SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (4); e2020011 DOI: 10.36141/svdld.v37i4.10136 

# Clinical Characteristics of Sarcoidosis in Asian Population: A 14-year Single Center Retrospective Cohort Study from Thailand

*Athiwat Tripipitsiriwat[1], Chulaluk Komoltri[2], Ruchira Ruangchira-urai[3], Patompong Ungprasert[2]*

[1]Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [2]Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3]Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

**Abstract.** *Background:* Little is known about epidemiology and clinical characteristics of sarcoidosis in Asian population. *Objectives:* This study aimed to examine the epidemiology and clinical characteristics of Thai patients with sarcoidosis, using databases of a tertiary care medical center. *Methods:* Potential cases of sarcoidosis were identified from two sources, the medical record-linkage system and the pathology database of Siriraj Hospital, Mahidol University in Bangkok, Thailand. Patients with ICD-10-CM codes for sarcoidosis were identified and retrieved from the medical record-linkage system from 2005 to 2018. Patients with histopathology positive for non-caseating granuloma were identified and retrieved from the pathology database from the same time period. All potential cases underwent individual medical record review to confirm the diagnosis of sarcoidosis which required compatible clinical pictures supported by presence of non-caseating granuloma, radiographic evidence of intrathoracic sarcoidosis and exclusion of other granulomatous diseases. *Results:* From 2005 to 2018, 89 confirmed cases of sarcoidosis were identified. 80.9% of them were female and mean age at diagnosis was 46.8 years (standard deviation (SD) 13.9 years). The majority of patients had intrathoracic disease (81 cases; 91.0%) but less than half had respiratory symptoms (34 cases; 41.9%). Extrathoracic disease was common in this cohort that pulmonary sarcoidosis was accompanied by extrathoracic involvement in 53 patients (65.4%). Sarcoid uveitis was the most common extrathoracic disease (35 cases; 39.3%), followed by cutaneous sarcoidosis (24 cases; 26.9%), extrathoracic lymphadenopathy (18 cases; 22.5%) and sarcoid arthropathy (4 cases; 4.5%). *Conclusion:* The current study examined clinical characteristics of sarcoidosis in an Asian population and found high prevalence of uveitis and marked female predominance. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (4): e2020011)*

**Key words:** sarcoidosis, epidemiology, non-caseating granuloma, uveitis, asian

## Introduction

Sarcoidosis is a chronic granulomatous disease of unknown etiology that is believed to be a result of complex interaction between host factors and environmental triggers (1, 2). It is known that epidemiology and clinical phenotype of sarcoidosis are influenced by ethnicity. For instance, the annual incidence of sarcoidosis is as high as 70 per 100,000 population among African-Americans but is as low as 1-2 per 100,000 population among Asians and Hispanics (2-7). Nonetheless, data on clinical manifestations of Asians with sarcoidosis are still relatively limited and most of the previously published studies are from East Asia (4, 5, 8-11). The current study identified cohort of patients with sarcoidosis from medi-

Received: 3 July 2020
Accepted after revision: 20 October 2020
Correspondence: Patompong Ungprasert, MD, MS
2 Wanglang Road, Bangkoknoi, Bangkok, Thailand 10700
Tel. +66 655898155
Fax +66 24113062
E-mail: p.ungprasert@gmail.com

cal record-linkage system of a tertiary care center in Thailand, a country in South East Asia.

## Methods

Approval for this study was obtained from the Faculty of Medicine Siriraj Hospital, Mahidol University Institutional Review Board [IRB no. 763/2561(EC2)]. Since there was no direct contact to the patients, the need for informed consent was waived. Potential cases of sarcoidosis were identified from two sources, the medical record-linkage system and the pathology database of the hospital. Patients with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes for sarcoidosis (D86 – D86.9) were identified and retrieved from the medical record-linkage system from 2005 to 2018. Patients with histopathology positive for non-necrotizing granuloma or non-caseating granuloma were identified and retrieved from the pathology database from the same time period. All potential cases retrieved from either source underwent individual medical record review to confirm the diagnosis of sarcoidosis. Diagnosis of pulmonary sarcoidosis required compatible clinical pictures supported by presence of non-caseating granuloma, radiographic evidence of intrathoracic sarcoidosis and exclusion of other granulomatous diseases, especially tuberculosis. Presence of caseous granuloma is also an acceptable alternative if extensive investigations for other causes of granulomatous inflammation, especially tuberculosis, were negative. The only exception for the requirement of histological confirmation was stage I pulmonary sarcoidosis that required only thoracic imaging evidence of symmetric bilateral hilar adenopathy. This diagnostic approach is in accordance with the guidance from the American Thoracic Society/ European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders (12). Diagnosis of extra-thoracic sarcoidosis was also based largely on compatible clinical pictures and presence of non-caseating granuloma. Exceptions included neurosarcoidosis, cardiac sarcoidosis and sarcoid uveitis because of the challenge with the inaccessibility of the affected organs. Diagnosis of neurosarcoidosis was accepted if the patient fulfilled at least probable criteria as described by Zajicek et al (13). Diagnosis of cardiac sarcoidosis was accepted if the patient fulfilled either the first or second diagnostic pathway as described by the Heart Rhythm Society in 2014 (14). Diagnosis of sarcoid uveitis was accepted if the patient fulfilled at least probable criteria as described by the International Workshop on Ocular Sarcoidosis in 2009 (15).

A standardized case record form was used to record demographics and disease characteristics Descriptive statistics (means, proportions, standard deviation etc.) were used to summarize the data. Analyses were performed using IBM SPSS version 22.0 (IBM Corp, Armonk, NY, USA).

## Results

From 2005 to 2018, 89 confirmed cases of sarcoidosis were identified. There was female predominance (80.9%) with mean age at diagnosis of 46.8 years (standard deviation [SD] 13.9 years) and mean follow-up time of 5.4 years (SD 4.5 years). The majority of patients with sarcoidosis in this cohort had intrathoracic disease (81 cases; 91.0%). About half of them had stage I pulmonary sarcoidosis (43 cases; 53.1%), followed by stage II (32 cases; 39.5%), III (5 cases; 6.2%) and IV (1 case; 1.2%). However, less than half of patients with intrathoracic disease were symptomatic (34 cases; 41.9%) with dyspnea and cough being the most common symptoms (25.9% and 22.2%, respectively). The yield of intrathoracic biopsy was fair that histopathology was positive for non-caseating granuloma in 52 of 68 patients (76.5%) who underwent biopsy. There was also a case that hilar lymph node biopsy was positive for caseous granuloma.

Extrathoracic disease was common in this cohort that pulmonary sarcoidosis was accompanied by extrathoracic involvement in 53 patients (65.4%). Isolated extrathoracic disease was observed in 8 patients. Sarcoid uveitis was the most common extrathoracic disease (35 cases; 39.3%; 4 males and 31 females), followed by cutaneous sarcoidosis (24 cases; 26.9%), extrathoracic lymphadenopathy (18 cases; 22.5%) and sarcoid arthropathy (4 cases; 4.5%). Less commonly involved organs included nervous system, kidney, parotid gland, liver, spleen, heart and bone. Calcium was tested in 56 patients and hypercalcemia was seen in 9 of them (16.1%). Biopsy of extrathoracic organs appeared to have a high sensitivity with

21 of 22 skin biopsies and all 8 extrathoracic lymph node biopsies showed evidence of non-caseating granuloma.

A total of 48 patients (53.9%) received at least one systemic treatment during the course of their illness. The most commonly prescribed systemic treatment was oral prednisolone (46 cases; 51.7%) followed by methotrexate (16 cases; 17.9%), azathioprine (8 cases; 9.0%) and chloroquine (3 cases; 3.4%). Topical and inhaled corticosteroids were also frequently used (31.5% and 6.7%, respectively). Information on demographics, disease characteristics, laboratory investigations and treatment of patients with sarcoidosis in this cohort are described in table 1.

**Table 1.** Characteristics of patient with sarcoidosis in the current study

| | **Mean or proportion (N = 89)** |
|---|---|
| Age at diagnosis in years (standard deviation) | 46.8 (13.9) |
| Duration of follow-up (standard deviation) | 5.4 (4.5) |
| Male | 17 (19.1%) |
| **Intrathoracic disease** | |
| Intrathoracic involvement -Stage I<br>-Stage II<br>-Stage III<br>-Stage IV | 81 (91.0%)<br>43 (53.1%)<br>32 (39.5%)<br>5 (6.2%)<br>1 (1.2%) |
| Pulmonary symptoms -Dyspnea<br>-Cough<br>-Chest pain | 34 (41.9%)<br>21 (25.9%)<br>18 (22.2%)<br>2 (2.5%) |
| **Extrathoracic disease** | |
| Uveitis | 35 (39.3%) |
| Skin | 24 (26.9%) |
| Joint | 4 (4.5%) |
| Nervous system | 3 (3.4%) |
| Kidney | 3 (3.4%) |
| Parotid gland | 3 (3.4%) |
| Liver | 2 (2.2%) |
| Spleen | 2 (2.2%) |
| Heart | 2 (2.2%) |
| Bone | 1 (1.1%) |
| Extrathoracic lymph node | 18 (22.5%) |
| Hypercalcemia | 9 out of 56 patients who had at least one calcium level checked (16.1%) |
| **Biopsy** (positive for non-caseous granuloma / number performed) | |
| Intrathoracic | 53/68 (77.9%)* |
| Skin | 21/22 (95.5%) |
| Extrathoracic lymph node | 8/8 (100.0%) |
| Parotid gland | 1/1 (100.0%) |
| Kidney | 1/1 (100.0%) |

*(continued)*

**Table 1** ***(continued)*****.** Characteristics of patient with sarcoidosis in the current study

| | **Mean or proportion (N = 89)** |
|---|---|
| **Treatment** | |
| Oral prednisolone | 46 (51.7%) |
| Methotrexate | 16 (17.9%) |
| Azathioprine | 8 (9.0%) |
| Chloroquine | 3 (3.4%) |
| Leflunomide | 1 (1.1%) |
| Sulfasalazine | 1 (1.1%) |
| Inhaled corticosteroids | 6 (6.7%) |
| Topical corticosteroids | 28 (31.5%) |

*One case was positive for caseous granuloma

## Discussion

The most prominent findings of this cohort are the high prevalence of uveitis and the marked female predominance. Prevalence of uveitis in this cohort was almost 40% which is far higher than previous reports from Europe and North America that observed the prevalence of around 10%-15% (2, 3, 6, 16). Similarly, two recent studies from China found prevalence of uveitis of only less than 6% (10, 11). Thus, the prevalence of uveitis in this cohort was strikingly high even compared with other non-Japanese Asian cohorts. This could indicate that uveitis is indeed very common among Thai patients with sarcoidosis or it could be a result of referral bias as the cohort was identified from a single tertiary care center.

There was a female predilection for sarcoid uveitis as almost 90% of patients with sarcoid uveitis in this cohort were females, which is consistent with data from other ethnic groups (2, 3, 6, 7). In fact, a study of predominantly white patients from the United States found that male sex was a significant protective factor against development of uveitis with odds ratio of 0.76 (16).

The female-to-male ratio of this cohort was about 4:1 which is much higher than slight female predominance with female-to-male ratio of less than 2:1 in cohorts of white and black patients (1, 2, 6) as well as studies from Korea and Japan (4, 5). Two studies from China showed a slightly higher female-to-male ratio of about 2.5:1 but is still lower than the current cohort (10, 11). The aforementioned high prevalence of uveitis may partially explain this as uveitis is more likely to occur in females with sarcoidosis than males with sarcoidosis.

More than 90% of patients in this cohort had intrathoracic disease although less than half had pulmonary symptoms. This phenomenon has also been observed in other ethnic groups (2, 5, 7). Therefore, it is advisable that thoracic imaging should be obtained when there is a clinical suspicion for sarcoidosis, even in the absence of respiratory symptoms.

Since histopathological confirmation is required to establish the diagnosis of sarcoidosis in most circumstances, selecting the site for biopsy is of clinical importance to physicians to maximize the yield and to avoid potential complications. The current study confirmed the relatively lower yield of transbronchial lung biopsy plus endobronchial biopsy and/or endoscopic ultrasound-guided core needle biopsy of hilar nodes with the false negative rate of about one-fourth of patients, similar to previous studies (17, 18). On the other hand, biopsy of skin rash and extrathoracic lymph node had a sensitivity to detect non-caseating granuloma of almost 100%, possibly due to the better accessibility to this tissue (19).

About half of patients in this cohort were treated with systemic corticosteroids and/or immunosuppressive agents. This is not unexpected as sarcoidosis, especially pulmonary sarcoidosis, can be asymptomatic and spontaneous regression is often observed (20). Nonetheless, the percentage of patients who received systemic therapy in this cohort is in the higher range compared with prior studies, which could be

the result of the clinical phenotype of our patients that had a high prevalence of sarcoid uveitis, an extrathoracic disease that often necessitates systemic immunosuppression.

The retrospective nature of the cohort is the main limitation. It is possible that the true prevalence of extrathoracic involvement could be higher than reported here because some subclinical diseases may not be recognized without dedicated examination and comprehensive laboratory screening. The other concern is the reliance on coding to identify cases of sarcoidosis. As coding error is common, it is possible that some patients with sarcoidosis maybe misclassified in the database (i.e., did not received the ICD-10-CM codes for sarcoidosis). Nonetheless, this study did not rely exclusively on the medical-record linkage system as cases were also identified based on histopathology which may help improving the comprehensiveness of case identification.

## Conclusion

The current study described clinical characteristics of sarcoidosis in an Asian population. The most prominent findings that are different from sarcoidosis in other ethnic groups included the high prevalence of uveitis and the marked female predominance.

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Credit authorship contribution statement**
Athiwat Tripipitsiriwat: Methodology, data curation, formal analysis, writing – original draft, validation
Chulaluk Komoltri: Methodology, writing – original draft, validation
Ruchira Ruangchira-urai: Methodology, data curation, writing – original draft, validation
Patompong Ungprasert: Methodology, data curation, formal analysis, writing – original draft, validation

## References


1. Judson MA, Boan AF, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. Sarcoidosis Vasc Diffuse Lung Dis. 2012;29:119-27.
2. Ungprasert P, Carmona EM, Utz JP, Ryu JH, Crowson CS, Matteson EL. Epidemiology of sarcoidosis 1946-2013: A population-based study. Mayo Clin Proc. 2016;91:183-8.
3. Cozier YC, Berman JS, Palmer JR, Boggs DA, Serlin DM, Rosenberg L, Sarcoidosis in black women in the United States: Data from the black women's health study. Chest. 2011;139:144-50.
4. Park JE, Kim YS, Kang MJ, Kim CJ, Han CH, Lee SM, et al. Prevalence, incidence and mortality of sarcoidosis in Korea, 2003-2015: A nationwide population-based study. Respir Med. 2018;144S:S28-S34.
5. Morimoto T, Azuma A, Abe S, Usuki J, Kudoh S, Sugisaki K, et al. Epidemiology of sarcoidosis in Japan. Eur Respir J. 2008;31:372-9.
6. Baughman RP, Field S, Costabel U, Crystal RG, Culver DA, Drent M, et al. Sarcoidosis in America. Analysis based on health care use. Ann Am Thorac Soc. 2016;13:1244-52.
7. Ungprasert P, Ryu JH, Matteson EL. Clinical manifestations, diagnosis and treatment of sarcoidosis. Mayo Clin Proc Inn Qual Out. 2019;3:358-75.
8. Yoon HY, Kim HM, Kim YJ, Song JW. Prevalence and incidence of sarcoidosis in Korea: a nationwide population-based study. Respir Res. 2018;19:518
9. Park JE, Kim YS, Kang MJ, Kim CJ, Han CH, Lee SM, et al. Prevalence, incidence and mortality of sarcoidosis in Korea, 2003-2015: a nationwide population-based study. Respir Med. 2018;144S:S28-S34
10. Zhou Y, Lower EE, Feng Y, Du S, Li H, Baughman R. Clinical characteristics of sarcoidosis in patients in the United States versus China. Sarcoidosis Vasc Diffuse Lung Dis. 2017;34:209-216.
11. Li CW, Tao RJ, Zou DF, Li MH, Xu X, Cao WJ. Pulmonary sarcoidosis with and without extrapulmonary involvement: a cross-sectional and observational study in China. BMJ Open. 2018;8:e018865.
12. Costabel U, Hunninghake GW (1999) ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J. 1999;14:735-7.
13. Zajicek JP, Scolding NJ, Foster O, Rovaris M, Evanson J, Moseley IF, et al. Central nervous system sarcoidosis – diagnosis and management. QJM. 1999;92:103-17.
14. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DM, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11:1305-23.
15. Herbort CP, Rao NA, Mochizuki M; members of Scientific Committee of First International Workshop on Ocular Sarcoidosis. International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop on Ocular Sarcoidosis (IWOS). Ocul Immunol Inflamm. 2009;17:160-9.
16. Birnbaum AD, French DD, Mirsaeidi M, Wehrli S. Sarcoidosis in the national veteran population: association of ocular inflammation and mortality. Ophthalmology. 2015;122:934-8.
17. de Boer S, Milne DG, Zeng I, Wilsher ML. Does CT scanning predict the likelihood of a positive transbronchial biopsy in sarcoidosis? Thorax. 2009;64:436-9.
18. Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial biopsy for sarcoidosis: a prospective study. Chest. 2001;120:109-14.
19. Ungprasert P, Wetter DA, Crowson CS, Matteson EL. Epidemiology of cutaneous sarcoidosis, 1976-2013: a population-based study from Olmsted County, Minnesota. J Eur Acad Dermatol Venereol. 2016;30:1799-804.
20. Pietinalho A, Ohmichi M, Lofroos AB, Hiraga Y, Selroos O. The prognosis of pulmonary sarcoidosis in Finland and Hokkaido, Japan. A comparative five-year of biopsy-proven cases. Sarcoidosis Vasc Diffuse Lung Dis. 2000;17:158-66.