Sarcoidosis

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FAQs

1. What is sarcoidosis and how does it affect you?
   Sarcoidosis is an inflammatory illness that affects one or more organs, however the lungs and lymph glands are the most typically affected. Inflammation causes abnormal lumps or nodules (granulomas) to form in one or more organs of the body. These granulomas may alter the normal structure and function of the organ(s).

2. What is the cause of sarcoidosis?
   The disease's cause is unknown, but genetic and environmental factors appear to have a role. So far, no consistent bacterial, fungal, or viral antigen has been isolated from sarcoidosis lesions.

3. How can sarcoidosis be diagnosed?
   In the majority of cases, a biopsy is required for diagnosis. Bronchoscopy is frequently used to perform endobronchial biopsies. The yield is substantial; even patients with normal chest radiographs may have good results. The presence of noncaseating granulomas with specific stains negative for fungi and mycobacteria is the most important histologic finding.

4. What are the differential diagnosis of sarcoidosis?
   Differential diagnoses include tuberculosis, fungal infection, histoplasmosis, coccidioidomycosis, bartonellosis, toxoplasmosis, brucellosis, sarcoid-like lesions caused by malignancy, immunodeficiency, and sarcoid-like lesions induced by drugs, among others.

5. What is the prognosis of sarcoidosis?
   Sarcoidosis is a harmless disease. Many sarcoidosis individuals never develop clinical disease that requires treatment, and many go into remission on their own.

6. What factors contribute to sarcoidosis mortality?
   The number of people who die from sarcoidosis is unknown. The consequences of end-stage lung disease - respiratory failure, right heart failure- are the leading cause of death in the United States.

7. Is sarcoidosis a cancerous condition?
   No, sarcoidosis is not a cancer.

8. What are the goals of sarcoidosis pharmacotherapy?
   Pharmacotherapy's goals are to reduce morbidity and prevent problems such as

organ complication.

9. How is sarcoidosis treated in patients who have pulmonary involvement?
   In patients with more severe stage II and III disease, corticosteroids can provide small improvements in functional vital capacity and radiographic appearance.

10. What are the stages of sarcoidosis?
    Sarcoidosis has four disease stages.

    1. Stage 0 (a normal radiograph)
    2. Stage I [bilateral hilar lymphadenopathy (BHL), variably associated with paratracheal adenopathy]
    3. Stage II (parenchymal infiltration with BHL)
    4. Stage III (parenchymal infiltration without BHL)
    5. Stage IV (overt pulmonary fibrosis and parenchymal infiltration; irreversible fibrosis

11. Will my sarcoidosis return if it goes away?
    Sarcoidosis can go away for a while and then come back in some circumstances. In some situations, people with sarcoidosis may have "flare ups" of symptoms during otherwise asymptomatic periods.

History of Sarcoidosis

History—Top 3-5 Things to Know (box)

1. Sarcoidosis is called 'mysterious disease' because the cause or etiologic agent is not known.
2. There is currently no cure for sarcoidosis.
3. Sarcoidosis is a systemic disease. It affects different parts of the body such as lungs, skin, eye, nymph node.
4. Common symptoms include: coughing, wheezing, shortness of breath, fever.

History—Main Entry

The first case of sarcoidosis was identified by Sir Jonathan Hutchinson (1828-1913). He described the patients to have multiple raised, dusty red patches on his feet, fingers and arms[1] (Mihailovic-Vucinic and Sharma 2005/p1/para1). Robert Willan (1757-1812), who is regarded as the father of dermatology introduced the term erythema nodsum, which was later associated with sarcoidosis by Swedish physician Sven Lofgren, in what is now referred to as Lofgren's Syndrome[1] (Mihailovic-Vucinic and Sharma 2005/p1/para1). Jorgen Schaumann was the first scientist to report systemic sarcoidosis in 1914.

Sarcoidosis is widely regarded as a 'mysterious disease' because the etiologic agent or cause is not known. Although, it can be simply described as an inflammation that occurs in different locations of the body, a comprehensive definition can be difficult because of the clinical, radiological, biochemical, genetic and immunological aspect of the disease[2] (Sharma 2005).

Inflammation is the normal immune response of the body as a result of the introduction of foreign particles or substances. Inflammation usually subsides when the antigen is removed from the body but some cases of sarcoidosis may persist for few months or even years. With respect to the course of disease or disease progression, sarcoidosis can be classified as acute or chronic. When the disease symptom develops quickly and then clear within a few month, this is known as acute sarcoidosis. However, when the disease persists for many years or the symptoms subsides and the reoccurs, this is known as chronic sarcoidosis[3] (Hunninghake and Costabel, 1999).

Sarcoidosis is usually associated with the lungs, however, other parts of the body such as eyes, skin, lymph nodes are also affected. Common symptoms include: coughing, wheezing, chest pain, shortness of breath, fever, night sweat and seizures. Although there is currently no cure for sarcoidosis,, treatment with corticosteroids is usually aimed to reduce inflammation. Chronic sarcoidosis may damage of vital organs of the body which will subsequently reduce the life expectancy of the patient. [4] (Nardi *et al.*, 2011)

Epidemiology

Epidemiology—Top 3-5 Things to Know (box)

1. The incidence and prevalence of sarcoidosis has consistently been observed to be highest in Nordic countries and among African Americans.
2. In addition to race and geographical location, sarcoidosis occurrence varies greatly by age and sex.
3. Sarcoidosis incidence is rare in childhood.

Epidemiology—Main Entry

Epidemiological studies are used the distribution of disease in a population, lack of knowledge of a specific etiologic agent has made epidemiology of sarcoidosis challenging. However, case-control studies that process large amount of data has provided more insight[5] (ACCESS, 1999). The differences in sarcoidosis incidence across ethnic groups has been widely reported with northern Europeans and African-Americans having the highest rates[6] (Benjamin *et al.*, 2007). The age-specific incidence of sarcoidosis varies across ethnic groups. In Japan, the peak incidence occurs in third decade of life[7] (Iannuzzi, 2003). Among Africa-Americans, sarcoidosis peak incidence is seen in the fourth decade of life for both female and male[8] (Valentonyte *et al.*, 2005).

Sarcoidosis occurrence varies substantially by age and sex, in addition to race and geographic region. It's unclear what causes this difference, but it suggests that sex plays a role in disease manifestation. There is a ten-year discrepancy in age at diagnosis between males and women in some groups. In Sweden, men were diagnosed at 45 years old, while women were diagnosed at 54 years old[9] (Arkema *et al.*, 2016). In Italy, men were diagnosed at the age of 47 and women at the age of 54[10] (Beghe *et al.*, 2017). Other demographics, such as Olmsted County, Minnesota (men 43 versus women 48 years old)[11] (Ungprasert, 2017) and a Spanish urban tertiary teaching hospital report (men 44 versus women 49 years old), show a smaller age gap[12] (Brito-Zeron, 2016). Except for one study from Estonia (average age in men 34, women 43 years old), the typical age of onset in most investigations was between 47 and 51 years old[13] (Lill, 2016). The variation in age at

diagnosis between men and women shows that the disease etiology differs between the sexes, which could be due to genetic factors or sex-specific environmental exposures, such as reproductive variables [12] (Brito-Zeron, 2016).

Sarcoidosis has a benign clinical course for the majority of individuals, but it is a chronic, life-threatening condition for a small percentage of them. According to a study by the French Epidemiologic Centre for Medical Causes of Death, death certificates often indicate sarcoidosis as the cause of death or as a significant contributing factor to death[14] (Jamilloux *et al.,* 2016). The age-standardized death rate was 3.6 per million at the time, and it has risen since then. Sarcoidosis-related mortality occurred at younger ages than the overall population, with men and women dying at equal ages, however women died less frequently. Using death certificate data from the National Center for Health Statistics, two studies from the United States showed pulmonary sarcoidosis-related age standardized mortality rates [15, 16] (Dwyer-Lindgren, 2017; Mirsaeidi, 2015). According to one study, the mortality rate from interstitial lung disease and pulmonary sarcoidosis increased from 2.7 to 5.5 fatalities per 100,000 from 1980 to 2014[15] (Dwyer-Lindgren, 2017). Another study, which used the same data source but covered the years 1999 to 2010, projected a death rate of 2.8 per 1 million due to sarcoidosis. Women had a greater mortality rate than men (3.3 versus 2.3), and African Americans had a higher mortality rate than white individuals (16 versus 1.3). Over the last decade, the sarcoidosis-related mortality rate in white people has increased statistically significantly[16] (Mirsaeidi, 2015).

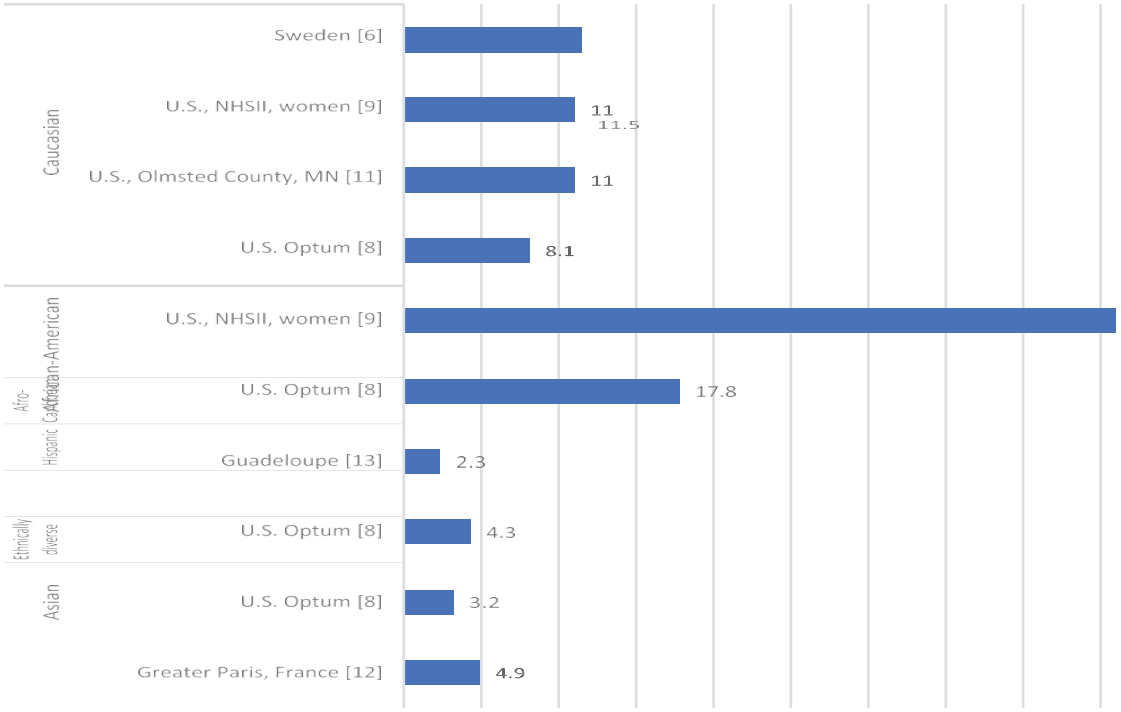


Figure 1. Incidence of sarcoidosis per 100,000 per year reported in the literature 2015–2017 categorized by ethnic group (Elizabeth and Arkema, 2018).

Etiology and Risk Factors

Etiology & Risk Factors—Top 3-5 Things to Know (box)

1. Obesity [body mass index (BMI) ⩾30 kg/m^2] is associated with increased incidence of sarcoidosis.
2. Sarcoidosis runs in the family as it can be transferred genetically.
3. Smoking and silica exposed worker are at major risk of sarcoidosis

Etiology and Risk Factors—Main Entry

Although the specific causes of sarcoidosis are unknown, a few elements have surfaced that provide insight into the disease's etiology.

Obesity

According to the Black Women's Health Study, a follow-up study of 59,000 African-American women showed that obesity [body mass index (BMI) 30 kg/m^2] at study baseline was associated with a 40% increased incidence of sarcoidosis[17] (Cozier, 2015). Obesity at the age of 18 and a cumulative weight gain of at least 30 kg since the age of 18 were also linked to a higher occurrence, according to researchers. The NHSII cohort, a follow-up study of approximately 116,000 primarily white (>98 percent) female registered nurses from 1989 to 2013, looked into the link between BMI and sarcoidosis. BMI at age 18 and a cumulative weight gain of at least 25 kg since age 18 were likewise linked to sarcoidosis incidence[18] (Dumas *et al.*, 2017).
While the exact mechanism by which obesity affects sarcoidosis is unknown, it is widely assumed that obesity's proinflammatory milieu plays a key role, as it does in other illnesses such as asthma[19] (Schipper, 2012).

Occupational risk

Certain vocations and industries, such as professional occupations, sales, lumbering occupations, working in rock wool factories, and dealing with glass wool, have been linked to an elevated risk of sarcoidosis, according to research [20] (Keller, 1971). Few studies of sarcoidosis risk have systematically explored occupational history as a risk factor for sarcoidosis, owing to the difficulties of quantifying occupational exposures over a lifetime. In a cohort study of silica-exposed employees in Sweden, researchers discovered that high exposure to silica dust (>0.048 mg/m3) was linked to an elevated risk of sarcoidosis (standardized incidence ratio 3.94; 95 percent confidence interval 1.07–10.08)[21] (Vihlborg *et al.*, 2017).

Family

Sarcoidosis risk is most likely influenced by genetic factors. Family members share several shared exposures, including occupation, in addition to DNA. The confluence of genetic and environmental risk factors in families frequently increases disease risk among family members. In a study of 179 African-American families based on an index sarcoidosis case diagnosed at Henry Ford Hospital in Detroit, Michigan, USA, it was discovered that siblings and parents of sarcoidosis cases have a 2.5-fold greater chance of developing the disease

[22] (Rybicki, 2001). Another study conducted in the UK in 2000 reported that 5.91 percent of sarcoidosis patients had at least one additional relative (first, second, or third degree) with biopsy-proven sarcoidosis, based on a questionnaire completed by 268 individuals [23] (McGrath, 2000).

Prognosis

Prognosis—Top 3-5 Things to Know (box)

1. Many sarcoidosis is usually benign and may resolve spontaneously.
2. Sarcoidosis is not a type of cancer and is more easily managed than cancer.
3. Stage IV pulmonary sarcoidosis is characterized by irreversible fibrosis and may lead to death.

Prognosis—Main Entry

Sarcoidosis is a benign condition. A large majority of sarcoidosis patients may never develop clinical disease that requires treatment, and many have spontaneous remission[24] (Rybicki *et al.*, 1998). During an average follow-up of 7 years in a study of individuals with radiological stage IV sarcoidosis, pulmonary hypertension was found in 30% of cases. In 12% of cases, long-term oxygen therapy was required. At ten years, the survival rate was 84 percent[25] (Nardi *et al.*, 2011).

Only 15-20% of patients experience functional impairment, which usually goes away on its own. For untreated patients, the total death rate is less than 5%. Advanced chest radiography stage, extrapulmonary illness (often cardiac and neurologic), and signs of pulmonary hypertension are all indicators of a bad prognosis. The initial chest radiography stage has been shown in multiple studies to be the most critical marker for prognosis.
Patients with advanced sarcoidosis who are waiting for a lung transplant have a significant mortality rate, with a median survival time of less than two years. The survival percentage of the patients reported was 66 percent after one year, 40 percent after two years, and 31 percent after three years. After transplantation, survival rates were 62 percent after one and two years, and 50 percent after three years [26] (Arcasoy, 2001).

Presentation and Diagnosis of Sarcoidosis

Presentation and Diagnosis—Top 3-5 Things to Know (box)

1. Pulmonary sarcoidosis can be categorized into 4 stages: Stage I, Stage II, Stage III and Stage IV.
2. Almost half of patients with pulmonary sarcoidosis are asymptomatic, especially those with stage I disease.
3. The combination of erythema nodosum, arthritis, and bilateral hilar adenopathy on chest radiography is termed *Löfgren syndrome*.
4. Presentation of lupus pernio shows a poor prognosis and increased chance of severe lung illness.

Presentation and Diagnosis—Main Entry

A well-defined round or oval granuloma made up of compact radially oriented epithelioid

cells with pale staining nuclei, a few multinucleate large cells, and a sparse ring of lymphocytes is the fundamental lesion in sarcoidosis (Figure 2). Histologic evidence of granulomatous inflammation, elimination of recognized causes of granulomatous inflammation other than sarcoidosis, and evidence of at least two different organs involved with the disease are the key criteria for diagnosing sarcoidosis. The multinuclear large cells are frequently seen in the granuloma's centre (Figure 3)[27] (Sharma, 2002).

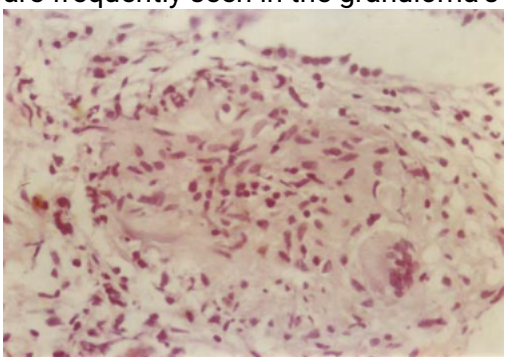


Figure 2: Early to intermediate sarcoid granuloma with epithelioid histiocytes and lymphocytes on the periphery and a large cell within the granuloma (early to intermediate sarcoid granuloma with epithelioid cells that is well confined and the presence of giant cell).

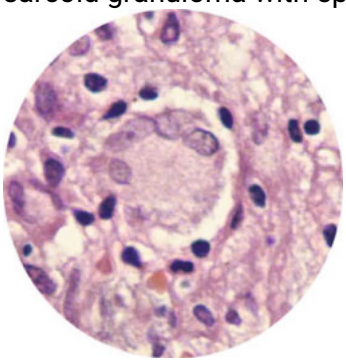


Figure 3: Giant cell

Physical Examination Findings

In most cases, histopathologic evidence is required to confirm the diagnosis of sarcoidosis. The presence of noncaseating granuloma in at least one organ is often regarded adequate for diagnosis, therefore tissue biopsy of every affected organ is not required. If the signs and symptoms match, sarcoidal involvement of the other organs is usually considered[28] (Judson, 2008). As a result, the easiest-to-access lesions, such as rash, conjunctival nodules, enlarged superficial lymph nodes, and enlarged lacrimal gland, are frequently used as biopsy sites. If these lesions aren't present or biopsy results aren't conclusive, biopsy of the intrathoracic lymph nodes and/or lung parenchyma is often the next best option[29] (Govender and Berman, 2015) since they affect approximately 95% of patients and the lesions are usually more accessible with a lower risk of consequences than other internal organs like the liver and kidneys[30] (Ungprasert *et al.*, 2016).

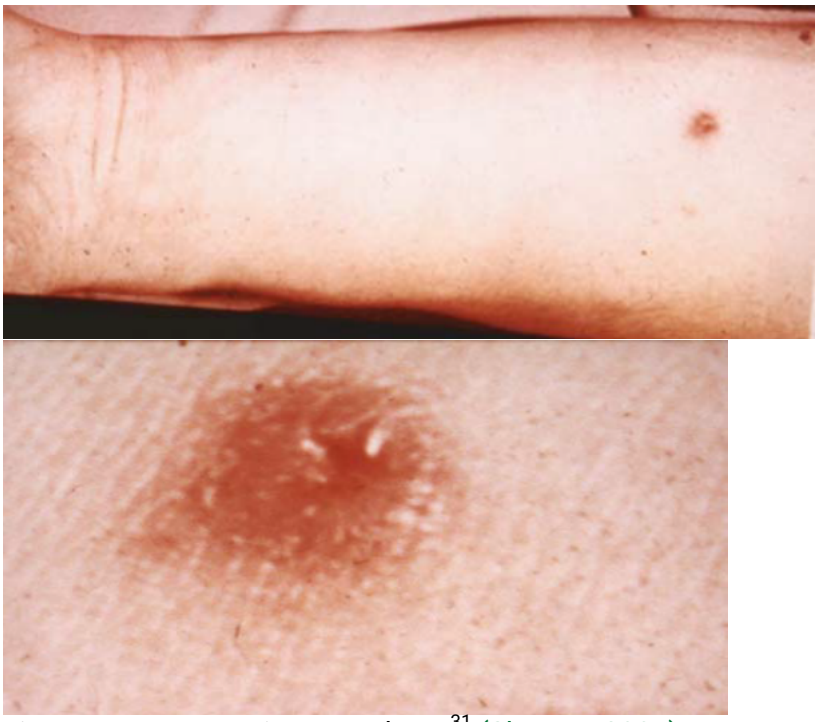
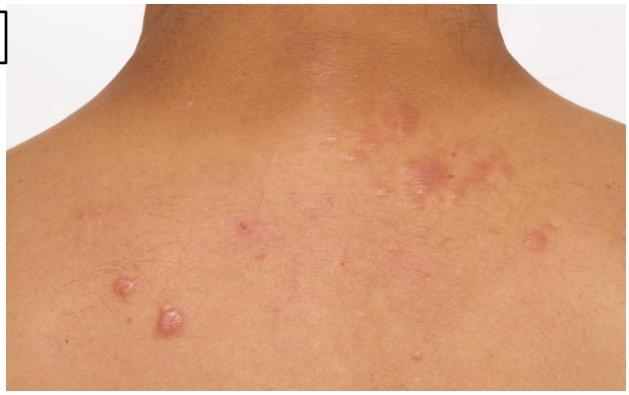


Figure 4: Nonceasating granuloma[31] (Sharma, 2005)

A



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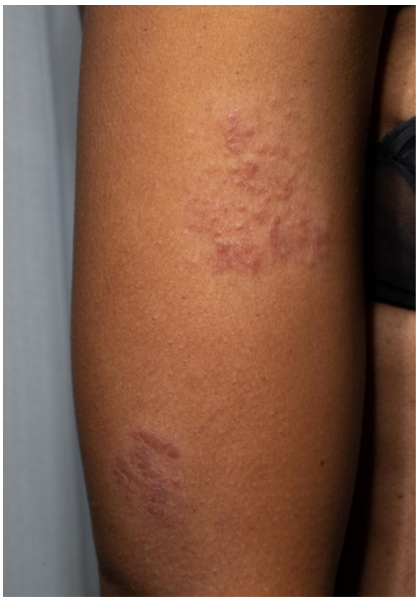

Figure 5[30] (Ungprasert *et al.*, 2016): A) Papular sarcoidosis as a cutaneous manifestation seen on the upper back region.
B) Plaque sarcoidosis as a cutaneous manifestation seen on the upper arms.

Diagnostic Workup

Skin

There are two types of skin lesions: specific and nonspecific. Biopsy of certain lesions reveals granulomatous inflammation. Inflammatory skin reactions without granulomatous inflammation are known as nonspecific skin lesions. The most prevalent nonspecific skin manifestation of sarcoidosis is erythema nodosum. The majority of cutaneous lesions are asymptomatic. The most common complaint is cosmetic disfigurement.

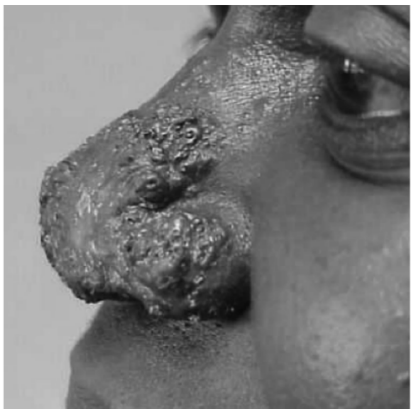

Figure 6. Lupus pernio, or disfiguring facial sarcoidosis affecting the nose[28] (Judson, 2008)

Lupus pernio is a type of sarcoidosis that causes indolent, red-purple, or violaceous skin lesions on the nose, cheeks, lips, and ears (Figure 6). These lesions can destroy cartilage and bone, especially around the nose, and are often disfiguring. Sarcoidosis patients with lupus pernio have a worse prognosis and have more severe lung illness.

Eye

Sarcoidosis can affect any region of the eye and is often the disease's most visible symptom. The most common ocular manifestation of sarcoidosis is uveitis[32] (Bradley *et al.*, 2002). Blurred vision, red eye, aching eye, and photophobia are all signs of anterior uveitis, which occurs in the anterior chamber[32] (Bradlet *et al.*, 2002). However, up to one-third of people with sarcoidosis-related anterior uveitis will experience no symptoms (a "quiet eye"). Retinal perivasculitis or scarring can occur as a result of posterior uveitis. Vision loss and blurred vision are possible side effects for the patient[33] (Ohara *et al.*, 2005).

Joint

Arthropathy, which affects 5% to 15% of sarcoidosis patients, is another typical extrathoracic symptom. Inflammatory arthritis, as opposed to arthralgia, is more common[30] (Ungprasert *et al.*, 2016). Joint discomfort is frequently one of the earliest signs of sarcoidosis, which leads to a diagnosis. Acute oligoarthritis with involvement of the major joints, particularly the ankle joint, is the most common manifestation (in over 90 percent of cases). Polyarthritis of the tiny joints of the hands is a fairly uncommon occurrence. Other systemic arthritides, such as rheumatoid arthritis, which can co-occur with sarcoidosis, must be considered first in these patients.

Laboratory Testing

Urine and blood tests

Blood and urine tests are low-risk, minimally invasive methods of determining what is going on within a person. They can aid medical professionals in determining the presence of disease, estimating the degree of organ involvement, and demonstrating the presence of inflammation. Such testing can help physicians narrow down the illnesses that are likely to produce reported symptoms in difficult-to-diagnose diseases like sarcoidosis.

Lung Imaging Test

The lungs are the most typically affected organ, with pulmonary sarcoidosis being detected in almost 90% of sarcoidosis cases.
Multiple tests may be required to rule out other illnesses before a diagnosis of pulmonary sarcoidosis may be made. One or more imaging studies on the lungs are usually conducted to confirm the presence of granulomas or other abnormalities.

Lung Biopsy

The lungs are one of the most common organs afflicted by sarcoidosis, and the illness is known as pulmonary sarcoidosis. If pulmonary sarcoidosis is suspected, a lung biopsy, along with additional testing, may be performed as part of the diagnosis. If an imaging scan, such as an X-ray or CT (computerized tomography) scan, reveals an abnormality, a lung biopsy is usually advised.

Lung function test

Lung function tests, also known as pulmonary function tests, are used to track the evolution of sarcoidosis and to diagnose it. These tests determine how well a patient's lungs function. Patients are frequently evaluated over time since such examinations are the best way to monitor the severity of sarcoidosis. This enables clinicians to decide whether the patient needs treatment or if the current treatment is enough.

Skin Biopsy Test

Sarcoidosis causes skin involvement in roughly 30% of all patients, which manifests as red nodules, lumps, and plaques. These symptoms can range in severity from minor to disfiguring, and they're frequently the first thing a patient notices and brings to their doctor's attention.
To determine the reason, a skin biopsy may be performed. A circle of skin tissue is removed, down to the first layer of fat beneath the skin, in this treatment. In a laboratory, the sample is examined for the presence of granulomas and inflammatory chemicals. In 81.6 percent of patients, punch biopsies can detect sarcoidosis[34] (Yanardag *et al.*, 2013).

Mediastinoscopy

The mediastinal area — the part of the chest cavity between the breastbone and the spinal column, just between the lungs — is examined with mediastinoscopy, a minor, minimally invasive surgery. It's used to look for enlarging lymph nodes in the chest and figure out what's causing them. As the "gold standard" for studying lymph nodes and other structures in the mediastinal area, mediastinoscopy can be helpful in detecting sarcoidosis[35] (Onat, 2017).

Imaging Studies

Scadding (1961)[36] classified posteroanterior (PA) chest radiographic findings as
1. Stage 0 (a normal radiograph),
2. Stage I [bilateral hilar lymphadenopathy (BHL), variably associated with paratracheal adenopathy] (Fig. 7),
3. Stage II (parenchymal infiltration with BHL) (Fig. 8),
4. Stage III (parenchymal infiltration without BHL) (Fig. 9)
5. Stage IV (overt pulmonary fibrosis and parenchymal infiltration; irreversible fibrosis) (Fig. 10)

Stage 0

A normal chest radiograph is seen in five to ten percent of patients at the time of initial presentation and/or during the course of the disease. Lung biopsy procedures would almost certainly indicate granulomatous inflammation in some of these patients [37,38] (Soskel and Sharma, 2000; Soskel and Sharma, 1992).

Stage I

Bilateral hilar lymphadenopathy (BHL) is a symptom of stage I pulmonary sarcoidosis, which affects more than half of all sarcoidosis patients. Enlargement of the bronchopulmonary, tracheobronchial, and paratracheal lymph nodes characterizes this condition. Between the swollen lymph nodes and the cardiovascular boundary, there is also a translucent area (clearer on the right side). BHL is linked to right paratracheal lymphadenopathy (25 percent)

or bilateral paratracheal lymphadenopathy (50 percent)[38] (Soskel and Sharma, 1992).

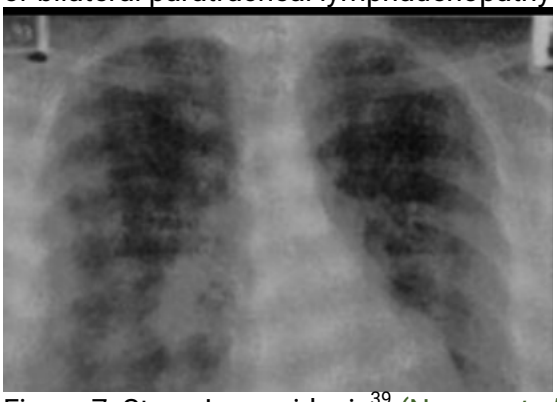

Figure 7: Stage I sarcoidosis[39] (Nunes *et al.*, 2007).

Clinical Feature of Stage I
BHL is a symptom of acute, reversible sarcoidosis, which is frequently linked with erythema nodosum.

Prognosis of Stage I
Within two years, 60 to 80 percent of patients with just BHL get complete remission of the radiographic signal; lymph nodes rarely grow again. Approximately 10% of patients have a long-term treatment plan (these are the patients with chronic skin lesions and bone cysts). The remaining 10% to 15% of patients with stage I disease may stay at the same stage or progress slowly to stage II[38] (Soskel and Sharma, 1992).

Stage II

Stage II pulmonary sarcoidosis is characterized by bilateral hilar adenopathy and parenchymal infiltrations, and it affects 25 to 30 percent of sarcoidosis patients. The pattern of infiltrates in the parenchyma is fairly diverse, and it is bilateral[40] (Lynch, 1997).

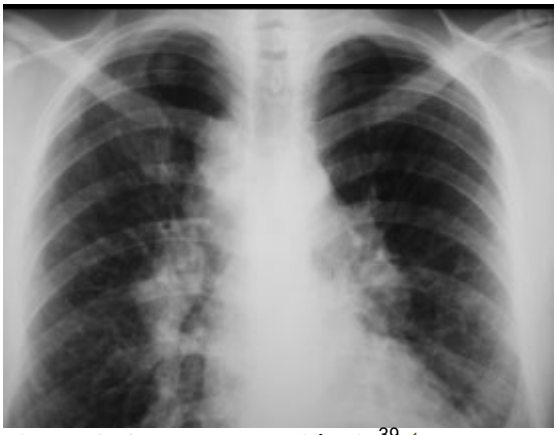

Figure 8: Stage II sarcoidosis[39] (Nunes *et al.*, 2007).

Clinical features of Stage II
Fever, weight loss, cough, and dyspnea are all symptoms that patients may experience. Patients are usually asymptomatic.

Prognosis of Stage II
Approximately 70% of individuals in stage II experience remission of symptoms. In the remaining 30%, symptoms stay stable or advance to stage III.

Stage III

Parenchymal infiltration without hilar adenopathy characterizes stage III pulmonary sarcoidosis. This stage of sarcoidosis affects around 15% of sarcoidosis patients. The presence of reticulonodular, acinar, or alveolar sarcoidosis on radiographs can be a sign of sarcoidosis. The most prevalent parenchymal abnormality is reticulonodular sarcoidosis, which is characterized by a mixture of linear densities and tiny nodules measuring 3mm to 5mm in diameter. The infiltration is generally always bilateral, while unilateral or isolated lung parenchyma involvement is possible. There is a propensity to keep apices and severe bases to a minimum. Segmental or lobar infiltrates with fluffy borders characterize acinar or alveolar sarcoidosis. Bronchograms in the air may be noticed[41] (Sharma, 2005).

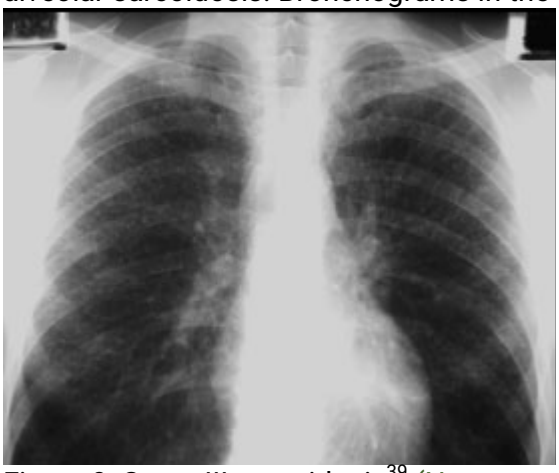

Figure 9: Stage III sarcoidosis[39] (Nunes *et al.*, 2007).

Clinical features of Stage III
Dry cough and dyspnea are common clinical characteristics, although productive cough due to bronchopulmonary infection and hemoptysis are uncommon.

Stage IV

Stage IV pulmonary sarcoidosis is characterized by irreversible fibrosis. The prevalence of sarcoidosis is estimated to be around 20% of all sarcoid patients. Irreversible fibrosis with hilar retraction, bullae development, and emphysema are among the lung lesions[42] (Miller *et al.*, 1995).

Clinical features of Stage IV
Patients have dyspnea, cough, and expectoration, as well as respiratory failure, pneumothorax, cor pulmonale, and aspergillosis.

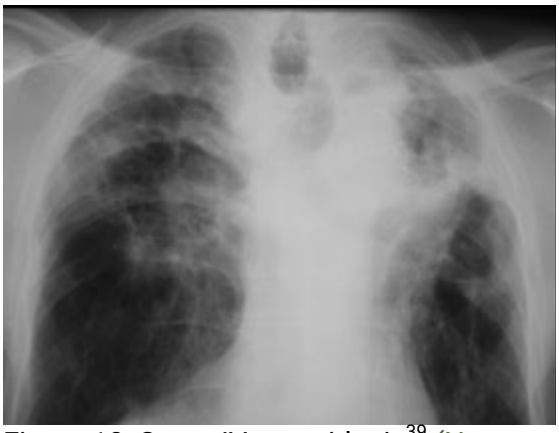

Figure 10: Stage IV sarcoidosis[39] (Nunes *et al.*, 2007).

Differential Diagnosis

The differential diagnosis of systemic disorders with epithelioid and large cells in granulomas include[43] (Prasse, 2016):

- Tuberculosis (*M. tuberculosis* infection) Atypical mycobacterial disease
- Fungal infection, histoplasmosis, coccidioidomycosis
- Bartonellosis, toxoplasmosis, brucellosis
- Sarcoid-like lesions caused by cancer
- Sarcoid-like lesions caused by immunodeficiency
- Sarcoid-like lesions caused by medications
- Heavy-metal-associated granulomatosis
- Chronic berylliosis
- Systemic vasculitis
- Isolated pulmonary disease: exogenous allergic alveolitis, silicosis.

Guideline Recommendations—Top Things to Know

American Thoracic Society Clinical Practice Guideline (Testing and Diagnostic Guidelines)[44] (Elliott *et al.,* 2020).

1. For patients with suspected sarcoidosis and mediastinal and/or hilar lymphadenopathy for whom it has been determined that tissue sampling is necessary, we suggest endobronchial ultrasound (EBUS)-guided lymph node sampling, rather than mediastinoscopy, as the initial mediastinal and/or hilar lymph node sampling procedure
2. For patients with sarcoidosis who have neither hepatic symptoms nor established hepatic sarcoidosis, we suggest baseline serum alkaline phosphatase testing to screen for hepatic sarcoidosis
3. For patients with extracardiac sarcoidosis who do not have cardiac symptoms or signs, we suggest performing baseline ECG to screen for possible cardiac

involvement
4. For patients with sarcoidosis in whom pulmonary hypertension (PH) is suspected, we suggest initial testing with TTE
5. For patients with sarcoidosis who have neither renal symptoms nor established renal sarcoidosis, we suggest baseline serum creatinine testing to screen for renal sarcoidosis

ERS clinical practice guidelines on treatment of sarcoidosis[45] (Baughman, 2021).

1. For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease, we suggest the addition of infliximab to improve and/or preserve FVC and QoL
2. For patients with chronic cutaneous sarcoidosis and cosmetically important active skin lesions which cannot be controlled by local therapy, we suggest oral glucocorticoids to reduce skin lesions.
3. For patients with evidence of functional cardiac abnormalities, including heart block, dysrhythmias, or cardiomyopathy, we recommend the use of glucocorticoids
4. For patients with neurosarcoidosis that have been treated with glucocorticoids and have continued disease, we suggest the addition of methotrexate
5. In patients with sarcoidosis who have troublesome fatigue, we suggest a pulmonary rehabilitation program and/or inspiratory muscle strength training for 6-12 weeks to improve fatigue.

Management

Management—Top 3-5 Things to Know (box)

1. Medical treatments are aimed to control symptoms, prevent complications and improve outcomes in patients.
2. It is important to monitor a patient's health closely for the first six months after medication has been stopped, which is usually the period of relapse also known as a flare.
3. Patients should be placed in a community or support group of others with sarcoidosis to help manage depression and anxiety which are common side effect of medications.

Management—Main Entry

Sarcoidosis management aims are to prevent or limit organ damage, alleviate symptoms, and improve the patient's quality of life. A pulmonologist's evaluation is strongly advised. A multidisciplinary approach may be required for patients with extrapulmonary involvement. An ophthalmologist, a cardiologist, a neurologist, and a nephrologist may be needed for ocular disease, cardiac disease, neurological disease, and renal disease, respectively.

Nonpharmacologic

Many people do not need therapy, and the condition can resolve on its own. Physical therapy, multimodal pulmonary rehabilitation, and maybe cognitive behavioral therapy are non-

pharmacological therapeutic alternatives.

Pharmacologic (summary and breakdown by class)

Corticosteroids

The mainstay of treatment is corticosteroids. When sarcoidosis necessitates treatment, corticosteroid medicines are the first line of defense. In most people, oral corticosteroids significantly reduce systemic inflammation, which slows, stops, or even prevents organ damage. Corticosteroids can be used alone or in combination with other drugs.

Methotrexate.

Methotrexate is one of the most often used corticosteroid-sparing therapy for sarcoidosis because of its effectiveness, low cost, and low risk of side effects when compared to other cytotoxic drugs at the dosages used to treat sarcoidosis. The medication can be administered orally or subcutaneously. Regular monitoring is essential due to the risk of hepatic and hematologic toxicity. Because the medication is removed by the kidneys, renal function should be monitored as well[46] (Schutt *et al.,* 2010).

Azathioprine

Azathioprine has been demonstrated to be as effective as methotrexate in the treatment of sarcoidosis in research. When methotrexate is contraindicated, such as when renal or hepatic function is impaired, it is considered as alternative[47] (Vorselaars *et al*., 2013). Azathioprine inhibits the development of circulating T and B cells while increasing circulating lymphocyte death. The activity of the enzyme thiopurine S-methyltransferase (TPMT), which is involved in drug metabolism, influences azathioprine toxicity.

Antimalarials

Based on early randomized trials that showed a long-term benefit, chloroquine and hydroxychloroquine have been widely used in the treatment of sarcoidosis[48] (Morse *et al.,* 1961). However, hydroxychloroquine is frequently favored because to its superior safety profile. Hydroxychloroquine has a number of modes of action, including interfering with antigen presentation, preventing T cell activation, inhibiting toll-like receptor signaling, and reducing inflammatory cytokines produced by T cells and B cells[49] (Schrezenmeier and Dorner, 2020). Hydroxychloroquine has been shown to be effective in the treatment of cutaneous illness, hypercalcemia, and neurosarcoidosis in some cases[50] (Baughman *et al.,* 2013).

Other Drugs
Cyclophosphamide or chlorambucil are drugs that are typically used when a condition has progressed to the point where other treatments have failed.

Topical corticosteroids: These medications can be found in a variety of forms (e.g., eye drops, skin creams, and respiratory sprays) and are used to treat minor sarcoidosis symptoms. They are less effective than steroid pills, although being much safer. Recent investigations have shown that pentoxifylline and thalidomide are effective in treating treatment-resistant lupus pernio.

Infliximab or adalimumab: These drugs, which are administered intravenously every 4-8 weeks or subcutaneously every 1-2 weeks, have lately been used to treat individuals with severe sarcoidosis. They're frequently utilized after other solutions have failed or aren't tolerated. They enhance the chance of infection by a large amount.

NSAIDs (nonsteroidal anti-inflammatory medicines [such as ibuprofen or aspirin]): These drugs can help ease arthritis and fever by reducing acute inflammation.

Monitoring for side effects, adverse effects, drug-drug interactions

The use of hydroxychloroquine is frequently associated with gastrointestinal adverse effects. Dyspepsia, mouth ulcers, myalgia, lethargy, jaundice, and blurred vision are all side effects of azathioprine. With azathioprine use, there is also evidence of a greater risk of opportunistic infections and perhaps cancer [51] (Drent *et al.*, 2020).
Cyclophosphamide has several major adverse effects, including bone marrow suppression and kidney damage. Infliximab increases the risk of infection considerably. Excessive weight gain, sleeplessness, acne, osteoporosis, and skin bruising are all common corticosteroid adverse effects.

Comorbidities

The presence of noncaseating granulomas in sarcoidosis affects various tissues, but the inflammatory process can also cause other comorbidities in sarcoidosis patients. Sarcoidosis is a complex systemic clinical scenario that is frequently complicated by the presence of various chronic diseases such as cancer, cardiovascular disease, autoimmune disease, and chronic liver disease[52,53] (Bonifazi *et al.*, 2015; Tuleta *et al.,* 2016).

Complications

Untreated pulmonary sarcoidosis can cause irreversible scarring in the lungs (pulmonary fibrosis), making breathing difficult and causing pulmonary hypertension in some cases. Inflammation can affect practically any region of the eye, resulting in retinal damage that can lead to blindness. Sarcoidosis can induce cataracts and glaucoma in some people. Sarcoidosis can also impair how the body manages calcium, resulting in kidney stones and decreased kidney function, kidney failure is a rare complication.[53] (Tuleta *et al.,* 2016).
Cardiac sarcoidosis causes granulomas in the heart, which can cause heart rhythm, blood flow, and normal cardiac function to be disrupted. This can result in death in rare cases. When granulomas form in the brain and spinal cord, a tiny number of persons with sarcoidosis experience difficulties with the central nervous system. For example, face paralysis can be caused by inflammation of the facial nerves.

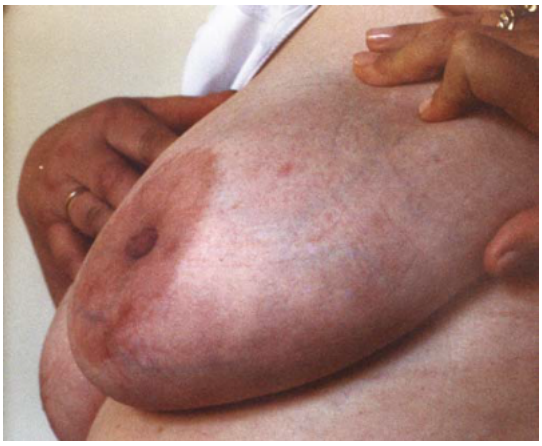

Figure 11: Sarcoidosis patient with breast cancer, which she developed four years after a chronic form of lung disease[54] (Lower *et al.*, 2001).

Patient Education

If a patient's sarcoidosis is in remission, the doctor may gradually reduce or eliminate their medications. They will, however, need to keep an eye out for a flare. Patients should contact their doctor if this occurs, as they may require additional treatment.

Flares can be unpredictable. They usually occur within six months of quitting medication. The longer a patient goes without experiencing symptoms, the less likely he or she is to experience a flare.

A healthy lifestyle can help a patient feel better while also preventing sarcoidosis from worsening. Increasing the intake of fruits and vegetables can have significant health benefits.

Avoid gaining weight. Maintain a regular physical activity schedule. Patients with sarcoidosis may find it difficult to exercise due to fatigue. Physical activity, on the other hand, can boost energy and alleviate other symptoms including shortness of breath and muscle weakness.

Patients must learn to handle stress and, if they smoke, quit. Other lung irritants, such as dust, chemicals, and secondhand smoke, should also be avoided.

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Artwork

Visual 1

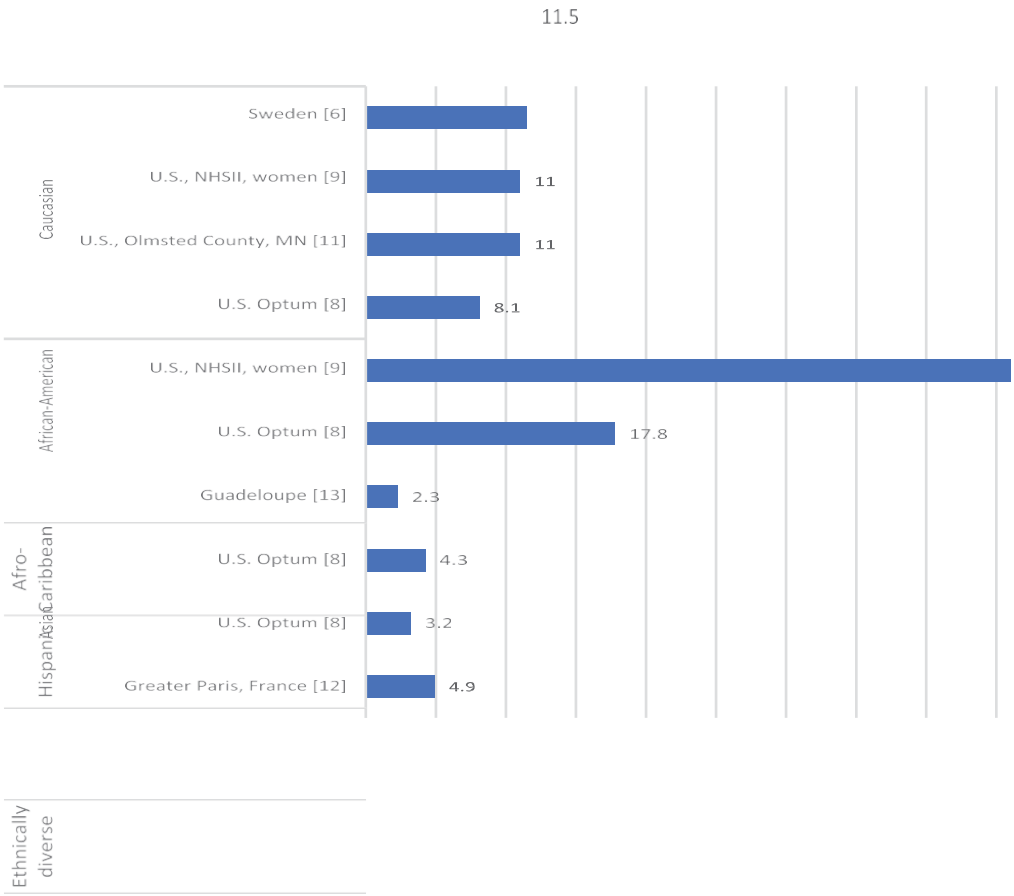

Figure 1. Incidence of sarcoidosis per 100,000 per year reported in the literature 2015–2017 categorized by ethnic group.

Visual 2

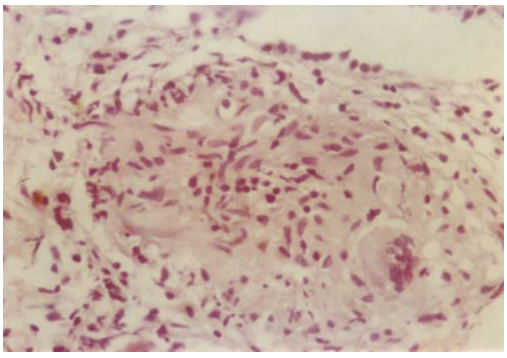

Figure 2: Early to intermediate sarcoid granuloma with epithelioid histiocytes and lymphocytes on the periphery and a large cell within the granuloma (early to intermediate sarcoid granuloma with epithelioid cells that is well confined and the presence of giant cell)

Visual 3

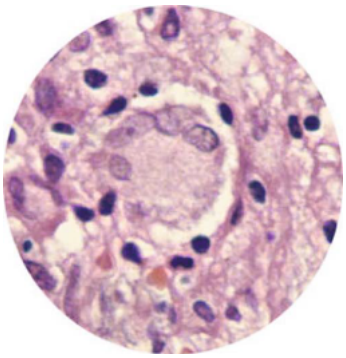

Figure 3: Giant cell

Visual 4

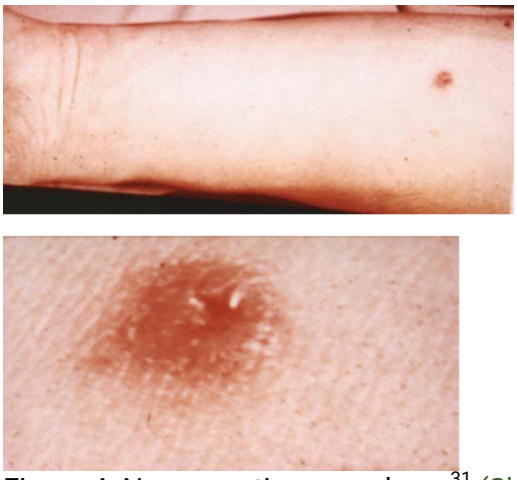

Figure 4: Nonceasating granuloma[31] (Sharma, 2005)

Visual 5

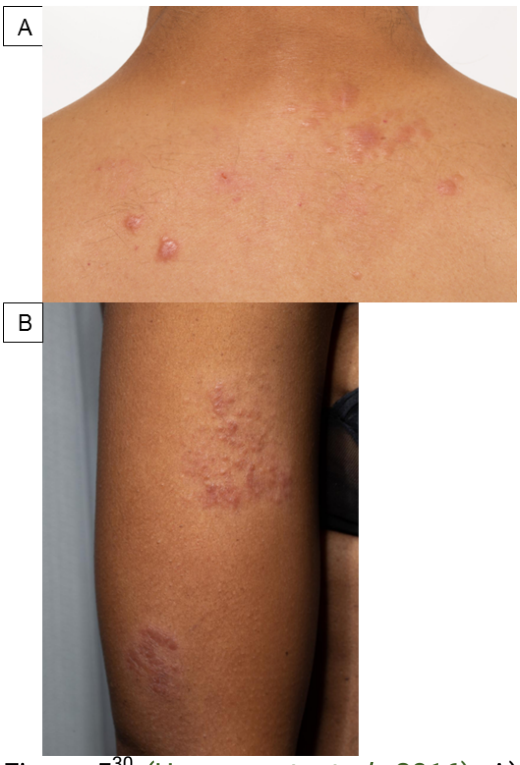

Figure 5[30] (Ungprasert *et al.*, 2016): A) Papular sarcoidosis as a cutaneous manifestation seen on the upper back region.
B) Plaque sarcoidosis as a cutaneous manifestation seen on the upper arms.

Visual 6

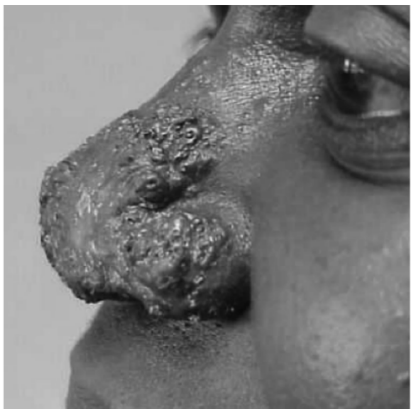

Figure 6. Lupus pernio, or disfiguring facial sarcoidosis affecting the nose[28] (Judson, 2008)

Visual 7

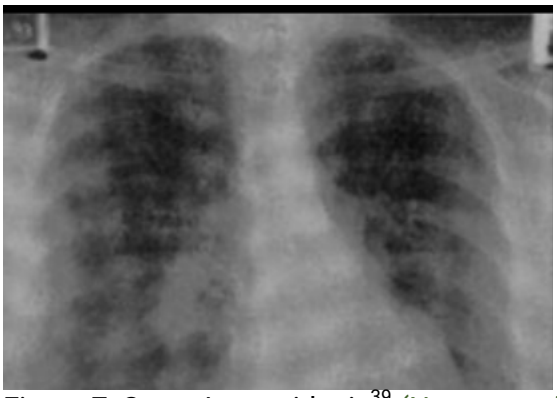

Figure 7: Stage I sarcoidosis[39] (Nunes *et al.*, 2007).

Visual 8

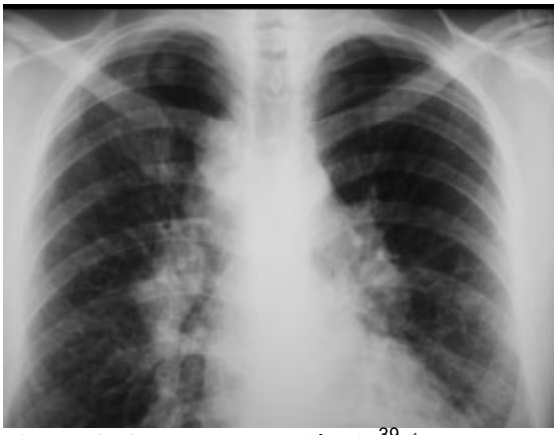

Figure 8: Stage II sarcoidosis[39] (Nunes *et al.*, 2007).

Visual 9

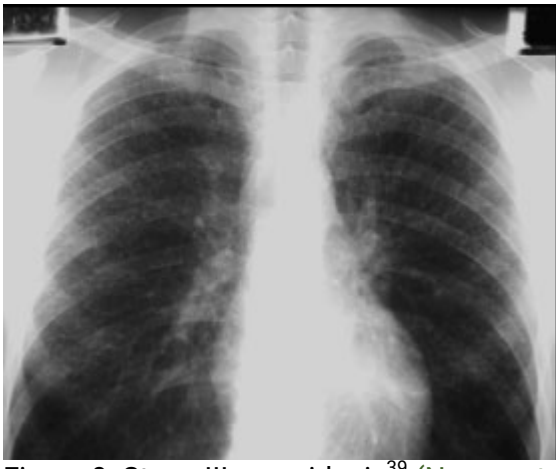

Figure 9: Stage III sarcoidosis[39] (Nunes *et al.*, 2007).

Visual 10

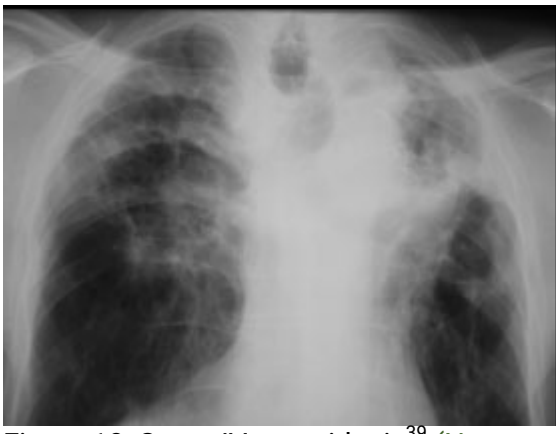

Figure 10: Stage IV sarcoidosis[39] (Nunes *et al.*, 2007).

Visual 11

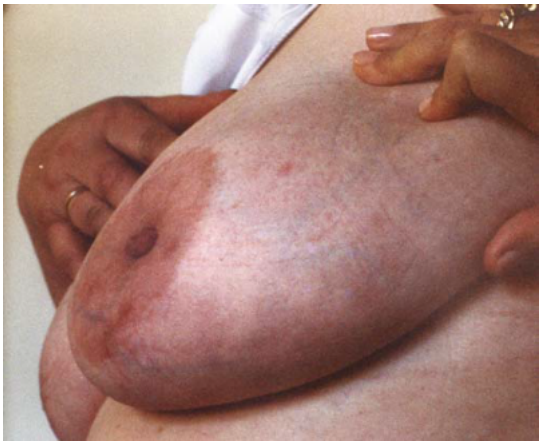

Figure 11: Sarcoidosis patient with breast cancer, which she developed four years after a chronic form of lung disease[54] (Lower *et al.*, 2001)

Visual 12

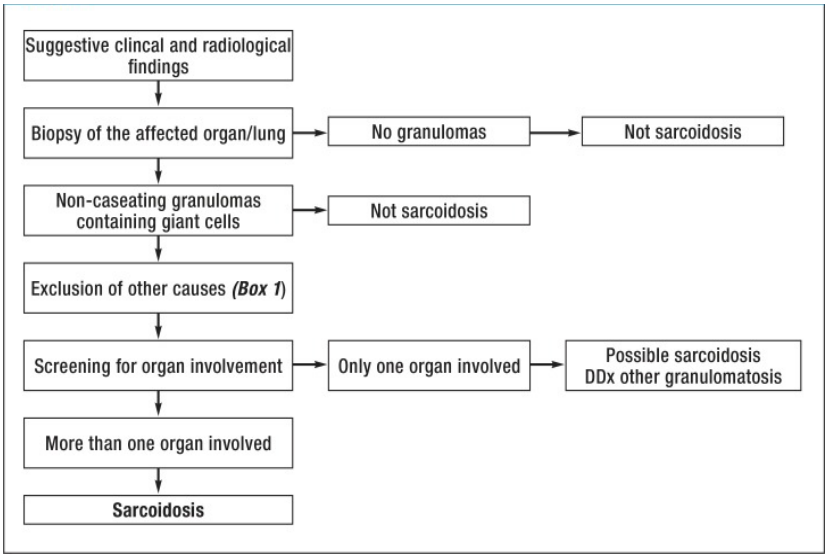

Figure 12: Algorithm for the diagnosis of sarcoidosis, modified from Baughman *et al.* (2011)[55]