Review Article

Sarcoidosis – A review article

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Abstract

Sarcoidosis is a granulomatous disorder of multiple organs, with lungs and lymphatic systems being the most frequently affected sites of the body. It was first reported in 1877 and has continued to engross both clinicians and scientists since that time. Because sarcoidosis being a diagnosis of exclusion, it demands the physician to rule out all the possible diagnosis. Most of the patients remain asymptomatic and this makes the disease remain unnoticed for a prolonged period. Later after years, the disease could be diagnosed after witnessing the patient being symptomatic or suffering from organ failures. It could affect middle aged people of any sexes, often its clinical features correlate with tuberculosis. On immunological and histopathological examination, it reveals noncaseating granuloma in simple terms. Glucocorticoids remain the standard drug now and then. Further research has to be done to know the exact pathogenesis, early detection and betterment in treatment plan of sarcoidosis. The current review article gives a brief knowledge about etiopathogenesis, Clinical features, upgraded diagnostic methods such as biomarkers detection and the organized treatment plan to treat sarcoidosis.

Keywords: Asteroid bodies, glucocorticoids, granulomatous, kveim-slitzbach skin patch test, sarcoidosis, Schaumann bodies

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INTRODUCTION

Sarcoidosis is a multisystem disorder of unrecognized etiology. It is also a chronic granulomatous disease primarily affecting lungs, lymphoid systems, and any organ system in the body. The histopathology of sarcoidosis reveals granulomas which are nonnecrotizing with a tightly packed macrophages in the center, epithelioid cells, multinucleated giant cells, and T-lymphocytes that are CD4 positive.[1,2] Since this is a diagnosis of exclusion, it is mandatory to exclude other granulomatous diseases. In 1877, Jonathan Hutchinson reported the first case of sarcoidosis at the King's College Hospital in London (United Kingdom). It still remains a challenge for clinicians to give sarcoidosis as a diagnosis even after many advancements have occurred. It has nonspecific symptoms and histopathology remains as a gold standard to confirm the diagnosis. This review article discusses about the etiology, pathogenesis, clinical manifestations, and the advancements in the management of sarcoidosis.[3]

EPIDEMIOLOGY

The prevalence of sarcoidosis is seen in people of all ages, regardless of race and ethnicity, with crest incidence seen in people aged between 20 and 39 years.[4,5] Highest incidence is seen among African Americans with an annual incidence

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of 17–35 per 100,000 population while the lowest annual incidence is observed among Asians and Hispanics (1–3/100,000).[6-12] There is a female predilection of 2:1 seen in Africans Americans.[12] It is more common among rural areas in particularly among nonsmokers.[13] Prevalence of sarcoidosis in India is 10–12 cases/1000 registrations yearly, as announced by a respiratory unit in western India.[14,15] Erythema nodosum (EN) in Europeans, chronic uveitis in U. S. blacks and lupus pernio in Puerto Ricans are the extra-thoracic manifestations encountered in specific populations. Unusual enitity in Blacks and Japanese is the sarcoid-related erythema nodosum.[16] Myocardial involvement is the frequent cause of death caused by sarcoidosis which is[17-19] followed by respiratory failure.[20,21] Mortality rate due to sarcoidosis is 1%–5%.

RISK FACTORS

The exact cause of sarcoidosis is unknown. The causes can be categorized under genetic factors, environmental factors, Infection and autoimmunity. Genetic factors that predispose to sarcoidosis includes the following risk loci like BTNL2, HLA-B, HLA-DPB1, ANXA11, IL23R, SH2B3/ATXN2, IL12B, NFKB1/MANBA and FAM177B. Environmental agents such as aluminium, zirconium, talc, pine tree pollen, clay, insecticide were the potent pathogens. Mycobacteria is the frequently and strongest pathogen associated with sarcoidosis, followed by *Leptospira* species, *Mycoplasma*, *Chlamydia pneumoniae* and *Borrelia burgdorferi*.

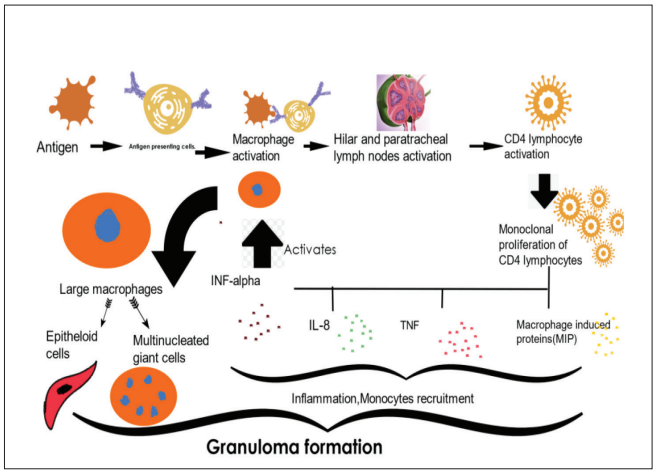
ETIOPATHOGENESIS OF SARCOIDOSIS

The etiology of sarcoidosis remains uncertain; however, there is improved understanding of its genetic factors, environmental associations, putative antigens and immunopathogenesis, and it probably results due to genetical susceptibility of individuals to specific environmental agents.[22]

Etiologic agents must be able to evoke the basic histologic hallmarks of sarcoidosis and account for the clinical heterogeneity and immunologic features of this disease.[23] The histological characteristic feature of sarcoidosis is well-organized, closely-packed, nonnecrotizing granulomas surrounded by lamellar hyaline collagen as described in Flow Chart 1.[24] Most researchers concur that environmental exposure, genetic factors, seemingly dysregulated immune system represented by an exaggerated T helper 1 (TH1) immune response are involved in pathogenesis of sarcoidosis.[25-28]

ROLE OF MYCOBACTERIA IN SARCOIDOSIS

There is similarity between sarcoidosis and tuberculosis (TB),



Flow Chart 1: Explaining the mechanism involved in the granuloma formation

in clinical, radiological and immunological features leading to the suggestion of mycobacteria as etiologic agent in sarcoidosis.[29-33] Favourable association between mycobacteria and sarcoidosis has been observed in various studies. Slow-growing mycobacteria species with low pathogenic potential, but with the ability of eliciting a type IV immune response, may be important in sarcoidosis.[34] Residues of Mycobacterial species are detected in the tissues of patients with sarcoidosis, in specific an intracellular protein, mycobacterial catalase– peroxidase (KatG), which could be a target of the adaptive immune response.[25] Other candidate mycobacterial antigens comprise superoxide dismutase and HSPs3,[25] early-secreted antigenic target of 6 kDa (ESAT6).

GENETIC FACTORS ASSOCIATED WITH SARCOIDOSIS

Sarcoidosis is a polygenic disease and various gene variants have been related with distinct phenotypes, prognosis and therapeutic response. The importance of interactions at the MHC binding site in the pathogenicity of sarcoidosis is supported by various studies.[24] Twin studies prove that monozygotic twins are more vulnerable for sarcoidosis than dizygotic twins.[35]

Human leucocyte antigen genotypes confer susceptibility, particularly a polymorphism in the butyrophilin-like 2 receptor gene (BTNL2-Costimulatory molecule within the MHC locus).[22] Hofmann and colleagues acknowledge an association of annexin A11 gene on chromosome 10q22.3. The annexin A11 gene is responsible for calcium signalling, vesicle trafficking, cell division, and apoptosis. Therefore, its deletion or dysfunction may influence apoptotic pathways in sarcoidosis.[35] The BTNL2 single-nucleotide polymorphism associated with sarcoidosis (rs2076530 G → A) may influence

T-lymphocyte activation and regulation.[36] Sarcoidosis is linked with the DR subtypes of class II ANTIGENS. HLADRB1∗ 03, HLA-DRB1∗ 11, HLA-DRB1∗ 12, HLA-DRB1∗ 14 and HLA-DRB1∗ 15 promote the risk of sarcoidosis whereas HLA-DRB1∗ 01 AND HLA-DRB1∗ 04, are negatively linked with sarcoidosis**.** HLA-DRB1∗ 03 is associated with Lofgren's syndrome.[35]

IMMUNOLOGICAL HALLMARKS

Natural killer T cells

Reduced numbers of NKT cells have been associated with sarcoid blood and Broncho alveolar lavage (BAL) fluid. Blood NKT cells obtained from patients with sarcoidosis and stimulated with a potent glycolipid stimulator, a-galactosyl ceramide, exhibited impaired production of interferon gamma.[36]

Toll like receptors

BAL cells obtained from sarcoidosis patients showed increased cytokine responses to TLR2/1 ligand 19-kDa lipoprotein of Mycobacterium TB. eTLR-2 promotor polymorphism-16934AA have a higher risk of developing a course of chronic course due to increased production of tumor necrosis factor-alpha (TNF-α).[36]

CLINICAL MANIFESTATIONS

It has got nonspecific manifestations and it primarily affects lungs and lymphoid system of the body. It has got organ-specific manifestations. 50% had extra thoracic symptoms, 95% of patients had thoracic engagement, and 2% had unaccompanied extra thoracic sarcoidosis as reported by ACCESS.[37]

Sarcoidosis may be acute, subacute or chronic in presentation**.** Lofgren syndrome is a triad comprising erythema nodosum, bilateral lymphadenopathy and polyarthritis are present. Whereas individuals suffering from subacute sarcoidosis have nonspecific signs such as fever, weight loss, frailty along with arthralgia and peripheral lymphadenopathy. Chronic sarcoidosis is linked with persistent lung engagement.

GENERALIZED SYMPTOMS

Majority of the sarcoidosis patients would be asymptomatic. Nonspecific symptoms like malaise, fatigue, fever and weight loss may occur in about one-third of sarcoidosis patients. Sarcoidosis seems to be an important and frequently neglected reason for fever of unknown origin.[38] Fever is generally low grade but temperature elevations of 39° to 40°C may be seen. Weight loss is usually bound to 2–6 kg during the 10–12 weeks before presentation. Occasionally, night sweats may occur.

PULMONARY SYMPTOMS

Lung with hilar and mediastinal lymph nodes is the most frequently affected organ (over 90% populations).[39] Fifty percent of the patients with pulmonary sarcoidosis are asymptomatic (stage) and rest of the patients will be presenting with dry cough, wheezing, dyspnea, chest tightness. Hemoptysis is rare. Certain atypical features like mucosal erythema, mucosal nodules, obstructive sleep apnea, hilar and mediastinal lymphadenopathy is seen. Conglomerate masses in the lungs will be well evident in radiographic image as linear opacities, ground-glass opacities[40,41] etc., [Table 1].

EXTRAPULMONARY MANIFESTATIONS

Cutaneous sarcoidosis

Most common extra thoracic manifestations of sarcoidosis. It has got an incidence of 20-40% individuals which can either be specific or non- specific.[42]

Sarcoidosis specific skin lesions

Papules/Plaques, subcutaneous nodules maybe present. Papule can be skin colored, violaceous, hypo/hyper pigmented, erythematous and are frequently found on extremities, head and neck region and least on the trunk. Subcutaneous nodules are due to Granulomatous inflammation of adipose tissue under the skin. These are multiple and painless nodules without overlying erythema, seen on extremities.[43] Other uncommon manifestations can be inflammation around scars, tattoos and lupus pernio.

Nonspecific skin lesions

Erythema nodosum. Painful erythematous nodules

Table 1: Scadding radiological staging of pulmonary sarcoidosis[40]

Stages	Radiographic Features	Frequency at Presenation
I	Mediastinal and hilar adenopathy(usually bilaterla)without pulmonary infiltrates	40-50%
II	Mediastinal and hilar adenopathy(usually bilateral) With pulmonary infiltrates	30-40%
III	Pulmonary infiltrates wothout adenopathy	15-20%
IV	Pulmonary fibrosis with volume loss,no adenopathy	2-5%

seen in anterior surface of lower extremities is the typical presentation. It usually represents acute form of sarcoidosis (i.e., Lofgren syndrome). Profuse sweating will also be present.

Scarring and non-scarring alopecia will be present. In nails, onycholysis, dystrophy, hyper keratosis and longitudinal ridging may be present.

Ocular sarcoidosis

Affects more than 40% of the individuals.[44-46] Affects any part of the eye, mostly causes uveitis and it is visualized on slit-lamp examination. Blindness results due to adhesions with the iris and lens.

According to involvement of eye, it can be further classified into anterior, posterior, intermediate and diffuse uveitis (PAN uveitis). Depending on the intraocular inflammation, it can be either anterior or posterior uveitis.

Anterior uveitis

Present with eye pain, erythematous around the limbus and visual loss. Usually seen in whites (over 80% cases).

POSTERIOR AND INTERMEDIATE UVEITIS

This is characterized by painless visual loss and floaters. It is more common in blacks.[47-49]

Nonuveitis ocular sarcoidosis

Conjunctivitis/:Scleritis, episcleritis, conjunctivitis/ conjunctival nodules, lacrimal gland involvement, orbital mass, and optic neuritis. It won't affect visual acuity.[43] Other manifestations include pain, hyperemia and photophobia.

Renal sarcoidosis

It is rare and seen in <3% populations.[39,50] Patients with sarcoidosis should be observed for the existence of renal impairment to prevent chronic kidney disease. Hence investigations like serum creatinine, blood urea nitrogen, estimated glomerular filtration rate, protein and calcium in both serum and urine, and screening of the urinary sediment for casts of red or white blood cells. 25-hydroxvitamin D3,

1,25-dihydroxyvitamin D3, and parathyroid hormone should be measured in sarcoidosis patients.[51] Chronic kidney disease with or without abnormal urine, pyuria, proteinuria is the typical presentation. Granulomatous interstitial nephritis is seen in <20% sarcoidosis patients.[52,53] Nephrolithiasis and nephrocalcinosis arises owing to hypercalcemia and hypercalciuria. Renal biopsy remains the standard method for the diagnosis renal sarcoidosis.

Cardiac sarcoidosis

It occurs in 20%–27% of populations.[54,55] Initially, the patients may be asymptomatic initially after which symptoms like palpitations, syncope or even sudden cardiac death can occur. Cardiac failure occurs due to Granulomatous inflammation of myocardium manifested as arrhythmia (commonly AV block is seen in 50% of patients followed by ventricular tachycardia and supraventricular arrhythmia) and cardiomyopathy. Cardiac sarcoidosis constitutes for two-thirds of all cases.[56]

Neurosarcoidosis

Neurosarcoidosis is reported in <10% of patients.[57,58] Unilateral or bilateral cranial neuropathy of facial and optic nerve is the most common manifestations in neurosarcoidosis.[59,60] The mechanism involved in cranial neuropathy could be either granulomatous inflammation of the epineural/perineural nerve itself or compressing of nerve by leptomeninges.[61,62] The lesions are most commonly found in the hypothalamus and pituitary glands, and may result in endocrine manifestations, including diabetes insipidus, adrenal and pituitary failure, and amenorrhoea–galactorrhoea syndrome.[63-65] Psychiatric manifestations like psychosis may be present. Spinal cord involvement is a rare manifestation presenting with leg weakness, parenthesis most often thoracic segment is involved.[66] Symptoms ranging from mononeuritis multiplex to Guillain–Barré-like syndromes, as well as polyneuropathy or polyradiculopathy, can occur. Patients usually present with pain, burning sensation and paresthesia which may be migratory or intermittent.[67,68] Cerebrospinal fluid analysis reveals high protein level and increased monocyte cell count. 50% of renal biopsies reveal only one-fifth of cases.[69,70] Since taking biopsy is more invasive and difficult, brain MRI is considered as most sensitive noninvasive test for neurosarcoidosis.

Musculoskeletal involvement in sarcoidosis

It involves 1%–13% of patients.[71,72] Acute arthritis with reference to sarcoidosis, most frequently arises in Lofgren syndrome (Bilateral hilar lymphadenopathy, Erythema nodosum and bilateral ankle swelling) which was explained in Table 2. Ankle swelling is predominantly due to soft tissue swelling and tenosynovitis. Chronic arthritis is extremely rare. Other manifestations like arthropathy, osteoporosis, osteopenia are usual. Nodular lesions, cystic lesions sffecting the joints, arthralgia may be present.[70,71] Axial sarcoidosis may involve the vertebral bodies or the joints of sacrum and ilium bones.

Gastrointestinal and hepatic involvement: It accounts for 0%–3.4% of cases[72]

The most affected hollow organ is stomach. The pathological

process involved in stomach is granulomatous infiltration of mucosa and muscular layer, which subsequently ends up in mucositis, ulcer, obstruction or strictures. About 20%of patients are asymptomatic and may present with sarcoid-related lesions. Patients with gastric sarcoidosis has tendency to present with epigastric pain. Other common symptoms include nausea, vomiting, diarrhea, weight loss etc. About 80%of patients were identified with granulomatous lesions in the liver biopsy on an autopsy study.[72] Common liver and spleen manifestations include hepatosplenomegaly, portal hypertension, intrahepatic cholestasis and impaired liver function.

Oral manifestation

Oral lesions are mostly asymptomatic and are not identified before the diagnosis is made. The most common extra-oral sites are salivary glands (parotid gland being affected 6%) and cervical lymph nodes. Buccal mucosa, lips, gingiva, tongue and palate are the most commonly affected intraoral sites. More than one site is involved only in few cases.[73] Oral lesions mostly evident as diffuse enlargements or nodular swellings, mostly localised at the sub mucosal level. Papule and superficial ulceration have also noted. Pain and dryness of tongue also evident in some rare cases.[74]

Endocrine and exocrine involvement

Its manifestations seen in 20%–50% of individuals.[75] Thyroid gland (5%) and parotid glands (5%–10%) are the frequently affected organs. Thyroid and parotid gland enlargement is most commonly seen.

Hypothermia, adrenal suppression hypothyroidism, hyperthyroidism, are rare.[22] It also influences hypothalamic-pituitary effects like diabetes insidious etc. Heerfordt's syndrome comprises the features of fever, parotid enlargement, facial palsy, and anterior uveitis.

Lymph node involvement

It is seen in 20% of patients. Peripheral lymphadenopathy is commonly seen. Cervical, axillary, epitrochlear, and inguinal are the most frequently involved lymph nodes. Affected lymph nodes are moderately swollen, and are usually nontender.[76-78] These are often round, granular in appearance, homogeneous echogenicity with distinct margin.[76]

HISTOPATHOLOGY

The typical feature of sarcoidosis would be well formed, noncaseating granuloma with mass of epithelioid cells and multinucleated giant cells. The granuloma is surrounded by lymphocytes and contains minimal or no central necrosis. Certain cytoplasmic inclusions like Asteroid bodies, Schaumann bodies, Hamazaki-Wesenberg bodies [illustrated in Figures 1 and 2] calcium oxalate crystals will also be present.[79,80]

Special stains can be used to differentiate sarcoidosis from other granulomatous diseases like fungal and mycobacterium diseases. Atypical mycobacterial infections and TB and can resemble sarcoidosis. These infections can be screened for by acid-fast staining.

Table 2: Criteria for diagnosing acute arthritis related to sarcoidosis

Arthritis of ankle symmetrically
Symptomatic for <2 months
40 years or below 40 years
EN reaching sensitivity and specificity of 93% and 99%

EN: Erythema nodosum

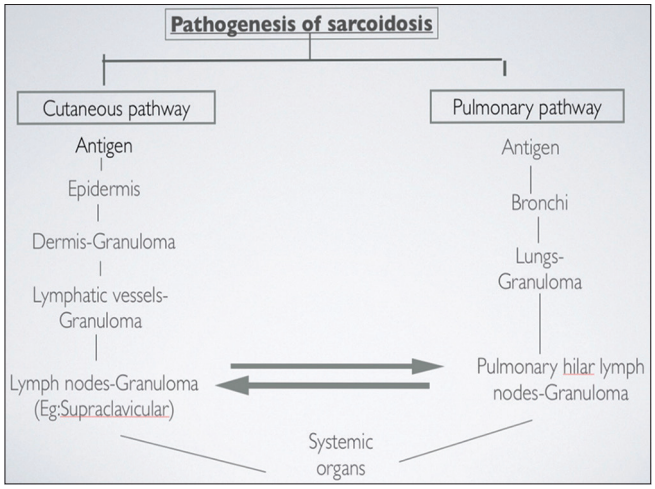


Figure 1: Pathogenesis of sarcoidosis

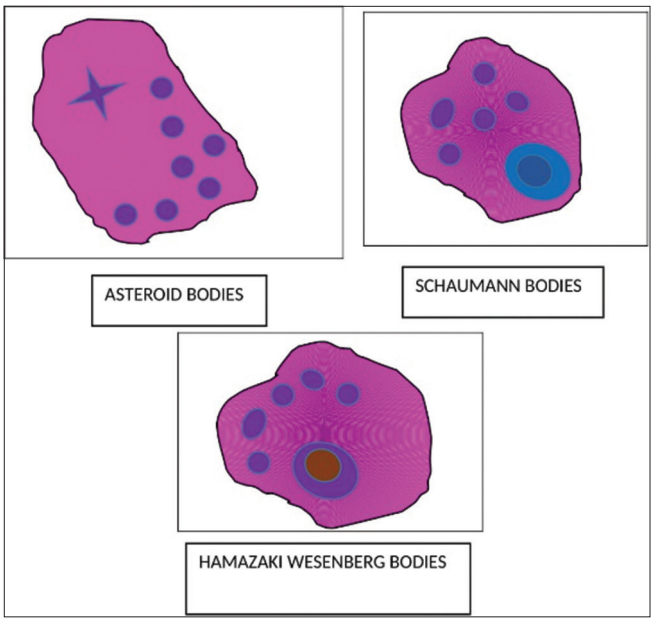


Figure 2: Inclusion bodies seen in sarcoidosis

Table 3: Investigations and differential diagnosis of sarcoidosis

Organ system	Clinical features	Investigations	Differential diagnosis
Lungs	Cough, dyspnoea	Chest radiograph, chest CT (may be necessary)	Noninfectious Hypersensitivity pneumonitis Pneumoconiosis: Beryllium (chronic beryllium disease), titanium, aluminum Drug reactions Aspiration of foreign materials Wegener's granulomatosis Chronic interstitial pneumonia like usual and lymphocytic interstitial pneumonia NSG Infectious Tuberculosis Atypical mycobacteriosis Cryptococcosis Aspergillosis Histoplasmosis Coccidioidomycosis Blastomycosis Pneumocystis carinii Mycoplasma, etc.
	Hilar lymphadenopathy	Chest radiography and CT, endoscopic ultrasonographic with needle aspiration	
		^{18}F-FDG PET (in selected patients), Gallium scan	
	Pulmonary hypertension	Brain natriuretic peptide, 6 min walk test, echocardiography, right heart catheterisation	
	Interstitial lung disease and pulmonary fibrosis	Chest radiograph, chest CT, bronchoscopy, surgical lung biopsy (if needed)	
	To assess pulmonary involvement and disease severity	Pulmonary function test	
Skin	Papules, nodules, plaques, erythe ma nodosum, lupus pernio	Skin biopsy if needed, except for EN and lupus pernio, which will usually be diagnosed clinically	Noninfectious Reaction to foreign bodies: Beryllium zirconium, tattooing, paraffin, etc. Rheumatoid nodules Infectious Tuberculosis Atypical mycobacteriosis Fungal infection
Heart	Conduction abnormalities, arrhythmia, ventricular tachycardia and ventricular fibrillation), sudden cardiac failure, death	Electrocardiograph, echocardiography, Holter monitoring, cardiac MRI, ^{18}F-FDG PET, thallium scan (in selected patients)	Noninfectious Giant cell myocarditis Acute rheumatic heart disease Granulomatosis with polyangiitis Erdheim-Chester arrhythmogenic right ventricular dysplasia Drugs/toxins Granulomatous lesions of unknown significance Infectious Bacteria - Tuberculosis, syphilis, *Tropheryma whippelii* Fungi - Aspergillosis
Nervous system	Cranial nerve palsy	Brain MRI	Noninfectious Chronic variable immunodeficiency Rosai-Dorfman disease Lymphomatoid granulomatosis Granulomatosis with polyangiitis Rheumatoid nodules Amyloidosis Cholesterol granuloma Foreign body Drugs/toxins/heavy metals Sarcoid-like reaction to tumor CNS malignancies Infectious Bacteria - Tuberculosis, brucella Fungi - Aspergillus, coccidioidomycosis, cryptococcosis Parasites - Amoeba, Toxoplasmosis, Schistosomiasis, *Taenia solium* Viruses: Varicella zoster, Herpes simplex
	Optic neuritis	Ophthalmologic evaluation	
	Hypopituitarism	Hormonal studies	
	Cognitive	Brain MRI, CSF dysfunction studies small finer	
	Polyneuropathy	Electromyography, nerve conduction defects	
Kidney	Hypercalcemia	Biopsy, renal ultrasonography, CT nephrolithiasis, renal urography, renal stones, renal failure, function test	Noninfectious Granulomatosis polyangiitis Chronic lymphocytic leukemia Infectious Bacteria - Tuberculosis Fungi - Histoplasmosis, Coccidioidomycosis Virus - Adenovirus
Liver	Mostly asymptomatic	Liver biopsy, liver function test	Noninfectious Crohn's disease Hodgkin's disease

Contd...

Table 3: Contd...

Organ system	Clinical features	Investigations	Differential diagnosis
			Non-Hodgkin's lymphomas GLUS syndrome Infectious Tuberculosis Brucellosis Schistosomiasis
Spleen	Splenomegaly	Abdominal ultrasonography, abdominal CT	Noninfectious Chronic variable immunodeficiency Sarcoid-like reaction to tumor Infectious Bacteria - Tuberculosis Fungi - Histoplasmosis Parasites - Leishmaniasis
Eyes	Uveitis, retinal vascular changes, lacrima l gland enlargement, conjunctival nodules	Opthalmologic evaluation, lacrimal gland biopsy (if necessary), gallium scan (in selected patients)	Noninfectious Inflammatory bowel disease ANCA vasculitides Vogt-Koyanagi-Harada diseases Blau syndrome Infectious Perinaud oculoglandular syndrome Bacteria - Tuberculosis , syphilis Viruses - Cytomegalovirus , Varicella zoster Fungi - Toxoplasmosis
Musculoske letal system	Proximal muscle weakness, myalgia, intramuscular nodules	Creatine kinase, MRI, ^{18}F-FDG PET, possible muscle biopsy	Noninfectious Non-Hodgkin lymphoma Crohn's disease Thymoma-myasthenia gravis Foreign body Primary biliary cirrhosis (primary biliary cholangitis) Infectious Bacteria - Tuberculosis, syphilis, brucella Fungi - *Pneumocystis jirovecii*, Cryptococcosis Virus - Human T-lymphotrophic virus 1
Hematologic	Anaemia, leukopenia	Complete blood count, bone marrow biopsy	Idiopathic thrombocytopenia purpura
Lymph nodes	Peripheral lymphadenopath y such as cervical lymph node enlargement Hilar and mediastinal lymph node enlargement	Biopsy of most accessible and safest site Chest radiograph, chest CT, endoscopic ultrasonography with needle aspiration (endobronchial or esophageal), gallium scan, ^{18}F-FDG PET (in selected patients)	Noninfectious Hodgkin's disease Non-Hodgkin's Lymphomas Granulomatous GLUS syndrome Infectious Tuberculosis Atypical mycobacteriosis Brucellosis Toxoplasmosis Granulomatous histiocytic necrotizing lymphadenitis (Kikuchi's disease) Cat-scratch disease
Exocrine and endocrine glands	Thyroid gland enlargement Parotid enlargement, isolated or associated with Heerfordt syndrome (uveoparotid fever)	FNAC, ultrasound is otope study Barium, gallium scan (in selected patients)	Noninfectious Granulomatosis polyangiitis Ductal obstruction (calculus, tumor) Crohn's disease Infectious Bacteria Tuberculosis Atypical mycobacteria

CT: Computed tomography, ^{18}F-FDG PET: ^{18}Fluorodeoxyglucose positron emission tomography, MRI: Magnetic resonance imaging, NSG: Necrotizing sarcoid granulomatosis, EN: Erythema nodosum, CSF: Cerebrospinal fluid, CNS: Central nervous system, GLUS: Granulomatous lesions of unknown significance, ANCA: Antineutrophilic cytoplasmic antibody, FNAC: Fine needle aspiration cytology

Fungal infections such as histoplasmosis should also be considered and staining has to be for the final diagnosis of sarcoidosis.

INVESTIGATIONS AND DIAGNOSIS

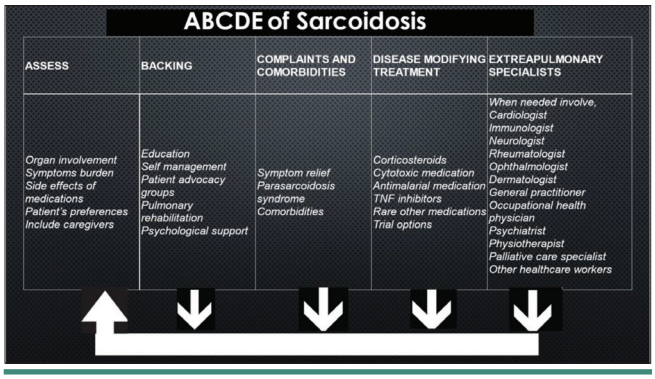
The various clinical manifestation exhibited by different

Table 4: Biomarker activity in sarcoidosis[40,82]

Serial number	Biomarkers	Indications
	Serum biomarkers for sarcoidosis	
A)	Macrophages	
1	Serum angiotensin-converting enzyme	Well known serum biomarker correlates with granuloma burden and radiological Stages II and III Sensitivity: 22%-86%; specificity: 54%-5% also increased in other inflammatory diseases like tuberculosis, histoplasmosis, Gaucher disease etc. Not significant when ACE inhibitors is used by patients
2	Lysozyme	Prognostic tool Mainly observed at the time of disease onset. Involved in granuloma formation Low sensitivity for sarcoidosis
3	Serum CD163	Prognostic tool CD163 levels alter under the influence of inflammatory mediators High sensitivity and low specificity Also increased in diseases like rheumatoid arthritis, MS, Crohn's disease
4	YKL40	Marker for granuloma burden Growth factor for fibroblast and vascular endothelial cells Comparatively higher in active sarcoidosis Patients
5	Neopterin	Nonspecific marker Low specificity
6	Serum amyloid A	Produced by liver during acute phase of sarcoidosis Clinical marker of inflammation Also elevated in rheumatoid arthritis, Crohn's disease etc.
7	CC chemokine Ligand 18	Prognostic marker Seen in patients with active disease Increased levels seen in most interstitial lung disease and gaucherie disease
8	Chitotriosidase	Good prognostic marker Elevated in case of progressive disease high sensitivity and specificity Also increased in Gaucher's disease, malaria, multiple sclerosis, atherosclerosis, Alzheimer's disease and tuberculosis
B)	Monocytes	Intermediate monocytes (CD14+/CD16+) and nonclassical monocytes (CD14−/CD16++) will be elevated Low specificity Also increased in cardiovascular diseases and interstitial lung disease
C)	T-cell	
1	Serum soluble interleukin 2 receptor	Diagnostic marker Also elevated in some hematological disorders, autoimmune diseases, also in patients with impaired renal function
D)	B cell	
1	B-cell activating factor	Low specificity Elevated levels seen in the multiple organ involvement (i.e., skin and eye involvement), decline in pulmonary function and more advanced chest radiographic stages (II/III)
2	Naive and memory B-cells	Naive B-cells increase Memory B-cells downregulated
3	Regulatory B-cells	Elevated in active sarcoidosis
	Bronchoalveolar lavage fluid biomarkers	
1	CD4/CD8 ratio	Not a specific biomarker Sensitivity: 54%-80% and specificity: 59%-80%
2	CD 103+CD 4+/CD4+ratio	Diagnostic tool
3	T-helper 17.1 cells	Immunological marker
4	Regulatory T-cells	Treg/Th17 ratio inversely related to disease activity
5	Neutrophils	Elevated in radiological stage (II/III)
6	Natural killer cells	Elevated in patients with impaired lung function
7	Natural-killer T cells	Reduced number of NKT cells seen
8	CXCL9, CXCL10, and CXCL11	Prognostic marker CXCL9 and CXCL11 associated with number of organs involved CXCL10 associated with higher dyspnea scores
9	krebs Von den lungen-6	Reflects damaged or regenerating Type II pneumocytes Elevated in radiological Stage IV pulmonary sarcoidosis (marker of severity)
	Future biomarkers of sarcoidosis	
1	JAK/STAT signaling	
2	mTOR signaling	
3	Hair cortisol	
4	Labeled PET-Tracers	

ACE: Angiotensin-converting enzyme, MS: Multiple sclerosis, NKT: Natural-killer T, JAK: Janus kinase, STAT: Signal transducer and activator of transcription, mTOR: Mammalian target of rapamycin, PET: Positron emission tomography

Table 5: Explaining the management of sarcoidosis



organs and the investigations to be done and their differential diagnosis are summarized in table 3.

SERUM BIOMARKERS FOR SARCOIDOSIS

Numerous biomarkers are in investigational procedures for the accurate diagnosis and formulating a successful treatment plan. The summary of all the markers and their indications are tabulated in the Table 4.

Treatment

Sarcoidosis is a life-threatening disease. Hence, timely diagnosis influences the prognosis of the sarcoidosis patients. In sarcoidosis patients, the medical intervention has to be carried out when the patient develops specific symptoms (worsening functional status) which fails to regress on its own, along with the imaging abnormalities. Management modality for sarcoidosis are tabulated in the Table 5. Glucocorticoids acts as a first line drug treatment and also has several side effects.[83,84]

Pulmonary sarcoidosis

In pulmonary sarcoidosis, the granulomatous inflammation in lungs leads to reduced forced vital capacity and diffusing capacity of lung for carbon monoxide from its baseline (10%–20% or more) denoting significant impairment of lung functions.[85]

- First line treatment: Glucocorticoids like prednisolone 20–40 mg/day for 1–3 months has to be given. Tapered dose of 5–10 mg daily for every 1–3 months, until a maintenance dose of 5–10 mg/d for approximately 1 year. Relapse may occur in 30% of patients after discontinuing or tapering steroids.[85] Most importantly, patients start depending on corticosteroid drugs
- Second line drugs: To overcome glucocorticoid toxicity, disease modified anti-rheumatic drugs (DMARD's) are recommended.[86,87] Methotrexate (10-25 mg weekly, oral or intramuscular) is most commonly used drug in pulmonary sarcoidosis.[88-91] Folic acid supplements have to be given along with methotrexate. Patient can develop complications like hepatotoxicity, bone marrow suppression. Onset of action is slow (i.e. 2–3 months). Other DMARD's with less efficacy are leflunomide(10–20mg/day),azathioprine(50–200mg/day), mycophenolate (500–3000 mg/day)
- Third line drugs: Another class of drugs would be TNF-α inhibitor like Infliximab, adalimumab etc. Infliximab is given intravenously at a dosage of 5 mg/kg body weight at 0, 2 and every 4–8 weeks thereafter. Adalimumab 40 mg subcutaneously for every 1–2 weeks can be given. Adverse reactions of these drugs have to be consider while administering drugs.

Extra pulmonary sarcoidosis

- Skin: Most of the skin lesions like erythema nodosum are self-regressing lesions. Hence no treatment is needed, in most of the patients. For some patients presenting with pain, either short course nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids can be prescribed.[61,92] Topical or intralesional administration of corticosteroids is the most preferred route for better efficacy and to reduce systemic toxicity. In severe cases, oral administrations also preferred. The second line drugs such as hydroxychloroquine and chloroquine also be prescribed.[61,93,94] Infliximab is prescribed when both the above-mentioned drugs fail to act upon the lesion. Other topical formulations like clobetasol, halobetasol, propionate can also be used
- Eyes: Uveitis is the most common eye lesion in sarcoidosis. Glucocorticoids in the form of eye drops can be used for anterior uveitis and periocular/intravitreal injection or implant for posterior uveitis. Other second and third line drugs like Azathioprine, Infliximab can also be used. Orbital debulking/decompression surgery is also needed[44]
- Joints: NSAIDs are the first line drug used in sarcoid arthropathy.[61] 1n unresponsive cases, hydroxychloroquine and methotrexate can be used
- Heart: Granulomatous inflammation of the myocardium results in arrhythmia, conduction defect, left ventricular dysfunction or right ventricular dysfunction.[95] Immunosuppressants like Glucocorticoids are the drug of choice in cardiac sarcoidosis. Prednisolone initial dose 40–60 mg daily with taper regimen has to be given. Some experts suggest taking cardiac fluorodeoxyglucose positron emission tomography (FDG PET) scan before initiating immunosuppressants.[96] In case of corticosteroids intolerance, methotrexate, azathioprine, mycophenolate has to be prescribed.

Other TNF-alpha inhibitors like Rituximab can be used. Infliximab is not used since it tends to exacerbate heart failure. In case of cardiac failure, other drugs like diuretics, beta blockers, angiotensin converting enzyme inhibitors also used.[97] For advanced cardiac failure, implantable cardioverter-defibrillator is used.

- Nervous system*:* Curative treatment is done only for transient lesions whereas palliative treatment is carried out for permanent neurological deficit like facial nerve palsy etc.[98] A short course of intravenous methyl prednisolone 1000 mg daily should be given in patients with severe manifestations like visual loss, altered mental status etc. Moderate dose of prednisone 0.5 mg/kg/day is prescribed for patients with peripheral nerve involvement. Higher dose of corticosteroids (Prednisone 1.0 mg/kg/day) should be given for patients with central nervous system involvement. Prednisone 20–25 mg/ daily should be given along with tapering dose. Drugs can be given in combinations like "Prednisolone+ DMARD's (Methotrexate)."

Neurosarcoidosis has got a high recurrence rate. In a retrospective study, they found that infliximab has got high efficacy over patients with refractory sarcoidosis. Intravenous immunoglobulin and TNF-alpha inhibitors also appears to be more effective options because about 70% of patients who received one of them or a combination of them did experience improvement within the 1st month of therapy.[99] For seizure experiencing patients, anti-epileptics has to be prescribed.[103]

- *Kidneys:* The ultimate risk of renal sarcoidosis is chronic kidney disease. Glucocorticoids along with DMARDs can also be taken.[100] In prolonged Glucocorticoids intake, hypercalcemia has to be checked periodically. Calcium levels become normal after inhaling corticosteroids 20-40 MD.=
- *GIT and liver involvement*: It is rarely affected and hence the treatment remains unclear. Glucocorticoids can be used as a first line of choice[43]
- *Oral cavity:* Asymptomatic lesions would heal slowly and require no treatment. Surgery is the first choice for nodular lesions. Corticosteroids be given for painful or progressive lesions.[101,102]

CONCLUSION

Sarcoidosis is a diagnosis of exclusion. After many research studies done in sarcoidosis patients, the exact etiology of sarcoidosis still remains inconclusive. Since it has got nonspecific symptoms and multi-organ involvement, diagnosis cannot be given purely based on clinical history. A lot of investigations like Kveim-slitzbach skin patch test, imaging tests like chest X-ray, computed tomography, magnetic resonance imaging and 18f FDG-PET scan plays a major role in arriving at a diagnosis of sarcoidosis. However, presence of noncaseating granuloma in histopathology gives a clue for the diagnosis. Glucocorticoids remains the first line drugs in treating sarcoidosis. Methotrexate, Infliximab also has good efficacy and used as second and third line of drug treatment. This review article gives a clear idea about the clinical manifestations, differential diagnosis and treatment plan for sarcoidosis. It will help clinicians for early and easy diagnosis and prompt treatment.

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Conflicts of interest

There are no conflicts of interest.

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