96.6 ± 4.5	98,8 ± 0.5	**0.018**
O^2 demand	3 (5.4)	-	0.548
FEV 1 (%)	91.1 ± 20.2	98.3 ± 8.9	0.08
FVC (%)	94.1 ± 21.1	98.9 ± 11.7	0.28
FEV1/FVC ratio	0.97 ± 0.1	1.0 ± 0.1	0.157

6 MWD: *six-minute walk distance;* ***BMI:*** *Body mass index;* ***FEV 1:*** *Forced expiratory volume in 1 second;* ***FVC:*** *Forced vital capacity;* ***NT-proBNP:*** *N terminal probrain natriuretic peptide;* ***O²:*** *Oxygen.*
* Numerical variables are displayed as mean ± standard deviation and categorical variables are displayed as percentages

Independent predictors of 6 MWD were evaluated using linear regression analyses. Regression model included age, BMI, FVC, LV GLS, RV GLS, E/e' ratio, SPAP and TAPSE. Older age (beta coefficient -0.20, %95 CI for B -3.5 – 0.079, p = 0.04) and higher SPAP (beta coefficient -0.28, %95 CI for B -4.7 – 0.45, p = 0.018) were found to be independent predictors of low 6 MWD (Table 5).

Discussion

In this study, we demonstrated that the submaximal exercise capacity as assessed by 6 MWT was significantly reduced in patients with sarcoidosis compared with control population. Even in the absence of clinically overt cardiac dysfunction, biventricular and atrial functions as assessed by STE were significantly impaired in patients with sarcoidosis. Moreover, SPAP values were significantly increased in patients with sarcoidosis despite the fact that there were no differences between patients with sarcoidosis and controls regarding pulmonary function tests. Finally, LV GLS and RV GLS were not independent predictors of 6 MWD in patients with sarcoidosis.

Recent studies have shown that several factors are associated with poor 6 MWT performance in patients with sarcoidosis (15-18). However, no previous study has examined the relationship between subclinical cardiac dysfunction using myocardial strain imaging and poor functional capacity. To the best of our knowledge this is the first study using STE to evaluate independent predictors of low 6 MWD in patients with sarcoidosis.

Previous studies have suggested that several parameters were associated independently with low 6 MWD. Almahad et al. demonstrated that FEV1 was an independent parameter of low 6 MWD (25). In same study, SPAP values measured by transthoracic echocardiography (TTE) were correlated with 6

Table 3. Conventional transthoracic echocardiographic findings of the patients with sarcoidosis and controls*

	Patients with sarcoidosis n = 56	**Controls n = 26**	**P value**
LVEDD (mm)	45.0 ± 4.7	44.5 ± 3.9	0.59
LVESD (mm)	28.9 ± 5.8	27.6 ± 3.9	0.31
LV EF (%)	64.5 ± 8.8	66.5 ± 5.5	0.28
RV basal diameter (mm)	30.2 ± 3.7	29.3 ± 4.0	0.32
RV/LV ratio	0.72 ± 0.7	0.73 ± 0.7	0,66
LA diameter (mm)	33.7 ± 3.4	32.6 ± 3.4	0.16
LAA (cm^2)	15.2 ± 3.5	14.6 ± 2.6	0.48
RAA (cm^2)	12.9 ± 2.7	12.5 ± 2.4	0.48
Septum (mm)	10.0 ± 1.4	10.2 ± 1	0.54
PW (mm)	9.5 ± 1.1	9.7 ± 1.0	0.48
LV mass (gr)	149.4 ± 36.2	147.7 ± 28.9	0.83
RV wall thickness (mm)	4.9 ± 0.9	4.3 ± 0.4	**0.007**
Tranmitral E velocity (cm/sec)	0.8 ± 0.2	0.8 ± 0.1	0.59
Transmitral A velocity (cm/sec)	0.8 ± 0.2	0.7 ± 0.1	0.18
Transmitral E-wave DT (msec)	199.3 ± 40.9	178.9 ± 24.9	**0.022**
Transmitral E/A ratio	1.0 ± 0.3	1.2 ± 0.3	**0.049**
Mitral lateral E' (cm/sec)	11.2 ± 3.7	13.0 ± 3.5	**0.03**
Mitral lateral A' (cm/sec)	10.8 ± 2.4	11.0 ± 3.0	0.747
Mitral lateral S' (cm/sec)	10.7 ± 2.9	10.6 ± 2.2	0.925
E/E' ratio (cm/sec)	7.5 ± 2.9	6.4 ± 1.6	0.079
Tricuspid lateral S' (cm/sec)	13.0 ± 2.4	13.9 ± 2.2	0.09
TAPSE (cm)	22.9 ± 4	25.5 ± 3.4	**0.005**
RV FAC (%)	45.4 ± 8.9	56.6 ± 7.9	< **0.001**
SPAP (mm Hg)	25.9 ± 9.5	18.8 ± 5.8	< **0.001**

DT: *Deceleration time;* ***FAC:*** *Fractional area change;* ***LA:*** *Left atrium;* ***LAA:*** *Left atrium area;* ***LV:*** *Left ventricular;* ***LVEDD:*** *LV end-diastolic diameter;* ***LVESD:*** *LV end-systolic diameter;* ***PW:*** *Posterior wall;* ***RAA:*** *Right atrium area;* ***RV:*** *Right ventricular;* ***SPAP:*** *Systolic pulmonary artery pressure;* ***TAPSE:*** *Tricuspid annular plane systolic excursion.*

* Numerical variables are displayed as mean ± standard deviation and categorical variables are displayed as percentages

MWD but not an independent predictor. In our study, we found that SPAP was an independent predictor for poor submaximal exercise capacity. In another study by Mirsaeidi et al. SPAP, BNP and DLCO had correlation with 6 MWD (6). Both of these studies had no control group and did not use STE parameters.

We also demonstrated that subclinical cardiac dysfunction parameters regarding LVGLS, RVGLS, atrial conduit and reservoir functions were significantly lower in patients with sarcoidosis. Similarly, Tigen et al. suggested that LV GLS, RV GLS and atrial conduit and reservoir functions were low in patients with sarcoidosis (7). Other studies showed that LV GLS and RV GLS were low in patients with sarcoidosis as well (8-10). However, these studies did not assess the effects of GLS on 6 MWD. In this study, we found that STE parameters were correlated with low 6 MWD but were not independent predictors.

Decreased LV GLS can be result of subclinical cardiac involvement or diastolic dysfunction. Previ-

Table 4. Comparison of two-dimensional speckle tracking echocardiography parameters between patients with sarcoidosis and controls*

	Patients with sarcoidosis n = 56	**Controls n = 26**	**P value**
LV GLS (- %)	16.7 ± 4.1	22.8 ± 3.2	**<0.001**
LV GCS (- %)	19.1 ± 5.7	28.1 ± 4.4	**<0.001**
RV GLS (- %)	17.0 ± 5.2	23.4 ± 3.2	**<0.001**
LA reservoir function (%)	27.7 ± 11.0	41.1 ± 9.8	**<0.001**
LA conduit function (%)	14.2 ± 7.2	20.6 ± 6.0	**<0.001**
RA reservoir function (%)	27.4 ± 10.2	40.5 ± 8.4	**<0.001**
RA conduit function (%)	13.7 ± 6.5	20.3 ± 5.2	**<0.001**

LA: *Left atrium;* ***LV GLS:*** *Left ventricular global longitudinal strain;* ***LV GCS:*** *LV global circumferential strain;* ***RA:*** *Right atrium;* ***RV GLS:*** *RV global longitudinal strain.*
* Numerical variables are displayed as mean ± standard deviation and categorical variables are displayed as percentages

Table 5. Linear regression analysis: Relationship between walking distance and significant correlated variables

	Univariate analysis		**Multivariate analysis***				
Variables	**R**	**P-value**	**95% CI**		**Standardised Coefficient**	**t-value**	**P-value**
					Beta		
Age	-0.44	0.001	- 3.52	-0.08	-0.21	-2.10	**0.04**
BMI	-0.28	0.012	-5.71	0.83	-0.14	-1.48	0.14
FVC	0.26	0.018	-0.34	1.43	0.12	1.23	0.22
E/e' ratio	-0.30	0.006	-9.58	3.89	-0.08	-0.84	0.40
SPAP	-0.49	0.001	-4.7	-0.46	-0.28	-2.42	**0.02**
TAPSE	0.27	0.015	-4.24	4.22	-0.01	-0.01	0.99
LV GLS	-0.42	0.001	-7.93	1.55	-0.18	-1.34	0.18
RV GLS	-0.47	0.001	-6.03	2.98	-0.09	-0.68	0.50

* Model R = 0.67, R^2 = 0.45

ous studies showed that patients with pulmonary sarcoidosis had LV diastolic dysfunction compared with controls (7, 26, 27). Accordingly, we found E/A ratio and E'-wave were low and NT-proBNP levels were high in patients with sarcoidosis compared with controls. Although E/E' ratio had correlation with low 6 MWD, it was not an independent predictor. RV GLS may be reduced as a result of RV involvement, secondary to LV dysfunction or comorbid lung disease resulting in elevated right-sided pressures. In our study, we didn't perform cardiac MRI (CMRI), positron emission tomography (PET) or endomyocardial biopsy to evaluate primary RV involvement and the patients with sarcoidosis had no overt cardiac dysfunction (EF> 50%) and no significant differences compared with controls for EF, FVC or FEV1. We suggest that decreased TAPSE and FAC and increased RV wall thickness in patients with sarcoidosis can be a consequence of elevated right-sided pressures. Moreover, we demonstrated that higher SPAP in patients with sarcoidosis was an independent predictor for poor functional capacity. PHT is a feared complication in patients with sarcoidosis and early diagnosis is essential. However adequate tricus-

pid regurgitation velocity need to calculate SPAP is not always present. Based on our findings, 6 MWT can be an important screening tool for the development of PHT when SPAP is not reliably measured through TTE. Myocardial strain imaging parameters act as an early marker of cardiac dysfunction. This study demonstrated that decreased LV GLS and RV GLS levels were correlated with poor submaximal exercise capacity, although not an independent predictor. Future studies are needed to explore the prognostic role of 2D myocardial deformation imaging in patients with sarcoidosis.

Study Limitations

Small sample cohort is an obvious limitation of the study due to low prevalence of sarcoidosis. Another limitation may be the lack of right heart catheterization data. Patients with mild PHT but no tricuspid regurgitation might have been missed using TTE. However, continuous measurement of pulse oximetry saturations during the 6 MWT in order to assess any desaturation could give more information for the exercise performance of the patients. Finally, comparison of STE findings with CMRI or PET findings in patients with subclinical cardiac involvement could be very demonstrative. Cost and availability of CMRI and PET is always a limiting factor however.

Conclusions

Although subclinical cardiac dysfunction was readily detected using two-dimensional STE parameters, there were no independent correlations with submaximal exercise capacity assesed by 6 MWT. Older age and higher SPAP were independent predictors of poor submaximal exercise capacity in patients with sarcoidosis.

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Safety of macitentan in sarcoidosis-associated pulmonary hypertension: a case-series

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Abstract. *Background:* Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis and is associated with higher morbidity and mortality. Currently, there are no approved PH-targeted therapies for sarcoidosis-associated pulmonary hypertension (SAPH). Macitentan is frequently used as treatment for pulmonary arterial hypertension, but no results are known in the SAPH population. *Objective:* We investigated the safety and effect of macitentan as treatment for SAPH. *Methods:* We retrospectively reviewed our patient database for all SAPH patients receiving macitentan as treatment, with a minimum follow-up of twelve months for monitoring safety. Safety outcomes included reported side-effects, hospitalisations and mortality. Furthermore, six-minutes walking distance, New York Heart Association functional class and NT-proBNP levels were collected. *Results:* Six cases (three men) with a median age of 64 years (range 52-74 years) were identified. During macitentan treatment, one patient experienced side effects and aborted therapy after five days of treatment and died 16 months later. Three patients were hospitalised during treatment for congestive heart failure. Four patients showed improvement of their functional class and three patients in exercise capacity after 12 months of therapy. *Conclusion:* Macitentan was well tolerated in five out of six cases with severe pulmonary sarcoidosis and PH. Functional capacity improved in four cases. Prospective controlled trials are warranted before therapeutic recommendations can be made. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 74-78)*

Key words: sarcoidosis, macitentan, pulmonary hypertension, endothelin receptor antagonist

Abbreviation list:
6-MWD: six-minute walking distance
FDG-PET: fluodeoxyglucose-positron emission tomography
FVC: forced vital capacity
mPAP: mean pulmonary artery pressure
NT-proBNP: N-terminal pro-brain natriuretic peptide
NYHA: New York Heart Association
PH: pulmonary hypertension
PVR: pulmonary vascular resistance
SAPH: sarcoidosis-associated pulmonary hypertension
RHC: right heart catheterization
WU: Wood Units

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Introduction

Pulmonary hypertension (PH) is a known complication of pulmonary sarcoidosis. Prevalence numbers range from 3% in early stage pulmonary sarcoidosis, up to 70% in patients awaiting lung transplantation.(1,2) Sarcoidosis-associated pulmonary

hypertension (SAPH) is associated with increased morbidity and mortality.(3,4) The underlying pathophysiological mechanism of SAPH remains unclear. Hypothesised mechanisms include destruction of the pulmonary vascular bed by pulmonary fibrosis, granulomatous vasculopathy, extrinsic compression from thoracic lymphadenopathy, mediastinal fibrosis and cardiac involvement. (4–6) Currently, there are no approved PH-targeted treatments for SAPH. Although endothelin receptor antagonists are well used in pulmonary arterial hypertension, studies have shown mixed results in SAPH.(7,8) To our best knowledge, the safety and effect of the endothelin receptor antagnost macitentan in SAPH patients has not been evaluated. We report the results of a single centre case-series.

Methods

The St. Antonius hospital is a tertiary referral centre for sarcoidosis and PH. We retrospectively reviewed our patient database between 2014-2018 to include all patients aged ≥18 years, diagnosed with both sarcoidosis and PH, received macitentan as treatment (mono- or dual therapy), and at least 12 months of follow-up for monitoring safety outcomes. The diagnosis of sarcoidosis was based on current clinical diagnostic guidelines.(9) PH was confirmed by right heart catheterization (RHC) and defined as a resting mean pulmonary artery pressure (mPAP) of ≥25mmHg. The decision to start treatment was made by a multidisciplinary team. Safety outcomes included side effects leading to (temporarily) aborting therapy, hospitalisation for heart failure or dyspnoea, and death.

Baseline was defined as start of PH-targeted treatment. At baseline, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, forced vital capacity (FVC), New York Heart Association (NYHA) functional class were measured and a six-minute walking distance (6-MWD) was obtained. Macitentan was administered at a dose of 10mg/day. If applicable, sildenafil was dosed 20mg three times daily. All outcome parameters were obtained by chart review. Written informed consent was obtained in all cases. The study was approved by the local institutional review board.

Results

Figure 1 shows the flowchart of case selection. In total, 27 patients with SAPH were identified between 2014-2018. Of these patients, 8 were treated with macitentan. Of these, 6 patients had a follow-up of at least twelve months, while the other two patients were recently started on macitentan. The baseline characteristics and outcome parameters of all cases are shown in table 1. Six patients (three men) with a median age of 64 years (range 52-74 years) were identified. All cases were Caucasian patients with biopsy confirmed sarcoidosis. RHC showed a median mPAP of 49 (27 – 66) mmHg and the pulmonary vascular resistance (PVR) was > 3 Wood Units (WU) in all cases.

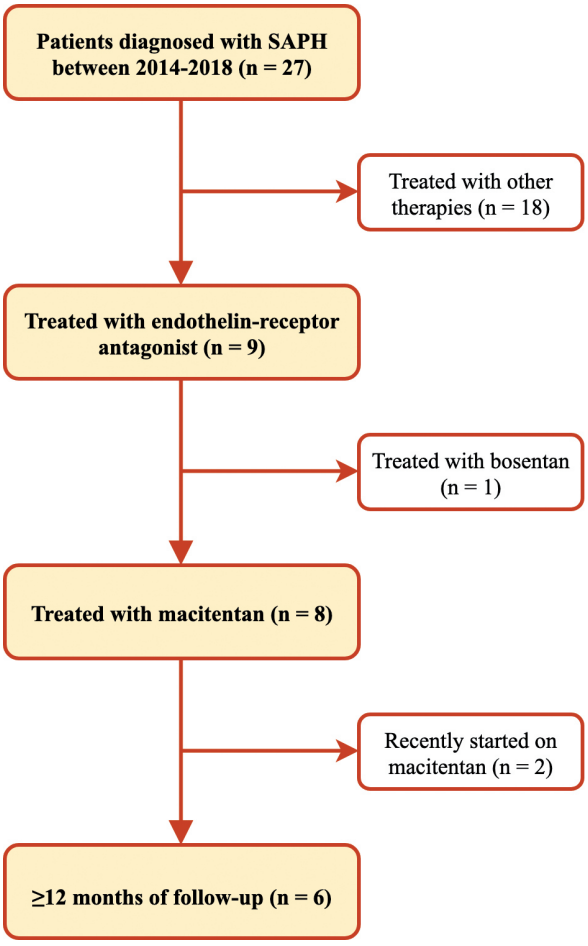

Fig. 1.

Table 1. Case characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Demographics						
Age (years)	60	74	64	52	69	65
Male / female	Female	Male	Male	Female	Female	Male
Time since sarcoidosis diagnosis (years)	8,3	4,3	20	0,2	22,5	12,2
Pulmonary function						
FEV1 (% predicted)	75.9	90.0	49.0	54.9	36.9	25.6
FVC (% predicted)	104.1	88.0	69.0	62.5	50.4	75.0
DLCO SB (% predicted)	76.4	25.0	-	40.3	13.9	57.1
Fibrosis on HRCT	Yes	Yes	No	No	Yes	Yes
Heamodynamics						
sPAP / dPAP (mmHg)	110/40	60/32	43/19	96/49	85/35	76/30
mPAP (mmHg)	63	37	27	66	55	43
PAWP (mmHg)	6	11	10	18	5	12
PVR (Wood Units)	10.3	10.4	3.2	11.3	13.9	7.2
Cardiac output (L/min)	5.6	2.5	5.3	4.3	3.6	4.6
Sarcoidosis treatment						
Supplemental oxygen use	No	Yes	Yes	Yes	Yes	No
Immunosuppressive treatment	No	Yes	Yes	Yes	No	Yes
Escalation of immunosuppressive treatment during follow-up	Yes	No	No	No	Yes	No
PH treatment						
Initial PH-targeted therapy	Macitentan	Macitentan	Dual	Macitentan	Dual	Sildenafil
Time before start dual treatment (months)	3	1	-	10	-	15
Follow-up duration (months)	42	12	12	42	36	18
Outcome parameters						
NYHA functional class at baseline	III	III	III	III	IV	III
NYHA functional class at 12 months	II	III	II	II	III	III
NYHA functional class at 24 months	II	III	II	II	III	IV
6-MWD at baseline (meters)	327	365	445	364	145	341
6-MWD at 12 months (meters)	439	-	457	367	340	244
6-MWD at 24 months (meters)	456	-	-	422	243	-
NT-proBNP at baseline (pg/mL)	136	959	52	3382	5875	346
NT-proBNP at 12 months (pg/mL)	110	1516	45	3512	343	688
NT-proBNP at 24 months (pg/mL)	38	-	-	1543	210	-

FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO SB: diffusing capacity of the lung for carbon monoxide single breath; HRCT: high resolution chest tomography; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; PH: pulmonary hypertension; NYHA: New York Heart Association; 6-MWD: six minute walking distance

Case 1 was 60-year old female with suspected fibrosing pulmonary sarcoidosis and severe PH. Macitentan was started after PH diagnosis. After two months, sarcoidosis was proven on biopsy and immunosuppressive therapy with methotrexate 15mg/week was initiated due to active disease on FDG-PET (fluodeoxyglucose-positron emission tomography) with compression of the pulmonary artery. At three months, echocardiography showed improved right ventricular function and sildenafil was added. At 7 months, immunosuppressive therapy was switched to azathioprine 100mg/day due to side effects (depressive thoughts). At one year, there was an improvement of mPAP (47mmHg), PVR (5.0WU), 6-MWD, and NYHA functional class. NT-proBNP levels and the FVC remained stable. During her 3.5 years follow-up, macitentan was well tolerated with no reported side effects.

Case 2 was a 74-year old male with fibrosing pulmonary sarcoidosis. RHC showed severe PH and macitentan was started. After four weeks, he was admitted for pneumonia and congestive heart failure. After recovery, sildenafil was added. At 12 months, no side effects were reported. NT-proBNP levels had increased, while NYHA functional class and FVC remained stable. A 6-MWD was not performed

during follow-up due to persisting disabilities after a cerebrovascular event.

Case 3 was 64-year old male with pulmonary sarcoidosis. After PH diagnosis, macitentan and sildenafil were started with good effect on NYHA functional class at 12 months while other outcome parameters remained stable or showed mild improvement. Macitentan was well tolerated.

Case 4 was a 52-year old female, with recently diagnosed pulmonary sarcoidosis and severe PH. Macitentan treatment was started with initial good effect on functional capacity. At 10 months, she was hospitalized due to congestive heart failure. After recovery, RHC was repeated which showed a mPAP of 58mmHg and PVR 12.5WU. Sildenafil was added and after 24 months all outcome parameters improved, while FVC remained stable. During 3.5 years follow-up, macitentan was well tolerated and the patient remained clinically stable.

Case 5 was 69-year old female patient with fibrosing pulmonary sarcoidosis and severely reduced exercise capacity. Dual treatment with macitentan and sildenafil was started. The FDG-PET showed enhanced inflammatory activity, and high-dosage prednisone was started at 6 weeks. At 12 months, there was an improvement in 6-MWD (340 vs 145m), NT-proBNP and NYHA functional class. FVC also improved during treatment (74.0% vs 50.4%). Echocardiography showed improvement in right ventricular function after 12 months. No side effects were reported during follow-up.

Case 6 was a 65-year old male patient with fibrosing pulmonary sarcoidosis. After PH diagnosis, initial treatment with sildenafil was started. After 12 months of treatment, RHC showed a mPAP of 47mmHg with no subjective improvement. FDG-PET revealed no signs of inflammatory activity and macitentan was initiated. Macitentan was not well tolerated and aborted after five days due to severe muscle aches and fatigue. Several days later, this patient was hospitalised for increasing dyspnoea and sildenafil was aborted due to no clinical improvement. The patient was discharged home with oxygen therapy and diuretics and died sixteen months later due to right ventricular failure.

Discussion

To the best of our knowledge, this is the first case series describing the safety and effect of macitentan, either as monotherapy or as dual treatment with sildenafil, as treatment for SAPH in predominantly patients with fibrosing pulmonary sarcoidosis. We found that macitentan was well tolerated in five patients, but one patient aborted macitentan therapy due to side effects and died sixteen months later.

Judson et al. investigated the role of the endothelin receptor antagonist ambrisentan as treatment for SAPH. They found that 11 out of 21 patients aborted ambrisentan therapy, mostly due to increasing dyspnoea.(7) In our case series, no patients aborted therapy due to dyspnoea. However three patients were hospitalised for dyspnoea due to congestive heart failure, but recovered with diuretic treatment. A known side-effect of a pulmonary vasodilator in parenchymal lung disease is the possible worsening of ventilation/perfusion mismatch, which could lead to increasing dyspnoea.(10,11) Unfortunately, we were not able to evaluate the effect of macitentan on gas exchange before and during treatment due to missing data for arterial blood gas analyses. The found rate of adverse events are in line with the MUSIC trial. This study showed that 12 months of macitentan therapy was well tolerated in patients with idiopathic pulmonary fibrosis, with 12.6% of patients aborting therapy due to adverse events.(12)

Furthermore, four patients showed improvement of their functional class and three patients in exercise capacity after 12 months of therapy. A possible confounder for this improvement is the escalating immunosuppressive treatment for increased sarcoidosis activity. It is known In pulmonary sarcoidosis that immunosuppressive treatment can improve FVC.(13) This could explain the functional improvement in case 5 as this was the only case with an improved FVC during follow-up compared to baseline. In all other cases the FVC remained stable.

In conclusion, this is the first case-series describing the safety and effect of macitentan therapy in SAPH. Macitentan was well tolerated in five out of six cases with severe pulmonary sarcoidosis and PH. Functional capacity improved in four out of six cases. However, results of this case series need to be interpreted with caution. Prospective controlled trials are warranted before therapeutic recommendations can be made.

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Desquamative interstitial pneumonia induced by metal exposure. A case report and literature review

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Abstract. *Background:* Forms of interstitial pneumonia secondary to exposure to an air-contaminant are varied and so far, insufficiently described. *Objectives/Methods:* We report here a case of a 57-year-old patient managed in our department for the exploration of MRC grade 2 dyspnoea and interstitial pneumonia. He mentioned multiple occupational and domestic exposures such as hens' excrements, asbestos and metal particles; he also had a previous history of smoking. *Results:* High-resolution computed tomography showed ground glass opacities predominating in posterior territories and surrounding cystic lesions or emphysematous destruction. The entire etiological assessment revealed only macrophagic alveolitis with giant multinucleated cells on the bronchoalveolar lavage. A surgical lung biopsy allowed us to refine the diagnosis with evidence of desquamative interstitial pneumonia and pulmonary granulomatosis. Finally, the analysis of the mineral particles in the biopsy revealed abnormally high rates of Zirconium and Aluminium. We were therefore able to conclude to a desquamative interstitial pneumonia associated with pulmonary granulomatosis linked to metal exposure (Aluminium and Zirconium). The clinical, functional and radiological evolution was favorable after a systemic corticosteroid treatment with progressive decay over one year. *Conclusion:* This presentation reports the first case to our knowledge of desquamative interstitial pneumonitis related to exposure to Zirconium and the third one in the context of Aluminium exposure. The detailed analysis of the mineral particles present on the surgical lung biopsy allows for the identification of the relevant particle to refine the etiological diagnosis, to guide the therapeutic management and to give access to recognition as an occupational disease.
(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (1): 79-84)

Key words: Interstitial lung disease, desquamative interstitial pneumonia, Aluminium lung, Metal analysis, Zirconium lung

I. Introduction

Forms of interstitial pneumonias secondary to exposure to an air-contaminant are varied and so far, insufficiently described. Based on the 2012 ATS/ERS classification of Interstitial Lung Disease (ILD), we can find these forms of pneumonia in each category of ILD (1). There is no separate class of ILD due to an air-contaminant. The identification of the causal agent remains difficult in a large amount of cases of ILD even if current recommendations insist on systematic investigation on possible exposure including medications, inhalation of organic antibodies or mineral particles… (2). Surgical lung biopsy is an

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important diagnostic tool and can be used to refine the diagnosis, but its use may be risky – 30-day and 90-day mortality up to 2.4% and 3.9% respectively in some series (3) – and should be indicated after a Multidisciplinary Discussion.

II. Case Report

A 57-year-old man was hospitalized in our service in 2017 to explore a mMRC grade 2 dyspnoea in the context of interstitial pneumonia on his chest X-ray.

His main medical history was emphysema of upper lobes diagnosed 5 years earlier, his follow-up consisted of a medical consultation with CT scan and pulmonary function test every 6 months (his last spirometry found a FEV1/VC ratio of 73% and a DLCO of 71%); he also presented a ventricular tachycardia which required the installation of a cardiac defibrillator. We did not find any significant family medical history.

This patient was living in a healthy house, but, reported multiple exposures. In his past work as a plumber, he was exposed to asbestos then he worked in a foundry with possible exposition to alloys of copper, bronze, iron, aluminium and zirconium compounds. He also described domestic exposures (hens of which he cleaned the excrement for 5 years) and during his current hobbies (welding, grinding); finally, he had a smoking history of 30 pack-years, stopping 10 years ago. His daily medications were amiodarone, bisoprolol and esomeprazole.

On examination, we found finger clubbing and dry crackles at the lung bases at auscultation; the remainder of the clinical examination was without particularity, we did not find in particular any extra thoracic sign or symptom such as arthralgia, myalgia or a dry eye or dry mouth syndrome.

High-resolution computed tomography (HRCT) showed ground glass opacities surrounding cystic lesions or emphysematous destruction; these anomalies predominated in posterior territories (Fig. 1a, 1b, 1c).

The antinuclear antibodies (ANA) were at 1/200, speckled type and nonspecific; the rest of the autoimmune evaluation was without particularity. The search for bird fancier's precipitin was negative

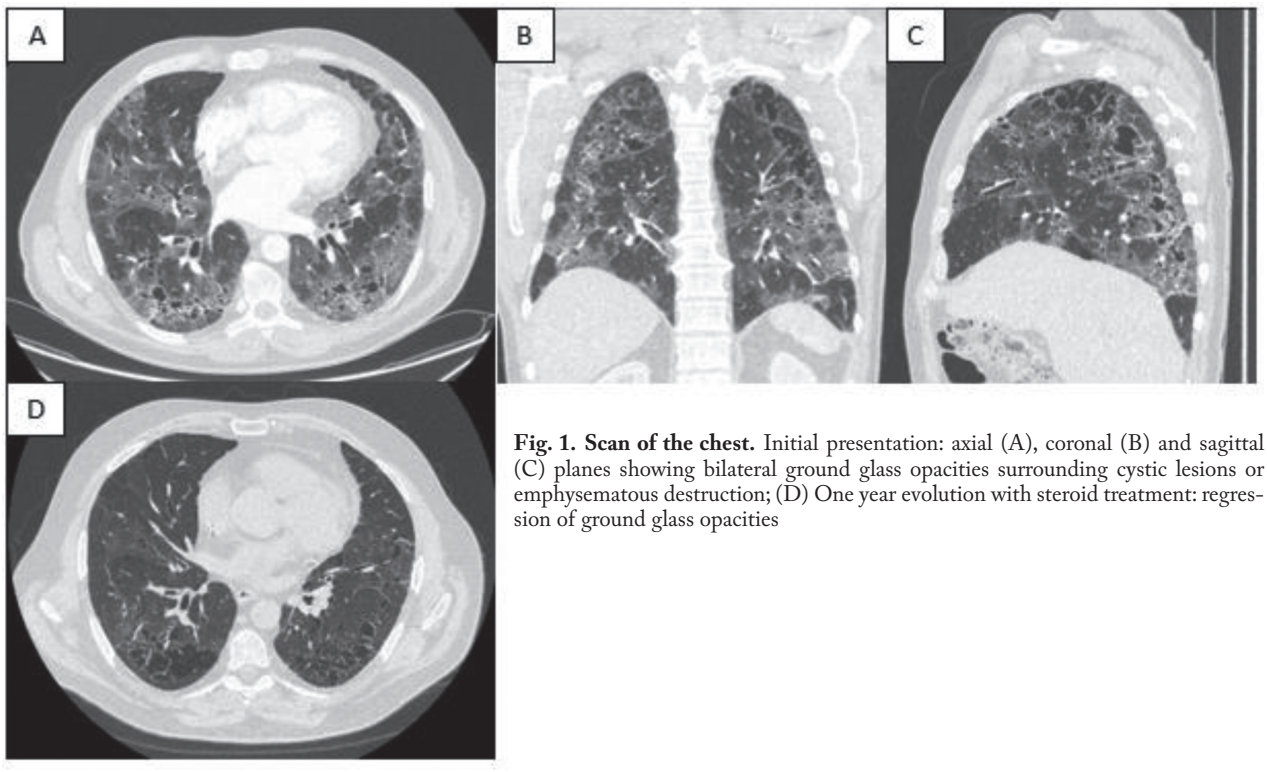

Fig. 1. Scan of the chest. Initial presentation: axial (A), coronal (B) and sagittal (C) planes showing bilateral ground glass opacities surrounding cystic lesions or emphysematous destruction; (D) One year evolution with steroid treatment: regression of ground glass opacities

especially for hens' excrements. Bronchoalveolar lavage (BAL) found a macrophagic alveolitis (presence of 180 elements/mm^3 including 80% macrophages, 5% lymphocytes, 10% neutrophils and 4.5% polynuclear cells eosinophils) with multinucleated giant cells. The bacteriological and mycobacteriological cultures were sterile. An accessory salivary gland biopsy showed no arguments for Sjögren's syndrome and the Schirmer's test was negative.

Pulmonary function tests were the following: FVC 2.72L or 73% of the predict values, FEV1/VC ratio of 77%, DLCO at 27% of predict values. During a 6 –minute walk test, the patient travelled a distance of 434m with an 83% O2 desaturation.

After a Multidisciplinary Discussion, it was decided to perform a surgical lung biopsy using video-assisted thoracoscopic surgery.

The left lower lobe biopsy led us to find outbreaks of desquamative interstitial pneumonitis with "plump" macrophages associated with emphysema lesions and with numerous giant-epithelioid granulomas without necrosis, sites of dusting. We did not find foamy macrophage that could evoke an amiodarone impregnation (Fig. 2).

Therefore, our conclusion was a Desquamative Interstitial Pneumonia associated with pulmonary granulomatosis.

We studied the mineral particles on the lung biopsy with the following method: the anatomopathological slides were analysed with an electronic scanning microscope (JEOL JSM-6010LV) coupled to a spectrometer EDX (EDS detector Oxford Aztec-DDI X MAXN 50), each mineral particle has a specific spectre. This analysis revealed abnormally high rates of zirconium compounds (5.2% versus 0.0%), aluminium compounds (4.4% versus 0.05%), aluminium oxide (2.0% versus 0.2%) and steel (14.0% versus 0.6%) in our patient compared to a reference population from the Forensic Institute of Lyon (Fig. 3) .

The diagnosis then retained in our patient is a Desquamative Interstitial Pneumonia associated with granulomas secondary to an exposure to metals: Aluminium, Zirconium compound and Steel.

Systemic corticosteroid therapy at a dose of 0.75 mg/kg was introduced for 3 months followed by a progressive decrease over 1 year.

The one-year evaluation showed (i) a clinical improvement: a reduction in dyspnoea to MRC grade 1 and an improvement of 80 meters over the distance covered in the 6-minute walk test; (ii) a functional improvement: the FVC was about 4.15L, i.e. 107% of predict values (gain of 34%) and the DLCO was 44% (gain of 17%); and (iii) a radiological improvement: the HRCT showed a marked improvement with the disappearance of the areas of ground glass opacities, however, there remained emphysematous zones that may correspond to its emphysematous medical history (fig. 1d).

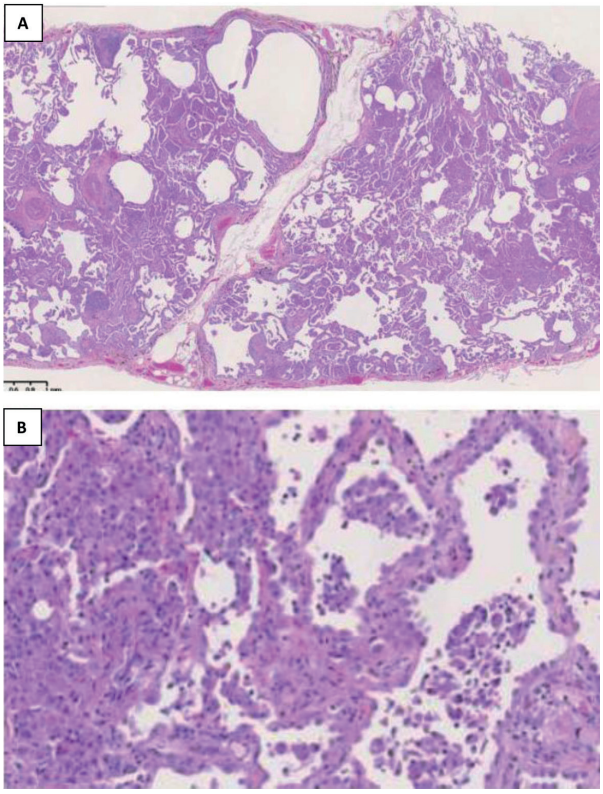

Fig. 2. Histological analysis of the lung biopsy.
(A) Left lower lobe biopsy (HPS coloration, x4): Emphysema and desquamative interstitial pneumonia patterns, "plump" macrophages. Numerous giant-epithelioid granulomas without necrosis, granulomas with micro calcifications and Schaumann bodies. (B) Left lower lobe biopsy (HPS coloration, x20): Pneumocytes hyperplasia, "plump" macrophages within alveolar spaces

III. Discussion

To our knowledge, this presentation reports the first case of desquamative interstitial pneumonitis related to exposure to Zirconium compound and the third one in a context of Aluminium exposure.

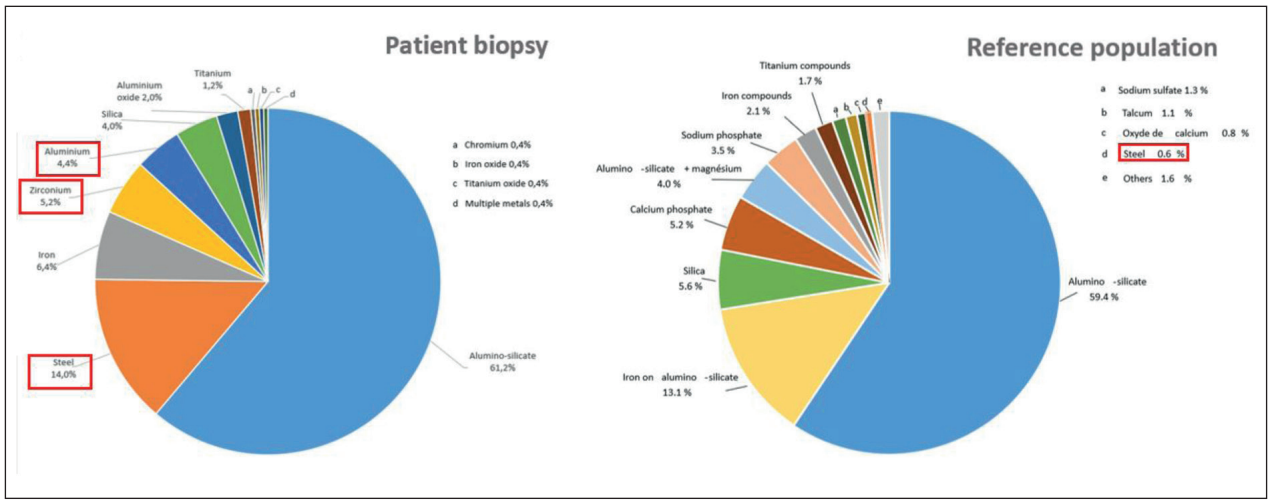

Fig. 3. Mineralogical analysis of lung biopsies. Repartition diagram of mineralogical particles observed with microscope. Comparison with a reference population (SEM-EDX in situ analysis of 53 blocks of pulmonary parenchyma from forensic institute of Lyon, 4050 particles analysed)

Metal lung disease is caused by an exposure to particles of metal alloys mostly composed of tungsten carbide and cobalt (4,5); among the first articles published that described the link between this exposure and pulmonary fibrosis, two were in Tours in 1974 and 1975 in cases of workers exposed to tungsten carbide and cobalt (6,7). A few clinical cases were described with other components such as aluminium, beryllium, copper, iron, nickel (8). The main pulmonary interstitial patterns that we can find in literature are giant cell interstitial pneumonia, usual interstitial pneumonia, hypersensitivity pneumonitis, granulomas, and bronchiolitis; histological patterns of desquamative interstitial pneumonia (DIP) are described in a very few cases.

DIP is one of the major idiopathic interstitial pneumonias, described for the first time in 1965 by Liebow (9). DIP concerns mainly men, aged between 40 and 60 years. Characteristic lesions in HRCT are bilateral ground glass opacities with a predilection for peripheral and lower lung zone; micronodular opacities can also be found with possible association with fibrosis patterns. BAL usually contains increased numbers of macrophages with an inconstant presence of giant cells. Increased numbers of neutrophils, eosinophils and lymphocytes have also been found but these findings are not very specific (10). In this context, a lung biopsy may be necessary to confirm the diagnosis. Some series of surgical biopsy showed a morbidity up to 7% (11) but the surgical approach used was thoracotomy. The advent of mini surgery and Enhanced Recovery After Surgery (ERAS) programs seem promising given that surgical biopsy shows a better concordance with the final diagnosis of ILD than transbronchial biopsies (12).

The main histologic feature is a diffuse and uniform accumulation of macrophages within alveoli; these macrophages have eosinophilic cytoplasm and mostly contain a granular light-brown pigment when DIP is associated to tobacco exposure; alveolar architecture is generally preserved (1). DIP's main aetiology is exposure to tobacco (58 to 91% of DIP's cases); epidemiological studies suggest other rare aetiologies such as infections, medications, rheumatoid arthritis and exposure to cannabis or anorganic particles.

Our research in medical literature led us to find seven cases of DIP secondary to a metal exposure , these results are collected in Table 1. We found two cases in a context of aluminium exposure, two in a context of tungsten exposure and five with multiple metal exposure. Two of these patients had only DIP patterns on their lung biopsies but the first one was an active smoker (13) and the authors did not mention the precise pathological findings of the other one (14). Thus, histological patterns of DIP seem to always be associated with other interstitial patterns: giant cell interstitial pneumonia, bronchiolitis, non-specific interstitial pneumonia or granulomas.

Table 1. Literature review

Exposition	Case	Histology
Aluminium	*Iijima 2017* (19)*: 1 case*	**DIP** + Non Specific Interstitial Pneumonia + Granulomas
	Herbert 1982 (14)*: 1 case*	**DIP** *(not detailed histology)*
Multiple exposures	*Mizutani 2016* (4)*: 1 case (Cobalt and Tungsten)*	**DIP** + Bronchiolitis
	Ju 2017 (13)*: 1 case (not detailed)*	**DIP** (Active smoker)
	Cai 2006 (20)*: 1 case (not detailed)*	**DIP** + Giant Cell Interstitial Pneumonia
	Davison 1983 (21)*: 1 case (Tungsten, Iron, Titanium)*	**DIP** + Giant Cell Interstitial Pneumonia
Tungsten	*Dai 2009 (12): 1 case*	**DIP** + Giant Cell Interstitial Pneumonia

In the present case, DIP patterns were associated with granulomas. We encountered DIP lesions incriminated on Aluminium and Zirconium exposure, as previously mentioned, we found two cases of DIP in aluminium-exposed patients but none with a Zirconium exposure. The imputability of Zirconium compounds in this pneumonia is particularly suspected as cases of pulmonary granulomatosis secondary to Zirconium exposure have been described (15). Moreover, 13% of the use of Zirconium consists in protecting the interior wall of furnaces and reactors used in manufacture of foundry crucibles; this corresponds to the professional activity of our patient in the foundry. Concerning Steel particles, they seem to be involved in the granulomatous component of this interstitial pneumonia as Catinon et al. has already described this association twice (16,17).

The other particularity of our case description lies in the favourable evolution after a systemic corticosteroid treatment. Corticosteroid therapy showed its efficiency in most DIPs induced by tobacco (10) but its use seems less obvious in cases of DIPs secondary to metal exposure with bad evolution despite corticosteroids (4,18) except in the description of Iijima et al. (19).

In conclusion, our case is the first one that describes a DIP secondary to a Zirconium exposure associated with Aluminium and Steel exposure. Our report shows that finding the relevant exposure is a challenging task that requires a complete interrogation including the patient's possible exposures. Moreover, a Multidisciplinary Discussion must be held to consider the need of a lung biopsy with the analysis of the mineral particles observed on the sampling. This analysis could be useful for epidemiological purposes, to support diagnosis or for therapeutic purposes for the eviction of the relevant particle. Patients could also benefit from this analysis for recognition as an occupational disease, and employers could guarantee protective measures to their employees.

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