ŚPIOŁEK, Olga, SIWIEC, Jan, SŁOWIKOWSKA, Aleksandra, TEOFILAK, Mateusz, SZATKOWSKA, Julia, SMYL, Natalia, SZTYLER-KRĄKOWSKA, Marcelina, WĄSOWICZ, Agnieszka, KĘDZIORA, Franciszek and FABIAN, Dariusz. A Comprehensive Review of Sarcoidosis: From Clinical Manifestations to Management Strategies. Journal of Education, Health and Sport. 2024;75:56452 eISSN 2450-3118.
https://dx.doi.org/10.12775/JEHS.2024.75.56452
https://apcz.umk.pl/JEHS/article/view/56452

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 26.11.2024. Revised: 16.12.2024. Accepted: 17.12.2024. Published: 20.12.2024.

A Comprehensive Review of Sarcoidosis: From Clinical Manifestations to Management Strategies

Authors:

Olga Śpiołek

LUX MED Sp. z o.o., Szturmowa 2, 02-678 Warsaw, Poland

olgaspiolek@gmail.com

ORCID: 0009-0008-6271-1242

Jan Siwiec

Międzyleski Specialist Hospital in Warsaw, Bursztynowa 2, 04-749 Warsaw, Poland

jjsiwiec@gmail.com

ORCID: 0000-0002-7193-7074

Aleksandra Słowikowska

National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland

aslowikowska0108@gmail.com

ORCID: 0009-0004-3705-822X

Mateusz Teofilak

Międzyleski Specialist Hospital in Warsaw, Bursztynowa 2, 04-749 Warsaw, Poland

teofilak.mateusz@gmail.com

ORCID: 0009-0007-3902-2484

Julia Szatkowska

Hospital of Our Lady of Perpetual Help in Wołomin, Gdyńska 1/3, 05-200 Wołomin, Poland

julka.szatkowska32@gmail.com

ORCID: 0009-0007-5084-9378

Natalia Maria Smyl

John Paul II Western Hospital in Grodzisk Mazowiecki, Daleka 11, 05-825 Grodzisk Mazowiecki, Poland

nataliamaria.smyl@gmail.com

ORCID: 0009-0003-9571-3432

Marcelina Paula Sztyler-Krąkowska

Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland

marcelina.sztyler@wp.pl

ORCID: 0009-0004-4817-9537

Agnieszka Alicja Wąsowicz

National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland

agnieszkawasowicz99@gmail.com

ORCID: 0009-0008-3256-793X

Franciszek Kędziora

Medical University of Białystok, Jana Kilińskiego 1, 15-089 Białystok, Poland

fkedzior@gmail.com

ORCID: 0009-0003-7833-1985

Dariusz Paweł Fabian
Specialist Provincial Hospital in Ciechanów, Powstańców Wielkopolskich 2, 06-400 Ciechanów
Dfabianstudy@gmail.com

ORCID: 0009-0006-7241-7245

Abstract

Introduction and purpose: Sarcoidosis is a complex, multi – system disease characterized by the formation of non – caseating granulomas that can affect nearly every organ in the body, though lungs and lymph nodes are the most commonly involved. The disease's clinical presentation is highly variable, ranging from asymptomatic cases to severe, organ-threatening manifestations, with significant implications for diagnosis and treatment. The aim of this study is to present current state of knowledge on clinical features, etiology, diagnosis and treatment methods of sarcoidosis.
Materials and methods: The review is based on the analysis of literature available on Pubmed, Google Scholar and UpToDate databases. To search for relevant scientific content the following keywords were used: sarcoidosis, symptoms, etiology, diagnosis, treatment, neurosarcoidosis, cutaneous sarcoidosis, cardiac sarcoidosis, Löfgren syndrome.
Conclusions: Despite numerous studies, the cause of sarcoidosis still remains unknown, which leaves a field for researchers for further investigation. Diagnosis of sarcoidosis is challenging, it typically involves histological confirmation through biopsy, supported by imaging studies, laboratory tests and need to exclude other causes. Treatment is limited, focused on alleviating the symptoms and preventing organ failure, therefore further research into more effective or targeted therapies is advisable.

Keywords: sarcoidosis; neurosarcoidosis; pulmonary fibrosis; cardiac sarcoidosis; Löfgren syndrome

1. Introduction

Sarcoidosis is a chronic multisystem inflammatory disease that may affect almost every organ of the human body. Most commonly it affects the lungs and lymph nodes[1]. Other organs that may be involved include the heart, nervous system, joints, skin, liver and eyes, leading to a wide range of clinical symptoms. Although the clinical manifestation may vary between the patients, the common factor and most characteristic histological observation of sarcoidosis is the formation of the non – caseating granulomas. A granuloma is defined as a distinct conglomeration of immune cells, primarily consisting of epithelioid macrophages and multinucleated giant cells, surrounded by of CD4+ T cells, and in lesser amounts with CD8+ T cells and B cells. This structure forms as a result of a dysregulated immune response to an unknown environmental trigger in genetically susceptible individuals, leading to granulomatous inflammation[2]. The severity and duration of the inflammation, as well as the specific organs affected, determine the clinical manifestation of the disease. The prognosis is also variable, with potential outcomes ranging from spontaneous resolution to chronic inflammation, which may be complicated by fibrosis or associated with irreversible organ failure[3].

2. Epidemiology

Epidemiology of sarcoidosis reveals significant variations based on geographic, racial, and demographic factors. It affects individuals of all ages, but typically presents between ages 25 and 45, with a second peak in women over 50 years of age[4]. It has a higher occurrence in women and non-smokers, particularly in rural communities[5]. The disease exhibits significant variability in prevalence across Europe, with higher incidence rates observed in northern regions compared to southern areas. For example, the incidence is highest in Sweden (64/100,000), while countries like Italy report rates of less than 10/100,000. In the United Kingdom, the incidence is around 20/100,000, in Germany it is about 9/100,000, and in Spain it is only 1.4/100,000[1]. In Poland, the average annual incidence of sarcoidosis is estimated at 7.5/100,000, based on a comprehensive analysis of hospital discharge records from 2008 to 2015, which included 23,097 patients[6]. Japan has a much lower rate of 1-2 per 100,000[7]. In the United States, the incidence is notably higher among African Americans, with rates approximately three times greater than those of Caucasians, reflecting a prevalence of 35.5-64/100,000 for Caucasians and 10-14/100,000 for African Americans[1]. Moreover, the disease exhibits a heightened severity among individuals of African American descent, whereas

individuals of Caucasian ethnicity are more predisposed to exhibit asymptomatic manifestations of the disease[8]. These disparities suggest that environmental and genetic factors may play crucial roles in the disease's manifestation across different populations.

3. Etiology and risk factors

The etiology of sarcoidosis has been a topic of research in the past years, yet it still remains unknown. The dominant conclusion is that the disease results from one or more environmental factors interacting with genetic factors. Occupational exposures, such as working in agriculture, using insecticides, and staying in the environments with mold or mildew, have been linked to increased sarcoidosis risk[9]. Additionally, working in occupations related to metals and combustible products, such as firefighting, has been linked to increased sarcoidosis risk[10]. Also, obesity, but not overweight, particularly in women with a BMI over 30, is associated with a higher likelihood of developing the disease[11]. What is interesting, current smoking appears to have a protective effect against sarcoidosis, while former smoking or non-ever smoking is linked to increased risk[12]. It is possibly since smoking inhibits function of T-lymphocytes and phagocytic activity of macrophages - its anti-inflammatory effect contributes to lowering the risk of sarcoidosis, which is a highly inflammatory disease[13]. Genetic factors also play a significant role, with familial aggregation studies indicating a heritability of 39%[14]. Furthermore, the presence of certain human leukocyte antigen (HLA) alleles can serve as predictive markers for the disease's clinical course, highlighting the role of genetic predisposition in sarcoidosis. For instance, the HLA-DRB1*04/*15 are linked to cardiovascular sarcoidosis, HLA-DRB1*04 is linked to uveitis, HLA-DRB1*03 and HLA-DQB1*0201 are associated with Löfgren's syndrome, which indicates shorter duration of the disease and favorable prognosis, while alleles HLA-DRB1*15 and HLA-DQB1*0601 relate to chronic sarcoidosis[15]. Overall, these findings suggest that sarcoidosis may arise from a complex interaction of environmental, lifestyle, and genetic factors.

4. Clinical manifestation

Clinical picture of sarcoidosis varies significantly between patients. It is estimated that 30-50% of patients will present with asymptomatic course of the disease[8]. This often leads to incidental findings during imaging studies, such as chest X-rays or computed tomography (CT) scans, which are performed for unrelated reasons[16]. The disease presents with variety of general symptoms and may be easily confused with other medical issues. For instance, fatigue, which affects up to 90% of symptomatic patients is often linked to other conditions, such as anxiety

and depression[17]. Other common constitutional symptoms include low-grade fever, weight loss, night sweats and lymphadenopathy. Additionally, patients may experience concentration disturbances, which can be attributed to comorbidities like sleep apnea[18].

In some patients very characteristic and acute onset can be observed, which is called Löfgren syndrome. It is characterized by a triad of symptoms: bilateral hilar lymphadenopathy, erythema nodosum, and arthritis with joint pain. It typically presents with fever[18,19]. Prognosis of this acute presentation of sarcoidosis is favourable, with many patients experiencing resolution of symptoms within two years[20]. Another rare but very characteristic manifestation of sarcoidosis is Heerfordt's syndrome, which is considered as its subacute variant. The classic presentation includes facial nerve palsy, painless enlargement of the parotid glands, anterior uveitis, and low-grade fever[21].

4.1. Pulmonary Sarcoidosis

Lungs are the most common organs affected by the disease, with approximately 90% of patients affected at some stage[22]. Symptoms are diverse and range from mild to severe, with the most frequent manifestations being dry cough, dyspnea, chest discomfort, and shortness of breath. These symptoms are observed in 30–50% of patients[23]. The severity of pulmonary sarcoidosis can vary from incidental radiographic abnormalities in asymptomatic individuals to chronic, progressive disease resistant to treatment. Pulmonary fibrosis, which develops in 20-25% of patients, is a significant concern, as it is associated with impaired lung function, extensive disease visible on high-resolution chest CT, and pulmonary hypertension—factors that are strong predictors of poor clinical outcomes[23,24]. Respiratory failure is the leading cause of death in patients with sarcoidosis. While thoracic radiologic abnormalities are present in 90% of patients, chest auscultation is often unremarkable, even in the presence of extensive infiltrates, and finger clubbing is rare[19,23]. Additionally, pulmonary symptoms are non-specific and can be easily mistaken for other respiratory conditions, such as asthma or chronic bronchitis[25]. As such, the diagnosis of pulmonary sarcoidosis can be challenging, particularly in the absence of prominent symptoms.

4.2. Extrapulmonary sarcoidosis

Sarcoidosis can manifest in various organs beyond the lungs, with skin involvement being the most common, affecting up to one-third of patients. Other frequent sites include the eyes, liver, and joints, followed by heart, nervous system, often leading to significant complications if untreated[26].

4.2.1. Cutaneous sarcoidosis

Lesions that can be observed on the skin include small purplish papules, plaques, and subcutaneous nodules. Erythema nodosum is the most frequent cutaneous manifestation, usually linked with acute sarcoidosis - it is characterized by painful, red nodules typically found on the calves. Itis not associated with granulomas and usually resolves within 6-8 weeks[8]. In contrast, lupus pernio, an indurated bluish discoloration, primarily affecting the nose and cheeks, is linked to a chronic course and poor prognosis[27]. In some cases, sarcoidosis can also lead to inflammation and granulomas formation in scar tissue or to granulomatous vasculitis[27,28]. The frequency and severity of skin involvement vary significantly among different ethnic groups, with African-Americans experiencing more severe manifestations compared to Caucasians[29].

4.2.2. Ocular sarcoidosis

This condition can affect many different ocular structures, leading to a range of clinical presentations. Uveitis is the most common manifestation, which can be anterior, intermediate or posterior uveitis. Anterior uveitis is characterized by symptoms such as eye pain, redness, and photophobia, often accompanied by mutton-fat keratic precipitates and iris nodules[30]. Intermediate uveitis may present with floaters and blurred vision, while posterior uveitis can lead to more severe complications like retinal vasculitis and macular edema[31]. Other ocular manifestations include conjunctival nodules, dry eye syndrome, and the most severe form of this condition - optic nerve involvement[32]. It can manifest as optic neuropathy, characterized by symptoms such as optic disc edema and potential optic atrophy if untreated, which can result in vision loss[30].

4.2.3. Cardiac sarcoidosis

In this severe manifestation of systemic sarcoidosis granulomatous inflammation affects all three layers of the heart, with a predominant involvement of the myocardium[4]. Symptoms can include cardiomyopathy, arrhythmia, shortness of breath, syncope, and palpitations. Advanced cases may lead to atrioventricular block, reduced left ventricular ejection fraction (<50%), and heart failure[4,19]. While 25% of sarcoidosis patients experience subclinical cardiac involvement, around 5% show clinical signs of heart damage, with another 30% exhibiting asymptomatic cardiac involvement[33,34]. Life threatening complications include myocardial infarction, ventricular arrythmias, which contribute to poor prognosis and can cause a sudden cardiac death[4].

4.2.4. Abdominal sarcoidosis

Sarcoidosis can manifest in various gastrointestinal organs, with the stomach being the most commonly affected. Symptoms often include epigastric pain, early satiety, and potential upper gastrointestinal bleeding due to ulcerations or antral narrowing caused by granulomatous infiltration. Esophageal involvement is rare, but when it occurs, it can lead to symptoms such as dysphagia and weight loss due to dysmotility or mechanical obstruction from granulomatous infiltration or lymphadenopathy. The condition may manifest as esophageal strictures or thickening, which can be observed through imaging techniques like barium swallow studies. The small intestine is the least commonly involved, presenting with diarrhoea and malabsorption[35]. Liver involvement is more frequent, with granulomas leading to conditions such as portal hypertension or cholestatic syndromes causing pruritus and jaundice[20,35,36]. Imaging studies, such as CT scans, often reveal hepatosplenomegaly and low-attenuation lesions in the liver[37].

4.2.5. Neurosarcoidosis

Neurosarcoidosis can present with a variety of neurological symptoms, often including cranial neuropathies, with facial nerve involvement being the most common, occurring in approximately 70% of cases. Other cranial nerves, such as the optic and vestibulocochlear nerves, may also be affected, leading to visual disturbances and hearing loss, respectively[38]. Patients may experience symptoms like headache, seizures, and cognitive dysfunction due to meningeal involvement[39]. Additionally, myelopathy is reported in up to 26% of patients, characterized by longitudinally extensive myelitis and associated imaging findings[39,40].

5. Diagnosis

The heterogeneity of presentation and disease course can make diagnosis and treatment challenging. The diagnosis of sarcoidosis is based on three primary criteria: a compatible clinical presentation, histological evidence of noncaseating granulomas, and the exclusion of other diseases that can cause similar histological or clinical features[2,8,41]. A multidisciplinary approach is essential, and many diagnostic tools may be effective and helpful in establishing the correct diagnosis.

5.1. Biopsy

The diagnosis of sarcoidosis typically requires histological confirmation through the presence of noncaseating granulomas obtained via biopsy. The selection of an appropriate

biopsy site is crucial. Biopsy of intrathoracic lymph nodes or lung parenchyma is typically preferred, as these areas are involved in over 95% of sarcoidosis cases and are more accessible, posing fewer risks compared to other internal organs such as the liver or kidneys[26]. Various methods for obtaining the lymph nodes can be used, including transbronchial lung biopsy (TBLB) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), with EBUS-TBNA showing a higher diagnostic yield compared to TBLB (80% vs. 53%) for detecting granulomas[42]. Moreover, some less invasive and easily accessible lesions, including rashes, conjunctival nodules, enlarged superficial lymph nodes, and lacrimal glands, may also serve as biopsy sites[26]. When cardiac sarcoidosis is suspected, endomyocardial biopsy can also be conducted. This method is a golden standard for detecting cardiac sarcoidosis, however a lot of false - negative results are obtained[4]. It is important to note that for patients presenting with Löfgren's syndrome, lupus pernio, or Heerfordt's syndrome—sampling of lymph nodes is generally not recommended, and the diagnosis can be made relying on the characteristic clinical picture[2]. While biopsy is generally sufficient for diagnosing sarcoidosis, it is important to remember that the presence of noncaseating granulomas on biopsy is not specific to sarcoidosis, as similar granulomas may be observed in other diseases[26].

5.2. Medical imaging

Radiologically, chest X-rays often reveal bilateral hilar adenopathy, which is a common initial finding in approximately 50% of cases, alongside pulmonary infiltrates that may progress to fibrosis in advanced stages[8]. The presence of these radiographic features, particularly in asymptomatic patients, can support the diagnosis, although definitive confirmation typically requires histological examination to exclude other granulomatous diseases[2,38].

High-resolution computed tomography (HRCT) is more sensitive than standard chest radiography in detecting pulmonary involvement. It can detect more subtle changes and assess the extent of pulmonary involvement more accurately[8,43]. HRCT is indicated when there is a clinical suspicion of the disease despite normal chest radiographs or when complications such as bronchiectasis or pulmonary fibrosis are suspected[8]. HRCT can reveal characteristic patterns such as nodular infiltrates with a bronchovascular and subpleural distribution, mediastinal lymphadenopathy and thickened interlobular septa, aiding in the identification of asymptomatic disease and guiding biopsy sites for histological confirmation[8,16,43].

Magnetic resonance imaging (MRI) is used most often in assessing cardiac and neurological involvement. In neurosarcoidosis, it can detect lesions in the brain and meninges. The findings often include multiple non-enhancing white matter lesions that may resemble

those seen in multiple sclerosis, making differentiation challenging[18]. Additionally, MRI can reveal abnormalities in the pituitary gland and spinal cord, with specific patterns such as the "trident sign" indicating sarcoidosis-associated myelopathy[18,26]. In cardiac sarcoidosis, MRI findings typically include multifocal areas of late gadolinium enhancement, indicating myocardial fibrosis, primarily located in the epicardial and mid-myocardial regions[26].

5.3. Laboratory findings

In sarcoidosis, laboratory abnormalities are not specific to the disease and provide limited diagnostic insight. Common findings include anemia, leukopenia, and an elevated erythrocyte sedimentation rate[2]. Serum angiotensin-converting enzyme (ACE) levels are often raised and are used by some clinicians to track treatment response[44]. Hypercalcemia is also notable due to the dysregulated metabolism of vitamin D, with macrophages in granulomas producing excessive 1,25-dihydroxyvitamin D[20]. It can lead to hypercalciuria and associated renal complications, including nephrocalcinosis and renal failure, particularly if left untreated[2]. Additionally, serum levels of soluble interleukin-2 receptor (sIL-2r) have emerged as a more sensitive biomarker, correlating with disease activity and multisystem involvement[45]. Overall, laboratory findings in sarcoidosis require careful interpretation within the broader clinical context, as they are usually not pathognomonic.

6. Treatment

The treatment approach should be personalized, considering the severity of the disease and the patient's quality of life[46]. Many cases are self – limiting: approximately 50% of individuals with sarcoidosis may not require treatment, as their condition can resolve without intervention, particularly in cases with limited organ involvement[47,48]. However, about 10-30% of patients may develop chronic, unremitting disease, leading to complications such as pulmonary fibrosis and respiratory failure[48]. The treatment approach mainly focuses on alleviating symptoms and preventing organ damage[49].

Glucocorticoids, particularly prednisone, are the first-line treatment for sarcoidosis. They are effective in reducing inflammation and controlling the immune response associated with granuloma formation[17,50]. Their mail role is to provide significant symptomatic relief and improve lung function. The initial treatment often involves a high dose of corticosteroids (20-40 mg per day), with a gradual tapering to lower maintenance doses (5-10 mg per day) to minimize side effects associated with long-term use[47,49]. Long-term use of corticosteroids can

lead to significant side effects, including osteoporosis, hypertension, and diabetes, necessitating careful monitoring and management[17,51].

In cases where patients do not respond adequately to glucocorticoids or experience intolerable side effects, alternative immunosuppressive agents may be considered. These include methotrexate, azathioprine, and cyclophosphamide, which can serve as steroid-sparing agents[17,43]. In comparative studies, methotrexate has demonstrated similar efficacy to azathioprine but with less associated toxicity[30,46]. The mechanism of action of methotrexate involves the inhibition of folate metabolism, which is crucial for the proliferation of lymphocytes and the production of inflammatory cytokines. This action helps to modulate the immune response, thereby reducing the inflammatory processes associated with sarcoidosis[47]. Despite its benefits, the use of methotrexate is not without risks. Patients may experience side effects such as gastrointestinal disturbances, liver toxicity, and bone marrow suppression. Therefore, regular monitoring of liver function tests and complete blood counts is recommended every 1-3 months during treatment[50].

Tumor necrosis factor (TNF) inhibitors, such as infliximab and adalimumab, have been utilized as third-line treatments for refractory sarcoidosis. They are effective with both pulmonary and extrapulmonary manifestations, especially in cases involving the skin and eyes. The use of TNF inhibitors requires careful monitoring due to potential complications, and the most common side effects include increased susceptibility to infections and allergic reactions[43,46,48,49].

7. Conclusions

Diagnosis of sarcoidosis still remains a challenge, particularly due to the rarity of disease and its heterogeneous clinical course. The disease can affect different organs and therefore multidisciplinary approach is recommended to ensure effective patient care. However, despite extensive research, treatment is not standardized and focuses only on alleviating the symptoms and preventing complications of chronic granulomatous inflammation. Further research is necessary to improve clinical protocols and produce higher-quality evidence for treatment strategies.

Disclosure

Author's contribution

Conceptualization: Olga Śpiołek, Jan Siwiec; methodology: Aleksandra Słowikowska, Marcelina Sztyler - Krąkowska, Natalia Smyl, Dariusz Fabian; formal analysis: Julia

Szatkowska, Franciszek Kędziora, Agnieszka Wąsowicz; check: Natalia Smyl, Mateusz Teofilak, Marcelina Sztyler - Krąkowska; formal analysis: Julia Szatkowska; investigation: Franciszek Kędziora; resources: Olga Śpiołek, Mateusz Teofilak; writing - rough preparation: Olga Śpiołek, Jan Siwiec, Aleksandra Słowikowska, Julia Szatkowska, Natalia Smyl; writing - review and editing: Franciszek Kędziora, Dariusz Fabian, Agnieszka Wąsowicz, Marcelina Sztyler - Krąkowska; visualization: Agnieszka Wąsowicz; supervision: Olga Śpiołek, Jan Siwiec; project administration: Olga Śpiołek.

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflict of Interest Statement: All authors declare no conflict of interest.

References:

1. Jain R, Yadav D, Puranik N, Guleria R, Jin JO. Sarcoidosis: Causes, diagnosis, clinical features, and treatments. *J Clin Med*. 2020;9(4). https://doi.org/10.3390/jcm9041081

2. Crouser ED, Maier LA, Baughman RP, et al. Diagnosis and Detection of Sarcoidosis An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2020;201(8):E26-E51. https://doi.org/10.1164/RCCM.202002-0251ST

3. Drent M, Crouser ED, Grunewald J. Challenges of Sarcoidosis and Its Management. *New England Journal of Medicine*. 2021;385(11):1018-1032. https://doi.org/10.1056/nejmra2101555

4. Shah HH, Zehra SA, Shahrukh A, et al. Cardiac sarcoidosis: a comprehensive review of risk factors, pathogenesis, diagnosis, clinical manifestations, and treatment strategies. *Front Cardiovasc Med*. 2023;10. https://doi.org/10.3389/fcvm.2023.1156474

5. Arkema E V., Cozier YC. Epidemiology of sarcoidosis: current findings and future directions. *Ther Adv Chronic Dis*. 2018;9(11):227-240. https://doi.org/10.1177/2040622318790197

6. Bogdan M, NitschOsuch A, Kanecki K, et al. Sarcoidosis among hospitalized patients in Poland: A study based on a national hospital registry. *Pol Arch Intern Med*. 2019;129(9):580-585. https://doi.org/10.20452/pamw.14927

7. Morimoto T, Azuma A, Abe S, et al. Epidemiology of sarcoidosis in Japan. *European Respiratory Journal*. 2008;31(2):372-379. https://doi.org/10.1183/09031936.00075307

8. Costabel U. Sarcoidosis: clinical update. *Eur Respir J Suppl*. 2001;32:56s-68s. http://www.ncbi.nlm.nih.gov/pubmed/11816825

9. Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis: Environmental and occupational risk factors. *Am J Respir Crit Care Med*. 2004;170(12):1324-1330. https://doi.org/10.1164/rccm.200402-249OC

10. Prezant DJ, Dhala A, Goldstein A, et al. The incidence, prevalence, and severity of sarcoidosis in New York City firefighters. *Chest*. 1999;116(5):1183-1193. https://doi.org/10.1378/chest.116.5.1183

11. Dumas O, Boggs KM, Cozier YC, Stampfer MJ, Camargo CA. Prospective study of body mass index and risk of sarcoidosis in US women. *European Respiratory Journal*. 2017;50(4):1701397. https://doi.org/10.1183/13993003.01397-2017

12. Dehara M, Sachs MC, Arkema E V., Grunewald J, Blomberg A. Modifiable lifestyle risk factors for sarcoidosis: a nested case–control study. *ERJ Open Res*. 2023;9(2). https://doi.org/10.1183/23120541.00492-2022

13. Hodge S, Hodge G, Ahern J, Jersmann H, Holmes M, Reynolds PN. Smoking alters alveolar macrophage recognition and phagocytic ability: Implications in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2007;37(6):748-755. https://doi.org/10.1165/rcmb.2007-0025OC

14. Rossides M, Grunewald J, Eklund A, et al. Familial aggregation and heritability of sarcoidosis: A Swedish nested case-control study. *European Respiratory Journal*. 2018;52(2). https://doi.org/10.1183/13993003.00385-2018

15. Starshinova AA, Malkova AM, Basantsova NY, et al. Sarcoidosis as an Autoimmune Disease. *Front Immunol*. 2020;10. https://doi.org/10.3389/fimmu.2019.02933

16. Mañá J, Rubio-Rivas M, Villalba N, et al. Multidisciplinary approach and long-term follow-up in a series of 640 consecutive patients with sarcoidosis. *Medicine (United States)*. 2017;96(29). https://doi.org/10.1097/MD.0000000000007595

17. Baughman RP, Valeyre D, Korsten P, et al. ERS clinical practice guidelines on treatment of sarcoidosis. *European Respiratory Journal*. 2021;58(6). https://doi.org/10.1183/13993003.04079-2020

18. Sève P, Pacheco Y, Durupt F, et al. Sarcoidosis: A clinical overview from symptoms to diagnosis. *Cells*. 2021;10(4). https://doi.org/10.3390/cells10040766

19. S.F. da Silva I, Costa Silva R, Sopa I, Peixoto L. Clinical Manifestations of Sarcoidosis. In: *Sarcoidosis - Diagnosis, Research, and Therapy of a Granulomatous Disease of Unknown Etiology [Working Title]*. IntechOpen; 2023. https://doi.org/10.5772/intechopen.1002282
20. Sanchez M, Haimovic A, Prystowsky S. Sarcoidosis. *Dermatol Clin*. 2015;33(3):389-416. https://doi.org/10.1016/j.det.2015.03.006
21. Denny MC, Fotino AD. The Heerfordt-Waldenström Syndrome as an Initial Presentation of Sarcoidosis. *Baylor University Medical Center Proceedings*. 2013;26(4):390-392. https://doi.org/10.1080/08998280.2013.11929014
22. Criado E, Sánchez M, Ramírez J, et al. Pulmonary sarcoidosis: Typical and atypical manifestations at high- resolution CT with pathologic correlation. *Radiographics*. 2010;30(6):1567-1586. https://doi.org/10.1148/rg.306105512
23. Spagnolo P, Rossi G, Trisolini R, Sverzellati N, Baughman RP, Wells AU. Pulmonary sarcoidosis. *Lancet Respir Med*. 2018;6(5):389-402. https://doi.org/10.1016/S2213-2600(18)30064-X
24. Abehsera M, Valeyre D, Grenier P, Jaillet H, Battesti JP, Brauner MW. Sarcoidosis with Pulmonary Fibrosis. *American Journal of Roentgenology*. 2000;174(6):1751-1757. https://doi.org/10.2214/ajr.174.6.1741751
25. Judson MA, Thompson BW, Rabin DL, et al. The diagnostic pathway to sarcoidosis. *Chest*. 2003;123(2):406-412. https://doi.org/10.1378/chest.123.2.406
26. Ungprasert P, Ryu JH, Matteson EL. Clinical Manifestations, Diagnosis, and Treatment of Sarcoidosis. *Mayo Clin Proc Innov Qual Outcomes*. 2019;3(3):358-375. https://doi.org/10.1016/j.mayocpiqo.2019.04.006
27. Marcoval J, Mañá J, Rubio M. Specific cutaneous lesions in patients with systemic sarcoidosis: Relationship to severity and chronicity of disease. *Clin Exp Dermatol*. 2011;36(7):739-744. https://doi.org/10.1111/j.1365-2230.2011.04128.x
28. Wei CH, Huang YH, Shih YC, Tseng FW, Yang CH. Sarcoidosis with cutaneous granulomatous vasculitis. *Australasian Journal of Dermatology*. 2010;51(3):198-201. https://doi.org/10.1111/j.1440-0960.2010.00630.x
29. Schupp JC, Freitag-Wolf S, Bargagli E, et al. Phenotypes of organ involvement in sarcoidosis. *European Respiratory Journal*. 2018;51(1). doi:10.1183/13993003.00991-2017
30. Baughman RP, Lower EE, Kaufman AH. Ocular sarcoidosis. *Semin Respir Crit Care Med*. 2010;31(4):452-462. https://doi.org/10.1055/s-0030-1262213
31. Pasadhika S, Rosenbaum JT. Ocular Sarcoidosis. *Clin Chest Med*. 2015;36(4):669-683. https://doi.org/10.1016/j.ccm.2015.08.009

32. Takase H. Characteristics and management of ocular sarcoidosis. *Immunol Med*. 2022;45(1):12-21. https://doi.org/10.1080/25785826.2021.1940740

33. Roberts WC, McAllister HA, Ferrans VJ. Sarcoidosis of the heart. *Am J Med*. 1977;63(1):86-108. https://doi.org/10.1016/0002-9343(77)90121-8

34. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *New England Journal of Medicine*. 2007;357(21):2153-2165. https://doi.org/10.1056/NEJMra071714

35. Ebert EC, Kierson M, Hagspiel KD. Gastrointestinal and hepatic manifestations of sarcoidosis. *American Journal of Gastroenterology*. 2008;103(12):3184-3192. https://doi.org/10.1111/j.1572-0241.2008.02202.x

36. Hena KM. Sarcoidosis Epidemiology: Race Matters. *Front Immunol*. 2020;11. https://doi.org/10.3389/fimmu.2020.537382

37. Gezer NS, Başara I, Altay C, et al. Abdominal sarcoidosis: Cross-sectional imaging findings. *Diagnostic and Interventional Radiology*. 2015;21(2):111-117. https://doi.org/10.5152/dir.2014.14210

38. Kidd DP. Neurosarcoidosis: Clinical manifestations, investigation and treatment. *Pract Neurol*. 2020;20(3):199-212. https://doi.org/10.1136/practneurol-2019-002349

39. Bradshaw MJ, Pawate S, Koth LL, Cho TA, Gelfand JM. Neurosarcoidosis: Pathophysiology, Diagnosis, and Treatment. *Neurology(R) neuroimmunology & neuroinflammation*. 2021;8(6). https://doi.org/10.1212/NXI.0000000000001084

40. Joubert B, Chapelon-Abric C, Biard L, et al. Association of prognostic factors and immunosuppressive treatment with long-term outcomes in neurosarcoidosis. *JAMA Neurol*. 2017;74(11):1336-1344. https://doi.org/10.1001/jamaneurol.2017.2492

41. Rossides M, Darlington P, Kullberg S, Arkema E V. Sarcoidosis: Epidemiology and clinical insights. *J Intern Med*. 2023;293(6):668-680. doi:10.1111/joim.13629

42. von Bartheld MB, Dekkers OM, Szlubowski A, et al. Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis. *JAMA*. 2013;309(23):2457. https://doi.org/10.1001/jama.2013.5823

43. Ibitoye RT, Wilkins A, Scolding NJ. Neurosarcoidosis: a clinical approach to diagnosis and management. *J Neurol*. 2017;264(5):1023-1028. https://doi.org/10.1007/s00415-016-8336-4

44. Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic Utility of Angiotensin-Converting Enzyme in Sarcoidosis: A Population-Based Study. *Lung*. 2016;194(1):91-95. https://doi.org/10.1007/s00408-015-9826-3

45. Grutters JC, Fellrath JM, Mulder L, Janssen R, van den Bosch JMM, van Velzen-Blad H. Serum Soluble Interleukin-2 Receptor Measurement in Patients With Sarcoidosis. *Chest*. 2003;124(1):186-195. https://doi.org/10.1378/chest.124.1.186

46. Wijsenbeek MS, Culver DA. Treatment of Sarcoidosis. *Clin Chest Med*. 2015;36(4):751-767. doi:10.1016/j.ccm.2015.08.015

47. Gerke AK. Treatment of Sarcoidosis: A Multidisciplinary Approach. *Front Immunol*. 2020;11. https://doi.org/10.3389/fimmu.2020.545413

48. Obi ON, Saketkoo LA, Russell AM, Baughman RP. Sarcoidosis: Updates on therapeutic drug trials and novel treatment approaches. *Front Med (Lausanne)*. 2022;9. https://doi.org/10.3389/fmed.2022.991783

49. Baughman RP, Lower EE. Treatment of Sarcoidosis. *Clin Rev Allergy Immunol*. 2015;49(1):79-92. https://doi.org/10.1007/s12016-015-8492-9

50. James WE, Baughman R. Treatment of sarcoidosis: grading the evidence. *Expert Rev Clin Pharmacol*. 2018;11(7):677-687. https://doi.org/10.1080/17512433.2018.1486706

51. Kampstra NA, Van Der Nat PB, Dijksman LM, et al. Results of the standard set for pulmonary sarcoidosis: Feasibility and multicentre outcomes. *ERJ Open Res*. 2019;5(4). https://doi.org/10.1183/23120541.00094-2019