MADEJ, Aleksandra, SENAT, Hanna, GRABOWSKA, Patrycja, BOLLA, Patrycja, SENAT, Aleksandra and MARCZYŃSKA, Zuzanna. Sarcoidosis. A review of diagnosis, clinical features and treatment. Journal of Education, Health and Sport. 2024;56:97-111. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.56.007
https://apcz.umk.pl/JEHS/article/view/47957
https://zenodo.org/records/10614612

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
Received: 10.01.2024. Revised: 27.01.2024. Accepted: 04.02.2024. Published: 04.02.2024.

Sarcoidosis. A review of diagnosis, clinical features and treatment

1. Aleksandra Madej MD, ORCID: 0009-0006-7757-8363, University Hospital, Zyty 26, 65-046 Zielona Gora, Poland, aleksandmad@gmail.com
2. Hanna Senat MD, ORCID: 0009-0009-3862-5827, Miedziowe Centrum Zdrowia S.A. Marii Skłodowskiej - Curie 66, 59-300 Lubin, hannasenat1@gmail.com
3. Patrycja Grabowska MD, ORCID: 0009-0000-3171-2746, Voivodeship Specialist Hospital of the NMP, Bialska 104/118, 42-202 Czestochowa, Poland grabowska0903@gmail.com
4. Patrycja Bolla MD, ORCID: 0009-0009-6118-2104, Faculty of Medicine, Wroclaw Medical University, Wybrzeze L. Pasteura 1, 50-367, Wroclaw, Poland, patrycjabolla@gmail.com
5. Aleksandra Senat, ORCID: 0009-0000-2523-4370, Faculty of Medicine, Wroclaw Medical University, Wybrzeze L. Pasteura 1, 50-367, Wroclaw, Poland, ola.senat@gmail.com
6. Zuzanna Marczyńska MD, ORCID: 0009-0007-5162-9836, Faculty of Medicine, Wroclaw Medical University, Wybrzeze L. Pasteura 1, 50-367, Wroclaw, Poland, zuzia.marczynska@gmail.com

Corresponding author
Aleksandra Madej MD,
+48-790212058, aleksandmad@gmail.com
University Hospital, Zyty 26, 65-046 Zielona Gora

ABSTRACT

Introduction: Sarcoidosis is a progressive chronic multisystemic inflammatory disease of unclear pathogenesis, which presents with noncaseating granulomas and is complicated to diagnose due to the variable clinical presentation of patients. Sarcoidosis may attack any organ, but especially the pulmonary, cutaneous, lymphatic, ocular, hepatic and splenic systems. The most frequent presentations are prolonged cough, rash, visual problems, peripheral lymphadenopathy, tiredness, and occasional abnormality of the chest X-ray. The diagnostic evaluation of sarcoidosis is difficult and often involves a combined effort of clinical data and appropriate imaging modalities.

Purpose: The purpose of this article is to review the available literature on the epidemiology, clinical manifestations and management of patients with sarcoidosis

Materials and method: The available literature in PubMed was reviewed to write the article, using the keywords ,,sarcoidosis", ,,cardiac sarcoidosis", ,,pulmonary sarcoidosis" and ,,cutaneous sarcoidosis".

Conclusion: Sarcoidosis is associated with a significant increase in patient mortality, as well as decreased quality of life and physical disability. Efforts to accurately predict disease progression allow for more comprehensive and personalized patient care. As a life threatening disease, sarcoidosis needs to be diagnosed early and treated appropriately.

Keywords: sarcoidosis, cardiac sarcoidosis, positron emission tomography, granuloma, epidemiology

1. Introduction:

Sarcoidosis refers to a multisystem systemic inflammatory disease of unclear etiology associated with the occurrence of non-necrotizing granulomas in various organs. It was first reported in 1889 by Besnier et al. Although sarcoidosis is still a disorder of uncertain etiology, the underlying molecular mechanisms of granuloma formation, such as genetic predisposition and environmental influences, are becoming better understood (1,2,3,4).

The unknown pathogenesis and the multisystem nature of the disorder have added to its complexity. Earlier data suggest that in at least 90% of patients with sarcoidosis, pulmonary manifestations are present. Apart from the lungs, it has been shown that the skin, liver, spleen, lymph nodes, respiratory tract, the heart and the central nervous system are also affected, accounting approximately for 10-30% of the disease. It occurs globally and has been described in all races and ethnics. There is no racial, gender, or age group that is resistant to sarcoidosis (5,6,7,8).

Symptoms of sarcoidosis vary according to the organ affected. Sarcoidosis can have a variety of clinical manifestations, from subtle to lethal. The pathogenesis of the disorder is unclear, but several reports have suggested that an unknown antigen that is processed by active macrophages triggers an immune response that is controlled by T cells and macrophages. The activated cells secrete different mediators, among them cytokines, chemokines and reactive oxygen species, which might be related to the progress of sarcoidosis. Numerous studies indicate that not only unidentified antigens, but genetic predisposition, environmental factors and, in some cases, autoimmune activation may be responsible for this disease (9,10,11,12).

There are two distinct courses of sarcoidosis: a transient course (in which 2/3 of patients develop a remission within 12-36 months) and a chronic phase (in which 10-30 % of patients will need long-term therapy) (13,14). Systemic treatment is often indicated for advanced life-threatening organ damage (pulmonary fibrosis, pulmonary hypertension, central nervous system (CNS) sarcoidosis, cardiac sarcoidosis, portal hypertension, etc.) or severe or disabling skin disease, laryngeal involvement, and/or posterior segment uveitis (15,16). Ethnic origin (especially African American and Afro-Caribbean), age older than 40 years at onset, systemic lupus erythematosus, chronic uveitides, sine and osseous lesions, CNS lesions, cardiac disease, massive hypercalcemia, nephrocalcinosis, and x-ray stages III and IV are related to a worse outcome (17).

Sarcoidosis patients have a lower average life expectancy compared to the population at large (18,19). In developed countries, the majority of sarcoidosis mortality occurs due to progressive pulmonary fibrosis resulting in lung failure, pulmonary hypertension as well as both, and less frequently due to cardiac and CNS sarcoidosis or portal hypertension (16,20,21).

2. Purpose: The purpose of this article is to review the available literature on the epidemiology, clinical manifestations, and management of patients with sarcoidosis

3. Materials and method: The available literature in PubMed was reviewed to write the article, using the keywords ,,sarcoidosis", ,,cardiac sarcoidosis", ,,pulmonary sarcoidosis" and ,,cutaneous sarcoidosis".

4. Epidemiology

The global incidence and frequency of sarcoidosis are not well documented because of the difficulties involved in determining the asymptomatic population. Sarcoidosis occurs in people of all ages, regardless of race or ethnicity, with a peak occurrence in those 20-39 years of age and a significantly higher incidence in women, non-smokers and in the countryside. A higher incidence of the condition has been reported in northern Europe (approximately 60 per 100,000) than in southern European countries, (<10 per 100,000) (22,23,24). The most frequent comorbid diseases in sarcoidosis patients are hyperlipidemia, overweight, thyroid

disorders, Diabetes mellitus, osteoporosis, chronic coronary heart disease, asthma, hypertension, chronic renal disease and chronic obstructive pulmonary disease (COPD). It is also commonly found in patients with some types of autoimmune disorders, among them autoimmune thyroid disorders, Sjögren's syndrome, rheumatoid arthritis and systemic sclerosis (25,26,27,28).

5. Etiology

Several investigations have suggested that genetic factors may be important in determining the risk and clinical course of sarcoidosis. To date, eleven sarcoidosis risk loci such as BTNL2, HLA-B, HLA-DPB1, ANXA11, IL23R, SH2B3/ATXN2, IL12B, NFKB1/MANBA, FAM177B, chromosome 11q13.1 and RAB23 have been reported (29,30).

Different types of environmental exposures, including wood stove, soil, tree pollen, inorganic particulate matter, insecticides, and nanoparticles, have been linked to an enhanced risk of incident sarcoidosis. Besides these, some occupational groups, such as hardware, yard and construction workers, metalworkers, naval personnel, firefighters, and teachers, are susceptible to sarcoidosis. Respirable silica exposure has also been suspected to trigger the onset of sarcoidosis (31,32,33,34).

Apart from all the previously mentioned factors, it has been suggested that pathogens such as mycobacteria may be involved in the pathogenesis of sarcoidosis, since granuloma formation is a major component of the immune response to these pathogens. Numerous microbial agents have been reported as potential inducers of the immune response in sarcoidosis, among them Leptospira species, Mycoplasma species, herpes virus, retrovirus, Chlamydia pneumoniae, Borrelia burgdorferi, Pneumocystis jirovecii, Mycobacterium. Patients receiving interferon α treatment for hepatitis C infection have been reported to develop sarcoidosis. Some research has indicated that hepatitis C infection alone may be associated with an increased risk of incident sarcoidosis. More likely, however, is that interferon α therapy may induce increased expression of interferon-γ and interleukin-2, thereby promoting granuloma development and sarcoidosis (35,36,37,38,39,40).Autoimmunity has not been studied as extensively but given the underlying pathological mechanism of sarcoidosis there is certainly potential for these conditions to play a contributing role in disease development.

A further major component of auto-immunity is the imbalance of the gut microbiota. There is overlap between sarcoidosis and other autoimmune diseases such as rheumatoid arthritis, autoimmune thyroid disease, Sjögren's syndrome and ankylosing spondylitis. Previous studies have investigated the importance of the microbiota in the pathogenesis of these autoimmune diseases; therefore, studying the microbiota of sarcoidosis patients and its association with other conditions may provide new opportunities for research into the mechanisms that underlie sarcoidosis (41,42).

6. Diagnosis

A variety of imaging modalities are used for diagnosis. Lung lesions are well visualized on a traditional chest x-ray. Abdominal organs and superficial lymph nodes may be seen with ultrasound. High-resolution computed tomography (HRCT) is an excellent tool for detecting lung invasion and mediastinal lymph node involvement, but at the expense of ionizing radiation exposure. There is often a mismatch between findings and functional limitation. Although HRCT may demonstrate diffuse lung involvement (especially of the fine-nodular type), lung function is frequently only slightly reduced. Magnetic resonance imaging (MRI) is useful for the identification and monitoring of cardiac and central nervous system (CNS) disease. Another option is 18F-FDG PET, which shows evidence of ongoing inflammation throughout all of the organs in which it is located(43,44).

It is generally agreed that an initially suspected sarcoidosis diagnosis must be biopsy-confirmed, as subsequent therapy often complicates confirmation, and it may not be possible to assess the possible need for further treatment. Pulmonary biopsy is the most widely used method because of the high prevalence of pulmonary involvement and the ease of access provided by bronchoscopy. The mediastinal lymph nodes are well accessible for biopsy by ultrasound-guided fine-needle aspiration (EBUS) (45).

7. Clinical features

The diagnosis of sarcoidosis is commonly made when abnormalities are found on a chest X-ray during a routine examination (occurring in up to almost 50% of the patients). Different stages of sarcoidosis have been described based on the

appearance of pulmonary infiltrates and/or lymphadenopathies on the chest radiograph. The symptoms are typically mild and non-specific, such as cough, dyspnea, chest pain, shortness of breath, and mild fever. Common systemic symptoms include tiredness, decreased body weight, and excessive night sweating. Coughing up blood is rarely seen. Sarcoidosis may present acutely, subacutely, or chronically; in the majority of patients, however, it is completely asymptomatic. Lofgren's syndrome, in which both erythema nodosum and bilateral hilar adenopathy are seen, is considered one of the more typical and acute presentations of sarcoidosis. Individuals with subacute sarcoidosis present with non-specific signs including weakness, fever, loss of weight, joint pain, and peripheral lymph node enlargement. The chronic form of sarcoidosis is recognized after severe ongoing pulmonary involvement, with a slowly progressive course and a large amount of individual variations (46,47,48).

8. Treatment

The decision of whether or not to treat a patient with sarcoidosis is preceded by the decision of the appropriate intervention. Treatment is not necessary for every patient. The choice to manage a patient with sarcoidosis is based on the evolution of certain symptoms and disease activity, as demonstrated by functional status deterioration and imaging findings. Follow-up of patients may be long-term, as a spontaneous recovery might happen in this time frame. The development of clinical deterioration and significant loss of quality of life are two important indicators for physicians to initiate interventional therapy. Treatment strategy must include not only physical, but also mental and emotional health. When initiating treatment, the first line of therapy is oral corticosteroids. Although corticosteroids have been shown to be effective in relieving symptoms and correcting organ damage, the risks of corticosteroid use are always a major issue. Therapy is frequently started at 0.5-0.75 mg of prednisolone per kg of body mass per day for 4 weeks and decreased by 10 mg per 4 weeks, based on the response. Sometimes the dose of 0.5-0.75 mg/kg of prednisolone is considered too high, and doses of 20 mg of prednisone may be used alternatively. When lung functioning has been improved, treatment may be stopped, typically in 6-12 months. Many of the patients with minor clinical signs, like skin changes, uveitis anterior or cough, should be started

on corticosteroids. Among those who require a systemic therapy, the majority will improve in a relatively short period of time, however, a small number of individuals experience chronic disease and do not improve in 2-5 years. Such chronic sufferers often require long-lasting therapy, which may require the administration of corticosteroids or adjunctive medications for over 5 years.

Secondary therapies include drugs such as azathioprine, methotrexate, cyclophosphamide, and hydroxychloroquine for symptom control, although each of these drugs has been found to be ineffective compared with steroid therapy (54,55,56,57).

9. Conclusion

Sarcoidosis is a complex disease of undetermined pathogenesis. Because of the varied clinical presentation of individuals with sarcoidosis, physicians performing a complete diagnostic evaluation must aim to identify all symptoms of the condition, even symptomless presentations, and to evaluate the general health status and quality of life of the patient. In order to improve disease control, a multidisciplinary approach remains the most appropriate way to provide patients with professional and highly efficient treatment. It is only through such a holistic perspective that the disease severity can be properly assessed and the proper treatment can be determined. In order to manage this rare disease, early detection is essential. Clinicians therefore urgently require the development of effective diagnostic instruments for the diagnosis and prediction of sarcoidosis.

Declarations

Funding

This research did not receive any specific grant from funding agencies.

Author contributions

Conceptualization, A.M., H.S. ; Methodology, P.G. and A.M. ; Validation, P.B. and A.S. ; Formal Analysis, Z.M.; Investigation, A.N. and A.M; Resources, A.M. ; Data Curation, H.S. and A.M. ; Writing – Original, A.M. ; Writing – Review & Editing, A.M. and A.S. ; Visualization, P.B. and P.G. ; Supervision, A.S.; Project Administration, A.N.

Conflicts of interest

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data availability

The data have not been made public, but are kept with the authors, if necessary.

Ethics approval

Written informed consent for publication was obtained from the patient. We complied with the policy of the journal on ethical consent.

References:

1. Sève P, Pacheco Y, Durupt F, Jamilloux Y, Gerfaud-Valentin M, Isaac S, Boussel L, Calender A, Androdias G, Valeyre D, El Jammal T. Sarcoidosis: A Clinical Overview from Symptoms to Diagnosis. Cells. 2021 Mar 31;10(4):766. doi: 10.3390/cells10040766. PMID: 33807303; PMCID: PMC8066110.
2. Jain R, Yadav D, Puranik N, Guleria R, Jin JO. Sarcoidosis: Causes, Diagnosis, Clinical Features, and Treatments. J Clin Med. 2020 Apr 10;9(4):1081. doi: 10.3390/jcm9041081. PMID: 32290254; PMCID: PMC7230978.

3. Besnier E.H. Lupus Pernio de La Face; Synovites Fongueuses (Scrofulo-Tuberculeuses) Symétriques Des Extrémités Supérieures. *Ann. Derm. Syph.* 1889;10:333–336.
4. Sakthivel P., Bruder D. Mechanism of Granuloma Formation in Sarcoidosis. *Curr. Opin. Hematol.* 2017;24:59–65. doi: 10.1097/MOH.0000000000000301.
5. Hunninghake G. Statement on sarcoidosis. *Am. J. Respir. Crit. Care Med.* 1999;160:736–755.
6. Baughman R.P., Teirstein A.S., Judson M.A., Rossman M.D., Yeager H., Jr., Bresnitz E.A., DePalo L., Hunninghake G., Iannuzzi M.C., Johns C.J., et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am. J. Respir. Crit. Care Med.* 2001;164:1885–1889. doi: 10.1164/ajrccm.164.10.2104046.
7. Li C.-W., Tao R.-J., Zou D.-F., Li M.-H., Xu X., Cao W.-J. Pulmonary sarcoidosis with and without extrapulmonary involvement: A cross-sectional and observational study in china. *BMJ Open.* 2018;8:e018865. doi: 10.1136/bmjopen-2017-018865.
8. Siltzbach L.E., James D.G., Neville E., Turiaf J., Battesti J.P., Sharma O.P., Hosoda Y., Mikami R., Odaka M. Course and prognosis of sarcoidosis around the world. *Am. J. Med.* 1974;57:847–852. doi: 10.1016/0002-9343(74)90160-0.
9. Miyara M., Amoura Z., Parizot C., Badoual C., Dorgham K., Trad S., Kambouchner M., Valeyre D., Chapelon-Abric C., Debré P., et al. The immune paradox of sarcoidosis and regulatory t cells. *J. Exp. Med.* 2006;203:359–370. doi: 10.1084/jem.20050648.
10. Iannuzzi M.C., Rybicki B.A., Teirstein A.S. Sarcoidosis. *N. Engl. J. Med.* 2007;357:2153–2165. doi: 10.1056/NEJMra071714.
11. Prior C., Knight R.A., Herold M., Ott G., Spiteri M.A. Pulmonary sarcoidosis: Patterns of cytokine release in vitro. *Eur. Respir. J.* 1996;9:47–53. doi: 10.1183/09031936.96.09010047.
12. Arkema E.V., Cozier Y.C. Epidemiology of Sarcoidosis: Current Findings and Future Directions. *Ther. Adv. Chronic Dis.* 2018;9:227–240. doi: 10.1177/2040622318790197.

13. Zissel G. Cellular activation in the immune response of sarcoidosis. *Semin. Respir. Crit. Care Med.* 2014;35:307–315. doi: 10.1055/s-0034-1376861.
14. Pereira C.A.C., Dornfeld M.C., Baughman R., Judson M.A. Clinical Phenotypes in Sarcoidosis. *Curr. Opin. Pulm. Med.* 2014;20:496–502. doi: 10.1097/MCP.0000000000000077.
15. Valeyre D., Prasse A., Nunes H., Uzunhan Y., Brillet P.-Y., Müller-Quernheim J. Sarcoidosis. *Lancet.* 2014;383:1155–1167. doi: 10.1016/S0140-6736(13)60680-7.
16. Nunes H., Bouvry D., Soler P., Valeyre D. Sarcoidosis. *Orphanet J. Rare Dis.* 2007;2:46. doi: 10.1186/1750-1172-2-46.
17. Nardi A., Brillet P.-Y., Letoumelin P., Girard F., Brauner M., Uzunhan Y., Naccache J.-M., Valeyre D., Nunes H. Stage IV Sarcoidosis: Comparison of Survival with the General Population and Causes of Death. *Eur. Respir. J.* 2011;38:1368–1373. doi: 10.1183/09031936.00187410.
18. Swigris J.J., Olson A.L., Huie T.J., Fernandez-Perez E.R., Solomon J., Sprunger D., Brown K.K. Sarcoidosis-Related Mortality in the United States from 1988 to 2007. *Am. J. Respir. Crit. Care Med.* 2011;183:1524–1530. doi: 10.1164/rccm.201010-1679OC.
19. Kirkil G., Lower E.E., Baughman R.P. Predictors of Mortality in Pulmonary Sarcoidosis. *Chest.* 2018;153:105–113. doi: 10.1016/j.chest.2017.07.008.
20. Morimoto T., Azuma A., Abe S., Usuki J., Kudoh S., Sugisaki K., Oritsu M., Nukiwa T. Epidemiology of Sarcoidosis in Japan. *Eur. Respir. J.* 2008;31:372–379. doi: 10.1183/09031936.00075307.
21. Jamilloux Y., Maucort-Boulch D., Kerever S., Gerfaud-Valentin M., Broussolle C., Eb M., Valeyre D., Seve P. Sarcoidosis-Related Mortality in France: A Multiple-Cause-of-Death Analysis. *Eur. Respir. J.* 2016;48:1700–1709. doi: 10.1183/13993003.00457-2016.
22. Peros-Golubicic T., Ljubic S. Cigarette smoking and sarcoidosis. *Acta Med. Croat.* 1995;49:187–193.
23. Siltzbach L.E. Current thoughts on the epidemiology and etiology of sarcoidosis. *Am. J. Med.* 1965;39:361–368. doi: 10.1016/0002-9343(65)90205-6.

24. Arkema E.V., Cozier Y.C. Epidemiology of sarcoidosis: Current findings and future directions. *Ther. Adv. Chronic Dis.* 2018;9:227–240. doi: 10.1177/2040622318790197.
25. Martusewicz-Boros M.M., Boros P.W., Wiatr E., Roszkowski-Śliż K. What comorbidities accompany sarcoidosis? A large cohort (n = 1779) patients analysis. *Sarcoidosis Vasc. Diffus. Lung Dis.* 2015;32:115–120.
26. Nowinski A., Puscinska E., Goljan-Geremek A., Bednarek M., Kaminski D., Gorecka D. Comorbidities associated with sarcoidosis—Results from long-term observational study. *Eur. Respir. J.* 2014;44:461.
27. Wu C.H., Chung P.I., Wu C.Y., Chen Y.T., Chiu Y.W., Chang Y.T., Liu H.N. Comorbid autoimmune diseases in patients with sarcoidosis: A nationwide case-control study in taiwan. *J. Dermatol.* 2017;44:423–430. doi: 10.1111/1346-8138.13654.
28. Carmi O., Berla M., Edelstein E., Levy Y. Coexisting systemic sclerosis-polymyositis and sarcoidosis: Case report and review of the literature. *J. Clin. Rheumatol. Pract. Rep. Rheum. Musculoskelet. Dis.* 2018;24:238–240. doi: 10.1097/RHU.0000000000000699.
29. Grunewald J., Spagnolo P., Wahlstrom J., Eklund A. Immunogenetics of disease-causing inflammation in sarcoidosis. *Clin. Rev. Allergy Immunol.* 2015;49:19–35. doi: 10.1007/s12016-015-8477-8
30. Fischer A., Ellinghaus D., Nutsua M., Hofmann S., Montgomery C.G., Iannuzzi M.C., Rybicki B.A., Petrek M., Mrazek F., Pabst S., et al. Identification of immune-relevant factors conferring sarcoidosis genetic risk. *Am. J. Respir. Crit. Care Med.* 2015;192:727–736. doi: 10.1164/rccm.201503-0418OC.
31. Kucera G.P., Rybicki B.A., Kirkey K.L., Coon S.W., Major M.L., Maliarik M.J., Iannuzzi M.C. Occupational risk factors for sarcoidosis in african-american siblings. *Chest.* 2003;123:1527–1535. doi: 10.1378/chest.123.5.1527.
32. Newman L.S., Rose C.S., Bresnitz E.A., Rossman M.D., Barnard J., Frederick M., Terrin M.L., Weinberger S.E., Moller D.R., McLennan G., et al. A case control etiologic study of sarcoidosis: Environmental and occupational risk factors. *Am. J. Respir. Crit. Care Med.* 2004;170:1324–1330. doi: 10.1164/rccm.200402-249OC.

33. Vihlborg P., Bryngelsson L., Andersson L., Graff P. Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in swedish iron foundries: A retrospective cohort study. *BMJ Open.* 2017;7:e016839. doi: 10.1136/bmjopen-2017-016839.
34. Izbicki G., Chavko R., Banauch G.I., Weiden M.D., Berger K.I., Aldrich T.K., Hall C., Kelly K.J., Prezant D.J. World trade center "sarcoid-like" granulomatous pulmonary disease in new york city fire department rescue workers. *Chest.* 2007;131:1414–1423. doi: 10.1378/chest.06-2114.
35. Newman L. Aetiologies of sarcoidosis. *Eur. Respir. Monogr.* 2005;32:23–48.
36. Vidal S., De la Horra C., Martin J., Montes-Cano M., Rodríguez E., Respaldiza N., Rodriguez F., Varela J., Medrano F., Calderón E. Pneumocystis jirovecii colonisation in patients with interstitial lung disease. *Clin. Microbiol. Infect.* 2006;12:231–235. doi: 10.1111/j.1469-0691.2005.01337.x.
37. Hirano A., Kataoka M., Nakata Y., Takeda K., Kamao T., Hiramatsu J., Kimura G., Tanimoto Y., Kanehiro A., Tanimoto M. Sarcoidosis occurring after interferon-alpha therapy for chronic hepatitis c: Report of two cases. *Respirology.* 2005;10:529–534. doi: 10.1111/j.1440-1843.2005.00745.x.
38. Trien R., Cooper C.J., Paez D., Colon E., Ajmal S., Salameh H. Interferon-alpha-induced sarcoidosis in a patient being treated for hepatitis c. *Am. J. Case Rep.* 2014;15:235–238.
39. Brjalin V., Salupere R., Tefanova V., Prikk K., Lapidus N., Jõeste E. Sarcoidosis and chronic hepatitis c: A case report. *World J. Gastroenterol.* 2012;18:5816–5820. doi: 10.3748/wjg.v18.i40.5816.
40. Ramos-Casals M., Mana J., Nardi N., Brito-Zeron P., Xaubet A., Sanchez-Tapias J.M., Cervera R., Font J. Sarcoidosis in patients with chronic hepatitis c virus infection: Analysis of 68 cases. *Medicine.* 2005;84:69–80. doi: 10.1097/01.md.0000157577.69729.e6.
41. Kaiser Y., Eklund A., Grunewald J. Moving target: Shifting the focus to pulmonary sarcoidosis as an autoimmune spectrum disorder. *Eur. Respir. J.* 2019;54:1802153. doi: 10.1183/13993003.021532018.
42. Grunewald J., Kaiser Y., Ostadkarampour M., Rivera N.V., Vezzi F., Lötstedt B., Olsen R.-A., Sylwan L., Lundin S., Käller M. T-cell receptor—

Hla-drb1 associations suggest specific antigens in pulmonary sarcoidosis. *Eur. Respir. J.* 2016;47:898–909. doi: 10.1183/13993003.01209-2015.

43. Lynch JP, 3rd, Hwang J, Bradfield J, Fishbein M, Shivkumar K, Tung R. Cardiac involvement in sarcoidosis: evolving concepts in diagnosis and treatment. *Semin Respir Crit Care Med.* 2014;35:372–390.
44. Koyama T, Ueda H, Togashi K, Umeoka S, Kataoka M, Nagai S. Radiologic manifestations of sarcoidosis in various organs. *Radiographics.* 2004;24:87–104.
45. Costabel U, Bonella F, Ohshimo S, Guzman J. Diagnostic modalities in sarcoidosis: BAL, EBUS, and PET. *Semin Respir Crit Care Med.* 2010;31:404–408.
46. Pierce T.B., Margolis M., Razzuk M.A. Sarcoidosis: Still a mystery? *Bayl. Univ. Med Cent. Proc.* 2001;14:8–12. doi: 10.1080/08998280.2001.11927724.
47. Hu X., Carmona E.M., Yi E.S., Pellikka P.A., Ryu J. Causes of death in patients with chronic sarcoidosis. *Sarcoidosis Vasc. Diffuse Lung Dis.* 2016;33:275–280.
48. Wirnsberger R.M., de Vries J., Wouters E.F., Drent M. Clinical presentation of sarcoidosis in the netherlands an epidemiological study. *Neth. J. Med.* 1998;53:53–60. doi: 10.1016/S0300-2977(98)00058-8.
49. Judson M.A., Baughman R.P., Costabel U., Mack M., Barnathan E.S. The potential additional benefit of infliximab in patients with chronic pulmonary sarcoidosis already receiving corticosteroids: A retrospective analysis from a randomized clinical trial. *Respir. Med.* 2014;108:189–194. doi: 10.1016/j.rmed.2013.11.019.
50. Pande A., Culver D.A. Knowing when to use steroids, immunosuppressants or biologics for the treatment of sarcoidosis. *Expert Rev. Respir. Med.* 2020;14:285–298. doi: 10.1080/17476348.2020.1707672.
51. James W.E., Judson M.A. Therapeutic strategies for pulmonary sarcoidosis. *Expert Rev. Respir. Med.* 2020;14:391–403. doi: 10.1080/17476348.2020.1721284.
52. Gibson G., Prescott R., Muers M., Middleton W., Mitchell D., Connolly C., Harrison B. British thoracic society sarcoidosis study: Effects of long term

corticosteroid treatment. *Thorax.* 1996;51:238–247. doi: 10.1136/thx.51.3.238.

53. Grunewald J., Grutters J.C., Arkema E.V., Saketkoo L.A., Moller D.R., Müller-Quernheim J. Sarcoidosis. *Nat. Rev. Dis. Primers.* 2019;5:45. doi: 10.1038/s41572-019-0096-x.
54. Muller-Quernheim J., Kienast K., Held M., Pfeifer S., Costabel U. Treatment of chronic sarcoidosis with an azathioprine/prednisolone regimen. *Eur. Respir. J.* 1999;14:1117–1122. doi: 10.1183/09031936.99.14511179.
55. Baughman R., Winget D., Lower E. Methotrexate is steroid sparing in acute sarcoidosis: Results of a double blind, randomized trial. *Sarcoidosis Vasc. Diffus. Lung Dis. Off. J. WASOG.* 2000;17:60–66.
56. Brill A.-K., Ott S.R., Geiser T. Effect and safety of mycophenolate mofetil in chronic pulmonary sarcoidosis: A retrospective study. *Respiration.* 2013;86:376–383. doi: 10.1159/000345596.
57. Korsten P., Mirsaeidi M., Sweiss N.J. Nonsteroidal therapy of sarcoidosis. *Curr. Opin. Pulm. Med.* 2013;19:516. doi: 10.1097/MCP.0b013e3283642ad0