We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Löfgren's Syndrome

Shiyu Wang and Shailendra Singh

Abstract

Löfgren's syndrome presents as acute sarcoid arthritis, with a triad of hilar adenopathy, acute polyarthritis and erythema nodosum. Löfgren's syndrome is self-limited, erythema nodosum, hilar adenopathy and acute polyarthritis usually resolve within a few weeks to months, however polyarthritis can last for up to 2 years. Treatment involves symptomatic control with NSAIDs/colchicine or oral glucocorticoids until symptoms resolve, if disease is resistant to these therapies, hydroxychloroquine, methotrexate or infliximab can be used. Löfgren's syndrome is a rare presentation of sarcoidosis occurring in only about 5–10% of sarcoid patients. It is, however, important to recognize as it is the most common form of acute sarcoid arthritis and prompt treatment can prevent unnecessary prolonged discomfort for patients.

Keywords: Löfgren's Syndrome, Sarcoidosis, Polyarthritis, Hilar adenopathy, Erythema nodosum

1. Introduction

Löfgren's syndrome is an acute manifestation of sarcoidosis. Sarcoidosis is a disease characterized by noncaseating granulomas throughout multiple body systems, most commonly involving the lungs (> 90% cases), often manifesting as hilar adenopathy. A small subset of patients (~10%) will develop joint symptoms, which can manifest as either acute or chronic arthritis. Löfgren's syndrome is the most common presentation of acute sarcoid arthritis, occurring in about 5–10% of sarcoid cases, presenting as classical triad of acute polyarthritis, erythema nodosum and hilar adenopathy.

2. Epidemiology

Sarcoidosis is a disease with prevalence of about 10 to 20 per 100,000 people, it affects a wide variety of patients, but there are certain predilections and patterns for higher disease activity. Geographic area, ethnicity, gender and age seem to play important roles in incidence and presentation of disease [1, 2]. Various geographic locations have been studied, and there seems to be clustering of sarcoidosis incidence around certain geographic areas, with northern countries (such as Scandinavia) having much higher incidence than other areas [3]. Ethnicity also has a distinct pattern, with African Americans, Scandinavians, Afro Caribbeans, Irish, Puerto Rican and North Africans having highest incidence, though this seems to be affected by geographical location as well [3, 4]. There are also differences in disease presentation between different ethnicities; African Americans seem to have more

severe disease presentation than Caucasians [2]. Lowest incidence occurs in Spain and Japan [3, 4]. Women are overall more affected by sarcoidosis than men, though interestingly, the age of diagnosis is almost 10 years later in women than men in many populations [3, 4]. There also seem to be difference in disease presentation between women and men, with women potentially experiencing more musculoskeletal related symptoms [3]. Sarcoidosis incidence also increases with family history of the disease; studies have shown that alleles on short arm of chromosome 6 seem to confer increased risk (HLA DR 11, 12, 14, 15, 17) or protection (HLA DRI, DR4) from disease [5].

Löfgren's syndrome follows many of the same epidemiologic trends of sarcoidosis. It affects women more than men, with Scandinavian ethnicity having the highest incidence [6, 7]. There also seems to be a temporal clustering of incidence, with rates highest in the months from March to July [6]. The age of onset was, however; significantly lower for Löfgren's syndrome than sarcoidosis, at 39 years old versus 47 years old [7]. There also are differences between sexes in regards to presentation, women are more likely to present with erythema nodosum, whereas men are more likely to have inflammation or arthritis of ankles without erythema nodosum [8]. Various genetic factors and alleles have been associated with Löfgren's syndrome, some protective and leading to better outcomes (HLA DQB1*0201, DRB1*03) while others are associated with more severe disease and worse outcomes (CCR2, HLA DQ2, DR3) [6, 9–12].

3. Etiology

The etiology of sarcoidosis, and by extension Löfgren's syndrome, is poorly understood. Granulomatous inflammation leads to eventual noncaseating granulomas in various organs. Formation of granulomas is due to exaggerated cell mediated immune response to antigens. The exact antigen(s) that stimulate sarcoidosis is unclear at this point in time. Many studies analyzing a large number of patients have not found one factor(s) that clearly causes sarcoidosis [13], possibly due to there being many different underlying causes of sarcoidosis that leads to similar presentations. Some of the possible etiologies explored to date are environmental exposures and infectious agents.

3.1 Environmental exposure

Certain chemical elements (Beryllium, Zirconium, Aluminum) have been shown to cause granulomatous disease in lungs of patients with occupational exposure to these elements, while they themselves do not cause sarcoidosis, various studies have investigated if other environmental exposures could [14–16]. Specifically, rescue workers exposed to World Trade Center dust and debris developed new onset sarcoidosis, possible due to exposure to a yet unknown component of the dust [17].

3.2 Infectious agent

Mycobacterium and Propionibacteria have been studied as possible causes of sarcoidosis [18, 19]. *Mycobacterium tuberculosis* causes granulomatous caseations similar to those seen in sarcoidosis, and there have been *Mycobacterium tuberculosis* components found in sarcoidosis tissue [20]. Propionibacteria acnes have also been found in lymph nodes of sarcoidosis patients [19]. Despite these findings, there has been no casual relationship found between these infectious agents and sarcoidosis. Further evidence to support an infectious etiology of sarcoidosis is that transplantations of various organs have been shown to induce sarcoidosis in recipient [21–23].

4. Pathophysiology

The pathophysiology of sarcoidosis, and by extension Löfgren's syndrome, involves activation of immune cells by as of yet unknown antigen(s). While the end result is granuloma formation, there are quite a few steps before this stage.

Antigen presenting cells (APCs), either macrophages or dendritic cells, phagocytose the as of yet unknown antigen(s), and then presents this antigen(s) to Helper CD4⁺ T cells. These Helper T cells then express various inflammatory cytokines including: interferon-gamma, Tumor necrosis factor (TNF), interleukin (IL)-2, IL-17 and IL-22 [24]. IL-17 recruits T Helper 17 (Th17) cells which then produce even more inflammatory cytokines, primarily interferon-gamma [25]. All these inflammatory mediators cause fusion of APCs into multinucleated giant cells, the APCs and multinucleated giant cells then cluster to form granulomas.

This process seems to occur most prominent and commonly in the lungs, with alveolar macrophages often the first to aggregate to form granulomas. This process can occur in other areas of the body, as evidenced by up to 30% of patients experiencing extrapulmonary symptoms (**Figure 1**) [26].

4.1 Erythema Nodosum and acute polyarthrititis

In Löfgren's syndrome, in addition to pulmonary granulomas (represented as hilar adenopathy), there are also manifestations of erythema nodosum and acute polyarthrititis. Erythema nodosum is caused by delayed type hypersensitivity reaction from exposure to antigens. Its exact pathophysiology is not fully understood, but may be due to immune complex deposition in venules of subcutaneous

Figure 1.
Non-caseating granuloma (Samir at the English-language Wikipedia, CC BY-SA 3.0 <<http://creativecommons.org/licenses/by-sa/3.0/>>, via Wikimedia Commons).

fat, inciting an inflammatory reaction and granuloma formation [27]. Acute polyarthritis also has poorly understood pathogenesis, but may be due increased inflammatory milieu within the body, leading to transient inflammatory arthritis.

5. Presentation

Löfgren’s syndrome presents classically as a triad of hilar lymphadenopathy, erythema nodosum and acute polyarthritis. Often constitutional symptoms occur concurrently with the above triad, most commonly manifesting as fever, fatigue and malaise. Age of onset is generally under or around 40 years of age. More rare symptoms include uveitis along with blurry vision and light sensitivity [28]. There is variability in presentation between different sexes [8].

5.1 Hilar lymphadenopathy

Hilar lymphadenopathy is a classic finding of pulmonary sarcoidosis, making it ubiquitous in Löfgren’s syndrome. It is a radiographic term for enlarged mediastinal lymph nodes, most often those surrounding the pulmonary hila or root of the lung, where the lungs connect to the trachea and heart. Often the enlargement is bilateral and symmetric, though the right side may be slightly more prominent. Chest radiograph is required for definitive diagnosis, and there are five stages, as discussed below. These stages do not represent disease activity, just anatomical findings on chest radiography [29]. Generally, hilar lymphadenopathy will regress within 1 year [30]. Though not exclusively caused by bilateral hilar lymphadenopathy, respiratory symptoms are often the first presentation that prompts obtaining a chest radiograph, where hilar lymphadenopathy is first discovered in a patient. These respiratory symptoms most commonly are coughing, dyspnea and chest pain (Table 1 and Figures 2 and 3).

5.2 Erythema Nodosum

Erythema nodosum presents as erythematous, tender, immobile nodules that are elevated and can join to form a plaque. Most commonly, they present on shins in Löfgren’s syndrome, though they can also appear on head and neck regions as well. These nodules are caused by subcutaneous inflammation, and are frequently accompanied by fevers and take a few days to develop. Spontaneous resolution typically occurs within eight weeks without scarring. There may be hyperpigmentation after resolution, but this is rare [27]. Relapsing erythema nodosum

Stages of Pulmonary Sarcoidosis	Features
Stage 0	Normal chest radiograph
Stage I	Bilateral hilar lymphadenopathy
Stage II	Bilateral hilar lymphadenopathy + Diffuse infiltrative lung damage
Stage III	Diffuse infiltrative lung damage
Stage IV	Lung fibrosis ¹

¹The Foundations in Diagnostic Pathology Series, Pulmonary Pathology – Chapter 17.

Table 1.
Stages of pulmonary sarcoidosis.

Figure 2.
Anterior–posterior and lateral chest radiograph of bilateral hilar lymphadenopathy (image courtesy of H. Bruce Dull, MD).

Figure 3.
Computed tomography of bilateral hilar lymphadenopathy (by James Heilman, MD - Own work, CC BY-SA 4.0, <https://commons.wikimedia.org/w/index.php?curid=49068286>).

can develop; this represents poor control or failure of treatment of underlying chronic condition. Erythema nodosum is also more commonly seen in women with Löfgren's syndrome, whereas men can have acute polyarthritis with no erythema nodosum (**Figure 4**) [8].

5.3 Acute polyarthritis

Acute polyarthritis in Löfgren's syndrome is typically symmetrical and oligoarticular (affecting 2 to 4 joints) initially. Most often, it involves the ankles bilaterally and then starts to affects other joints of the lower extremities such as knees and

Figure 4.

Erythema nodosum of lower extremities (by James Heilman, MD - Own work, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=11520780>).

can also affect wrists and elbow joints as well. Bilateral ankle arthritis seems to be the most common initial manifestation of acute polyarthritis. Rarely, small joints of hands bilaterally can be involved [30]. Arthritis generally resolves within a few months, though it can persist up to 2 years, even with treatment. Cases of recurrent arthritis after treatment have also been described [31]. Men present with acute polyarthritis more commonly [8].

6. Evaluation and diagnosis

There are no definitive test or classification criteria for Löfgren's syndrome, and though the classic triad of hilar lymphadenopathy, erythema nodosum and acute polyarthritis are highly specific (> 95%), there are instances where not all components are presents in patients with Löfgren's syndrome [32]. For successful evaluation of a patient with Löfgren's syndrome, an accurate and detail history and physical must first be performed, usually followed up with a chest radiograph to confirm diagnosis. Biopsies may be indicated for definitive diagnosis of sarcoidosis if chest radiograph or other forms of imaging are inconclusive. Laboratory testing is generally not required.

6.1 History and physical exam

A detailed and accurate history and physical exam is essential for evaluation and diagnosis of Löfgren's syndrome. Chronicity and specificity symptoms need to be elucidated and investigated. Importantly, history should uncover onset and location of acute polyarthritis, and whether there has been any migration of arthritis. Underlying arthritis or arthralgias should also be clarified, to ensure that the acute polyarthritis is indeed new and acute in nature, not a continuation of previous disease. Constitutional symptoms should also be inquired about, as acute onset of fever very often accompanies both the acute polyarthritis and development of erythema nodosum. Ask about respiratory symptoms, as they can be the first sign

of previously unknown hilar lymphadenopathy. Keep in mind the differences in presentation between men and women, as women may not have presentation of acute polyarthritis and just erythema nodosum, whereas men may not present with erythema nodosum.

Physical exam should include detailed examination of lower extremities, neck and head regions for erythema nodosum. Joint examination of lower extremities as well as hands, wrists and elbows should be performed to see if there is pain, tenderness, swelling, redness and heat. Monitoring temperature can also be useful in determining if there is accompanying fever with these symptoms. A detailed cardiac, pulmonary and abdominal exam should be performed as hilar adenopathy and sarcoidosis in general can cause various manifestations and physical changes in these areas.

6.2 Chest radiography

Chest radiography should be obtained at least once on all patients suspected with Löfgren's syndrome, it is an essential step to establishing if there is hilar lymphadenopathy. Section 5.1 describes findings and diagnostic criteria for hilar lymphadenopathy on chest radiograph. If chest radiography is inconclusive, high resolution computed tomography (HRCT) scan can be performed, and provides more detailed imaging and analysis of mediastinum, able to identify in more detail the precise location and extent of lymphadenopathy [33]. HRCT is not routinely recommended for evaluation and diagnosis of Löfgren's syndrome.

6.3 Biopsies

Biopsies are generally limited to cases of Löfgren's syndrome where HRCT or other imaging modalities cannot detect sarcoidosis, and/or disease is refractory to treatment or deviates from expected course. It is utilized to definitively obtain tissue samples that confirm diagnosis of sarcoidosis. Generally, bronchoalveolar lavage (BAL) is performed with endobronchial or transbronchial biopsies, endobronchial ultrasound (EBUS) biopsy can also be used for various positions and angles to attempt a needle aspiration biopsy of lymphadenopathy. A triad of CD4 to CD8 cell ratio > 4, lymphocyte percentage > 16% and presence of noncaseating granulomas has 100% positive predictive value and 81% negative predictive value for diagnosis of sarcoidosis [34].

6.4 Laboratory and genetic testing

Laboratory testing is generally not required for evaluation and diagnosis of Löfgren's syndrome. Many laboratory testing is non-specific and do not provide additional value. Exceptions may include angiotensin-converting enzyme (ACE) and ionized calcium. Studies have shown that patients with elevated ACE and ionized calcium may have increased risk for prolonged arthritis [35]. Tuberculosis skin or interferon-gamma testing should be performed at least once on patients suspected with Löfgren's syndrome to rule out tuberculosis, which can mimic erythema nodosum as well as hilar adenopathy.

Genetic testing is not required for evaluation and diagnosis of Löfgren's syndrome. Though some alleles and genes have been associated with Löfgren's syndrome, they are more for academic research purposes rather than to diagnose the disease. Associations include: HLA DQB1*0201 and DRB1*03 have been found to be protective and lead to better outcomes, and CCR2, HLA DQ2 and DR3 have been found to be risk factors for worse outcomes [9–12].

7. Differential diagnoses

Many conditions and diseases can cause erythema nodosum, polyarthritis and associated fever. These including: infections, drug reactions, malignancies, inflammatory bowel disease and other rheumatologic conditions. While chest radiograph with findings of hilar adenopathy can significantly increase specificity for Löfgren's syndrome, it is not always necessary and a detailed history and physical should be able to differentiate many of the other differential diagnoses listed below.

7.1 Infections

A wide variety of infections can cause erythema nodosum and arthritis, which can manifest as reactive arthritis or infectious arthritis. These include bacterial: streptococcus, chlamydia, yersinia, salmonella, campylobacter and tuberculosis. Fungal: coccidiomycosis, histoplasmosis, blastomycosis. Viral: hepatitis B and infectious mononucleosis. Reactive and infectious arthritis generally present initially in the knee joint, which can overlap with Löfgren's syndrome, and the arthritis are also usually self-limited and acute. Therefore it can be difficult to distinguish between the two without chest radiography, but presence of hilar lymphadenopathy should exclude most of the infections listed above. The exception to this is tuberculosis, which can also present with hilar adenopathy, thus it is necessary to obtain tuberculosis skin or interferon-gamma testing to rule out tuberculosis infection.

7.2 Drug reactions

Drug reactions that can cause erythema nodosum include: oral contraceptives, penicillins, sulfonamides, bromides, iodides and TNF Alpha inhibitors. Though drug reactions can cause fever, very rarely do they cause arthritis. Cessation of offending drug also often resolves symptoms. Thus, if there is no presence of acute polyarthritis, distinguishing a drug reaction from Löfgren's syndrome is clear.

7.3 Malignancies

Malignancies that can cause erythema nodosum include lymphoma, leukemia and carcinomas. These malignancies can also be associated with fever, but also very rarely cause arthritis. They can, however, cause hilar lymphadenopathy, thus it is important to delineate presence of acute polyarthritis.

7.4 Inflammatory bowel disease (IBD)

Ulcerative colitis and Crohns disease can cause erythema nodosum with associated fever as well as enteropathic arthritis. Enteropathic arthritis can present sporadically and intermittently, and can be mistaken for acute polyarthritis. Therefore, it is difficult to distinguish between inflammatory bowel disease and Löfgren's syndrome, chest radiography should be obtained to detect for presence of hilar adenopathy. IBD generally does not cause hilar lymphadenopathy.

7.5 Other rheumatologic conditions

Rheumatologic conditions such as Behcet disease and Sweet syndrome can also cause erythema nodosum, arthritis with associated fevers. Behcet syndrome causes polyarthritis of lower extremity joints, very similar to Löfgren's syndrome. Sweet

syndrome itself does not cause arthritis, but is associated with rheumatoid arthritis, IBD and Behcet syndrome, all of which can cause arthritis. Sweet syndrome is associated with a characteristic rash that present as erythematous plaques, which should be differentiated from erythema nodosum. Neither condition is associated with hilar lymphadenopathy, thus chest radiography should be obtained to distinguish them from Löfgren's syndrome.

8. Treatment/management

Löfgren's syndrome is largely a self-limited disease, the erythema nodosum, acute polyarthritis and hilar lymphadenopathy resolves usually within a few weeks to months, most cases resolve within 1 year. Polyarthritis has been known to last up to 2 years. Treatment is largely supportive and goal is symptomatic control. NSAIDs are first line for anti-inflammatory properties to ameliorate discomfort of fever, erythema nodosum and arthritis; colchicine can also be used for this purpose. In severe or refractory cases, glucocorticoids can be used, which needs to be tapered off of once symptoms have been resolved. Further interventions with methotrexate or hydroxychloroquine can also be used, and infliximab beyond that [36].

9. Prognosis

Prognosis of Löfgren's syndrome is excellent; most patients achieve complete resolution of symptoms without recurrence in 6 months to 2 years. Cases have been described of recurrence of symptoms or progression to chronic disease, but these are exceedingly rare [35].

10. Conclusions

Löfgren's syndrome is a rare disease that is often misdiagnosed or under diagnosed. The constellation of symptoms of erythema nodosum, acute polyarthritis (most commonly bilaterally in ankle and under 2 months since time of onset) as well as hilar lymphadenopathy in a young patient (under 40 years of age) should raise very high suspicions for this disease. Prompt recognition and treatment of this disease can save much stress and pain for patients afflicted by it.

Conflict of interest

The authors declare no conflict of interest.

IntechOpen

Author details

Shiyu Wang^{1*} and Shailendra Singh²

1 White River Health System, Batesville, AR, USA

2 Unity Healthy System, Searcy, AR, USA

*Address all correspondence to: shiyuwang0@gmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Thomas KW, Hunninghake GW. Sarcoidosis. *JAMA*. 2003 Jun 25;289(24):3300-3303. doi: 10.1001/jama.289.24.3300. PMID: 12824213.
- [2] Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med*. 1997 Apr 24;336(17):1224-34. doi: 10.1056/NEJM199704243361706. Erratum in: *N Engl J Med* 1997 Jul 10;337(2):139. PMID: 9110911.
- [3] Arkema EV, Cozier YC. Epidemiology of sarcoidosis: current findings and future directions. *Ther Adv Chronic Dis*. 2018;9(11):227-240. Published 2018 Aug 24. doi:10.1177/2040622318790197
- [4] Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol*. 1997 Feb 1;145(3):234-241. doi: 10.1093/oxfordjournals.aje.a009096. PMID: 9012596.
- [5] Baughman RP, Lower EE, du Bois RM. Sarcoidosis. *Lancet*. 2003 Mar 29;361(9363):1111-1118. doi: 10.1016/S0140-6736(03)12888-7. PMID: 12672326.
- [6] Visser H, Vos K, Zanelli E, Verduyn W, Schreuder GM, Speyer I, Breedveld FC, Hazes JM. Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. *Ann Rheum Dis*. 2002 Jun;61(6):499-504. doi: 10.1136/ard.61.6.499. PMID: 12006321; PMCID: PMC1754119.
- [7] Rubio-Rivas M, Franco J, Corbella X. Sarcoidosis presenting with and without Löfgren's syndrome: Clinical, radiological and behavioral differences observed in a group of 691 patients. *Joint Bone Spine*. 2020 Mar;87(2):141-147. doi: 10.1016/j.jbspin.2019.10.001. Epub 2019 Oct 11. PMID: 31606494.
- [8] Grunewald J, Eklund A. Sex-specific manifestations of Löfgren's syndrome. *Am J Respir Crit Care Med*. 2007;175(1):40-44. doi:10.1164/rccm.200608-1197OC
- [9] Sato H, Grutters JC, Pantelidis P, Mizzon AN, Ahmad T, Van Houte AJ, Lammers JW, Van Den Bosch JM, Welsh KI, Du Bois RM. HLA-DQB1*0201: a marker for good prognosis in British and Dutch patients with sarcoidosis. *Am J Respir Cell Mol Biol*. 2002 Oct;27(4):406-412. doi: 10.1165/rcmb.4782. PMID: 12356573.
- [10] Grunewald J, Eklund A. Löfgren's syndrome: human leukocyte antigen strongly influences the disease course. *Am J Respir Crit Care Med*. 2009 Feb 15;179(4):307-312. doi: 10.1164/rccm.200807-1082OC. Epub 2008 Nov 7. PMID: 18996998.
- [11] Spagnolo P, Renzoni EA, Wells AU, Sato H, Grutters JC, Sestini P, Abdallah A, Gramiccioni E, Ruven HJ, du Bois RM, Welsh KI. C-C chemokine receptor 2 and sarcoidosis: association with Löfgren's syndrome. *Am J Respir Crit Care Med*. 2003 Nov 15;168(10):1162-1166. doi: 10.1164/rccm.200303-456OC. Epub 2003 Jul 25. PMID: 12882757.
- [12] Kremer JM. Histologic findings in siblings with acute sarcoid arthritis: association with the B8,DR3 phenotype. *J Rheumatol*. 1986 Jun;13(3):593-597. PMID: 3488404.
- [13] Rybicki BA, Iannuzzi MC, Frederick MM, Thompson BW, Rossman MD, Bresnitz EA, Terrin ML, Moller DR, Barnard J, Baughman RP, DePalo L, Hunninghake G, Johns C, Judson MA, Knatterud GL, McLennan G, Newman LS, Rabin DL, Rose C, Teirstein AS, Weinberger SE, Yeager H, Cherniack R; ACCESS Research Group. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). *Am J Respir Crit Care Med*. 2001 Dec

- 1;164(11):2085-2091. doi: 10.1164/ajrccm.164.11.2106001. PMID: 11739139.
- [14] Balmes JR, Abraham JL, Dweik RA, Fireman E, Fontenot AP, Maier LA, Muller-Quernheim J, Ostiguy G, Pepper LD, Saltini C, Schuler CR, Takaro TK, Wambach PF; ATS Ad Hoc Committee on Beryllium Sensitivity and Chronic Beryllium Disease. An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease. *Am J Respir Crit Care Med*. 2014 Nov 15;190(10):e34-e59. doi: 10.1164/rccm.201409-1722ST. PMID: 25398119.
- [15] Werfel U, Schneider J, Rödelserperger K, Kotter J, Popp W, Woitowitz HJ, Zieger G. Sarcoid granulomatosis after zirconium exposure with multiple organ involvement. *Eur Respir J*. 1998 Sep;12(3):750. doi: 10.1183/09031936.98.12030750. PMID: 9762810.
- [16] Cai HR, Cao M, Meng FQ, Wei JY. Pulmonary sarcoid-like granulomatosis induced by aluminum dust: report of a case and literature review. *Chin Med J (Engl)*. 2007 Sep 5;120(17):1556-1560. PMID: 17908469.
- [17] Izbicki G, Chavko R, Banauch GI, Weiden MD, Berger KI, Aldrich TK, Hall C, Kelly KJ, Prezant DJ. World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. *Chest*. 2007 May;131(5):1414-1423. doi: 10.1378/chest.06-2114. Epub 2007 Mar 30. PMID: 17400664.
- [18] Ferrara G, Valentini D, Rao M, Wahlström J, Grunewald J, Larsson LO, Brighenti S, Dodo E, Zumla A, Maeurer M. Humoral immune profiling of mycobacterial antigen recognition in sarcoidosis and Löfgren's syndrome using high-content peptide microarrays. *Int J Infect Dis*. 2017 Mar;56:167-175. doi: 10.1016/j.ijid.2017.01.021. Epub 2017 Jan 31. PMID: 28159576.
- [19] Ishige I, Eishi Y, Takemura T, Kobayashi I, Nakata K, Tanaka I, Nagaoka S, Iwai K, Watanabe K, Takizawa T, Koike M. Propionibacterium acnes is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes from subjects without sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2005 Mar;22(1):33-42. PMID: 15881278.
- [20] Saboor SA, Johnson NM, McFadden J. Detection of mycobacterial DNA in sarcoidosis and tuberculosis with polymerase chain reaction. *Lancet*. 1992 Apr 25;339(8800):1012-1015. doi: 10.1016/0140-6736(92)90535-b. PMID: 1349051.
- [21] Burke WM, Keogh A, Maloney PJ, Delprado W, Bryant DH, Spratt P. Transmission of sarcoidosis via cardiac transplantation. *Lancet*. 1990 Dec 22-29;336(8730):1579. doi: 10.1016/0140-6736(90)93354-r. PMID: 1979389.
- [22] Bhagat R, Rizzieri DA, Vredenburg JJ, Chao NJ, Folz RJ. Pulmonary sarcoidosis following stem cell transplantation: is it more than a chance occurrence? *Chest*. 2004 Aug;126(2):642-644. doi: 10.1378/chest.126.2.642. PMID: 15302757.
- [23] Ionescu DN, Hunt JL, Lomago D, Yousem SA. Recurrent sarcoidosis in lung transplant allografts: granulomas are of recipient origin. *Diagn Mol Pathol*. 2005 Sep;14(3):140-145. doi: 10.1097/01.pas.0000176765.26047.6f. PMID: 16106194.
- [24] Sakthivel P, Bruder D. Mechanism of granuloma formation in sarcoidosis. *Curr Opin Hematol*. 2017 Jan;24(1):59-65. doi: 10.1097/MOH.0000000000000301. PMID: 27755127.
- [25] Broos CE, Hendriks RW, Kool M. T-cell immunology in sarcoidosis: Disruption of a delicate balance between helper and regulatory T-cells. *Curr Opin Pulm Med*. 2016 Sep;22(5):476-483. doi:

10.1097/MCP.0000000000000303.
PMID: 27379969.

[26] Judson MA. The Clinical Features of Sarcoidosis: A Comprehensive Review. *Clin Rev Allergy Immunol*. 2015 Aug;49(1):63-78. doi: 10.1007/s12016-014-8450-y. PMID: 25274450.

[27] Kunz M, Beutel S, Bröcker E. Leucocyte activation in erythema nodosum. *Clin Exp Dermatol*. 1999 Sep;24(5):396-401. doi: 10.1046/j.1365-2230.1999.00511.x. PMID: 10564331.

[28] Ponhold W. Das Löfgren-Syndrom: Die akute Form der Sarkoidose [The Löfgren syndrome: acute sarcoidosis (author's transl)]. *Rontgenblätter*. 1977 Jun;30(6):325-7. German. PMID: 897518.

[29] Roberto J. Barrios, Chapter 17 - Other Interstitial Lung Diseases, Editor(s): Dani S. Zander, Carol F. Farver, In *The Foundations in Diagnostic Pathology Series, Pulmonary Pathology*, Churchill Livingstone, 2008, Pages 348-373, ISBN 9780443067419, <https://doi.org/10.1016/B978-0-443-06741-9.50023-9>.

[30] Visser H, Vos K, Zanelli E, et al. Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. *Ann Rheum Dis*. 2002;61(6):499-504. doi:10.1136/ard.61.6.499

[31] Johard U, Eklund A. Recurrent Löfgren's syndrome in three patients with sarcoidosis. *Sarcoidosis*. 1993 Sep;10(2):125-127. PMID: 8140298.

[32] MAYOCK RL, BERTRAND P, MORRISON CE, SCOTT JH. MANIFESTATIONS OF SARCOIDOSIS. ANALYSIS OF 145 PATIENTS, WITH A REVIEW OF NINE SERIES SELECTED FROM THE LITERATURE. *Am J Med*. 1963 Jul;35:67-89. doi: 10.1016/0002-9343(63)90165-7. PMID: 14046006.

[33] Koyama T, Ueda H, Togashi K, Umeoka S, Kataoka M, Nagai S. Radiologic manifestations of sarcoidosis

in various organs. *Radiographics*. 2004 Jan-Feb;24(1):87-104. doi: 10.1148/rg.241035076. PMID: 14730039.

[34] Winterbauer RH, Lammert J, Selland M, Wu R, Corley D, Springmeyer SC. Bronchoalveolar lavage cell populations in the diagnosis of sarcoidosis. *Chest*. 1993 Aug;104(2):352-361. doi: 10.1378/chest.104.2.352. PMID: 8339618.

[35] Sejdic A, Graudal N, Baslund B. Clinical and biochemical presentation of sarcoidosis with high and normal serum angiotensin-converting enzyme. *Scand J Rheumatol*. 2018 Nov;47(6):487-490. doi: 10.1080/03009742.2017.1420818. Epub 2018 Jun 22. PMID: 29929412.

[36] Zisman DA, Shorr AF, Lynch JP 3rd. Sarcoidosis involving the musculoskeletal system. *Semin Respir Crit Care Med*. 2002 Dec;23(6):555-570. doi: 10.1055/s-2002-36520. PMID: 16088651.