Review

SARCOIDOSIS ASSOCIATED WITH RHEUMATIC AUTOIMMUNE DISEASE

Gabriela CEOBANU[1], Gina GHEORGHE[2,3], Vlad Alexandru IONESCU[3]

[1] *Clinical Hospital "Sfanta Maria", Bucharest, Romania*
[2] *University of Medicine and Pharmacy Carol Davila, Bucharest, Romania*
[3] *Department of Gastroenterology, Emergency Clinical Hospital of Bucharest, Romania*

Address for correspondence: Gabriela Ceobanu, Clinical Hospital "Sfanta Maria", Bucharest, Romania; gabriela.ceobanu@ymail.com

Abstract

Sarcoidosis is a multisystem inflammatory disease of incompletely elucidated etiology. It is characterized by the formation of non-caseating granulomas which can be found in any organ or tissue. The most commonly affected organ is the lung and the typical presentation is with bilateral hilar lymphadenopathy, pulmonary infiltrates, and cutaneous and ocular symptoms. However, as the granulomatous reaction can take place in any organ and tissue, sarcoidosis can have variable clinical presentations. It is well documented that sarcoidosis may mimic a great array of autoimmune and non-autoimmune diseases. Moreover, it can also coexist with these disorders, which makes the diagnostic pathway all the more challenging.

Keywords: sarcoidosis, autoimmune disease, non-caseating granuloma

DOI https://doi.org/10.56082/annalsarscimed.2021.1.7

Introduction

Sarcoidosis is a systemic inflammatory disease characterized by a granulomatous reaction leading to the formation of non-caseating granulomas in different organs and systems.

The prevalence of sarcoidosis is dependent on the geographic location and it has been observed that it is the highest in Nordic countries [1]. In 2016, studies were conducted in the USA and Sweden, estimating a prevalence as high as 160 cases per 100,000 people in Sweden and 50 cases per 100,000 people in the USA, reaching the highest rates of sarcoidosis worldwide [2,3].

Sarcoidosis is seen more frequently in females; the median age at diagnosis varies between 35 and 50 years [4].

Pulmonary involvement is seen in more than 90% of sarcoidosis patients and they usually present with dyspnea, dry cough, and chest tightness [5]. 30-50% of patients have extra-pulmonary manifestations, out of which skin and eye involvement are the most common manifestations [6]. Sarcoidosis may present acutely as Lofreg's syndrome, which is characterized by the presence of fever, bilateral hilar lymphadenopathy, erythema nodosum, and bilateral ankle arthritis, or it may present with non-specific signs and symptoms like fever, weight loss, and malaise [7].

Pathogenesis

Although the pathogenesis of sarcoidosis is yet to be fully understood, it is assumed that the formation of granulomas is the result of cellular immune activation after exposure to an environmental or infectious agent, in genetically susceptible individuals [8]. It is

believed that the triggering antigen responsible for the inflammatory reaction may not be successfully eliminated, thus leading to ongoing inflammation. It has been suggested that, because the lung is the most affected organ in sarcoidosis, the antigen triggering the disease may have an aerogenous source [9]. Sarcoidosis is considered a T-cell mediated disease; interaction between T lymphocytes and macrophages leads to the release of pro-inflammatory cytokines by T-helper cells. T-helper-17 cells in particular have been found to play a key role in the pathogenesis of sarcoidosis [10]. An increased number of Th17 cells has been found in both the lung and the peripheral blood in patients with active sarcoidosis compared with healthy individuals. Furthermore, high levels of IL-17 have been found in sarcoid granulomas, supporting the idea that IL-17 is involved in granuloma formation and maturation [10,11].

Sarcoidosis and rheumatic autoimmune diseases

Co-occurrence of sarcoidosis and rheumatic autoimmune diseases has been largely studied, Telium being the first to suggest a relation between these two entities. Sarcoidosis does not meet the criteria for an autoimmune disorder, but its coexistence with various autoimmune diseases has been well documented [12]. Up to the present time, this association has been analyzed in different settings: case reports, population-based studies as well as in four studies that specifically investigated the overlap of sarcoidosis and immune-mediated diseases [13, 14, 15, 16].

A study conducted in Turkey aimed to determine the characteristics and frequency of autoimmune diseases associated with sarcoidosis [13]. The diseases most frequently coexisting with sarcoidosis were ankylosing spondylitis and rheumatoid arthritis. Other concomitant autoimmune rheumatic disorders were Sjogren's syndrome and systemic sclerosis. Compared to patients with isolated sarcoidosis, patients with an associated rheumatic disease had more interphalangeal joint involvement, rheumatoid factor positivity, and a higher erythrocyte sedimentation rate.

A Taiwan case-control study that compared 1237 sarcoidosis patients with 4948 age and sex-matched subjects, showed a significant association of autoimmune comorbidities in sarcoidosis patients (17,6%) in comparison to controls (9,4%). The most significantly associated autoimmune disease was Sjogren's syndrome, followed by ankylosing spondylitis [14]. Other rheumatic autoimmune comorbidities were systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis, and systemic sclerosis, however, no statistical significance was identified.

A systematic epidemiological study conducted in the UK which enrolled 1510 patients sought to investigate the rate of sarcoidosis occurrence before and/or after a variety of immune-mediated and other chronic inflammatory diseases [15]. A significant association was found between sarcoidosis and systemic lupus erythematosus (OR 8.33; 95% CI 2.71 to 19.4).

Another study conducted by Brito-Zeron included 1737 patients diagnosed with sarcoidosis and it aimed to analyze the association of immune-mediated diseases (IMD) and sarcoidosis [16]. One in six patients had comorbid IMD, thus supporting the frequent co-occurrence of IMDs. Significant associations were demonstrated between sarcoidosis and Sjogren syndrome, antiphospholipid syndrome, systemic sclerosis, ankylosing spondylitis, and psoriatic arthritis, and less strongly between sarcoidosis and systemic lupus erythematosus and inflammatory myopathies. Like all the other studies which analyzed sarcoidosis and Sjogren syndrome overlap, this study supported the notion that pre-existing sarcoidosis does not exclude a concomitant diagnosis of Sjogren syndrome.

Cases of systemic vasculitis, adult-onset Still disease, psoriasis, and polymyalgia rheumatica have also been reported in association with sarcoidosis [17-20].

A study that involved 154 patients diagnosed with sarcoidosis showed an overall autoimmune disease (AD) prevalence of 12.3% in sarcoidosis patients compared to the general population (3-5%) [21]. An increased level of the erythrocyte sedimentation rate, reflecting immunoglobulin change secondary to immune dysfunction, was a risk factor for AD co-occurrence in sarcoidosis patients. The study found that despite AD absence, patients with sarcoidosis had a higher probability of being autoantibody-positive; nevertheless, this observation is yet to be confirmed after a longer period of follow- up.

Table 1. Rheumatic autoimmune diseases most frequently associated with sarcoidosis

Rheumatic autoimmune comorbidity	Author	Comments
Sjogren's syndrome	Gorek et al. 2015 [22]	• The acceptance of sarcoidosis as an exclusion classification criterion for Sjogren's syndrome (SS) may result in under-diagnosis of SS
	van de Loosdrecht et al. 2001 [23]	• Pulmonary and exocrine gland involvement in primary SS should prompt the consideration of sarcoidosis in the differential diagnosis • In case of co-occurrence of sarcoidosis and primary SS, with muscular involvement, sarcoid myopathy should be included in the differential diagnosis
	Santiago et al. 2014 [24]	• Sarcoidosis and SS overlap appears to be associated with increased extrapulmonary involvement in sarcoidosis
	Ramos-Casals et al. 2004 [25]	• Sarcoidosis and primary SS have similar pathogenic, immunogenetic, and clinical characteristics • The differentiation between coexistence and mimicry of sarcoidosis and SS may be facilitated by focusing on these three elements: the immunologic pattern, the presence of extra glandular involvement, and the histologic analysis of the minor salivary gland biopsy
Rheumatoid arthritis	Zickuhr et al. 2017 [26]	• All patients with sarcoidosis and rheumatoid arthritis were seropositive
	Kucera et al. 1989 [27]	• The positivity of HLA-DR4 may be a risk factor for the co-occurrence of sarcoidosis and rheumatoid arthritis
	Kobak et al. 2015 [28]	• The study raises awareness of the possibility of sarcoidosis development after anti-tumor necrosis factor-alpha administration in patients with rheumatoid arthritis • Given the high prevalence of both sarcoidosis and rheumatoid arthritis, it is likely that their association is merely coincidental

Ankylosing spondylitis	Alishiri et al. 2020 [29]	• Patients with pulmonary sarcoidosis and ankylosing spondylitis (AS) overlap may be safely treated with anti-TNF monoclonal antibodies
	Wafa et al. 2018 [30]	• Patients with sarcoidosis and AS co-occurrence rarely associated HLA-B27 positivity, suggesting that a different genetic profile and different mechanisms may be involved in the pathogenesis of this entity • Most cases of associated SA and sarcoidosis are reported as TNF-alpha antagonist-induced
	Erb et al. 2005 [31]	• Sarcoidosis patients had a higher prevalence of radiographic sacroiliitis (6.6%) compared to spondylarthritis prevalence in the general population (1.9%)
	Kobak et al. 2014 [32]	• The two different genetic backgrounds on which sarcoidosis and AS develop (MHC class II and MHC class I, respectively) suggest a coincidence rather than a common etiopathogenesis
Systemic lupus erythematosus (SLE)	Prieto-Pena et al. 2021 [33]	• Sarcoidosis and SLE co-occurrence was more common in young female adults in the fourth decade of life • Considering the low prevalence of acute lupus pneumonitis or chronic ILD in SLE, pulmonary involvement presenting as ILD in lupus patients should lead to the consideration of sarcoidosis co-existence
	Papaioannides et al. 2004 [34]	• SLE developed after discontinuation of chronic steroid therapy for pulmonary sarcoidosis
	Umeki et al. 2001 [35]	• Sarcoidosis developed after cessation of oral prednisolone used in SLE patient
	Enzenauer et al. 1992 [36]	• Sarcoidosis and SLE share some similarities regarding immune dysfunction: cellular and humoral immune abnormalities including hyperreactivity of the immune system, hypergammaglobulinemia, and defective cell-mediated immune function
Systemic sclerosis	Senda et al. 2014 [37]	• Co-occurrence of sarcoidosis and systemic sclerosis (SSc) was common in females and patients with limited SSc • Male patients with sarcoidosis-SSc overlap syndrome predominantly had anti-Scl-70 antibodies (78%) • Female patients with sarcoidosis-SSc overlap syndrome showed positivity for anti-centromere antibodies

	Suga et al. 2011 [38]	• Despite the incidence rates seen in sarcoidosis and SSc (50-400/million/year and 20/million/year, respectively), overlap cases seem to have a lower incidence than expected • The lower incidence of sarcoidosis and early/active SSc co-occurrence could be explained by the Th1/Th2 paradigm, as sarcoidosis is a Th1 dominant condition and early and active-stage SSc is Th2-polarized
	Nakamura et al. 2020 [39]	• Considering the weaker Th2 background in ACA-positive SSc patients [40], sarcoidosis may preferentially manifest in limited SSc • Sarcoidosis may shift the Th1/Th2 balance towards Th1, thus diminishing SSc activity

The reason why some autoimmune rheumatic diseases (ARDs) co-occur with sarcoidosis more frequently than others is unknown. One explanation could be that some ARD share more common immunopathogenic mechanisms with sarcoidosis. The paucity of multicentric large-scale studies analyzing sarcoidosis-ARD overlap syndromes precludes the validation of certain mechanisms underlying this association of diseases.

Conclusions

Sarcoidosis is a systemic granulomatous disease of incompletely elucidated etiology, characterized by the presence of non-caseating granulomas which can form in any tissue or organ. The association between sarcoidosis and autoimmune rheumatic diseases has been described in multiple case reports and population-based studies. The presence of immunological similarities between sarcoidosis and autoimmune diseases suggests a possible common etiopathogenesis. The coexistence of sarcoidosis and other autoimmune diseases represents a diagnostic challenge and the physician should differentiate between co-occurrence and mimicry. A high level of suspicion is warranted as the association of these diseases carries significant implications in clinical practice.

Author Contributions:

G.C. conceived the original draft preparation. G.C., G.G., and V-A.I. were responsible for conception and design of the review. VA.I., and G.C. were responsible for the data acquisition. G.C., and G.G. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. G.C., G.G., and VA.I. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article".

Acknowledgements: *None***.**

References

[1] Arkema EV, Cozier YC. Epidemiology of sarcoidosis: current findings and future directions. *Ther Adv Chronic Dis*. 2018;9(11):227-240.

[2] Baughman RP, Field S, Costabel U, et al. Sarcoidosis in America. Analysis based on health care use. *Ann Am Thorac Soc* 2016;13:1244–1252.

[3] Arkema EV, Grunewald J, Kullberg S, et al. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. *Eur Respir J* 2016;48:1690–1699.

[4] Ungprasert P, Carmona EM, Utz JP, et al. Epidemiology of sarcoidosis 1946-2013: a population-based study. *Mayo Clin Proc.* 2016;91(2):183–188.

[5] Ungprasert P, Ryu JH, Matteson EL. Clinical Manifestations, Diagnosis, and Treatment of Sarcoidosis. *Mayo Clin Proc Innov Qual Outcomes*. 2019;3(3):358-375.

[6] Judson MA, Boan AD, Lackland D.T. 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(2):119–127

[7] Korsten P, Tampe B, Konig MF, et al. Sarcoidosis and autoimmune diseases: differences, similarities, and overlaps. *Curr Opin Pulm Med.* 2018;24(5):504-512.

[8] Bennett D, Bargagli E, Metella Refini R, et al. New concepts in the pathogenesis of sarcoidosis. *Expert Review of Respiratory Medicine*. 2019;13(10):981-991

[9] Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA*. 2011;305(4):391-9

[10] Facco M, Cabrelle A, Teramo A, et al. Sarcoidosis is a Th1/Th17 multisystem disorder. *Thorax*. 2011;66:144-50.

[11] Ten Berge B, Paats MS, Bergen IM, et al. Increased IL-17A expression in granulomas and in circulating memory T cells in sarcoidosis. *Rheumatology* (Oxford). 2012;51:37-46.

[12] l2. Sharma OP. Sarcoidosis and other autoimmune disorders. *Curr Opin Pulm Med*. 2002;8(5):452-6

[13] Yildiz F, Kobak Ş, Semİz H, et al. Concomitant autoimmune diseases in patients with sarcoidosis in Turkey. *Arch Rheumatol*. 2020;35(2):259-263.

[14] Wu CH, Chung PI, Wu CY, et al. Comorbid autoimmune diseases in patients with sarcoidosis: A nationwide case-control study in Taiwan. *J Dermatol*. 2017;44(4):423-430.

[15] Rajoriya N, Wotton CJ, Yeates DGR, et al. Immune-mediated and chronic inflammatory disease in people with sarcoidosis: disease associations in a large UK database. *Postgraduate Medical Journal.* 2009;85(1003):233–237.

[16] Brito-Zerón P, Pérez-Alvarez R, Feijoo-Massó C, et al; SarcoGEAS-SEMI Registry. Coexistence of immune-mediated diseases in sarcoidosis. Frequency and clinical significance in 1737 patients. *Joint Bone Spine.* 2021;88(6):105236.

[17] Poudel J, Risal U, Sigdel KR, et al. Case report: Co-existence of sarcoidosis and Takayasu arteritis. *Wellcome Open Res*. 2020;5:73 .

[18] Semiz H, Kobak S. Coexistence of sarcoidosis and adult-onset Still disease. *Reumatol Clin* (Engl Ed). 2019;15(5):e18-e20.

[19] Khalid U, Gislason GH, Hansen PR. Sarcoidosis in patients with psoriasis: a population-based cohort study. *PLoS ONE*. 2014;9:e109632.

[20] Bejerano C, Blanco R, González-Vela C, et al. Refractory polymyalgia rheumatica as presenting manifestation of large-vessel vasculitis associated to sarcoidosis. Successful response to adalimumab. *Clin Exp Rheumatol,* 2012;30(1 Suppl 70):S94-7.

[21] Shi TY, Wen XH, Shi XH, et al. Associations between sarcoidosis,

autoimmune diseases, and autoantibodies: a single-center retrospective study in China. *Clin Exp Med*. 2021. Epub ahead of print. PMID: 34191227.

[22] Dilektasli A, Demirdöğen E, Durmus E, et al. Coexistence of sarcoidosis and Sjögren's Syndrome: a case report. *Chest.* 2015;148:384A.

[23] van de Loosdrecht AA, Kalk W, Bootsma H, et al. Simultaneous presentation of sarcoidosis and Sjögren's syndrome. *Rheumatology*. 2001;40(1):113-115.

[24] Santiago T, Santiago M, Rovisco J, et al. Coexisting primary Sjögren's syndrome and sarcoidosis: coincidence, mutually exclusive conditions or syndrome? *Rheumatol Int.* 2014;34(11):1619-22.

[25] Ramos-Casals M, Brito-Zerón P, García-Carrasco M, et al. Sarcoidosis or Sjögren syndrome? Clues to defining mimicry or coexistence in 59 cases. *Medicine* (Baltimore). 2004;83(2):85-95

[26] Zickuhr L, Hajj-Ali R. AB0338 Heads-up! sarcoidosis and rheumatoid arthritis co-exist. *Annals of the Rheumatic Diseases*. 2017;76:1167.

[27] Kucera, Richard F. A possible association of rheumatoid arthritis and sarcoidosis. *Chest.* 1989;95(3):604–606.

[28] Kobak Ş, Karaarslan AA, Yilmaz H, et al. Co-occurrence of rheumatoid arthritis and sarcoidosis. *BMJ Case Rep*. 2015;bcr2014208803.

[29] Alishiri G, Rahmanian E, Ramezanpour M. Coincidence of sarcoidosis with ankylosing spondylitis in a 48-year-old woman: a therapeutic challenge. *Hospital Practices and Research.* 2020;5(2):75-78.

[30] Wafa H, Saoussen M, Dhia K, et al. Sarcoidosis and spondyloarthritis: A coincidence or common etiopathogenesis? *Caspian J Intern Med.* 2018;9(1):100-103.

[31] Erb N, Cushley MJ, Kassimos DG, et al. An assessment of back pain and the prevalence of sacroiliitis in sarcoidosis. *Chest.* 2005;127(1):192-6.

[32] Kobak S, Sever F, Ince O, et al. The prevalence of sacroiliitis and spondyloarthritis in patients with sarcoidosis. *Int J Rheumatol*. 2014;2014:289454.

[33] Prieto-Peña D, Ferrer-Pargada D, Atienza-Mateo B, et al. Coexisting sarcoidosis and systemic lupus erythematosus: a case report and literature review. *Acta Reumatol Port*. 2021;46(2):177-185.

[34] Papaioannides D, Korantzopoulos P, Latsi P, et al. Systemic lupus erythematosus developing in a patient with pulmonary sarcoidosis. *Joint Bone Spine*. 2004;71:442–4.

[35] Umeki K, Sawamura D, Sugawara T. Sarcoidosis developing after stopping oral prednisolone for systemic lupus erythematosus. *Acta Derm Venereol.* 2001;81:74.

[36] Enzenauer RJ, West SG. Sarcoidosis in autoimmune disease. *Semin Arthritis Rheum*. 1992;22(1):1-17.

[37] Senda S, Igawa K, Nishioka M, et al. Systemic sclerosis with sarcoidosis: case report and review of the published work. *J Dermatol.* 2014;41(5):421-423

[38] Suga H, Asano Y, Tamaki Z, et al. A case of systemic sclerosis with sarcoidosis. *Acta Derm Venereol.* 2011;91:718-20.

[39] Nakamura K, Sato S, Asano Y. Overlapping systemic sclerosis and sarcoidosis with mutually exclusive disease activities: a case report and analysis of previous studies. *Eur J Dermatol*. 2020;30(1):50-52.

[40] Denton CP, Khanna D. Systemic sclerosis. *Lancet.* 2017;390:1685-99.