JOURNAL OF WORLD SCIENCE
https://jws.rivierapublishing.id/index.php/jws
Volume 3 No. 2 February 2024
P-ISSN: 2828-8726
E-ISSN: 2828-9307

SARCOIDOSIS: EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS, AND DIAGNOSIS

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ABSTRACT
Interstitial lung disease is a lung condition with wide variations. There are over 200 disorders classified under interstitial lung disease, including sarcoidosis. Sarcoidosis is a systemic disease characterized by the formation of non-caseating granulomas involving the lungs, lymphatic system, skin, and eyes. Clinical manifestations of sarcoidosis vary greatly, ranging from asymptomatic to severe symptoms with uncertain prognosis. The cause of sarcoidosis remains unknown, though several hypotheses suggest its association with genetic, environmental, infectious, and autoimmune factors. The main pathogenesis involves the formation of non-caseating granulomas involving various types of innate and adaptive immune cells. Based on its clinical presentation, sarcoidosis is classified into two types: Lofgren syndrome and non-Lofgren syndrome. Diagnosis of this disease can be established through clinical examination, radiological imaging, and biopsy revealing non-caseating granulomas. Corticosteroid therapy remains the primary treatment option, alongside immunosuppressive and biological therapies for advanced-stage sarcoidosis.

Keywords: Noncaseating Granuloma, Interstitial Lung Disease, Sarcoidosis, Lofgren's Syndrome.

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INTRODUCTION

Interstitial lung disease is a lung disease that has vast variations. There are more than 200 disorders that fall into the group of interstitial lung diseases. Interstitial lung disease includes areas with various cell types such as fibroblasts, myofibroblasts, macrophages, and many matrix components such as collagen, elastin, and proteoglycans. These matrix components lie between the alveolar epithelium and the vascular endothelium. Interstitial lung disease is a rare disease. The most common interstitial lung disease is idiopathic pulmonary fibrosis (IPF). This disease has a low survival rate (Putra et al., 2017).

Interstitial lung disease has several classifications. As seen in Figure 1, the classification currently used divides interstitial lung disease into five groups, namely autoimmune-related interstitial lung disease, idiopathic interstitial pneumonia, hypersensitivity pneumonitis, sarcoidosis, and other forms of interstitial lung disease. One form of interstitial lung disease is pulmonary sarcoidosis (Cottin et al., 2018) . In this literature review, the author will discuss the epidemiology, definition, clinical picture, diagnosis, and management of sarcoidosis.

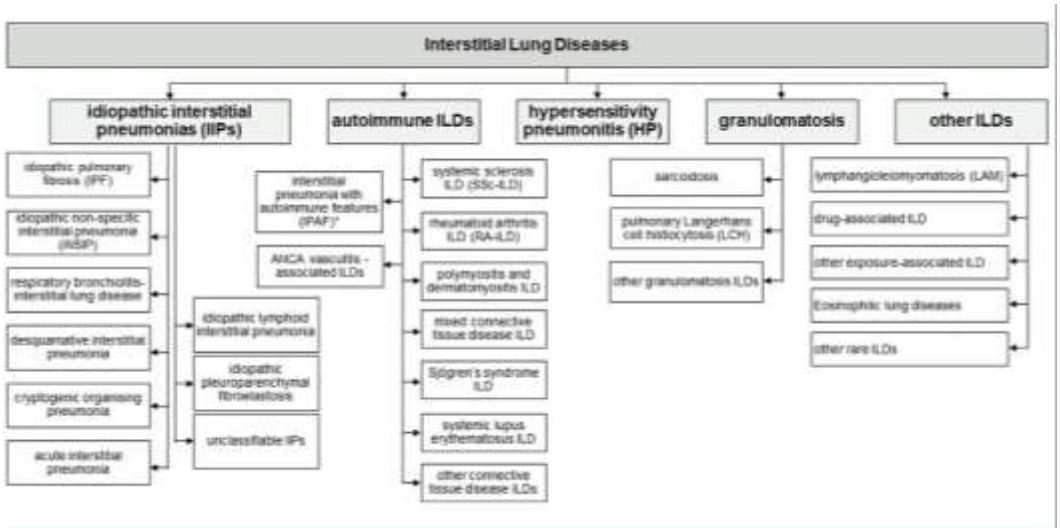

Figure 1. Classification of Interstitial Lung Disease

Based on the background above, the objective of this research is to understand the characteristics of interstitial lung disease, specifically sarcoidosis. This study is expected to provide a deeper understanding of the variations in clinical symptoms, possible causes, and diagnostic methods of this disease. With a better understanding of sarcoidosis, it is hoped to improve the ability to diagnose and manage this condition, as well as to benefit patients through increased effectiveness of therapy and care.

METHOD

The method used involves a literature review to gather current information on interstitial lung disease, particularly sarcoidosis, including variations in clinical symptoms, possible causes, and diagnostic methods used. This is based on data sources from both online and offline references, including books, journals, and articles related to the topic.

RESULTS AND DISCUSSION

Sarcoidosis is a systemic disease characterized by the formation of noncaseating granulomas involving the lungs. Lung involvement can reach 90%, while other organs that can be affected include the lymphatic system, skin, and eyes. The clinical manifestations of sarcoidosis vary widely, ranging from asymptomatic to causing severe symptoms with an undetermined prognosis (Sikjær et al., 2021). Sarcoidosis was first identified by Jonathan Hutchinson in 1869 in a 58-year-old coal dock worker (Spagnolo, 2015). Sarcoidosis has an acute, subacute, and chronic onset and can attack various organs, especially the lungs (Sikjær et al., 2021).

Several other organs can be involved in this disease, including the lymphatic system, skin, eyes, liver, spleen, nervous disorders, and heart. The proportion of involvement of other organs can be seen in Table 1 (Polverino et al., 2020). Sarcoidosis is very difficult to diagnose because it often resembles various diseases, including infections, vasculitis, drug reactions, and malignancies. Sarcoidosis is generally benign, and most patients do not require treatment. Complete resolution occurs in almost 50% of cases, and only a third of cases of this disease develop into chronic and progressive disease (Bernardinello et al., 2021).

Table 1. Organ Involvement in Sarcoidosis

Organ	Frequency (%)
Lungs	90
Skin (excluding erythema nodosum)	16
Erythema nodosum	8
I measured	12
Extrathoracic lymph node	15.2
Liver	12
Spleen	7
Nerve	5
Heart	2

Epidemiologist

Sarcoidosis occurs worldwide and most commonly affects young and middle-aged people of all races and genders. The incidence of this disease is most common in Scandinavian countries. Data in Sweden shows the incidence of this disease reached 11.5 per 100,000 population. This data is higher than that of the United States, which reached 8-11 per 100,000 people, and Canada's 6.8 per 100,000 people. The incidence of this disease in the East Asian region is lower. Data in South Korea shows the incidence of this disease reaches 0.5-1.3 per 100,000 population. The incidence and prevalence of this disease can be seen in Table 2 (Arkema & Cozier, 2020).

Table 2. Incidence and Prevalence of Sarcoidosis

Country	Prevalence per 100,000	Incidence per 100,000 per year
Australia		4.7
Belgium	2	0.3
Canada	143	6,8
Croatia		3.3
Czech Republic	63.1	4.4
Denmark		7.2
Finland	28	11.4
French	30	4.9
Greece	5.9	1.07
Ireland	28	
Italy	49	
Japan	3.7	1
Poland	6.5	5.9
Saudi Arabia	13	
South Korea	4.69	0.48
Sweden	160	11.5
Switzerland	121	7
Taiwan	2,2	
Türkiye		4
English	11	
United States of America	60	8.3

Etiology

The leading cause of sarcoidosis has not yet been found, but several researchers have hypothesized that it can cause sarcoidosis. Sarcoidosis develops due to complex immune interactions with environmental exposures and a person's genetic factors. Several hypotheses that can cause this disease include genetic factors, environmental exposure, infection, and autoimmune. Sarcoidosis is frequently reported in patients with autoimmune thyroid disease, Sjogren's syndrome, and systemic sclerosis. This disease is also often found in patients with airway diseases such as asthma and chronic obstructive pulmonary disease (Jain et al., 2020).

Genetic factors

Various studies show that genetic factors play an essential role in determining the risk and clinical development of sarcoidosis. Eleven loci associated with the risk of sarcoidosis have been identified, namely butyrophilin like 2 (BTNL2), human leukocyte antigen B (HLA-B), human leukocyte antigen beta chain 1 (HLA-DPB1), annexin A11 (ANXA11), interleukin 23 receptor (IL -23R), SH2 adapter protein 3 (SH2B3), ataxin 2 (ATXN2), IL-12B, nuclear factor kappa B subunit 1 (NFKB1/MANBA), family with sequence similarity 177 member B (FAM177B), chromosome 11q13.1 and ras-related protein (RAB 23). A study showed that familial sarcoidosis occurred in 17% of African Americans, and only 1.4% of Spaniards showed the same risk. Granuloma-encoding genetic variations also play a role in this process (Jain et al., 2020).

In a Case Control Etiologic Study of Sarcoidosis (ACCESS) research, there is a family history factor in this disease. Siblings have five times the risk of developing sarcoidosis, and monozygotic siblings have an 80-fold higher risk of developing sarcoidosis. Genomic studies also show that several HLA and non-HLA alleles are associated with the development of this disease. Transforming growth factor beta (TGF- β), tumor necrosis factor-alpha (TNF- α), toll-like receptor 4 (TLR-4), and the subgenre HLA-DRB1*0301/DQB1*0201 are considered significant indicators for susceptibility to sarcoidosis (Jain et al. al., 2020).

Environmental factor

Various environmental factors, such as exposure to wood stoves, soil, tree pollen, inorganic particulates, insecticides, and nanoparticles, are thought to be associated with an increased risk of sarcoidosis. In addition, marines, firefighters, and some workers involved in plantation materials, building supplies, and metalwork are susceptible to sarcoidosis. Exposure to silica dust is also associated with this disease. This hypothesis is strengthened by reports that workers at the World Trade Center, especially firefighters, experienced an increase in the incidence of sarcoid-like diseases (Newman & Newman, 2012).

Infection

Several other studies have also identified infectious agents that trigger the immune response in sarcoidosis, namely Leptospira sp, Mycoplasma sp, herpes viruses, retroviruses, Chlamydia pneumoniae, Borrelia burgdorferi, Pneumocystis jirovecii, Mycobacterium tuberculosis, and Propionibacterium sp. Mycobacterium tuberculosis infection is considered to be one of the causes of sarcoidosis. This is because granuloma production is a critical factor in the immune response to this agent. Isolation of these bacterial proteins, mainly the early secreted antigenic target 6 (ESAT6), catalase-peroxidase (KatG), and superoxide dismutase A (SoD A) proteins from sarcoidosis patient tissue, shows that these bacteria are the strongest candidates for sarcoidosis. Other studies also

show that hepatitis C patients who receive interferon alpha (IFN- α) therapy can develop sarcoidosis. Administration of IFN-γ therapy will increase the expression of gamma interferon (IFN- γ) and IL-2, which stimulate granuloma formation and increase the incidence of sarcoidosis (Jain et al., 2020).

Autoimmune

Autoimmunity may help explain the immunopathogenesis of sarcoidosis, especially sarcoid etiology. Major histocompatibility complex (MHC) class II molecules on antigen-presenting cells have autoantigens that are recognized by T cell receptors in sarcoidosis patients. There is a strong association between MHC class II alleles and the T cell receptor subfamily in the clinical course of sarcoidosis. Vimentin, an MHC class II peptide, can function as an antigen and activate T cells in sarcoidosis patients. T cells carrying the TCR V α2.3/V β22 chain accumulate in the lungs of patients with Lofgren's syndrome (Zissel & Müller-Quernheim, 2016).

Pathogenesis

Natural immune response

The natural immune system provides the first protection against invading microbes, as seen in Figure 2. Host cells will express receptors on the cell surface, endosomal membrane, or in the cytoplasm to recognize pathogen-associated molecular patterns (PAMP) found in bacteria, viruses, fungi, and protozoa. One of the receptors expressed is nucleotide-binding oligomerization domain and leucine-rich repeat-containing receptors (NLRs). This receptor is one of the inflammatory components of the NLRP-inflammasome. This inflammatory component is a large multiprotein complex consisting of adapter proteins such as caspase-1. The formation of this protein results in the activation of caspase-1, which activates IL-1 $\beta$and IL-18 (Lee et al., 2020).

Increased NLRP-inflammasome and caspase-1 were found in the granulomas of patients with cardiac sarcoidosis. This study also showed an increase in IL-1 released by alveolar macrophages and unstimulated monocytes from sarcoidosis patients. In addition to caspase-1, the transcription factor hypoxia-inducible factor 1-alpha (HIF-1 α) also increases the production of IL-1 $\beta$and IL-17 because HIF-1 is expressed in the central granulomatous tissue and giant cells in pulmonary sarcoidosis patients. Shamaei et al.'s research also showed an increase in type 2 (M2) macrophages in the lymph nodes and non-lymphatic tissue of sarcoidosis patients (Lee et al., 2020).

In the research, Matsuyama et al. also showed a decrease in the expression of mucosal-associated invariant T-cells (MAIT) in the peripheral blood of sarcoidosis patients, which produce pro-inflammatory cytokines including IFN- $\gamma$and TNF- α. Increased expression of programmed cell death (PD-1) was also found in this study. In addition, researchers also reported an increase in the number and frequency of MAIT cells in the bronchoalveolar cavities in sarcoidosis patients with lung parenchymal involvement. A decrease in natural immune cells, such as natural killer (NK) cells, was also found in sarcoidosis patients (Lee et al., 2020).

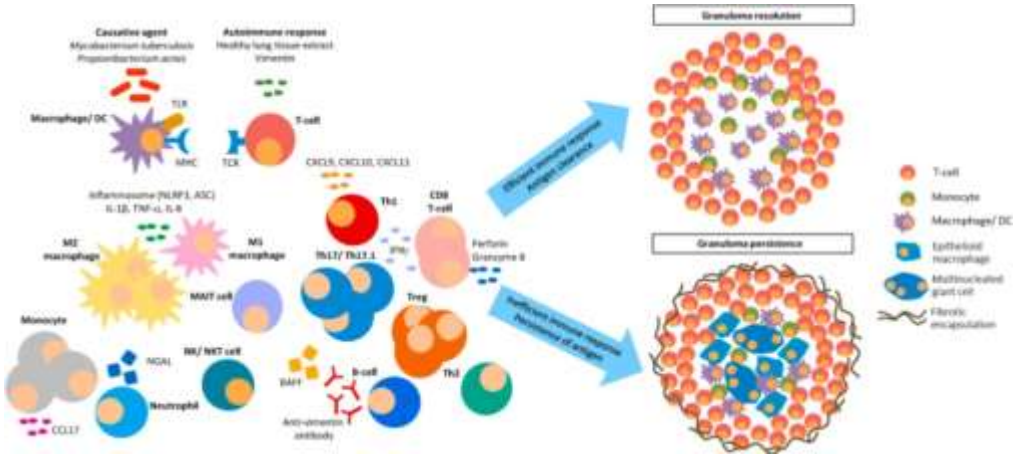

Figure 2. Natural and Adaptive Immune Responses in Granuloma Formation

Adaptive immune response

In addition to macrophages and dendritic cells, the sarcoid granulomas that form consist of infiltrating T cells and B cells. Analysis of lymphocyte profiles in lymph nodes taken from endobronchial ultrasound-guided transbronchial needle aspiration shows an increased ratio of CD4 $^{+}$ T cells/CD8 $^{+}$ T cells compared to accumulating. bronchoalveolar sarcoidosis patients. Several recent studies have demonstrated an essential role for adaptive immune system cells in the development of sarcoidosis. The increase in adaptive immune cells in sarcoidosis patients can be seen in Table 3 (Lee et al., 2020).

Table 3. Adaptive Immune Responses in Sarcoidosis

Sample	Findings
Blood, bronchoalevolar smear	Increased T helper 1 (Th1) cytokines, decreased proliferation, increased apoptosis and PD-1 expression in CD4 T cells, increased percentage of chemokine receptor 4 (CCR4 $^{+}$) $^{CD4+}$ T cells, increased TGF production by PD-1 $^{+, CD4+}$ T cells and helper T cells 17, increased T-reg cells, increased percentage of naïve B cells, decreased percentage of memory B cells.
Serum	Increased chemokine ligand 9 (CXCL9), CXCL10 and CXCL11, Increased vimentin antibody levels, increased B cell activation factor
Lymph nodes	Increased percentage of Th cells 17.1

Granuloma Formation in Sarcoidosis

Granuloma is a differentiation of immune cells with a lymphoid-like structure. Sarcoid granulomas are often found in the lungs, lymph nodes, eyes, and skin. The process of granuloma formation begins when aggregated macrophages are converted into epithelioid cells, which then form immature granulomas. Inflammatory signals cause macrophages and monocytes or dendritic cells to fuse to form multinucleated giant cells. Macrophages will then activate and attract T lymphocyte cells to the site of inflammation to form mature granulomas. Granuloma formation occurs due to the failure of antigen elimination. Granulomas function to protect antigens from spreading. The structure of sarcoid granuloma consists of two segments, namely the core and the

crust. The granuloma core consists of groups of macrophages, epithelioid cells, and multinucleated giant cells, while the crust area consists of high levels of T lymphocytes and few B lymphocytes (Sakthivel & Bruder, 2017).

In the process of chronic granuloma formation, as seen in Figure 3, alveolar macrophages will present antigens to MHC class II thereby converting CD4 $^{+}$ T cells. naïve to activated CD4 $^{+}$ T cells . CD4 $^{+}$ T cells will release IFN- and migrate to the site of inflammation guided by the chemokine receptor CXCR3. Apart from CXCR3, these cells also excrete the cytokine tumor necrosis factor-like cytokine 1A (TLA1) to interact with death receptor 3 (DR3) and produce high amounts of matrix metalloproteinase-9. This will make macrophages increasingly activated, thereby releasing TLR9. Activation of TLR9 will increase CXCL10 so that it will attract more Th 1 lymphocytes to the granuloma. Activated macrophages will also increase the regulation of interleukin-1 receptor-associated kinase 1 (IRAK-1) and receptor-interacting protein 2 (RIP 2) expression, which will increase the production of IL-1 βand IL-6. This cytokine is used for the differentiation of Th 17 lymphocytes. The accumulation of Th 17 produces the cytokines IL-17 and IL-22 (Sakthivel & Bruder, 2017).

In the process of acute granuloma formation that occurs in Lofgren's syndrome, alveolar macrophages present vimentin to class II HLA-DR3 molecules, thereby activating CD4 T lymphocytes that carry the Va2.3/Vb22 TCR chain. These specific T lymphocytes secrete high amounts of IL-17 and IL-22 and γlow amounts of IFN-. In addition, Treg cells that accumulate in granulomas will show increased levels of inducible costimulator (ICOS), thereby increasing IL-10 secretion by Tregs and creating an immunosuppressive state. B lymphocyte cells also have a role in the formation of acute granulomas. This is indicated by an increase in Propionibacterium acnes-specific immunoglobulin A antibodies in Lofgren syndrome patients (Sakthivel & Bruder, 2017).

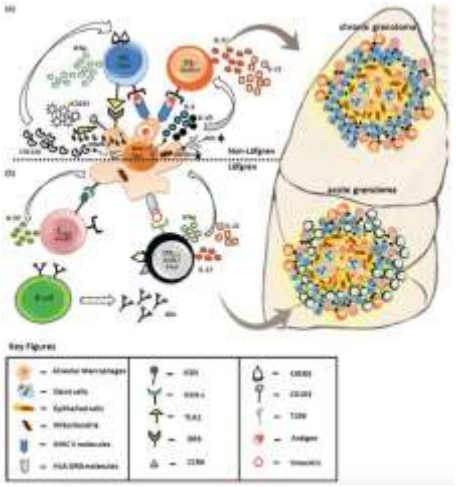

Figure 3. Granuloma Formation in Sarcoidosis

Resolution and Persistence of Granulomas in Sarcoidosis

The granuloma that forms can undergo resolution or be persistent, as seen in Figure 4. Exposure to an unknown antigen can cause the resolution or progression of the granuloma. Granuloma resolution occurs when peptide antigens are presented by HLA-DR3 molecules on dendritic cells or macrophages and recognized by specific T cell receptors segment variable chain 8 (TRBV8), α-chain variable 2.3 (TRAV 2.3) and CD4 $^{+}$TRAV 2.3^{+}TRBV22^{+} T cells. The resulting immune response is so efficient that the antigen can be eliminated, and the granuloma is resolved. On the

other hand, granuloma development occurs if antigen recognition does not occur properly. This could be due to the peptide antigen not being presented by the HLA-DR3 molecule or T cell inactivation (Grunewald et al., 2019).

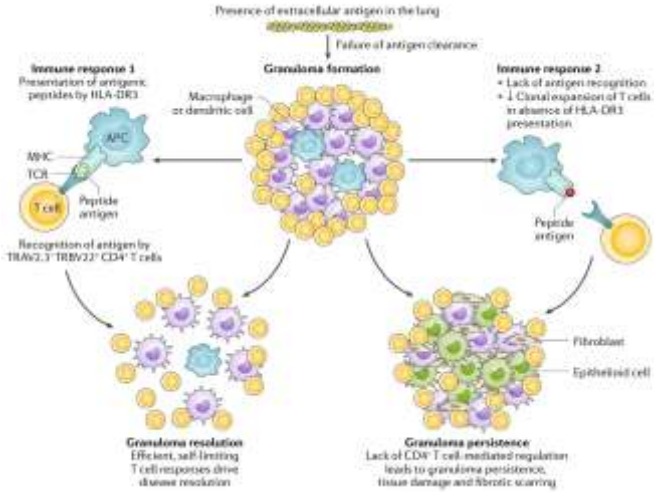

Figure 4. Process of Resolution and Persistence of Granuloma in Sarcoidosis

Pathology

A diagnosis of sarcoidosis can be made by looking at clinical and radiological images. However, pathological images can also support this diagnosis. Based on pathology, a non-caseating granuloma can be found on biopsy, as seen in Figure 5. Granuloma is an area of inflammation formed by epithelioid cells, lymphocytes, leukocytes, and plasma cells. Epithelioid cells can fuse to form multinucleated giant cells located at the edges and center of the granuloma. Giant cells can reach a diameter of 50 microns, consist of abundant cytoplasm, and contain more than 20 small cell nuclei. The nuclei of these small cells will be scattered at the edges and are called Langerhans-type giant cells. Apart from that, it can also be spread in the cytoplasm in so-called giant cells similar to foreign objects. These granulomas can be found in various organs. The choice of organ biopsy must consider the risks and complications that may occur (Tana et al., 2022).

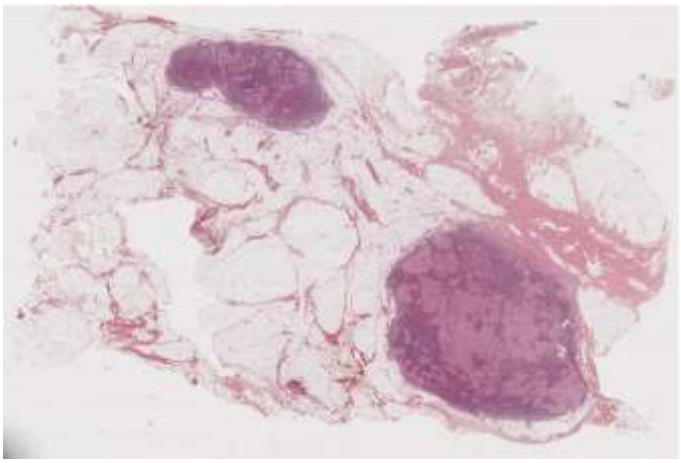

Figure 5. Histopathology of Granulomas in Sarcoidosis

Clinical Features

The clinical manifestations of sarcoidosis are very diverse because the disease affects various organs. The onset of this disease can be acute, subacute, or chronic. Based on the hypothesis, this difference is due to different immunological features. Based on clinical and immunological features, sarcoidosis is divided into Lofgren's syndrome and non-Lofgren's syndrome. In most cases, this disease can heal spontaneously within two years. The number of recoveries decreases if the disease occurs for five years, so in its development, this disease can be divided into acute onset, namely for two years, and chronic for three to five years (Polverino et al., 2020).

Lofgren's syndrome

Lofgren's syndrome is characterized by symptoms of fever, erythema nodosum, arthritis, and bilateral hilar lymphadenopathy with an acute onset. This syndrome is strongly associated with the HLA B8 serotype HLA-B*. The acute onset of the disease is associated with spontaneous resolution and an excellent prognosis. In patients in Europe and Sweden, this syndrome has a good prognosis even without therapy. In general, patients with Lofgren's syndrome will improve after administering corticosteroids. Apart from Lofgren's syndrome, acute-onset sarcoidosis can also be found in Heerfordt-Waldenstrom syndrome. This syndrome is a rare form of sarcoidosis. This rare form of sarcoidosis is characterized by typical symptoms such as parotitis, facial paralysis, anterior uveitis, and fever. Radiological images show typical enlargement of the parotid glands and enlarged lymph nodes (Polverino et al., 2020).

NonLofgren's syndrome

NonLofgren's syndrome is another form of sarcoidosis with a subacute to chronic onset. This form is more heterogeneous. The clinical features of this disease are cough, shortness of breath, arthralgia, fatigue, chest pain, muscle pain, night sweats, and weight loss. Fatigue is a widespread complaint in patients. This complaint is felt by 50-70% of patients, which causes a decrease in quality of life and disability. Chronic sarcoidosis is associated with an increased risk of developing fibrosis, pulmonary arterial hypertension, and permanent loss of lung function, affecting quality of life. Extrapulmonary manifestations associated with a poor prognosis are lupus pernio, chronic uveitis, chronic hypercalcemia, nephrocalcinosis, cystic bone lesions, and myocardial involvement. An overview of the clinical manifestations of sarcoidosis can be seen in Table 4 (Polverino et al., 2020).

Table 4. Clinical Features of Sarcoidosis Based on Organs Affected

Organ	Clinical picture
Lungs	Dry cough, wheezing, shortness of breath, fatigue. Acute: pleural effusion, pericardial effusion, pneumothorax, lymph nodes Chronic: pulmonary fibrosis and respiratory failure
Lymph gland	Peripheral lymphadenopathy, swollen and painless lymph nodes.
Endocrine (thyroid and parotid glands)	Thyroid dysfunction, enlargement of the parotid gland, affects the hypothalamic-pituitary axis, causing diabetes insipidus.
Skin	Erythema nodosum, nodules, paul and plaque
Eye	Pain, photophobia, and hyperemia are often associated with Lofgren's syndrome.

Organ	Clinical picture
Bone	Osteoporosis, osteopenia, arthritis, arthralgia, and cystic lesions.
Upper respiratory tract	Regarding the larynx, pharynx, and nose
Kidney	Nephrocalcinosis, interstitial nephritis, and renal failure.
Heart	Heart failure, arrhythmia, and syncope
Nerve	Facial weakness, meningeal inflammation, encephalopathy, vasculopathy, seizures and hydrocephalus.
Liver and spleen	Enlarged liver and spleen, intrahepatic cholestasis, portal hypertension, changes in liver function.

Radiological Features

Lung imaging is essential to help establish the diagnosis in all patients with suspected sarcoidosis. Chest X-rays are routinely used to evaluate patients with suspected sarcoidosis. Chest X-rays often reveal bilateral hilar lymph node enlargement, which occurs in 50-85% of patients, and parenchymal changes, which occur in 25-60% of patients. In the 1960s, Guy Scadding developed a sarcoidosis staging system based on chest radiographs. The staging system based on Scadding is shown in Figure 6 and Table 5 (Bernardinello et al., 2021; Jain et al., 2020; Sève et al., 2021).

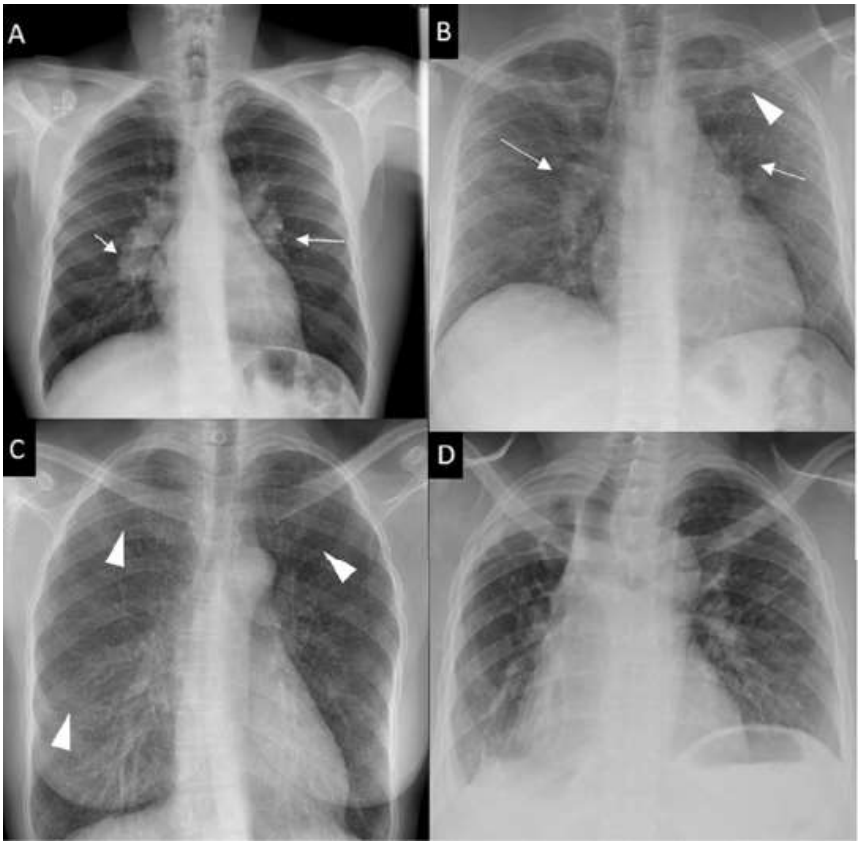

Figure 6. Scadding staging system chest x-ray. (A) Stage I bilateral hilar lymph node enlargement (white arrow), (B) Stage II bilateral hilar lymph node enlargement and left upper lobe infiltrate

(white arrow), (C) Stage III pulmonary infiltrate without lymph node enlargement, (D) Stage IV pulmonary fibrosis

Table 5. Scadding Staging System

Staging	Radiological picture
0	There are no abnormalities
I	Bilateral hilar lymph node enlargement
II	Bilateral hilar lymph node enlargement and parenchymal infiltrates
III	Parenchymal infiltrate without hilar lymph node enlargement on regular chest X-ray
IV	Advanced fibrosis with distortion of the normal lung, especially in the middle and upper lobes, with evidence of bronchiectasis, hilar retraction, bullae, cysts, and rarely honeycombing.

Another imaging that can be used to help diagnose sarcoidosis is thoracic high-resolution computed tomography (HRCT). This imaging has a higher sensitivity for detecting abnormalities in the hilus, mediastinum, and parenchyma. Based on this imaging, typical lesions of sarcoidosis include micronodules scattered along the veins, bronchi, vasculature, and pleura. Micronodules can turn confluent, causing conglomeration images such as masses and distortion of the lung parenchyma. The appearance of this conglomerated mass is sometimes surrounded by many micronodules resembling a galaxy sign. The appearance of thoracic HRCT abnormalities can also be divided into typical and atypical, as shown in Table 6, figures 7 and 8 (Bernardinello et al., 2021; Cozzi et al., 2018).

Table 6. Typical and Atypical Features of Sarcoidosis on HRCT

Typical picture	Atypical picture
Nodules with lymphatic spread in the peri broncho vascular interstitial spaces and interlobular septa	Atypical picture of isolated, unilateral, enlarged lymph nodes with calcification
Bilateral hilar lymph node enlargement	Pulmonary masses and nodules
Fibrotic changes: linear and reticulated opacities, thickening of interlobular septa, traction bronchiectasis, and reduction in lung volume	Interstitial fibrosis: bullae, cysts, honeycomb-shaped opacities in the upper and middle lobes of the lung, emphysema
Predominant in the upper and middle lobes of the lung	Ground-glass opacity
	Pleural involvement: pneumothorax, effusion, and pleural thickening
	Linear opacity: thickening of the interlobular septa
	Hello Sign
	Airway involvement: atelectasis, mosaic-attenuation, tracheobronchial changes

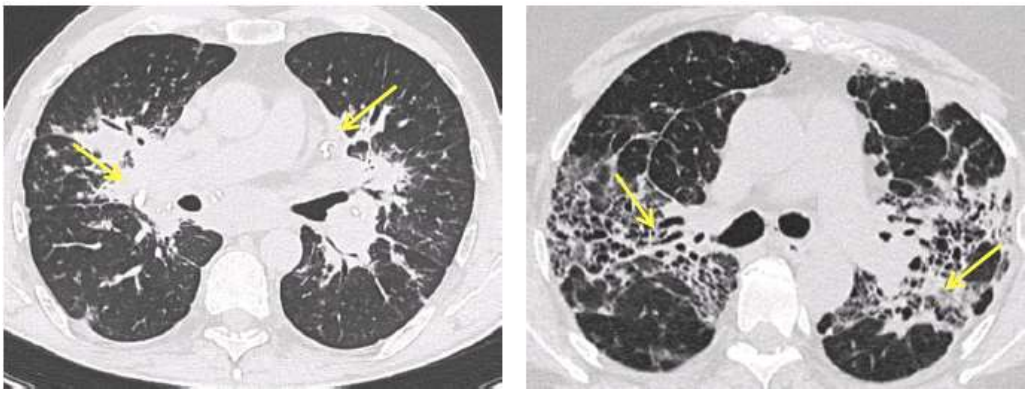

Figure 7. Typical sarcoidosis lesions, (C) bilateral hilar lymph node enlargement, (D) cystic fibrosis with traction bronchiectasis in the perihilar upper lobe

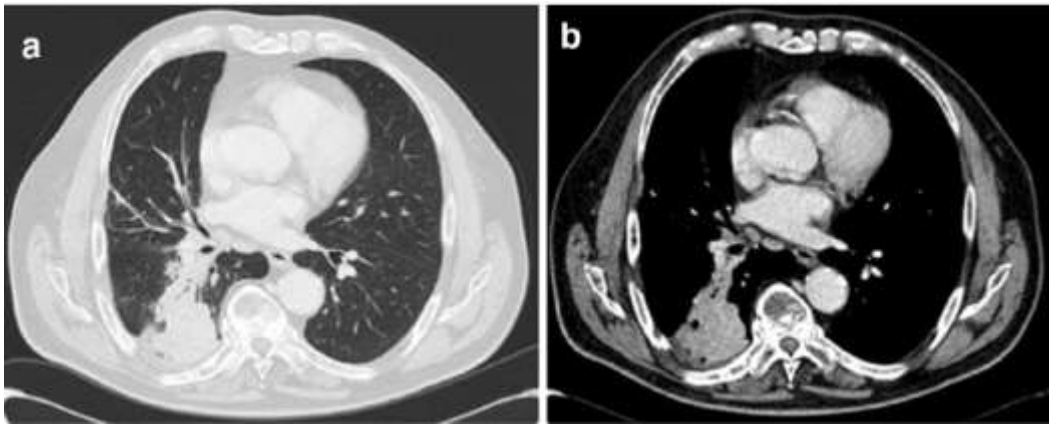

Figure 8. Atypical lesions, (a) and (b) peripheral consolidation with air bronchogram in the lower lobe of the right lung resembling a mass in malignancy and organizing pneumonia

Diagnosis

The diagnosis of sarcoidosis is a challenge for every clinician. This is due to the involvement of many organs, causing various clinical manifestations. Physical and radiological examinations supported by biopsy results of noncaseating granulomas can confirm the diagnosis of sarcoidosis. In patients with clear clinical manifestations such as Lofgren's syndrome and Heerfordt's syndrome, diagnosis based on clinical examination and chest x-ray is considered sufficient. In other cases, the diagnosis of sarcoidosis must be confirmed histologically. There is an algorithm that can be used to help diagnose sarcoidosis, as shown in Figure 9 (Spagnolo et al., 2018).

The clinical diagnosis of sarcoidosis can be made in patients based on clinical and radiological findings. Another supporting examination that can be used is a biopsy. If the biopsy results show granulomatous inflammation and there are still alternative diagnoses, the diagnosis of sarcoidosis cannot be made. However, if an alternative diagnosis is not available, then sarcoidosis may be diagnosed. The results of the biopsy examination did not show granulomatous inflammation. However, there were additional suggestive features, which included a negative tuberculin test, serum angiotensin converting enzyme more than twice the standard limit, bronchoalveolar lymphocytosis more than twice the average value, $CD4^+/CD8^+$ ratio more than 3.5 in bronchoalveolar calculi and hypercalciuria make the diagnosis of sarcoidosis possible (Spagnolo et al., 2018).

The extensive involvement of the lungs in this disease means that the role of bronchoscopy is vital to help confirm the diagnosis. A cobblestone appearance can be found in the mucosa of patients with sarcoidosis. Apart from that, another action that can be taken is cellular analysis of bronchoalveolar smears. On cellular analysis examination, an increase in the number of lymphocytes > 25% and an increase in the $CD4^+$ /$CD8^+$ ratio are often found. An increase in the $CD4^+$ /$CD8^+$ ratio > 3.5 has a specificity of 93-96%, even though the sensitivity is only 53-59%. However, in other studies, an increase in the $CD4^+$/$CD8^+$ ratio > 10 has a specificity value of > 99% for diagnosing sarcoidosis (Bernardinello et al ., 2021).

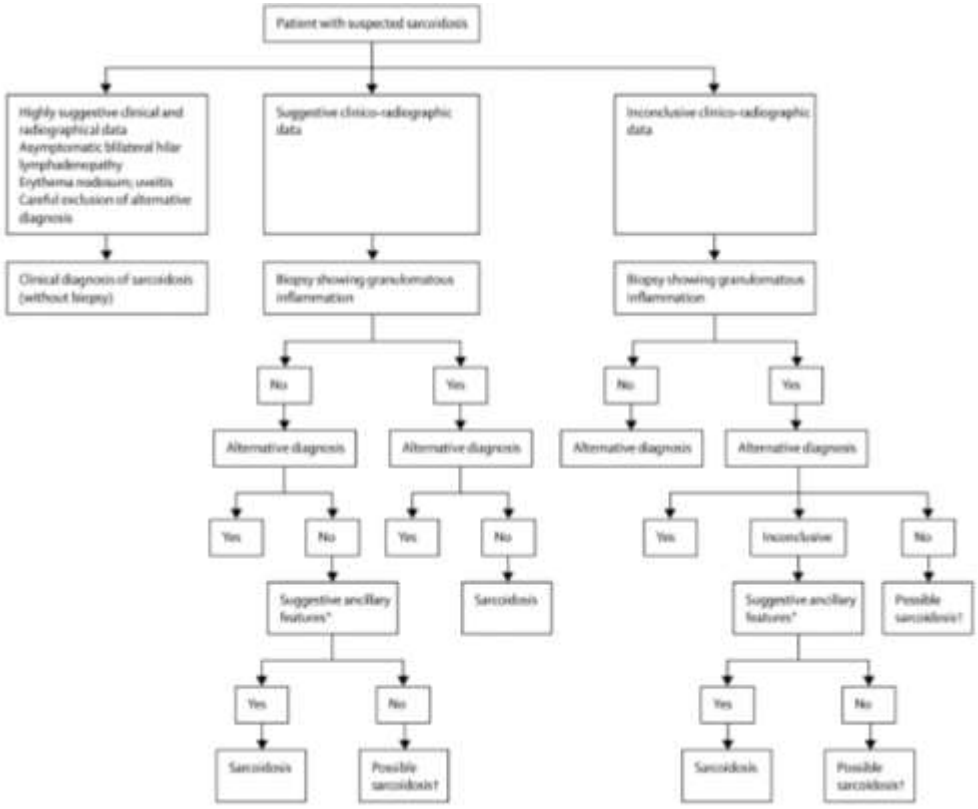

Figure 9. Sarcoidosis Diagnosis Flow

Another modality that can be used to help confirm the diagnosis is transbronchial needle aspiration (TBNA) using endobronchial ultrasonography (USG) guidance (EBUS-TBNA). This modality can be used to sample the enlarged hilar lymph nodes frequently found in sarcoidosis patients. This modality has a success rate of 84% in helping to diagnose stage I sarcoidosis and 77% in stage II. The use of EBUS-TBNA is superior when compared to transbronchial lung biopsy (TBLB). In patients with suspected sarcoidosis, sampling is recommended from lymph nodes in different locations. This influences the positivity rate for sarcoidosis diagnosis. The recommended location for lymph node sampling is in the suitable subcarinal and paratracheal regions (Bernardinello et al., 2021; Crouser et al., 2020).

In sarcoidosis with parenchymal involvement, transbronchial lung biopsy can be an option to help confirm the diagnosis. The TBLB procedure has a success rate of 50-75% in sarcoidosis patients with parenchymal involvement. This success rate decreases to 12% if this modality is used to diagnose stage I sarcoidosis patients. Sampling using this method must be carried out based on the

results of the patient's chest CT scan. This is to avoid sampling lung parenchyma that has minimal abnormalities, namely in the lower lobes. 8-10 biopsies must be taken to increase the positivity rate. The procedure is relatively safe but carries risks such as bleeding and pneumothorax (Bernardinello et al., 2021).

Alternative diagnosis

Alternative diagnoses of sarcoidosis are diverse. This is due to the absence of a gold standard and specific etiology for this disease, so the diagnosis of sarcoidosis remains one of exclusion. In addition, features of granulomatous inflammation can also be found in various conditions, including bacterial, mycobacterial, and fungal infections, and occupational lung diseases such as chronic beryllium disease and silicosis. Granulomatous inflammation can also occur as a result of an immunological response to antigens or the use of malignant drugs. Alternative diagnoses of sarcoidosis are listed in Table 7 (Bernardinello et al., 2021)

Table 7. Alternative Diagnosis of Sarcoidosis

	Sarcoidosis	Tuberculosis	Chronic beryllium disease and silicosis	Sarcoid-like reactions
Clinical manifestations	Often asymptomatic, dry cough, shortness of breath, weight loss and fever	Weight loss, cough, purulent phlegm, coughing up blood, fever	Dry cough and shortness of breath	Often asymptomatic
Exposure history	Not known	Travel history to endemic countries, history of contact with TB patients	History of exposure to beryllium or silica	Drugs, malignancy, or implantation of medical devices
Radiological findings	Symmetrical and bilateral enlargement of hilar lymph nodes, perilymphatic and peri broncho vascular nodules, cavities (rare)	Enlarged hilar lymph nodes are usually asymmetrical, cavitary (often), randomly distributed nodules.	Enlarged bilateral hilar lymph nodes, egg-shell appearance of the lymph nodes	Depends on the underlying cause
Laboratory	Hypercalcemia and hypercalciuria, increased serum angiotensin-converting enzyme, increased soluble interleukin-2 receptor (sIL-2R), and peripheral lymphopenia.	Mantoux test: positive, Interferon-gamma release assay (IGRA): positive, increased serum angiotensin-converting enzyme	Mantoux test: negative, increased serum angiotensin-converting enzyme	Depending on the underlying cause, possible increase in serum angiotensin-converting enzyme, Mantoux test: negative
Histopathology	Noncaseating granuloma	Caseous granuloma	Noncaseating granulomas,	It can be differentiated

	Sarcoidosis	Tuberculosis	Chronic beryllium disease and silicosis	Sarcoid-like reactions
			sclerotic nodules, silica particles	from sarcoid granuloma
Bronchoscopy and bronchoalveolar sampling	Lymphocytosis, $CD4^+/CD8^{+\text{ ratio}} > 3.5$	Mycobacterium tuberculosis culture was positive	Lymphocytosis, Beryllium lymphocyte proliferation test: positive	Depends on the underlying cause

Management

Management of sarcoidosis differs depending on the patient's condition. Not all sarcoidosis patients require hospital treatment. Hospitalization of sarcoidosis patients depends on disease progression characterized by decreased functional status and worsening chest radiographs or HRCT imaging. Worsening clinical conditions and a significant reduction in quality of life are the two main indications for starting treatment. Treatment of sarcoidosis patients should include the mental, emotional, and physical. The first-line therapy is corticosteroids. Corticosteroids function to inhibit the activation of macrophages and lymphocytes and modulate cytokines that play a role in granulomatous inflammation. Corticosteroids have been proven to relieve symptoms and restore organ function, although the use of corticosteroids has many risks (Jain et al., 2020; Polverino et al., 2020).

Corticosteroid treatment begins with prednisolone 0.5-0.75 mg/kg BW every day for 4 weeks. It is tapered off to 10 mg every 4 weeks, depending on the disease response. This therapy takes 6-12 months and can be measured by improvements in lung function. This treatment can be started in patients who have mild clinical features such as skin lesions, anterior uveitis, or cough. Most patients who require systemic treatment will recover, and only a small group will experience chronic disorders for up to two to five years (Jain et al., 2020).

Immunosuppressants can be given to patients if corticosteroid administration does not give good results, relapses, or they cannot tolerate the side effects of corticosteroids. This treatment is the recommended second line. Methotrexate is an antimetabolite, immunosuppressant, and anti-inflammatory recommended in patients. In several studies, methotrexate was safely given to sarcoidosis patients with involvement of the lungs, eyes, skin, and central nervous system. The dose of methotrexate that can be given is 5-7.5 mg per week and can be increased every week (Polverino et al., 2020).

Methotrexate can be given orally or intramuscularly. This drug has a slow onset, so treatment evaluation can be carried out after being given for six months. Methotrexate has several side effects, including toxicity in the liver and lungs, increased risk of infection, and myelosuppression. Therefore, 5 mg folic acid supplementation every week and checking blood, liver, and kidney function must be carried out periodically. Other immunosuppressants that can be used as a substitute for methotrexate are mycophenolate mofetil, azathioprine, and leflunomide. However, their effectiveness is still far below that of methotrexate (Polverino et al., 2020).

The third line of treatment that can be given to sarcoidosis patients is TNF-antagonist biological therapy α. This therapy is given to patients who have progressive, life-threatening disease despite corticosteroids and at least one second-line immunosuppressant agent. Infliximab is a monoclonal antibody that functions to neutralize TNF-α. In research study, the administration of infliximab could increase 2.5% forced vital capacity and improve lung parenchyma. Infliximab is well tolerated by patients who have features of progressive sarcoidosis (Polverino et al., 2020).

CONCLUSION

Sarcoidosis is a systemic disease characterized by the formation of noncaseating granulomas that primarily involve the lungs and other organs. The cause of sarcoidosis is still unclear, but several hypotheses explain that several things, including genetic factors, environmental factors, infection, and autoimmune can cause it. The pathogenesis of sarcoidosis is the formation of noncaseating granulomas involving the innate and adaptive immune systems. Based on the clinical picture, sarcoidosis can be divided into two, namely Lofgren's syndrome and non-Lofgren's syndrome. Based on radiological images, sarcoidosis has a typical appearance, namely bilaterally symmetrical enlargement of the hilar lymph nodes, predominance in the upper and middle fields of the lung, peribronchovascular nodules, and pulmonary fibrosis at an advanced stage. The diagnosis of sarcoidosis can be made based on clinical, radiological, and biopsy images, with histopathological images showing noncaseating granulomas. Several diseases can resemble sarcoidosis, including tuberculosis and chronic beryllium disease. Treatment for sarcoidosis can be given according to the severity of the symptoms, and administration of corticosteroids is still the primary choice. In progressive sarcoidosis, immunosuppressants and TNF-α antagonist biological therapy can be considered.

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