Sarcoidosis

Subjects: Pathology
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Sarcoidosis is a multisystem granulomatous disease with nonspecific clinical manifestations that commonly aects the pulmonary system and other organs including the eyes, skin, liver, spleen, and lymph nodes. Sarcoidosis usually presents with persistent dry cough, eye and skin manifestations, weight loss, fatigue, night sweats, and erythema nodosum.

Keywords: sarcoidosis ; biomarkers ; diagnosis ; cause ; management

1. Introduction

Sarcoidosis is not influenced by sex or age, although it is more common in adults (< 50 years) of African-American or Scandinavians decent. Diagnosis can be dicult because of nonspecific symptoms and can only be verified following histopathological examination. Various factors, including infection, genetic predisposition, and environmental factors, are involved in the pathology of sarcoidosis. Exposures to insecticides, herbicides, bioaerosols, and agricultural employment are also associated with an increased risk for sarcoidosis. Due to its unknown etiology, early diagnosis and detection are dicult; however, the advent of advanced technologies, such as endobronchial ultrasound-guided biopsy, high-resolution computed tomography, magnetic resonance imaging, and 18F-fluorodeoxyglucose positron emission tomography has improved our ability to reliably diagnose this condition and accurately forecast its prognosis. In a recent review published in the Journal of Clinical Medicine (https://doi.org/10.3390/jcm9041081) discusses the causes and clinical features of sarcoidosis, and the improvements made in its prognosis, therapeutic management, and the recent discovery of potential biomarkers associated with the diagnostic assay used for sarcoidosis confirmation.

2. The cause of Sarcoidosis

The exact cause of sarcoidosis is not known. Many researchers have hypothesized the role of genetic susceptibility, environmental factors, putative antigens, and autoimmunity in the development of this disease, but no single cause has been identified to date.

2.1. Genetic Factors

Various studies suggest that genetic factors could play a crucial role in establishing the risk and clinical development of sarcoidosis[1]. Eleven sarcoidosis risk loci (BTNL2, HLA-B, HLA-DPB1, ANXA11, IL23R, SH2B3/ATXN2, IL12B, NFKB1/MANBA, FAM177B, chromosome 11q13.1, and RAB23) have been identified to date[2]. A previous study reported that familial sarcoidosis occurred in 17% of African-Americans[3], while only 1.4% of Spanish people exhibited this same risk[4]. According to A Case-Control Etiologic Sarcoidosis Study (ACCESS) the chance of developing sarcoidosis is five-fold among siblings[5]. Monozygotic siblings with sarcoidosis had an 80-fold higher risk of developing the condition, although the estimated risk of developing sarcoidosis in dizygotic twins was only seven-fold[6].

Genome wide association studies have demonstrated that several HLA and non-HLA alleles are associated with the development of this disease[7]. HLA-DRB1*0301/ DQB1*0201[8], transforming growth factor β (TGF-β)[9], tumor necrosis factor α (TNF-α)[10], and Toll-like receptor 4 (TLR-4)[11] are all considered significant indicators for susceptibility to sarcoidosis[12][13].

2.2. Environmental Risk Factors

Various environmental factors, including exposure to *wood stoves,* soil, tree pollen, inorganic particulates, insecticides, and nanoparticles, have been associated with an increased risk for developing sarcoidosis. In addition to these factors, some workers, such as those involved in hardware, gardening materials, building supplies, and metal work as well as ship servicemen in the navy, fire workers, and educators, are prone to sarcoidosis[14][15][16]. It has been suggested that silica exposure also triggers the risk of sarcoidosis[17]. The underlying hypothesis for this association is that the environment is

an important risk factor for the development of sarcoidosis, which has been further strengthened by reports that US World Trade Center workers exposed to the crash debris, in particular firefighters; all experienced an increased risk for developing sarcoidosis or “sarcoid-like” disease[18].

2.3. Infection

In addition to all of the factors mentioned above, infectious agents such as mycobacteria, have been suggested to be associated with the development of sarcoidosis, because the production of granulomas is a key factor in the immune defense response against these agents. Studies have identified numerous microbial agents as a potential eliciting agents of the immune response in sarcoidosis including *Leptospira* species, *Mycoplasma* species, herpes virus, retrovirus, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, [19] *Pneumocystis jirovecii*[20], *Mycobacterium (M.tb)*[21], and *Propionibacterium species*[22]. Isolation of *M.tb.* DNA, from tissue specimens collected from sarcoidosis patients, with sequences specific to mycobacterial proteins, such as ESAT-6, Kat G, and SoD A, illustrate that *Mycobacterium* is the strongest candidate for infection-mediated sarcoidosis[23][24][25]. It has been reported that patients treated with interferon α therapy for hepatitis C infection developed sarcoidosis[26][27]. A few studies have suggested that hepatitis C infection on its own could increase the risk of developing sarcoidosis. However, it seems more likely that therapy with interferon α increases interferon-γ and interleukin-2 expression, stimulating granuloma formation and thus sarcoidosis[28][29].

2.4. Autoimmunity

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. Although no disease-specific auto-antibodies have been observed, it has been shown that the major histocompatibility complex (MHC) class II molecules on antigen-presenting cells possess an autoantigen that is recognized by the T-cell receptor (TCR) of the responding T-cells in sarcoidosis patients[30][31]. Vimentin-derived peptides are the most plausible candidate for the activation of both T-cells and B-cells in the lung[32]. Autoimmunity presents a as a novel spectrum for sarcoidosis immunopathogenesis and may help elucidate sarcoid etiology[33][34][35].

Another important aspect of autoimmunity is the imbalanced gut microbiome. Gianchecchi et al. reported the associations between the presence of microbiome dysbiosis and the development of autoimmune conditions[36]. Sarcoidosis overlaps with other autoimmune diseases, including rheumatoid arthritis, autoimmune thyroid disease, Sjogren’s syndrome, and ankylosing spondylitis[37]. The role of the microbiota in these autoimmune diseases has been evaluated in previous studies and been shown to lay a significant role in their pathogenesis[38]; thus, study of the microbiome of sarcoidosis patients and its correlation with other diseases could open new avenues for investigating the underlying causes of this disease[39][40].

3. Immunopathogenesis of sarcoidosis

Many etiological agents, including infectious microbes, as well as organic and inorganic compounds, contribute to the development of sarcoidosis. These antigens are first cleared by the immune system, but this is not infallible and some undegraded antigens may remain in the cells, which can initiate an immune feedback loop. In response to this feedback loop, the antigen-presenting cells (APCs), such as dendritic cells (DCs), alveolar macrophages (AMs), and alveolar epithelial cells, produce high levels of TNF-α, and secrete interleukins-12, -15, and -18, macrophage inflammatory protein-1 (MIP-1), monocyte chemoattractant protein-1 (MCP-1), and granulocyte macrophage colony-stimulating factor (GM-CSF)[41]. These APCs also present antigens to CD4+ T-cells initiating granuloma construction, a critical feature of sarcoidosis. The growth of these granulomas establishes the primary abnormality in most cases of sarcoidosis. Sarcoid granulomas are ordered, structured masses comprised of macrophages and their derivatives, epithelioid cells, giant cells, and T-cells.

Activated CD4+ T-cells can differentiate into two distinct subsets, namely, T helper 1 (Th1) and T helper 2 (Th2) cells, based on their cytokines profile. Th1 cells predominantly secrete interleukin-2 (IL-2) and interferon-*gamma (IFN-y)*, while IL-4 and IL-13 are the major secretions of Th2 cells. Resolution or maintenance of granuloma is determined by the proportion of Th1 and Th2 cells, respectively. Alveolar macrophages are activated in the Th2 milieu and stimulate fibroblast and collagen proliferation culminating in progressive fibrosis[42].

Incapacitation of Tregs is also a key feature of granuloma maintenance. It is presumed that infiltrating Tregs fail to reduce the exaggerated inflammatory response, thereby contributing to granuloma persistence and integrity. Tregs also release transforming growth factor β (TGF-β) that may contribute to fibrosis and granuloma organization[43].

Th17 and Th17.1 cells have only recently been linked to the pathogenesis of sarcoidosis[44]. These cells are recruited to the disease site and are involved in the construction of the granuloma. The balance between Th17 and Treg cells is thought to be disrupted in sarcoidosis[45] and is an important factor in its prognosis[46]. The regulation of antigen processing, antigen presentation to the APCs, and cytokine release are all controlled through genetic elements and may link the various causal factors of sarcoidosis together[47][48][49].

References

1. Johan Grunewald; Paolo Spagnolo; Jan Wahlström; Anders Eklund; Immunogenetics of Disease-Causing Inflammation in Sarcoidosis. *Clinical Reviews in Allergy & Immunology* **2015**, *49*, 19-35, 10.1007/s12016-015-8477-8.
2. Annegret Fischer; David Ellinghaus; Marcel Nutsua; Sylvia Hofmann; Courtney G. Montgomery; Michael C. Iannuzzi; Benjamin A. Rybicki; Martin Petrek; Frantisek Mrazek; Stefan Pabst; et al. Identification of Immune-Relevant Factors Conferring Sarcoidosis Genetic Risk. *American Journal of Respiratory and Critical Care Medicine* **2015**, *192*, 727-736, 10.1164/rccm.201503-0418oc.
3. Benjamin A. Rybicki; Michael C. Iannuzzi; Epidemiology of Sarcoidosis: Recent Advances and Future Prospects. *Seminars in Respiratory and Critical Care Medicine* **2007**, *28*, 22-35, 10.1055/s-2007-970331.
4. Estrella Fernandez Fabrellas; Epidemiología de la sarcoidosis. *Archivos de Bronconeumología* **2009**, *43*, 92-100, 10.1157/13098420.
5. Benjamin A. Rybicki; Michael C. Iannuzzi; Margaret M. Frederick; Bruce W. Thompson; Milton D. Rossman; Eddy A. Bresnitz; Michael L. Terrin; David R. Moller; Juliana Barnard; Robert P. Baughman; et al. Familial Aggregation of Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine* **2001**, *164*, 2085-2091, 10.1164/ajrccm.164.11.2106001.
6. Asger Sverrild; Vibeke Backer; Kirsten Ohm Kyvik; Jaakko Kaprio; Nils Milman; Claus Bo Svendsen; Simon Francis Thomsen; Heredity in sarcoidosis: a registry-based twin study. *Thorax* **2008**, *63*, 894-896, 10.1136/thx.2007.094060.
7. Manfred Schürmann; Philipp Reichel; Bertram Müller-Myhsok; Max Schlaak; Joachim Müller-Quernheim; Eberhard Schwinger; Results from a Genome-wide Search for Predisposing Genes in Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine* **2001**, *164*, 840-846, 10.1164/ajrccm.164.5.2007056.
8. Mami Ishihara; Shigeaki Ohno; Takako Ishida; Hitoshi Ando; Taeko Naruse; Yoshisuke Nose; Hidetoshi Inoko; Molecular genetic studies of HLA class II alleles in sarcoidosis. *Tissue Antigens* **1994**, *43*, 238-241, 10.1111/j.1399-0039.1994.tb02331.x.
9. Stefan Pabst; T. Franken; J. Schönau; S. Stier; G. Nickenig; R. Meyer; D. Skowasch; C. Grohé; Transforming growth factor- gene polymorphisms in different phenotypes of sarcoidosis. *European Respiratory Journal* **2010**, *38*, 169-175, 10.1183/09031936.00120410.
10. S. Sharma; B. Ghosh; Association of TNF polymorphisms with sarcoidosis, its prognosis and tumour necrosis factor (TNF)-α levels in Asian Indians. *Clinical & Experimental Immunology* **2007**, *151*, 251-259, 10.1111/j.1365-2249.2007.03564.x.
11. S. Pabst; G. Baumgarten; A. Stremmel; M. Lennarz; P. Knüfermann; A. Gillissen; H. Vetter; C Grohé; Toll-like receptor (TLR) 4 polymorphisms are associated with a chronic course of sarcoidosis. *Clinical & Experimental Immunology* **2006**, *143*, 420-426, 10.1111/j.1365-2249.2006.03008.x.
12. Grunewald, J. Role of genetics in susceptibility and outcome of sarcoidosis. Semin. Respir. Crit. Care Med. 2010, 31, 380–389.
13. Iannuzzi, M.C. Genetics of sarcoidosis. Semin. Respir. Crit. Care Med. 2007, 28, 15–21.
14. 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.
15. Lee S. Newman; Cecile S. Rose; Eddy A. Bresnitz; Milton Rossman; Juliana Barnard; Margaret Frederick; Michael L. Terrin; Steven E. Weinberger; David R. Moller; Geoffrey McLennan; et al. A Case Control Etiologic Study of Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine* **2004**, *170*, 1324-1330, 10.1164/rccm.200402-249oc.
16. Kira L. Newman; Lee S. Newman; Occupational causes of sarcoidosis. *Current Opinion in Allergy and Clinical Immunology* **2012**, *12*, 145-150, 10.1097/aci.0b013e3283515173.
17. Per Vihlborg; Ing-Liss Bryngelsson; Lena Andersson; Pål Graff; Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries: a retrospective cohort study. *BMJ Open* **2017**, *7*, e016839, 10.1136/bmjopen-2017-016839.

18. Gabriel Izbicki; Robert Chavko; Gisela I. Banauch; Michael D. Weiden; Kenneth I. Berger; Thomas K. Aldrich; Charles B. Hall; Kerry J. Kelly; David J. Prezant; World Trade Center “Sarcoid-Like” Granulomatous Pulmonary Disease in New York City Fire Department Rescue Workers. *Chest* **2007**, *131*, 1414-1423, 10.1378/chest.06-2114.

19. L.S. Newman; Aetiologies of sarcoidosis. *Sarcoidosis* **2005**, *32*, 23-48, 10.1183/1025448x.00032003.

20. S. Vidal; C. De La Horra; J. Martin; M. A. Montes-Cano; E. Rodríguez; N. Respaldiza; J.M. Varela; Francisco J. Medrano; Enrique Calderón; Pneumocystis jirovecii colonisation in patients with interstitial lung disease. *Clinical Microbiology and Infection* **2006**, *12*, 231-235, 10.1111/j.1469-0691.2005.01337.x.

21. Wonder P. Drake; Lee S Newman; Mycobacterial antigens may be important in sarcoidosis pathogenesis. *Current Opinion in Pulmonary Medicine* **2006**, *12*, 359-363, 10.1097/01.mcp.0000239554.01068.94.

22. Ikuo Ishige; Yoshinobu Eishi; Tamiko Takemura; Intetsu Kobayashi; Koh Nakata; Isao Tanaka; Sakae Nagaoka; Kazuro Iwai; Kunitomo Watanabe; Touichiro Takizawa; et al. Propionibacterium acnes is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes from subjects without sarcoidosis.. *Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG* **2005**, *22*, 33-42, .

23. Shannon S Allen; Whitney Evans; James Carlisle; Rana Hajizadeh; Michele Nadaf; Bryan E Shepherd; David T Pride; Joyce E Johnson; Wonder P. Drake; Superoxide dismutase A antigens derived from molecular analysis of sarcoidosis granulomas elicit systemic Th-1 immune responses. *Respiratory Research* **2008**, *9*, 36-36, 10.1186/1465-9921-9-36.

24. Song, Z.; Marzilli, L.; Greenlee, B.M.; Chen, E.S.; Silver, R.F.; Askin, F.B.; Teirstein, A.S.; Zhang, Y.; Cotter, R.J.; Moller, D.R. Mycobacterial catalase-peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis. J. Exp. Med. 2005, 201, 755–767.

25. Drake,W.P.; Dhason, M.S.; Nadaf, M.; Shepherd, B.E.; Vadivelu, S.; Hajizadeh, R.; Newman, L.S.; Kalams, S.A. Cellular recognition of mycobacterium tuberculosis esat-6 and katg peptides in systemic sarcoidosis. Infect. Immun. 2007, 75, 527–530.

26. Atsushi Hirano; Mikio Kataoka; Yasunari Nakata; Katsuyuki Takeda; Takayuki Kamao; Junichi Hiramatsu; Goro Kimura; Yasushi Tanimoto; Arihiko Kanehiro; Mitsune Tanimoto; et al. Sarcoidosis occurring after interferon-alpha therapy for chronic hepatitis C: Report of two cases. *Respirology* **2005**, *10*, 529-534, 10.1111/j.1440-1843.2005.00745.x.

27. Hasan Salameh; Remi Trien; Chad J. Cooper; David Paez; Edgardo Colon; Shajeea Ajmal; Interferon-alpha-induced sarcoidosis in a patient being treated for hepatitis C. *American Journal of Case Reports* **2014**, *15*, 235-238, 10.12659/ajcr.890180.

28. Vadim Brjalin; Riina Salupere; Valentina Tefanova; Kaiu Prikk; Natalia Lapidus; Enn Jõeste.; Sarcoidosis and chronic hepatitis C: A case report. *World Journal of Gastroenterology* **2012**, *18*, 5816-5820, 10.3748/wjg.v18.i40.5816.

29. Manuel Ramos-Casals; Juan Mañá; Norma Nardi; Pilar Brito-Zerón; Antoni Xaubet; José Maria Sánchez-Tapias; Ricard Cervera; Josep Font; Sarcoidosis in Patients With Chronic Hepatitis C Virus Infection. *Medicine* **2005**, *84*, 69-80, 10.1097/01.md.0000157577.69729.e6.

30. Johan Grunewald; Ylva Kaiser; Mahyar Ostadkarampour; Natalia V. Rivera; Francesco Vezzi; Britta Lötstedt; Remi-André Olsen; Lina Sylwan; Sverker Lundin; Max Käller; et al. T-cell receptor–HLA-DRB1 associations suggest specific antigens in pulmonary sarcoidosis. *European Respiratory Journal* **2015**, *47*, 898-909, 10.1183/13993003.01209-2015.

31. Jan Wahlström; Jörn Dengjel; Ola Winqvist; Ira Targoff; Bengt Persson; Hüseyin Duyar; Hans-Georg Rammensee; Anders Eklund; Robert Weissert; Johan Grunewald; et al. Autoimmune T cell responses to antigenic peptides presented by bronchoalveolar lavage cell HLA-DR molecules in sarcoidosis. *Clinical Immunology* **2009**, *133*, 353-363, 10.1016/j.clim.2009.08.008.

32. Gernot Zissel; Joachim Müller-Quernheim; Specific antigen(s) in sarcoidosis: a link to autoimmunity?. *European Respiratory Journal* **2016**, *47*, 707-709, 10.1183/13993003.01791-2015.

33. Ylva Kaiser; Anders Eklund; Johan Grunewald; Moving target: shifting the focus to pulmonary sarcoidosis as an autoimmune spectrum disorder. *European Respiratory Journal* **2019**, *54*, 1802153, 10.1183/13993003.021532018.

34. Anna Starshinova; Anna M. Malkova; Natalia Y. Basantsova; Yulia S. Zinchenko; Igor V. Kudryavtsev; Gennadiy A. Ershov; Lidia A. Soprun; Vera A. Mayevskaya; Leonid P. Churilov; Piotr K. Yablonskiy; et al. Sarcoidosis as an Autoimmune Disease. *Frontiers in Immunology* **2020**, *10*, 2933, 10.3389/fimmu.2019.02933.

35. Anna Häggmark; Carl Hamsten; Emil Wiklundh; Cecilia Lindskog; Cecilia Mattsson; Eni Andersson; Ingrid E. Lundberg; Hans Grönlund; Jochen M. Schwenk; Anders Eklund; et al. Proteomic Profiling Reveals Autoimmune Targets in Sarcoidosis. *American Journal of Respiratory and Critical Care Medicine* **2015**, *191*, 574-583, 10.1164/rccm.201407-1341oc.

36. Elena Gianchecchi; Alessandra Fierabracci; Recent Advances on Microbiota Involvement in the Pathogenesis of Autoimmunity. *International Journal of Molecular Sciences* **2019**, *20*, 283, 10.3390/ijms20020283.

37. Peter Korsten; Björn Tampe; Maximilian F. Konig; Elena Nikiphorou; Sarcoidosis and autoimmune diseases. *Current Opinion in Pulmonary Medicine* **2018**, *24*, 504-512, 10.1097/mcp.0000000000000500.
38. Fengna Chu; Mingchao Shi; Yue Lang; Donghui Shen; Tao Jin; Jie Zhu; Li Cui; Gut Microbiota in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis: Current Applications and Future Perspectives. *Mediators of Inflammation* **2018**, *2018*, 1-17, 10.1155/2018/8168717.
39. André Becker; Giovanna Vella; Valentina Galata; Katharina Rentz; Christoph Beisswenger; Christian Herr; Jörn Walter; Sascha Tierling; Hortense Slevogt; Andreas Keller; et al. The composition of the pulmonary microbiota in sarcoidosis – an observational study. *Respiratory Research* **2019**, *20*, 46, 10.1186/s12931-019-1013-2.
40. Pleiades T. Inaoka; Masato Shono; Mishio Kamada; J. Luis Espinoza; Host-microbe interactions in the pathogenesis and clinical course of sarcoidosis. *Journal of Biomedical Science* **2019**, *26*, 45, 10.1186/s12929-019-0537-6.
41. Carlo Agostini; Fausto Adami; Gianpietro Semenzato; New pathogenetic insights into the sarcoid granuloma. *Current Opinion in Rheumatology* **2000**, *12*, 71-76, 10.1097/00002281-200001000-00012.
42. Thomas A. Wynn; Luke Barron; Macrophages: Master Regulators of Inflammation and Fibrosis. *Seminars in Liver Disease* **2010**, *30*, 245-257, 10.1055/s-0030-1255354.
43. Branton, M.H.; Kopp, J.B.; Tgf-beta and fibrosis. *Infect* **1999**, *1*, 1349–1365, .
44. Jelle R. Miedema; Ylva Kaiser; Caroline E. Broos; Marlies S. Wijsenbeek; Johan Grunewald; M. Kool; Th17-lineage cells in pulmonary sarcoidosis and Löfgren's syndrome: Friend or foe?. *Journal of Autoimmunity* **2018**, *87*, 82-96, 10.1016/j.jaut.2017.12.012.
45. Hui Huang; Zhiwei Lu; Chunguo Jiang; Jia Liu; Yan Xun Wang; Zuojun Xu; Imbalance between Th17 and Regulatory T-Cells in Sarcoidosis. *International Journal of Molecular Sciences* **2013**, *14*, 21463-21473, 10.3390/ijms141121463.
46. Yongzhe Liu; Lan Qiu; Yanxun Wang; Halimulati Aimurola; Yuyue Zhao; Shan Li; Zuojun Xu; The Circulating Treg/Th17 Cell Ratio Is Correlated with Relapse and Treatment Response in Pulmonary Sarcoidosis Patients after Corticosteroid Withdrawal. *PLoS ONE* **2016**, *11*, e0148207, 10.1371/journal.pone.0148207.
47. Adrian Kelly; John Trowsdale; Genetics of antigen processing and presentation. *Immunogenetics* **2018**, *71*, 161-170, 10.1007/s00251-018-1082-2.
48. Jamie A Lee; Robert S. Sinkovits; Dennis Mock; Eva L Rab; Jennifer Cai; Peng Yang; Brian Saunders; Robert C Hsueh; Sangdun Choi; Shankar Subramaniam; et al. Components of the antigen processing and presentation pathway revealed by gene expression microarray analysis following B cell antigen receptor (BCR) stimulation. *BMC Bioinformatics* **2006**, *7*, 237-237, 10.1186/1471-2105-7-237.
49. David Bennett; Elena Bargagli; Rosa Metella Refini; Paola Rottoli; New concepts in the pathogenesis of sarcoidosis.. *Expert Review of Respiratory Medicine* **2019**, *13*, 981-991, 10.1080/17476348.2019.1655401.
