SARCOIDOSIS

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Definition

Sarcoidosis is a multisystem granulomatous disorder of unknown origin, commonly affecting young adults. and usually presenting with bilateral hilar lymphadenopathy, pulmonary infiltration and skin or eye lesions. Beryllium poisoning can produce a clinical and histological picture identical to sarcoidosis, though contact with this element is now strictly controlled.

Epidemiology and etiology

- Sarcoidosis can affect people of any age , but usually starts in adults aged between 20 and 40. It is rare in childhood.
- Sarcoidosis affects people from all ethnic backgrounds, but it tends to be more common in African Americans and Northern Europeans.
- Arabs and Chinese are rarely affected.

Epidemiology and etiology

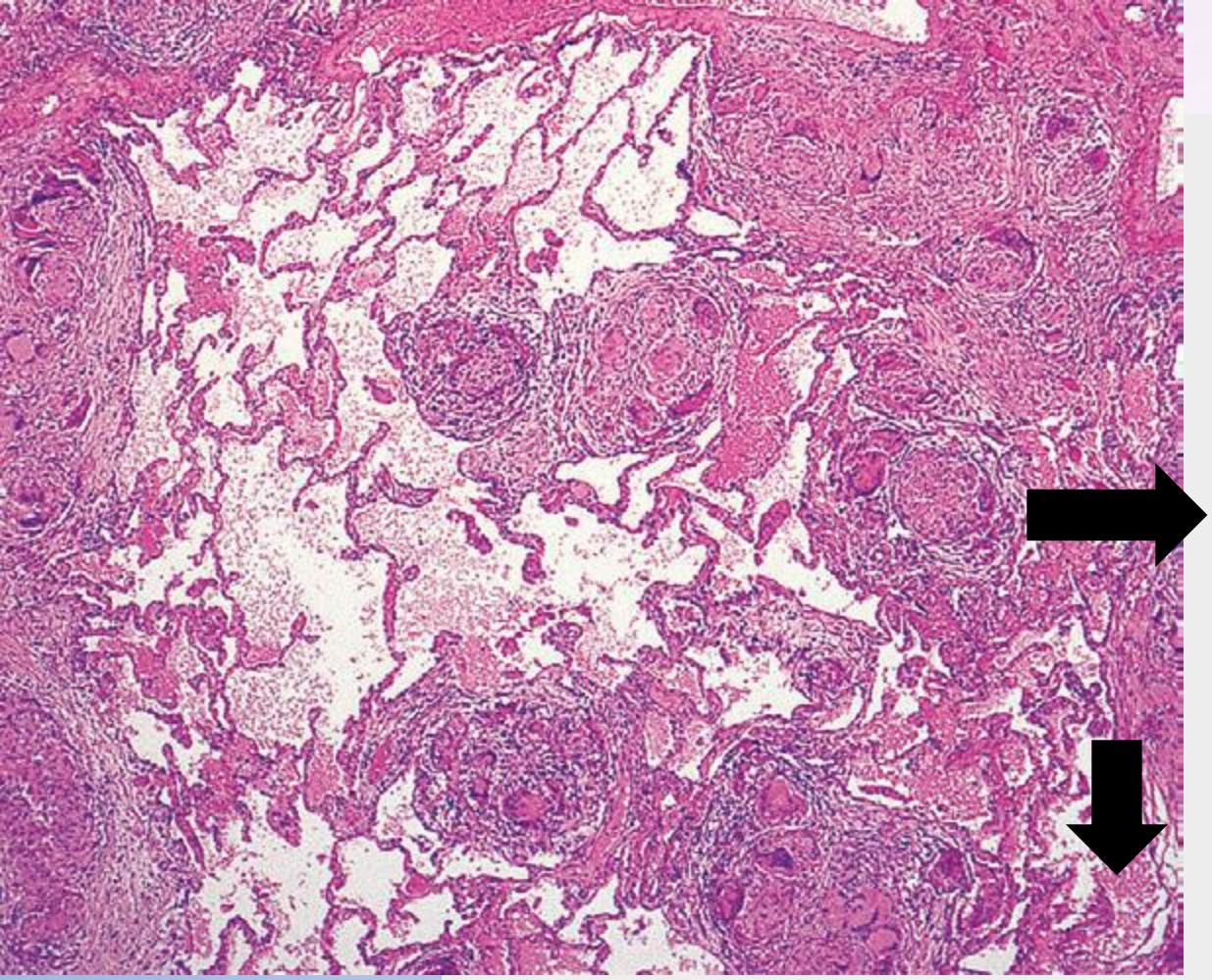
- The tendency for sarcoid to present in spring and summer has led to speculation about the role of infective agents, including mycobacteria, propionibacteria and viruses like Epstein-Barr virus , but the cause remains elusive.
- Genetic susceptibility supported by familial clustering; a range of class II HLA alleles(HLA-DRB1) confer protection from or susceptibility to the condition. First degree relatives have an increased risk for developing sarcoidosis.
- Sarcoidosis occurs less frequently in smokers.

Pathophysiology

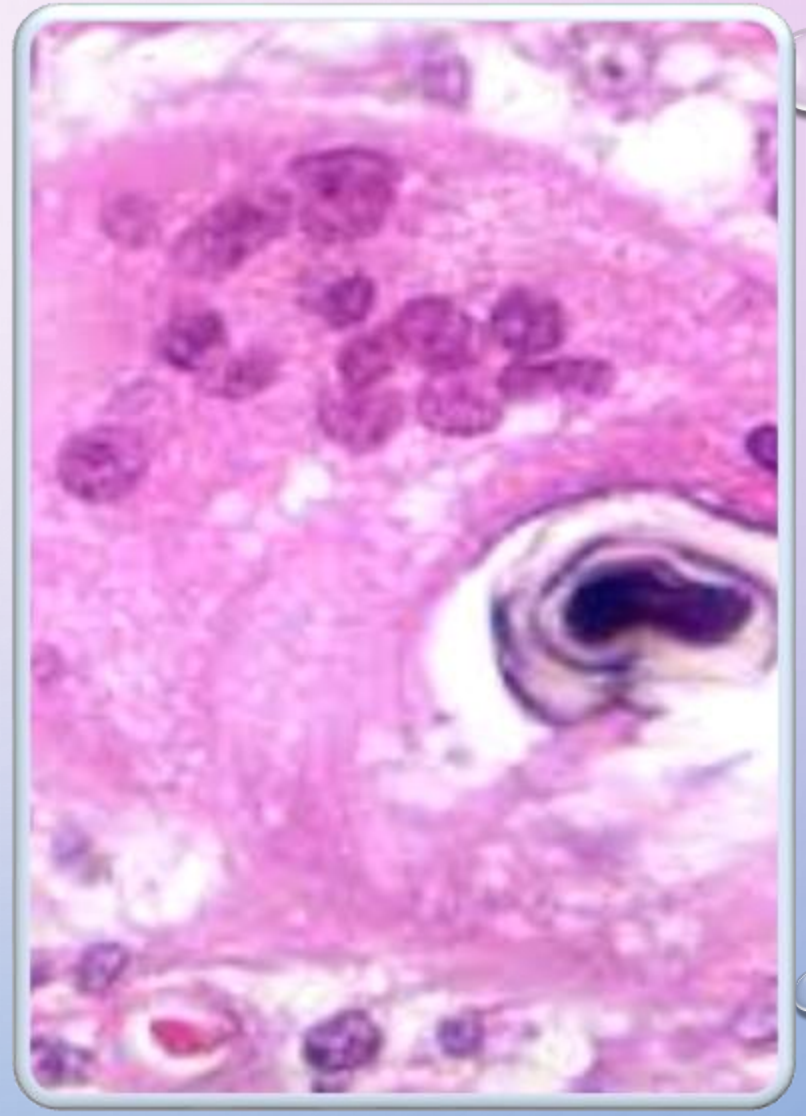
- The unknown antigen triggers a cell-mediated immune response that is characterized by the accumulation of T cells and macrophages, release of cytokines and chemokines, and organization of responding cells into granulomas. The inflammatory process leads to formation of noncaseating granulomas, the pathologic hallmark of sarcoidosis.

Pathophysiology

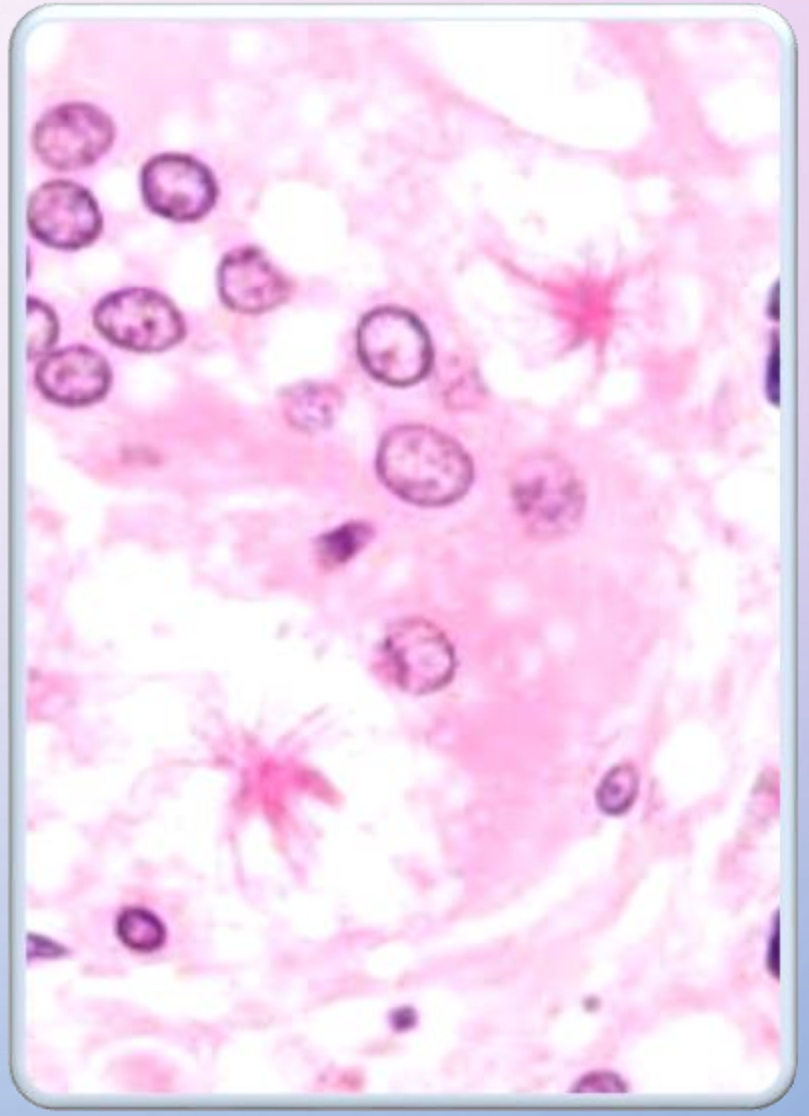
Granulomas occur most commonly in the lungs and lymph nodes but can involve any organ and cause significant dysfunction. Granulomas in the lungs are distributed along lymphatics, with most occurring in peribronchiolar, subpleural, and perilobular regions. Granuloma accumulation distorts architecture in affected organs.



Schaumann bodies



Astroid bodies



Clinical features

- Sarcoidosis can affect almost any organ.
- Symptoms and signs depend on the site and degree of involvement and vary over time, ranging from spontaneous remission to chronic indolent illness.
- Most cases are probably asymptomatic and thus go undetected or detected incidentally by routine chest x-ray.

Clinical features

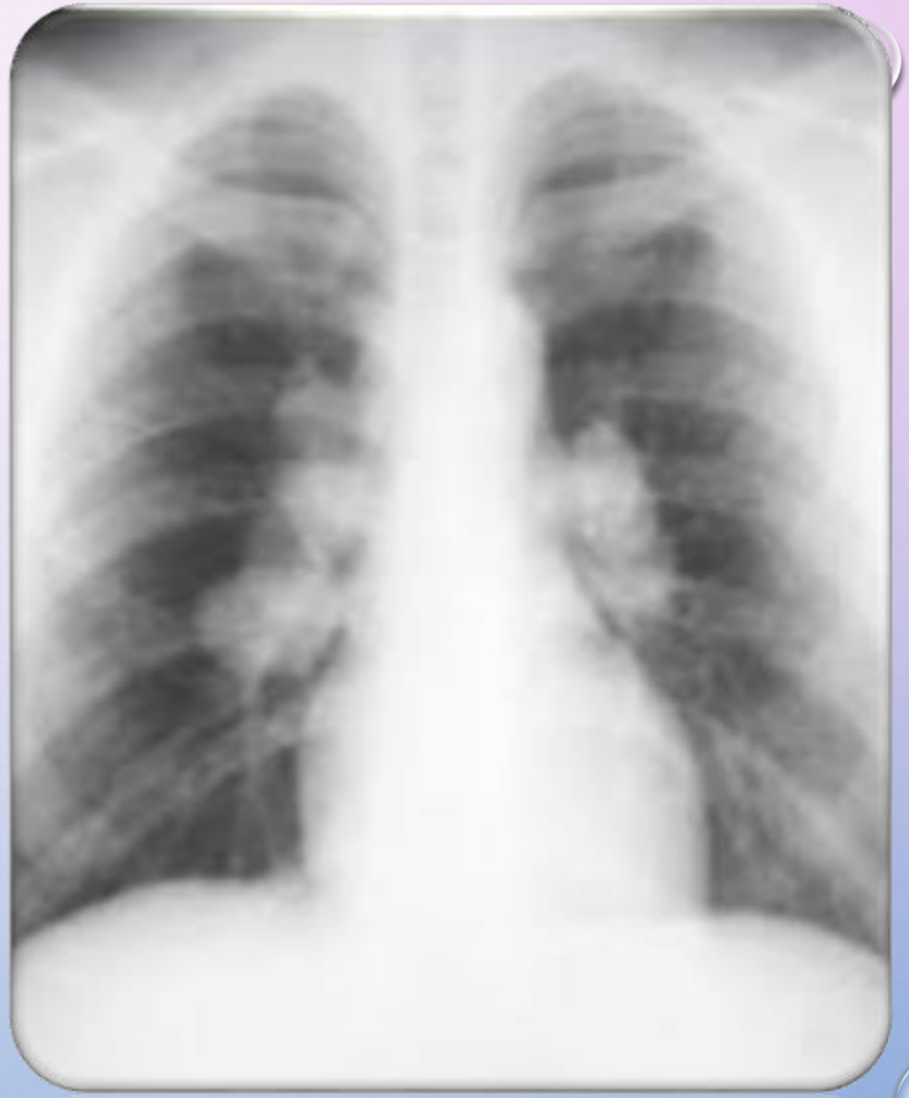
- Pulmonary disease occurs in > 90% of adult patients.
- Symptoms and signs may include dyspnea, cough and chest discomfort.
- Constitutional symptoms are also common including: fatigue, malaise, weakness, anorexia, weight loss, and low-grade fever.
- Sarcoidosis can manifest as fever of unknown origin.
- Systemic involvement causes various symptoms, which vary by race, sex, and age. Blacks are more likely than whites to have involvement of the eyes, liver, bone marrow, peripheral lymph nodes, and skin; erythema nodosum is an exception. Women are more likely to have erythema nodosum and eye or nervous system involvement. Men and older patients are more likely to be hypercalcemic.

Pulmonary sarcoidosis

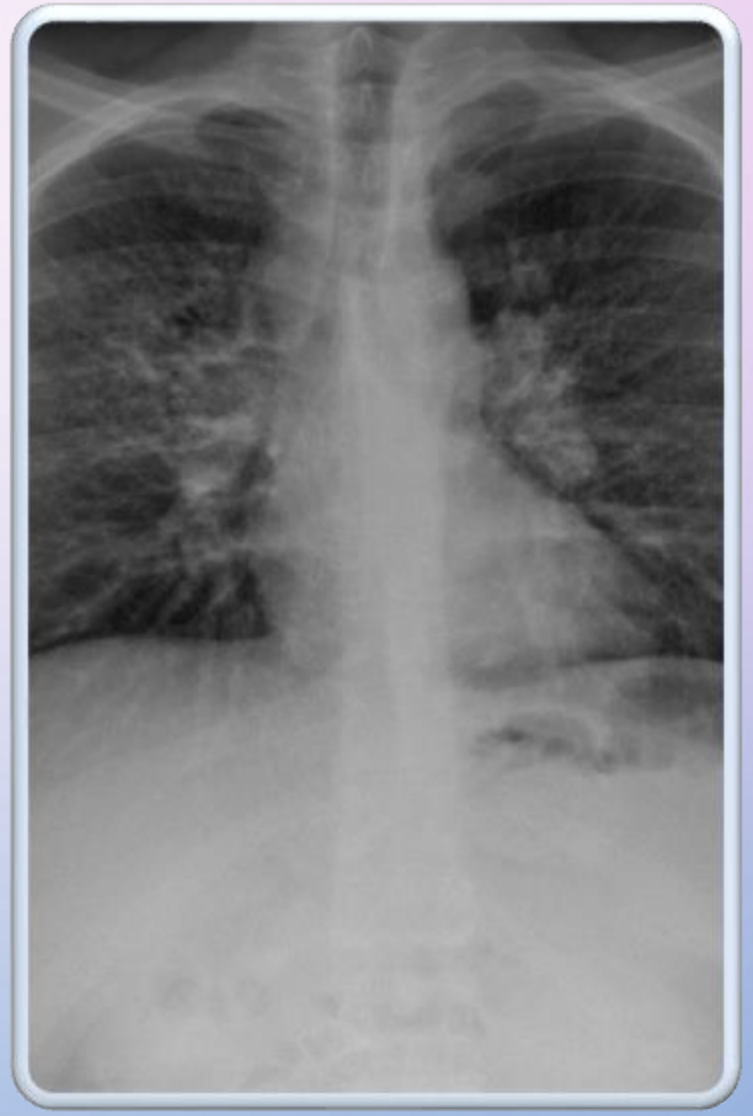
- Pulmonary disease may present in a more insidious manner with cough, exertional breathlessness and radiographic infiltrates.
- There are four stages of pulmonary involvement based on radiological stage of the disease, which is helpful in prognosis:
- Stage I: bilateral hilar lymphadenopathy (BHL) alone
- Stage II: BHL with pulmonary infiltrates
- Stage III: pulmonary infiltrates without BHL
- Stage IV: fibrosis.

Stage 1: bilateral hilar lymphadenopathy alone.

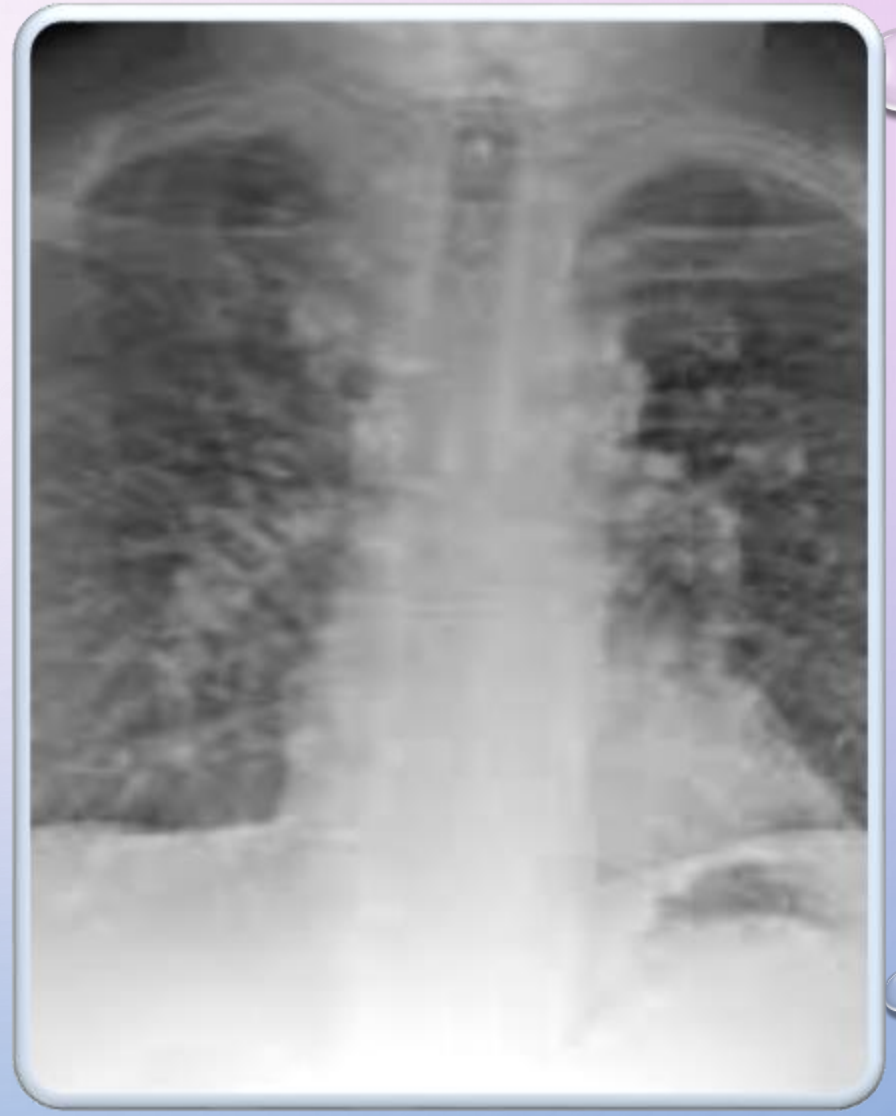
Bilateral hilar lymphadenopathy is a characteristic feature of sarcoidosis, which is usually symptomless and only detected on chest x-ray.



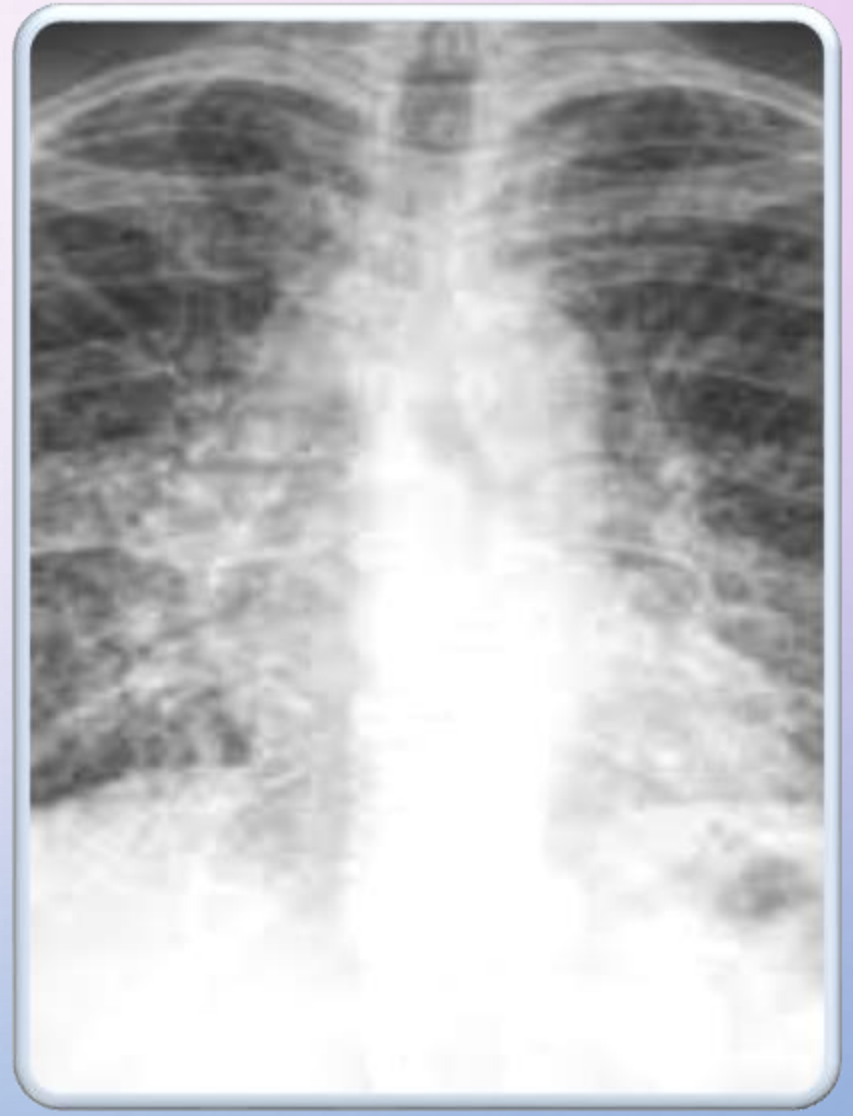
Stage 2 : bilateral hilar lymphadenopathy with pulmonary infiltrate.



Stage 3 : pulmonary infiltrate without bilateral hilar lymphadenopathy.



Stage 4 : Pulmonary fibrosis.



Complications of pulmonary sarcoidosis

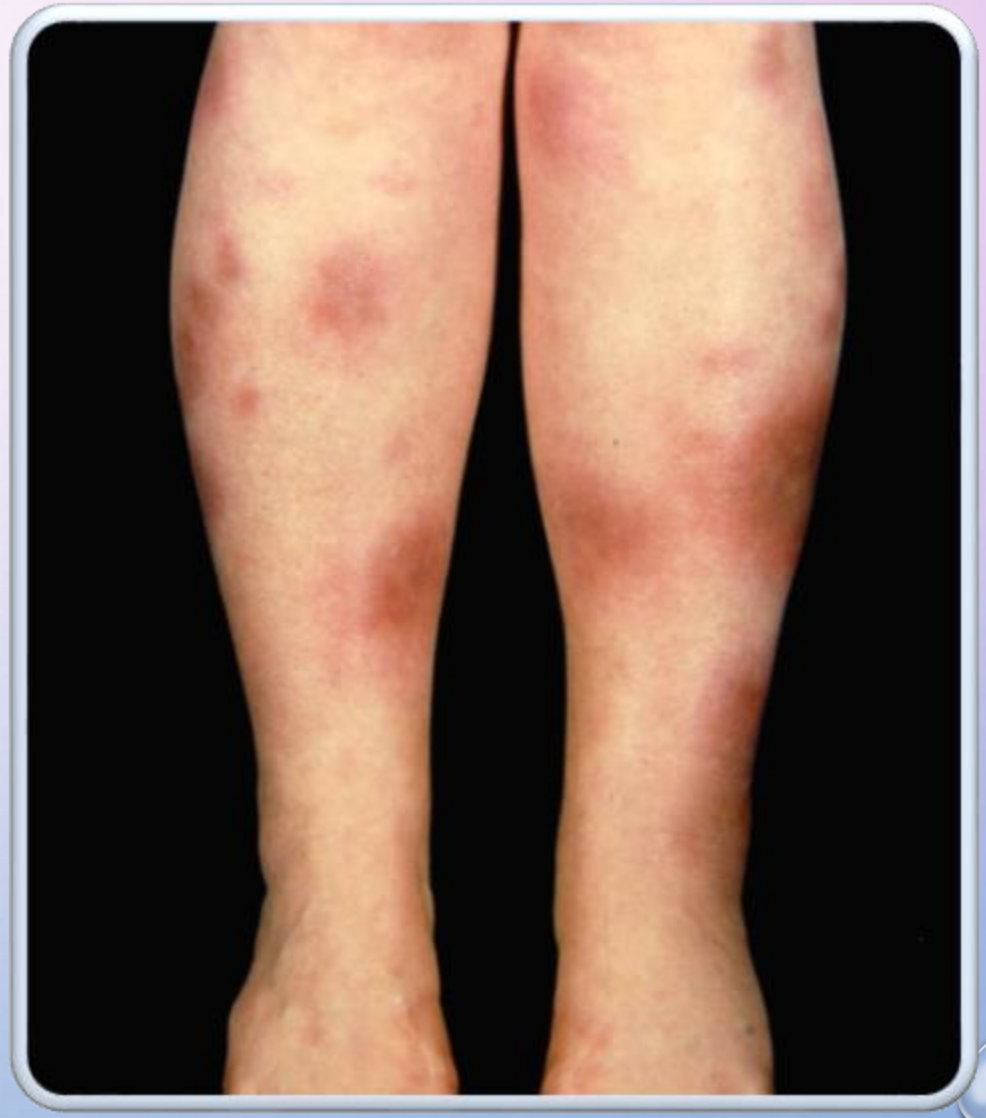
- Complications such as bronchiectasis, aspergilloma, pneumothorax, pulmonary hypertension, cor pulmonale and sudden cardiac death have been reported but are rare.

Extrapulmonary manifestations

- The skin is affected in 20% to 35% of patients with sarcoidosis, and skin lesions are often present at the time of diagnosis.
- Cutaneous manifestations of sarcoidosis that are caused by granulomas are referred to as specific for sarcoidosis, whereas other lesions are considered nonspecific.
- The most common nonspecific cutaneous manifestation is erythema nodosum, which typically manifests as painful nodules on the lower legs, usually in the setting of an acute presentation of sarcoidosis.

Erythema nodosum

Reddish, painful, tender lumps most commonly located in the shins.



Extrapulmonary manifestations

•Specific forms of cutaneous sarcoidosis occur in many patterns, with the most common being papular, maculopapular, and plaque lesions. Papular lesions occur commonly on the face, often around the eyes, whereas maculopapular lesions tend to favor the neck and trunk

- •both are associated with milder pulmonary disease and a good prognosis, whereas plaque lesions are more often associated with chronic disease requiring steroid treatment.

- •A unique lesion of sarcoidosis, termed lupus pernio (unrelated to systemic lupus erythematosus) causes distinctive violaceous, indurated lesions on the face, •these lesions are often disfiguring and may damage underlying soft tissue and bony structures, causing nasal ulcerations, septal perforation, and deformity ,bony cysts may develop under affected areas.
- •Lupus pernio associated with more frequent pulmonary parenchymal involvement and more aggressive systemic disease

Skin sarcoidosis

Specific forms of cutaneous sarcoidosis: popular, maculopapular and plaque lesions.

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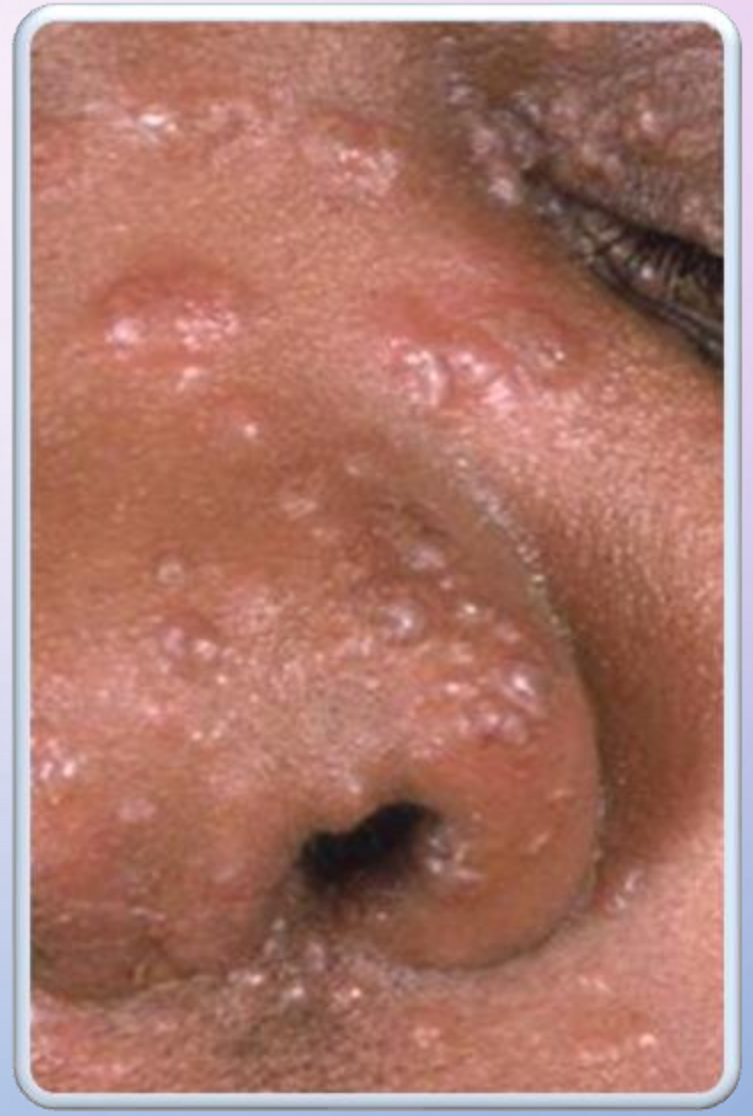
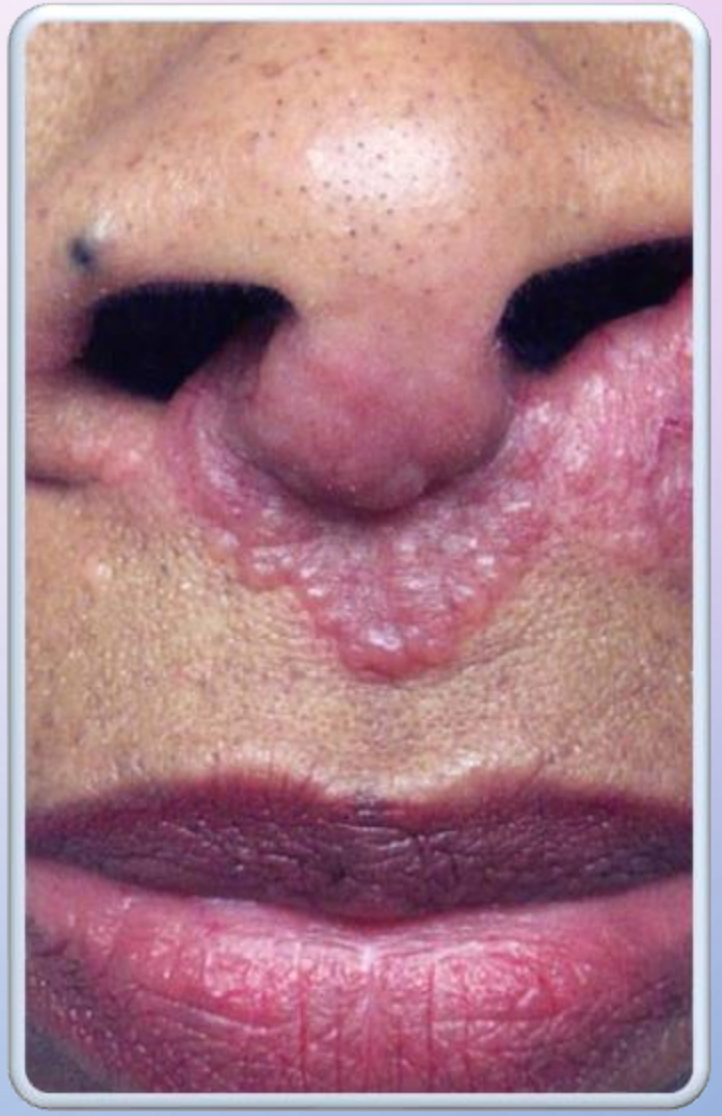


Lupus pernio

Bluish-red or violaceous nodules and plaques over the nose, cheeks and ears.



Extrapulmonary manifestations

- Eye lesions:

- The eye is the third most frequently involved organ, affected in between 10% and 60% of patients.
- • Ocular inflammation is most often bilateral, and the anterior segment is involved in 70% to 85% of cases. Involvement of the posterior segment occurs less frequently.
- Uveitis is the most common ocular manifestation and can be vision-threatening; thus, all patients diagnosed with sarcoidosis should have an ophthalmologic evaluation . Symptoms of uveitis may include tearing, photophobia, pain .
- Conjunctivitis and retinal lesions have also been reported.
- Uveoparotid fever is a syndrome of bilateral uveitis and parotid gland enlargement together with occasional development of facial nerve palsy and is sometimes seen with sarcoidosis.

Extrapulmonary manifestations

- Metabolic manifestations: Hypercalcemia is found in 10% of established cases. Hypercalcemia and hypercalciuria can lead to the development of renal calculi and nephrocalcinosis. The cause of the hypercalcemia is an increase in circulating 1,25-dihydroxyvitamin D3, with 1 α-hydroxylation occurring in sarcoid macrophages in the lung in addition to that taking place in the kidney.

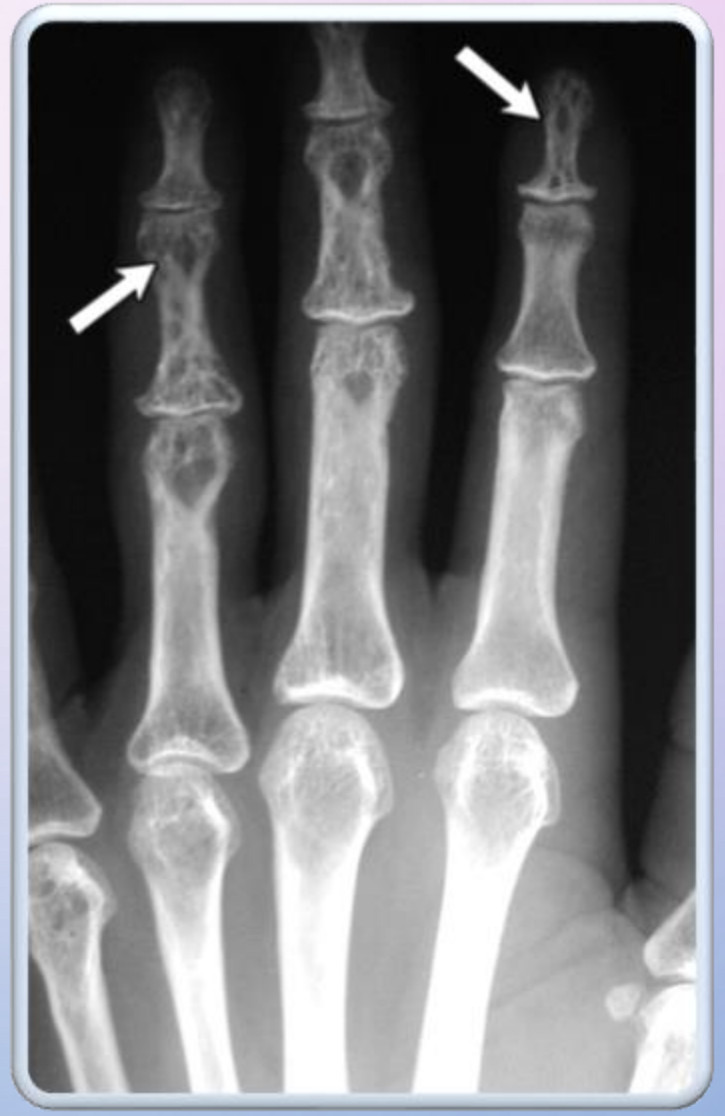
Extrapulmonary manifestations

- Bone and joint involvement: acute polyarthritis with fever, bones and joints are most commonly involved.
- Muscle involvement is rare.

Bone sarcoidosis

- Radio-graphically, bone manifestations follow 3 distinct patterns, namely: lytic , permeative, and destructive.
- A lytic pattern results from focal areas of imbalanced bone destruction and bone formation, resulting in net bone resorption and cyst formation. Bone cysts are often associated with overlying skin disease, either on the hands and feet, for example associated with dactylitis, or on the face underlying skin lesions of lupus pernio.

Punched out lytic lesions in the phalanges



Extrapulmonary manifestations

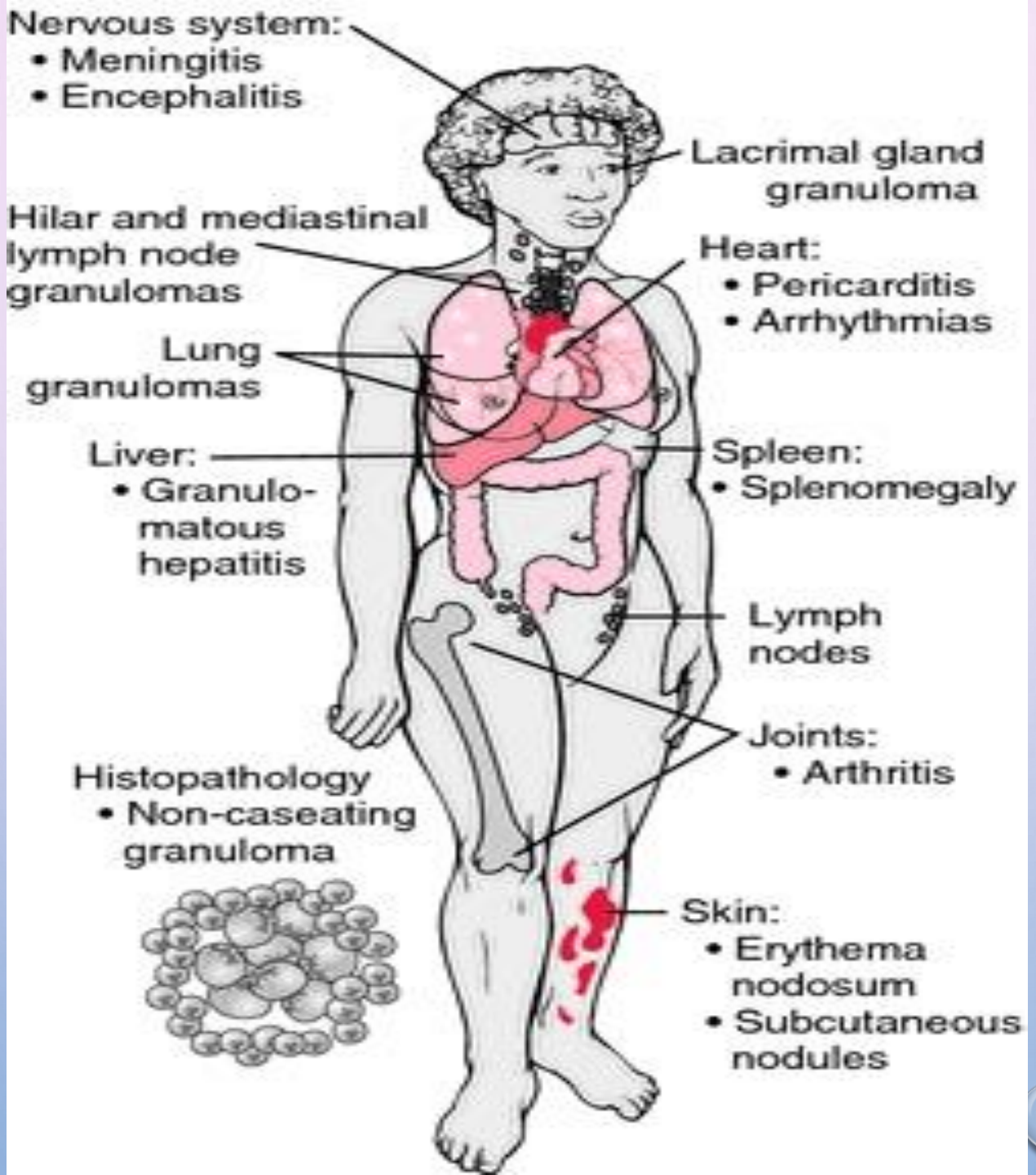
- Hepatosplenomegaly: Sarcoidosis is a cause of hepatosplenomegaly, though it is rarely of any clinical consequence. Liver biopsy is occasionally performed when the diagnosis is in doubt and will show granulomas.
- Neuro sarcoidosis: Cranial nerves are most commonly affected. If facial nerve is affected this can lead to facial nerve palsy. The hypothalamus and the pituitary gland can also be affected. when hypothalamus is affected diabetes insipidus can occur.

Extrapulmonary manifestations

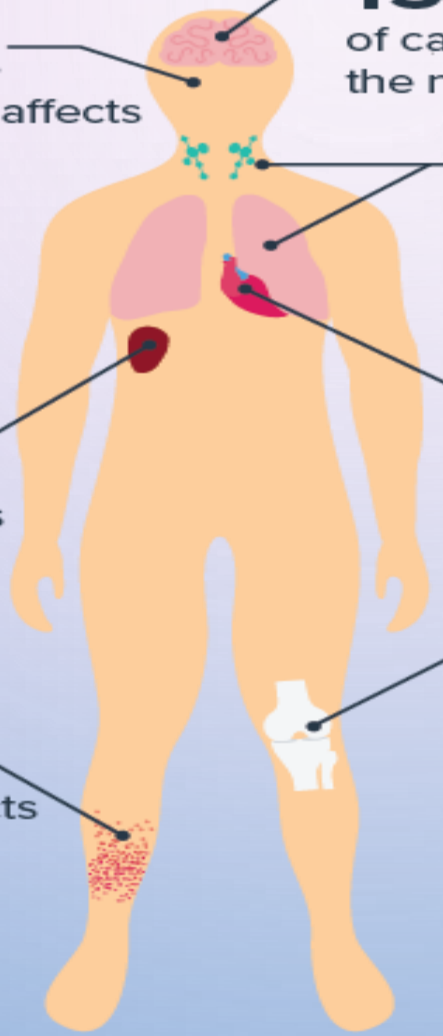
- Cardiac sarcoidosis : Is rare but can be serious.
- Ventricular dysrhythmias, conduction defects and cardiomyopathy with congestive cardiac failure and sudden cardiac death are seen.
- Screening should be done to exclude cardiac involvement: ECG,ECHO and Holter monitoring.
- Diagnosis of cardiac sarcoidosis is made by: nuclear imaging, cardiac PET\MRI and heart biopsy (rare, but gives an absolute result because of patchy involvement of myocardium).

Prognosis

- 50% of patients have spontaneous remission, remission occurs within the first 3 years after diagnosis. Fewer than 10% of these patients relapse after 2 years.
- Sarcoidosis is thought to be chronic in up to 30% of patients.
- Prognosis is worse for patients with extrapulmonary sarcoidosis and for blacks.
- Good prognostic signs include: Löfgren syndrome (triad of acute polyarthritis, erythema nodosum, and hilar adenopathy)
- Poor prognostic signs include: Chronic uveitis, Lupus pernio, Chronic hypercalcemia, Neurosarcoidosis, Cardiac involvement, Extensive pulmonary involvement and/or development of pulmonary hypertension.


Nervous system:
• Meningitis
• Encephalitis
Lacrimal gland granuloma
Hilar and mediastinal lymph node granulomas
Heart:
• Pericarditis
• Arrhythmias
Lung granulomas
Liver:
• Granulo-matous hepatitis
Spleen:
• Splenomegaly
Lymph nodes
Joints:
• Arthritis
Histopathology
• Non-caseating granuloma
Skin:
• Erythema nodosum
• Subcutaneous nodules

Effects of Sarcoidosis



15%
of cases affects
the nervous system

25%
of cases affects
the eyes

90%
of cases affects
the lungs and
lymph nodes

10%
of cases affects
the heart

65%
of cases affects
the liver

33%
of cases affects the
bones and joints

25%
of cases affects
the skin

Table 3. Differential Diagnosis for Pulmonary Sarcoidosis

Category	*Specific disease*
Exposures/toxins	Drug-induced hypersensitivity (e.g., adalimumab [Humira], etanercept [Enbrel], infliximab [Remicade], methotrexate)
	Foreign body granulomatosis (aspiration or intravenous injection of foreign materials)
	Hypersensitivity pneumonitis
	Pneumoconioses (aluminum, beryllium, cobalt, talc, titanium, zirconium)
Immunodeficiency	Chronic granulomatous disease
	Common variable immunodeficiency
Infections	Bacterial (brucellosis, nontuberculous mycobacteria, tuberculosis)
	Fungal (aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*)
	Parasitic (echinococcosis, leishmaniasis, schistosomiasis, toxoplasmosis)
	Viral (human immunodeficiency virus)
Inflammations	Bronchocentric granulomatosis (usually associated with asthma and allergic bronchopulmonary aspergillosis)
	Eosinophilic granulomatosis (pulmonary Langerhans cell histiocytosis)
	Lymphocytic interstitial pneumonitis
Malignancy	Lymphoma
	Lymphomatoid granulomatosis
	Sarcoid-like granuloma reactions (primary tumors, regional lymph nodes)
Vasculitis	Churg-Strauss syndrome
	Granulomatosis with polyangiitis (Wegener granulomatosis)

Information from reference 1.

Investigations

- Imaging: CXR \CT → chest x-ray is less sensitive than CT for thoracic manifestations of sarcoidosis.
- Lung function tests: Show a restrictive lung defect in patients with pulmonary infiltration or fibrosis. There is a decrease in TLC, FEV1 and FVC, and DLCO. Lung function is usually normal in patients who present with extrapulmonary disease or who only have hilar adenopathy on chest x-ray.
- Laboratory studies: Raised ESR , lymphopenia and mild eosinophilia. Hypercalcemia may be present (reflecting increased formation of calcitrol – 1,25-dihydroxyvitamin D3 – by alveolar macrophages), particularly if the patient has been exposed to strong sunlight, elevated levels of serum alkaline phosphatase, elevated levels of serum ACE (Angiotensin Converting Enzyme) and hypergammaglobulinemia.
- Serum ACE levels should be tested regularly to check the severity of the disease and to monitor the response to therapy.

Investigations

- **Transbronchial biopsy:** Is the most useful investigation, usually shows non-caseating granulomas.
- **Bronchoalveolar lavage**: BAL fluid typically contains an increased CD4:CD8 T-cell ratio>3.5 while in hypersensitivity pneumonitis CD4:CD8 T-cell ratio <3.5.

Confirmation of the diagnosis

There are three criteria for diagnosing sarcoidosis:

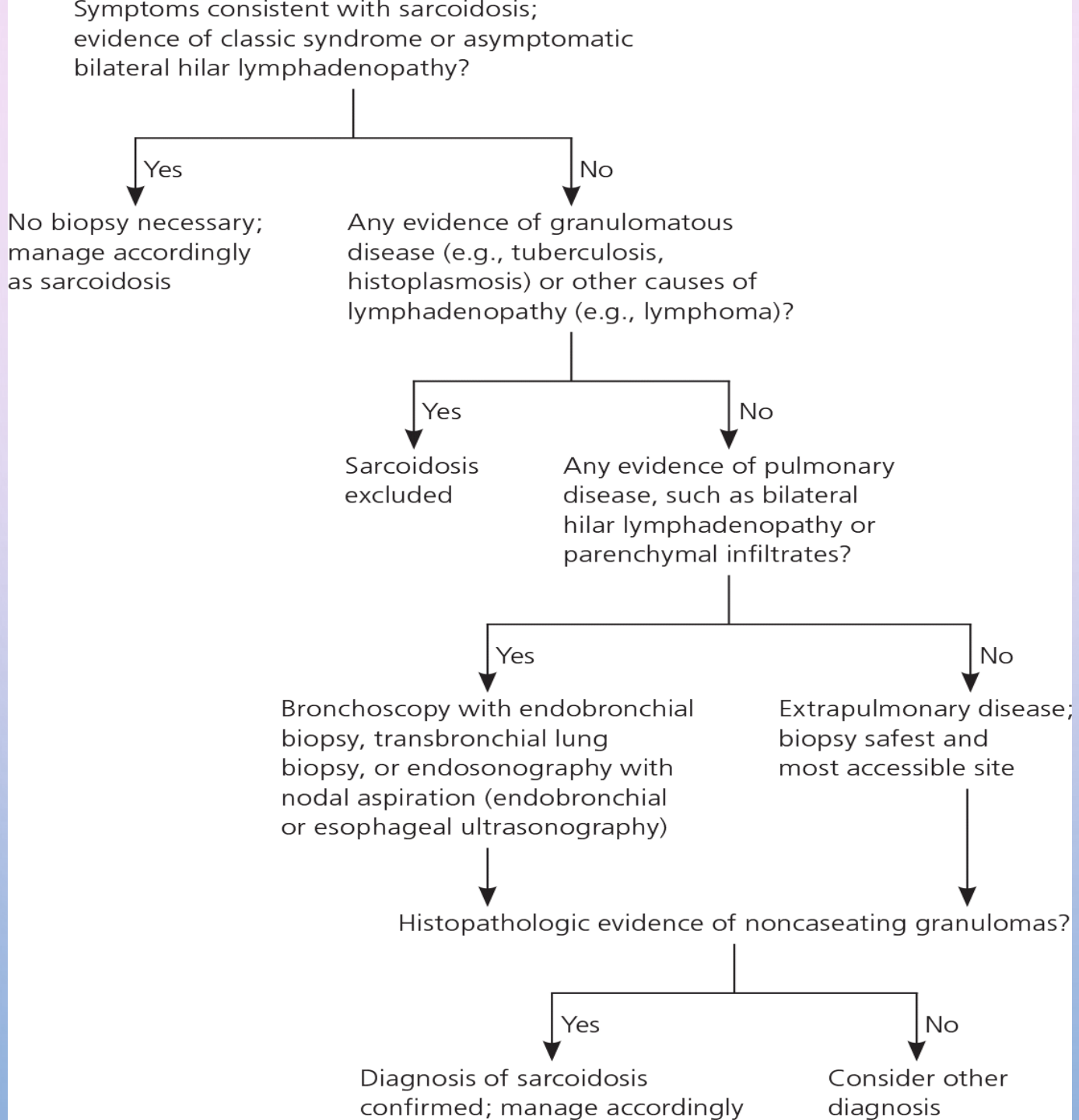
(1) a compatible clinical and radiologic presentation

(2) pathologic evidence of noncaseating granulomas

(3) exclusion of other diseases with similar findings

Confirmation of the diagnosis

- Certain sarcoidosis-specific syndromes, such as löfgren and heerfordt syndromes, can be diagnosed based on clinical presentation alone, avoiding the need for tissue biopsy.
- An asymptomatic patient with stage 1 sarcoidosis (Bilateral hilar lymphadenopathy on chest radiography) without suspected infection or malignancy does not require invasive tissue biopsy because the results would not affect the recommended management approach.
- If there would be an indication for treatment with a confirmed diagnosis, pathologic evidence of noncaseating granulomas should be obtained from the most accessible and safest biopsy site.


Symptoms consistent with sarcoidosis; evidence of classic syndrome or asymptomatic bilateral hilar lymphadenopathy?
Yes
No
No biopsy necessary; manage accordingly as sarcoidosis
Any evidence of granulomatous disease (e.g., tuberculosis, histoplasmosis) or other causes of lymphadenopathy (e.g., lymphoma)?
Yes
No
Sarcoidosis excluded
Any evidence of pulmonary disease, such as bilateral hilar lymphadenopathy or parenchymal infiltrates?
Yes
No
Bronchoscopy with endobronchial biopsy, transbronchial lung biopsy, or endosonography with nodal aspiration (endobronchial or esophageal ultrasonography)
Extrapulmonary disease; biopsy safest and most accessible site
Histopathologic evidence of noncaseating granulomas?
Yes
No
Diagnosis of sarcoidosis confirmed; manage accordingly
Consider other diagnosis

Treatment is not indicated for patients

with asymptomatic stage I or II sarcoidosis

because spontaneous resolution is common.

eTable A. Indications for Treatment of Sarcoidosis

Topical therapy

Skin lesions

Anterior uveitis

Cough or airway obstruction

Nasal polyps

Systemic therapy

Pulmonary compromise with symptomatic stage II to III disease, persistent infiltrates, decline in lung function

Cardiac disease

Neurosarcoidosis

Ocular disease not responding to topical therapy

Symptomatic hypercalcemia

Lupus pernio

NOTE: *Indications listed from most to least common.*

Information from Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. *1999;160(2):736-755.*

Treatment of pulmonary sarcoidosis

Corticosteroids remain the mainstay of treatment for patients with significant symptomatic or progressive stage II or III disease, or serious extrapulmonary disease.

Prednisone is recommended at a starting dosage of 20 to 40 mg per day for four to six weeks. If the patient's condition is stable or improved, the dosage should be tapered slowly to approximately 5 to 10 mg per day. If there is no clinical response after three months of steroid therapy, a response to longer courses is unlikely. Treatment should be continued for a minimum of 12 months before tapering off.

Moderate or severe impairment of pulmonary function may predict mortality in patients with sarcoidosis who are infected with SARS-CoV-2. As in patients with other inflammatory lung diseases, during the COVID-19 pandemic, immunosuppressants should be used judiciously.

eTable B. Most Commonly Used Medications for Sarcoidosis

Medication	*Dosage*	*Indication by organs involved*	*Significant adverse effects*	*Monitoring*
Prednisone	20 to 40 mg per day initially; 5 to 10 mg per day for long-term therapy	Pulmonary, cardiac, neurologic, ocular, cutaneous,† renal‡	Weight gain, diabetes mellitus, osteoporosis, hypertension, infections	Weight, glucose level, bone density, blood pressure
Methotrexate	10 to 15 mg per week	Pulmonary, cardiac, neurologic, ocular, cutaneous†	Nausea, leukopenia, liver/pulmonary toxicity, infections	Complete blood count, renal/liver indices every 1 to 3 months
Azathioprine (Imuran)	50 to 200 mg per day	Pulmonary, renal,‡ neurologic	Nausea, leukopenia, liver toxicity, infections	Consider thiopurine methyl-transferase level and phenotype before initiation; complete blood count and liver function tests every 1 to 3 months
Leflunomide (Arava)	10 to 20 mg per day	Pulmonary, ocular, cutaneous	Nausea, diarrhea, liver toxicity, rash, peripheral neuropathy	Liver function tests every 1 to 3 months
Hydroxychloroquine (Plaquenil)	200 to 400 mg per day	Cutaneous,† pulmonary, cardiac, neurologic, renal‡	Retinopathy, rash, neuromyopathy	Eye examination every 6 to 12 months
Infliximab (Remicade)	5 mg per kg intravenously at weeks 0, 2, and 6, then monthly thereafter	Pulmonary, neurologic, cutaneous,† renal‡	Infections (especially reactivation of TB), allergic reactions, antibody formation	TB assessment at initiation; close monitoring during infusions
Adalimumab (Humira)	40 mg subcutaneously every 1 to 2 weeks	Pulmonary, neurologic, cutaneous,† renal‡	Infections (especially reactivation of TB), allergic reactions	TB assessment at initiation; close monitoring during injections

NOTE: *Medications listed in order of preferred use.*

NA = not available; TB = tuberculosis.

**—Estimated retail price for one month's treatment based on information obtained from http://www.drugs.com (accessed July 2015) and http://www.goodrx.com (accessed January 11, 2016). Generic price listed first; brand price listed in parentheses.*

†—*Use if the cutaneous indication is cosmetically disfiguring (e.g., lupus pernio), symptomatic, ulcerating, or progressive; otherwise, local therapies may be sufficient.*

‡—*Renal disease includes hypercalcemia, nephrolithiasis, nephrocalcinosis, and acute interstitial nephritis.*

Information from Vorselaars AD, Cremers JP, Grutters JC, Drent M. Cytotoxic agents in sarcoidosis: which one should we choose? Curr Opin Pulm Med. *2014;20(5):479-487.*

Treatment of extrapulmonary sarcoidosis

- Cutaneous involvement can be treated with topical agents, systemic treatment.
- Ocular involvement can be treated with topical corticosteroids and systemic therapy.
- Cardiac sarcoidosis Often responds to corticosteroids and immunosuppressant therapy, heart transplantation has been required in patients with end-stage cardiomyopathy.
- Calcium metabolism patients with active sarcoidosis are advised to reduce dietary calcium and calcium supplement intake, avoid sunlight, and drink adequate amounts of fluids.

Evaluation

- Upon diagnosis, all patients should get:

➢Referral to ophthalmologist

➢Annual ECG

➢Annual PFTs \chest x-ray

➢Follow up routine labs (LFTs, KFTs)

THANK YOU