SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2017; 34; 115-121 DOI: 10.36141/svdld.v34i2.5966

Etiologies of consecutive series of non-necrotizing granulomas

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Abstract. *Background:* Sarcoidosis is an idiopathic granulomatous disease characterized by variable organ involvement and non-necrotizing granulomas. *Objectives:* To determine how often non-necrotizing granulomas are not secondary to sarcoidosis. *Methods:* A retrospective review was conducted to evaluate all biopsies performed at Mayo Clinic in Jacksonville, Florida from January 1, 1996, to December 31, 2013, showing non-necrotizing granulomas. *Results:* Three hundred and eight biopsies showing non-necrotizing granulomas met inclusion criteria. The average age was 58.2 years, 60.7% were female, and 85% were Caucasian. The most common symptoms were pulmonary (74.6% of cases), and the most common objective finding was lymphadenopathy (33.8%). The organs biopsied included lung parenchyma (65.3%), intrathoracic lymph nodes (25%), other lymph nodes (1.6%), liver (1.3%), airway (1.3%), skin (1.3%), kidney (0.7%), bone marrow (0.7%), gastrointestinal (0.7%), and one each from the brain, heart, bone, bladder, spleen, tendon, and eye. The suspected diagnosis was confirmed in 224 cases (72.7%). From the remaining 84 cases (27.3%), suspected sarcoidosis was refuted in 9, the initial diagnosis was changed to sarcoidosis in 37 (44%), and in 38, it was changed to a different diagnosis. Sarcoidosis was the final diagnosis in 173 (56%). *Conclusion:* Sarcoidosis was the leading cause of non-necrotizing granulomas, but in 44% of cases, there was an alternate diagnosis. We estimate that more than a quarter of the initial diagnoses will be changed based on biopsy results and clinical course. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 115-121)*

Key words: non-necrotizing granulomas, sarcoidosis, mycobacteria, vasculitis

Introduction

In 1877, Dr. Jonathan Hutchinson first described sarcoidosis based on dermatologic findings. In 1899, Dr. Caesar Boeck coined the term "sarcoidosis" because the skin nodules were characterized by sharply defined foci of epithelioid and giant cells, which resembled sarcoma (1). Despite being characterized 200 years ago, we still do not fully understand this disease.

In United States, sarcoidosis is the cause of lung granuloma most commonly encountered by surgical pathologists (2). However, several other conditions also cause non-necrotizing granulomas in the lung, and there are no pathognomonic histologic features of sarcoidosis (3).

The non-necrotizing granulomas of sarcoidosis are discrete, well-formed, and interstitial. The lymphangitic distribution of granulomas represents an advantage, since, the lymphatics run in the pleura, interlobular septa, and bronchovascular bundles in the lung, which explains the high diagnostic yield of transbronchial biopsies (4).

Received: 21 November 2016
Accepted after revision: 11 January 2017
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Previous Presentations: This study was presented as an abstract at the CHEST National Meeting at Austin, TX on October 29, 2014.

The prevalence of sarcoidosis differs by sex, racial group, and location. In United States, it most commonly affects middle-aged African-American women. Other ethnic groups have been included in some cohorts, but there is very little data to compare (5, 6). The epidemiology of sarcoidosis remains problematic because of the variability in presentation, lack of sensitive and specific tests, and the rate of under-recognition and misdiagnosis.

The vast majority of patients (30% to 60%) are asymptomatic (6). When symptoms are present, they vary widely. The most common symptoms are dry cough, dyspnea, chest pain, fever, night sweats, fatigue, and skin rashes (erythema nodosum, papules, nodules), and there are occasionally findings of neurologic or cardiac dysfunction, which can represent life-threatening presentation of this disease.

The diagnosis remains difficult and requires typical clinical and radiological findings, histological evidence of non-necrotizing epithelioid cell granulomas, and thorough exclusion of other causes (5). As such, sarcoidosis is a diagnosis of exclusion when there is no other apparent cause of non-necrotizing granulomas, which may only become apparent later in the clinical course.

Granulomas are common biopsy findings, particularly in the lung. The first step is to classify them by the presence of necrosis. The most common causes of necrotizing granulomas are infections such as mycobacteria, endemic fungi, and parasites; and vasculitis, which would point toward granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis.

If interstitial pneumonia is documented, hypersensitivity pneumonitis, lymphocytic interstitial pneumonitis, and giant-cell interstitial pneumonitis should be considered. If peribronchiolar or perivascular distribution of foreign material and non-necrotizing granulomas is seen, aspiration or intravenous drug use should be considered, respectively. Lymphocytic distribution of non-necrotizing granulomas could be related with occupational exposures like berylliosis and silicosis (3).

Our study aimed to determine the frequency of histologically confirmed non-necrotizing granulomas that were proven to be sarcoidosis and how often alternative diagnoses were made, both at the time of the initial diagnosis and during the subsequent clinical course.

Methods

The study was approved by the Mayo Clinic Institutional Review Board (#13-007753). Independent patients with variations of the terms "non-necrotizing granuloma" and "non-caseating granulomas" were electronically identified in pathology reports from Florida from January 1, 1996, to December 31, 2013. Cases of intestinal biopsies ordered for inflammatory bowel disease follow-up and for follow-up of administration of bacillus Calmette-Guérine for bladder cancer were excluded.

A chart review described the symptoms, initial diagnosis, type of biopsy, source of sample, imaging, pulmonary function tests, laboratory data, treatment, and subsequent clinical course to identify whether the initial diagnosis was altered. All data was entered into REDCap Software,(7) and the analysis was performed using JMP® (SAS, JMP, Cary, NC) and Microsoft Excel (Microsoft, Redmond, WA).

Descriptive statistics are presented as means with their standard deviations. Significant differences in proportions were tested with Fisher's exact test, and differences in continuous variables were tested with the Manny-Whitney test with a significance threshold of $p<0.05$. In trying to identify potential clinical variables that would predict the diagnosis of sarcoidosis, a multivariate logistic regression model was created incorporating covariates of age, sex, lymphadenopathy, constitutional symptoms, fatigue, and skin manifestations.

Results

Between 1996 and 2013, 433 patients with biopsy-proven non-necrotizing granulomas were identified. After exclusion of 125 patients with inflammatory bowel disease and bladder cancer surveillance, 308 cases were eligible for analysis. The mean age was 58.28 years; 60.7% were female; 85% were Caucasian, and 7% were African American.

Symptoms were present in 294 (95.45%) patients. Two hundred thirty (74.6%) had respiratory complaints, including cough, dyspnea, and hemoptysis. Constitutional compromise was seen in 104 (33.8%): fatigue, weight loss, fever, and night sweats. Other reported symptoms were gastrointestinal (11.4%), skin (9.09%), musculoskeletal (5.9%), oph-

thalmological (4.9%), neurological (4.6%), genitourinary (2.9%), and vague cardiac symptoms (2.9%). Lymphadenopathy was documented in 104 (33.8%), hilar or mediastinal in 80 (76.9%), extra-thoracic in 10 (9.6%), and both intra- and extrathoracic lymphadenopathy in 14 (13.5%) (Supplemental Table 1).

Biopsies were performed of the lung (65.3%), hilar/mediastinal lymph nodes (25%), other lymph nodes (1.6%), liver (1.3%), airway (1.3%), skin (1.3%), kidney (0.7%), bone marrow (0.7%), gastrointestinal (0.7%), and of one each of the brain, heart, bone, bladder, spleen, tendon, and eye. These were obtained by surgical procedure, endobronchial ultrasound-guided transbronchial needle aspiration, transbronchial forceps biopsies, percutaneous fine needle aspiration, endoscopic ultrasound-guided needle aspiration, endobronchial forceps biopsies, mediastinoscopy, bronchoscopic endobronchial biopsies, and endoscopic mucosal biopsies in 45.8%, 19.8%, 19.5%, 9.09%, 2.6%, 1.3%, 1.3%, and 0.7%, respectively.

Before the biopsies, the most common differential diagnosis was sarcoidosis (132, 42.9%), followed by lung malignancy (9.4%), pulmonary fibrosis (5.5%), interstitial lung disease (4.9%), and metastatic process (3.6%).

After biopsy, the initial suspected diagnoses were confirmed in 224 (72.7%) cases. In the remaining 84 cases where the suspected diagnosis was refuted, 9 (9/132, 6.8%) cases of suspected sarcoidosis were changed (one case each) to nonsmall cell lung cancer, idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, large-cell lymphocytic leukemia, mycobacterium avium complex infection, lymphoproliferative disorder, aspergilloma, and reactive lymphadenopathy. Thirty-seven cases with an initial suspicion of lung malignancy (24.3%), metastatic disease (13.5%), lymphoma (8.1%), solitary lung nodule of unclear etiology (8.1%), unspecified diagnosis presenting with hemoptysis (5.4%), infection (5.4%), and one each of skin nevus, lymphoproliferative disorder, renal cell carcinoma, pulmonary arteriovenous malformation, respiratory bronchiolitis-associated interstitial lung disease, shortness of breath, connective tissue disease-associated interstitial lung disease, nonalcoholic steatohepatitis, acute interstitial nephritis, chronic obstructive pulmonary disease, pulmonary fibrosis, acute kidney injury, and IPF were confirmed after biopsy to be sarcoidosis. In the remaining 38 cases, the pre- and post-diagnosis was not sarcoidosis (Table 1).

Table 1. Change in diagnosis

Final diagnosis sarcoidosis from nonsarcoidosis initial diagnosis	
Lung Malignancy	9
Metastatic Disease	5
Lymphoma	3
Lung nodule	3
Hemoptysis	2
Infectious disease	2
Nevus	1
Lymphoproliferative disorder	1
Renal cell carcinoma	1
Pulmonary arteriovenous malformation	1
Respiratory bronchiolitis-associated interstitial lung disease	1
Shortness of breath	1
Connective tissue disease-associated interstitial lung disease	1
Nonalcoholic steatohepatitis	1
Acute interstitial nephritis	1
Emphysema	1
Pulmonary fibrosis	1
Acute kidney injury	1
IPF	1
Final diagnosis nonsarcoidosis from sarcoidosis initial diagnosis	
Nonsmall cell lung cancer	1
IPF	1
Hypersensitivity pneumonitis	1
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	1
Large granular lymphocytic leukemia	1
MAC	1
Lymphoproliferative disorder	1
Aspergilloma	1
Reactive lymphadenopathy	1
Final diagnoses nonsarcoidosis from nonsarcoidosis initial diagnosis	
Hypersensitivity pneumonitis	5
Nonspecified granulomatous disease	5
Pulmonary nodules	4
MAC	3
Normal tissue	2
Organizing pneumonia	2
Lymphoma	2
Reactive lymphadenopathy	2
Infectious process	1
Squamous cell carcinoma	1
Neutrophilic alveolitis	1
Kikuchi syndrome	1
Viral pneumonitis	1
Recurrent aspiration pneumonia	1
Breast cancer	1
Right middle lobe syndrome	1
Limited granulomatosis with polyangiitis	1
Asthma	1
Acute hypersensitivity reaction	1
Chronic obstructive pulmonary disease	1
Eosinophilic pneumonia	1

IPF: Idiopathic Pulmonary Fibrosis;
MAC: mycobacterium Avium-Complex

Overall, the most common final diagnosis was sarcoidosis in 173 patients (56.2%), followed by hypersensitivity pneumonitis (6.8%), IPF (2.9%), mycobacterium avium complex infection (2.9%), nondiagnostic granulomatous findings (2.6%), lung adenocarcinoma (2.6%), and others (Table 2).

Table 2. Final diagnosis in patients with non-necrotizing granulomas

Final diagnosis	Absolute	Relative
Sarcoidosis	173	56.17
Hypersensitivity pneumonitis	21	6.82
Idiopathic Pulmonary Fibrosis	9	2.92
Mycobacterium avium-intracellulare	9	2.92
Granulomatous disease	8	2.60
Adenocarcinoma	8	2.60
Chronic obstructive pulmonary disease	7	2.27
Squamous cell carcinoma	5	1.62
Interstitial lung disease	4	1.30
Reactive lymphadenopathy	4	1.30
Pulmonary nodules	4	1.30
Pulmonary fibrosis	4	1.30
Organizing pneumonia	3	0.97
Nonsmall cell lung cancer	3	0.97
Metastatic disease	3	0.97
Infectious process	2	0.65
Lung transplant	2	0.65
Lymphoma	2	0.65
Connective tissue disease-associated interstitial lung disease	1	0.32
Acute hypersensitivity reaction	1	0.32
Acute intermittent porphyria	1	0.32
Aspergilloma	1	0.32
Asthma	1	0.32
Bacterial pneumonia	1	0.32
Benign metastasizing leiomyoma	1	0.32
Bladder cancer	1	0.32
Breast cancer	1	0.32
Bronchiectasis	1	0.32
Carcinoid tumor	1	0.32
Chronic granulomatous conjunctivitis	1	0.32
Chronic inflammation	1	0.32
Cirrhosis	1	0.32
Crohn's disease	1	0.32
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	1	0.32
Eosinophilic pneumonia	1	0.32
Epidermal inclusion cyst	1	0.32
Flexor tenosynovitis	1	0.32
Histoplasmosis	1	0.32
Inflammatory process	1	0.32
Kikuchi syndrome	1	0.32
Lymphangioleiomyomatosis	1	0.32
Large granular lymphocytic leukemia	1	0.32
Limited granulomatosis with polyangiitis	1	0.32
Lung abscess	1	0.32
Lymphoproliferative disorder	1	0.32
Negative for malignancy	1	0.32
Neutrophilic alveolitis	1	0.32
Normal tissue	1	0.32
Nonspecific interstitial pneumonia	1	0.32
Pancreatic adenocarcinoma	1	0.32
Recurrent aspiration pneumonia	1	0.32
Right middle lobe syndrome	1	0.32
Sarcoma	1	0.32
Submassive pulmonary embolism	1	0.32
Viral pneumonitis	1	0.32

There were no significant differences in age (54.8 versus 62.7 years, *P*=.08) and sex (63% versus 58%, *P*=.35) among those with and without confirmed sarcoidosis diagnosis, but lymphadenopathy (hilar, mediastinal, other) was documented in 91 of the 173 cases of sarcoidosis and in only 13 of the 135 cases with other diagnoses (*P*<.0001) (Figures 1 and 2).

To characterize all of the features of both sarcoidosis and nonsarcoidosis, we reviewed pulmonary function tests (PFTs), documented similar distribution of PFT patterns for both sarcoidosis and nonsarcoidosis diagnosis of non-necrotizing granulomas (Supplemental Table 2). PFT results of 132/173 patients with a final diagnosis of sarcoidosis including: normal for 49 (37.1%), obstructive pattern for 25 (18.9%), restrictive pattern for 25 (18.9%), isolated diffusion abnormality for 15 (11.4%), nonspecific pulmonary function pattern for 9 (6.8%), and mixed obstructive-restrictive pattern for 7 (5.3%), while in the nonsarcoidosis group, PFT results in 94 cases were normal for 29 (30.9%), obstructive pattern for 20 (21.3%), restrictive pattern for 20 (21.3%), isolated diffusion abnormality for 12 (12.7%), mixed obstructive-restrictive pattern for 6 (6.4%), and nonspecific pattern for 5 (5.3%).

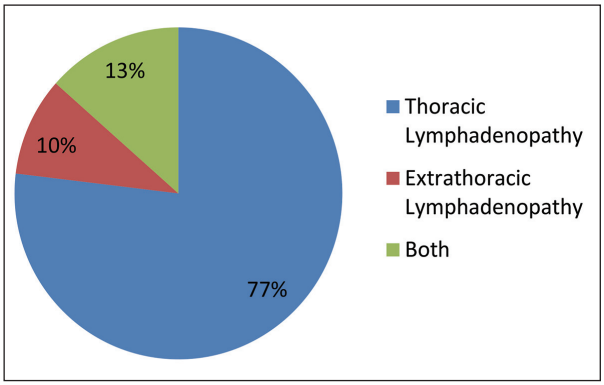

Fig. 1. Presence of lymphadenopathy

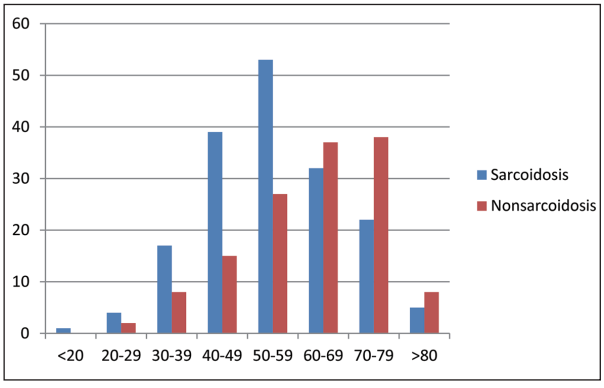

Fig. 2. Age group by diagnosis

The imaging tests included chest radiograph and computed tomography (CT). Chest radiography was performed in 231 patients. Out of the 129 radiographs in patients with final a diagnosis of sarcoidosis, the most important findings were thoracic lymphadenopathy in 78 (60.5%) and infiltrate in 46 (35.7%). No masses were found in this group. In 102 radiographs in patients with nonsarcoidosis as the final diagnosis, the most important findings were infiltrate in 49 (48%), masses in 3 (2.9%), and thoracic lymphadenopathy in only 7 cases (6.9%). A total of 63 CT scans of the chest were performed, of which 37 (58.7%) were performed for patients whose final diagnosis was sarcoidosis and 26 (41.3%) for patients with other nonsarcoidosis diagnosis. The most prominent findings from the CT chest scans in the sarcoidosis group were: thoracic lymphadenopathy in 28 (75.7%), nodules in 13 (35.1%), infiltrate in 4 (10.8%), and fibrosis in 4 (10.8%). In the nonsarcoidosis group, the most prominent findings on CT were thoracic lymphadenopathy in 9 (34.6%), ground-glass opacities in 9 (34.6%), and nodules in 8 (30.8%).

By multivariate analysis, the presence of lymphadenopathy (hilar, mediastinal, and other) and lower age were independently associated with the diagnosis of sarcoidosis.

Discussion

Our study examined all cases in the electronic medical record over a period of 17 years that had a biopsy revealing non-necrotizing granulomas. Three hundred eight cases were divided into those whose final diagnosis was sarcoidosis and those who a different final diagnosis. The 173 cases of sarcoidosis appear to be representative of the known epidemiology of this disease in United States.

There were fewer African American patients in our study compared to others studies (8). but this was comparable to the largest series for sarcoidosis regarding sex and age (9). Prior studies found the disease onset to be between 20 and 40 years of age

(10, 11). whereas the peak age group in our study was 50 to 59 years of age, which reflects the demographics our institution's patients.

The major goal of our study was to find the frequency of sarcoidosis in patients with non-necrotizing granulomas present on biopsy and document the alternative diagnosis for this pathology. Our study found that 84 (27%) cases changed diagnosis over time: to sarcoidosis in 37, from sarcoidosis to another diagnosis in 9, and from nonsarcoidosis diagnosis to other nonsarcoidosis diagnosis in 38. This might imply that observation should be the initial approach in up to 30% of patients with positive isolation of non-necrotizing granulomas before to label the case as a Sarcoidosis or even worse start therapy for it.

One of the weaknesses of our study is its retrospective nature, which can lead to biases in selection and outcome data. We have to acknowledge that in the cases we reviewed, the clinical evidence alone was not enough to obtain a diagnosis, which led to the need for biopsy.

Because the diagnosis of sarcoidosis remains challenging, we went back to look for clues that could help clarify the diagnosis; however, after a multivariate analysis, only the presence of lymphadenopathy and age of presentation were statistically significant predictors. This is consistent with previous reports where lymphadenopathy, mostly hilar or mediastinal, was the most common presentation of this disease (9, 11).

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Supplemental tables

Supplemental Table 1: Subjective Findings in Patients with Non-Necrotizing Granulomas

	Sarcoidosis		Nonsarcoidosis	
	Yes	No	Yes	No
Symptoms Present	170	3	124	11
Pulmonary Symptoms	122		108	
Dyspnea	72		64	
Cough	79		67	
Hemoptysis	6		7	
Constitutional	64		40	
Fever	8		12	
Weight Loss	17		15	
Night Sweats	11		8	
Fatigue	46		24	
Gastrointestinal	18		17	
Skin	19		9	
Ocular	11		4	
Renal	6		3	
Cardiac	7		2	
Neurological	12		2	
Musculoskeletal	11		7	

Supplemental Table 2: Pulmonary function test patterns in sarcoidosis and nonsarcoidosis

	Sarcoidosis	Nonsarcoidosis
Pulmonary Function Tests	132	94
Normal	49	29
Restrictive Pattern	25	20
Obstructive Pattern	25	20
Mixed Restrictive-Obstructive	7	6
Nonspecific Pattern	9	5
Isolated Diffusion Abnormality	15	12