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 engage both clinicians and scientists since that time. Because sarcoidosis is 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

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...
of 17–35 per 100,000 population while the lowest annual incidence is observed among Asians and Hispanics (1–3/100,000). There is a female predilection of 2:1 seen in Africans Americans. Prevalence of sarcoidosis in India is 10–12 cases/1000 registrations yearly, as announced by a respiratory unit in western India. 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 entity in Blacks and Japanese is the sarcoid-related erythema nodosum. Myocardial involvement is the frequent cause of death caused by sarcoidosis which is followed by respiratory failure. 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.

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. The histological characteristic feature of sarcoidosis is well-organized, closely-packed, nonnecrotizing granulomas surrounded by lamellar hyaline collagen as described in Flow Chart 1. 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.

ROLE OF MYCOBACTERIA IN SARCOIDOSIS

There is similarity between sarcoidosis and tuberculosis (TB), in clinical, radiological and immunological features leading to the suggestion of mycobacteria as etiologic agent in sarcoidosis. 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. 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. Other candidate mycobacterial antigens comprise superoxide dismutase and early-secreted antigenic target of 6 kDa (ESAT6).

GENETIC FACTORS ASSOCIATED WITH SARCOIDOSIS

Sarcoïdosis 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. Twin studies prove that monozygotic twins are more vulnerable for sarcoidosis than dizygotic twins.

Human leucocyte antigen genotypes confer susceptibility, particularly a polymorphism in the butyrophilin-like 2 receptor gene (BTNL2-Costimulatory molecule within the MHC locus). 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. The BTNL2 single-nucleotide polymorphism associated with sarcoidosis (rs2076530 G → A) may influence...
T-lymphocyte activation and regulation.\[16\] Sarcoidosis is linked with the DR subtypes of class II ANTIGENS. HLA-DRB1*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 Löfgren's syndrome.\[15\]

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, α-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. Löfgren 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. Hemoptyis 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.,\[40\] 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 |
|-------|
| Stages | Radiographic Features | Frequency at Presentation |
| I | Mediastinal and hilar adenopathy (usually bilateral) without pulmonary infiltrates | 40-50% |
| II | Mediastinal and hilar adenopathy (usually bilateral) With pulmonary infiltrates | 30-40% |
| III | Pulmonary infiltrates without 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
riding 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
heart 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.[54,56] 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 amenorrhea–
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 polynuropathy 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. 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. 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.

Endocrine and exocrine involvement
Its manifestations seen in 20%–50% of individuals. 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. 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. These are often round, granular in appearance, homogeneous echogenicity with distinct margin.

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.

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                                                                          |
|                  | Hilar lymphadenopathy                                 | Chest radiography and CT, endoscopic ultrasonographic with needle aspiration  | Hypersensitivity pneumonitis                                                            |
|                  |                                                        | ¹⁸F-FDG PET (in selected patients), Gallium scan                            | Pneumoconiosis: Beryllium (chronic beryllium disease), titanium, aluminum               |
|                  | Pulmonary hypertension                               | Brain natriuretic peptide, 6 min walk test, echocardiography, right heart    | Drug reactions                                                                          |
|                  |                                                        | catheterisation                                                               | Aspiration of foreign materials                                                         |
|                  | Interstitial lung disease and pulmonary fibrosis      | Chest radiograph, chest CT, bronchoscopy, surgical lung biopsy (if needed)   | Wegener’s granulomatosis                                                                |
|                  | To assess pulmonary involvement and disease severity  | Pulmonary function test                                                       | Chronic interstitial pneumonia like usual and lymphocytic interstitial pneumonia        |
| Skin             | Papules, nodules, plaques, erythema nodosum, lupus    | Skin biopsy if needed, except for EN and lupus pernio, which will usually be  | NSG                                                                                     |
|                  | pernio                                                 | diagnosed clinically                                                          |                                                                                         |
| Heart            | Conduction abnormalities, arrhythmia, ventricular     | Electrocardiograph, echocardiography, Holter monitoring, cardiac MRI, ¹⁸F-FDG| Noninfectious                                                                          |
|                  | tachycardia and ventricular fibrillation, sudden      | PET, thallium scan (in selected patients)                                     | Giant cell myocarditis                                                                  |
|                  | cardiac failure, death                                 |                                                                               | Acute rheumatic heart disease                                                           |
|                  |                                                        |                                                                               | Granulomatosis with polyangiitis                                                        |
|                  |                                                        |                                                                               | Erdheim-Chester arrhythmogenic right ventricular dysplasia                              |
|                  |                                                        |                                                                               | Drugs/toxins                                                                            |
|                  |                                                        |                                                                               | Granulomatous lesions of unknown significance                                          |
| Nervous system   | Cranial nerve                                          | Brain MRI palsy                                                               | Infectious                                                                              |
|                  | Optic neuritis                                         | Ophthalmologic evaluation                                                     | Bacteria - Tuberculosis, syphilis, *Tropheryma whippelli*                               |
|                  | Hypopituitarism                                        | Hormonal studies                                                              | Fungi - Aspergilosis                                                                    |
|                  | Cognitive                                              | Brain MRI, CSF dysfunction studies small finer                                | Noninfectious                                                                          |
|                  | Polyneuropathy                                         | Electromyography, nerve conduction defects                                    | Chronic variable immunodeficiency                                                       |
| Kidney           | Hypercalccmia                                          | Biopsy, renal ultrasonography, CT nephrolithiasis, renal urography, renal    | Rosai-Dorfman disease                                                                   |
|                  |                                                        | stones, renal failure, function test                                          | Lymphomatoid granulomatosis                                                             |
| Liver            | Mostly asymptomatic                                    | Liver biopsy, liver function test                                            | Granulomatosis with polyangiitis                                                        |
|                  |                                                        |                                                                               | Noninfectious                                                                          |

Contd...
Table 3: Contd...

| Organ system | Clinical features | Investigations | Differential diagnosis |
|--------------|------------------|----------------|------------------------|
| Spleen       | Splenomegaly     | Abdominal ultrasonography, abdominal CT | Non-Hodgkin’s lymphomas, GLUS syndrome, Infectious Tuberculosis, Brucellosis, Schistosomiasis, Noninfectious Chronic variable immunodeficiency, Sarcoid-like reaction to tumor |
| Eyes         | Uveitis, retinal vascular changes, lacrimal gland enlargement, conjunctival nodules | Ophthalmologic evaluation, lacrimal gland biopsy (if necessary), gallium scan (in selected patients) | Noninfectious Infectious Chronic variable immunodeficiency, Sarcoid-like reaction to tumor, Tuberculosis, Fungi - Histoplasmosis, Parasites - Leishmaniasis |
| Musculoskeletal system | Proximal muscle weakness, myalgia, intramuscular nodules | Creatine kinase, MRI, ¹⁸F-FDG PET, possible muscle biopsy | Noninfectious Infectious Non-Hodgkin lymphoma, Crohn’s disease, Thymoma-myxastenia gravis, Foreign body, Primary biliary cirrhosis (primary biliary cholangitis), Blau syndrome, ANCA vasculitides, Vogt-Koyanagi-Harada diseases |
| Hematologic | Anaemia, leukopenia | Complete blood count, bone marrow biopsy | Idiopathic thrombocytopenia purpura |
| Lymph nodes | Peripheral lymphadenopathy 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, ¹⁸F-FDG PET (in selected patients) | Noninfectious Infectious Hodgkin’s disease, Non-Hodgkin’s Lymphomas, Granulomatous GLUS syndrome, Tuberculosis, Atypical mycobacteriosis, Brucellosis, Toxoplasmosis, Granulomatous histiocytic necrotizing lymphadenitis (Kikuchi’s disease), Cat-scratch disease, Ductal obstruction (calculus, tumor) |
| Exocrine and endocrine glands | Thyroid gland enlargement, Parotid enlargement, isolated or associated with Heerfordt syndrome (uveoparotid fever) | FNAC, ultrasound is otopy study, Barium, gallium scan (in selected patients) | Noninfectious Infectious Granulomatous lesions of unknown significance, ANCA, 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                                      | Well known serum biomarker correlates with granuloma burden and radiological Stages II and III |
| 1             | Serum angiotensin-converting enzyme             | Sensitivity: 22%-86%; specificity: 54%-5% also increased in other inflammatory diseases like tuberculosis, histoplasmosis, Gaucher disease etc. |
| 2             | Lysozyme                                        | Mainly observed at the time of disease onset. Involved in granuloma formation |
| 3             | Serum CD163                                      | Low sensitivity for sarcoidosis                                             |
| 4             | YKL40                                           | Markers for granuloma burden                                               |
| 5             | Neopterin                                       | Nonspecific marker                                                         |
| 6             | Serum amyloid A                                 | Produced by liver during acute phase of sarcoidosis                        |
| 7             | CC chemokine Ligand 18                         | Also elevated in rheumatoid arthritis, Crohn’s disease etc.                |
| 8             | Chitotriosidase                                  | diagnosed in case of progressive disease high sensitivity and specificity   |
| **B) Monocytes** |                                              |                                                                             |
| 1             | Intermediate monocytes (CD14+/CD16+) or nonclassical monocytes (CD14−/CD16++) will be elevated |                                                                             |
| 2             | Low specificity                                 |                                                                             |
| **C) T-cell** |                                              |                                                                             |
| 1             | Serum soluble interleukin 2 receptor            | Diagnostic marker                                                         |
| 2             | Naive and memory B-cells                        | Memory B-cells downregulated                                               |
| 3             | Regulatory B-cells                              | Elevated in active sarcoidosis                                             |
| **Bronchoalveolar lavage fluid biomarkers** |                                                |                                                                            |
| 1             | CD4/CD8 ratio                                   | Not a specific biomarker                                                   |
| 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                                                         |
| 9             | krebs Von den lungen-6                          | Reflects damaged or regenerating Type II pneumocytes                       |
| **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
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.[80]
- 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.[83] 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] In 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.[93] 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.[89] In case of corticosteroids intolerance, methotrexate, azathioprine, mycophenolate has to be prescribed.
Other TNF-alpha inhibitors like Rituiximab 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.\[100\]

- **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\[48\]

- **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-slitizbach 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 noncascading 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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**REFERENCES**

1. Thomas KW, Hunninghake GW. Sarcoidosis. JAMA 2003;289:3300-3.
2. Chen ES, Moller DR. Sarcoidosis – scientific progress and clinical challenges. Nat Rev Rheumatol 2011;7:457-67.
3. Hutchinson J. Anomalous disease of the skin of the fingers: Case of livid papillary psoriasis. Illus. Clin Surg 1877;1:42-3.
4. 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;160:736-55.
5. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007;357:2153-65.
6. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: A 5-year study in a health maintenance organization. Am J Epidemiol 1997;145:234-41.
7. Baughman RP, Field S, Costabel U, Crystal RG, Calver DA, Drent M, et al. Sarcoidosis in America: Analysis based on health care use. Ann Am Thorac Soc 2016;13:1244-52.
8. Ungprasert P, Carmona EM, Utz JP, Ryu JH, Crousew CS, Matteson EL. Epidemiology of sarcoidosis 1946-2013: A population-based study. Mayo Clin Proc 2016;91:183-8.
9. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata IJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax 2006;61:980-5.
10. Arkema EV, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: A nationwide register-based assessment in Sweden. Eur Respir J 2016;48:1690-9.
11. Morimoto T, Azuma A, Abe S, Usuki J, Kudoh S, Sugisaki K, et al. Epidemiology of sarcoidosis in Japan. Eur Respir J 2008;31:372-9.
12. Park JE, Kim YS, Kang MJ, Kim CJ, Han CH, Lee SM, et al. Prevalence, incidence, and mortality of sarcoidosis in Korea, 2003-2015: A nationwide population-based study. Respir Med 2018;148S: S28-34.
13. Peros-Golubicić T, Ljubić S. Cigarette smoking and sarcoidosis. Acta Med Croatica 1995;49:187-93.
14. Sharma S, Mohan A. Sarcoidosis in India: Not so rare. J Indian Acad Clin Med 2004;5:12-21.
15. Gupta SK, Gupta S. Sarcoidosis in India: A review of 125 biopsy-proven cases from eastern India. Sarcoidosis 1990;7:43-9.
66. Sohn M, Culver DA, Judson MA, Scott TE, Tavee J, Nozaki K. Spinal cord neurosarcoidosis. Am J Med Sci 2014;347:195-8.
67. Nozaki K, Judson MA. Neurosarcoidosis: Clinical manifestations, diagnosis and treatment. Presse Med 2012;41:e331-48.
68. Tavee JO, Karwa K, Ahmed Z, Thompson N, Parambil J, Culver DA. Sarcoidosis-associated small fiber neuropathy in a large cohort: Clinical aspects and response to IVIG and anti-TNF alpha treatment. Respir Med 2017;126:135-8.
69. Joseph FG, Scolding NJ. Neurosarcoidosis: A study of 30 new cases. J Neurol Neurosurg Psychiatry 2009;80:297-304.
70. Nesrime A, Zahra AF, Taoufik H. Musculoskeletal involvement in sarcoidosis. J Bras Pneumol 2014;40:175-82.
71. Conte G, Zughni F, Colloni M, Renne G, Bellomi M, Petralia G. Sarcoidosis with bone involvement mimicking metastatic disease at (18) F-FDG PET/CT: Problem solving by diffusion whole-body MRI. Eacancermedicalscience 2015;9:537.
72. Hercules HD, Bethlem NM. Value of liver biopsy in sarcoidosis. Arch Pathol Lab Med 1984;108:831-4.
73. Radochová V, Radocha J, Laco J, Slezák R. Oral manifestation of sarcoidosis: A case report and review of the literature. J Indian Soc Periodontol 2015;19:582-5.
74. Porter N, Heyson JH, Randeva HS. Endocrine and reproductive manifestations of sarcoidosis. QJM 2003;96:533-61.
75. Ozgul M, Cetinkaya E, Kirkil G, Ozgul G, Abul Y, Acat M, et al. Lymph node characteristics of sarcoidosis with endobronchial ultrasound. Endose Ultrasound 2014;3:232-7.
76. Koo HJ, Kim MY, Shin SY, Shin S, Kim SS, Lee SW, et al. Evaluation of mediastinal lymph nodes in sarcoidosis, sarcoid reaction, and malignant lymph nodes using CT and Fdg-Pet/CT. Medicine (Baltimore) 2015;94:e1095.
77. Robinson LA, Smith P, Sengupta DJ, Prentice JL, Sandin RL. Molecular analysis of sarcoidosis lymph nodes for microorganisms: A case-control study with clinical correlates. BMJ Open 2013;3:e004065.
78. Judson MA. The diagnosis of sarcoidosis. Clin Chest Med 2008;29:415-27, viii.
79. Govender P, Berman JS. The diagnosis of sarcoidosis. Clin Chest Med 2015;36:585-602.
80. Crouzer ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2020;201:e26-51.
81. Kraaijvanger R, Janssen Bonás M, Vorselaars AD, Veltkamp M. Biomarkers in the diagnosis and prognosis of sarcoidosis: Current use and future prospects. Front Immunol 2020;11:1443.
82. Migita K, Sasaki Y, Ishizuka N, Arai T, Kiyokawa T, Sueatsukito E, et al. Glucocorticoid therapy and the risk of infection in patients with newly diagnosed autoimmune disease. Medicine (Baltimore) 2013;92:285-93.
83. Maradit Kremers H, Reinalda MS, Crowson CS, Davis JM 3rd, Hunder GG, Gabriel SE. Glucocorticoids and cardiovascular and cerebrovascular events in polymyalgia rheumatica. Arthritis Rheum 2007;57:279-86.
84. Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, de Bois R, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vascul Dis Diffuse Lung Dis 1999;16:149-73.
85. Carmona EM, Kalra S, Ryu JH. Pulmonary sarcoidosis: Diagnosis and treatment. Mayo Clin Proc 2016;91:946-54.
86. Schutt AC, Bullington WM, Judson MA. Pharmacotherapy for pulmonary sarcoidosis: A Delphi consensus study. Respir Med 2010;104:717-23.
87. Paramothayan S, Lasserson T. Treatments for pulmonary sarcoidosis. Respir Med 2008;102:1-9.
88. Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: Results of a double blind, randomized trial. Sarcoidosis Vascul Dis Diffuse Lung Dis 2000;17:60-6.
89. Lower EE, Baughman RP. The use of low dose methotrexate in refractory sarcoidosis. Am J Med Sci 1990;299:153-7.
90. Vucicin VM. What is the future of methotrexate in sarcoidosis? A study and review. Curr Opin Pulm Med 2002;8:470-6.
91. Marchell RM, Judson MA. Cutaneous sarcoidosis. Semin Respir Crit Care Med 2010;31:442-51.
92. Zic JA, Horowitz DH, Arzubiaga C, King LE Jr. Treatment of cutaneous sarcoidosis with chloroquine. Review of the literature. Arch Dermatol 1991;127:1034-40.
93. Webster GF, Razsi LK, Sanchez M, Shupack JL. Weekly low-dose methotrexate therapy for cutaneous sarcoidosis. J Am Acad Dermatol 1991;24:451-4.
94. Hamzeh NY, Wamboldt FS, Weinberger HD. Management of cardiac sarcoidosis in the United States: A Delphi study. Chest 2012;141:154-62.
95. Charoenthaitawee P, Beanlands RS, Chen W, Dorbala S, Miller EJ, Murthy VL, et al. Joint SNMMI-ASN expert consensus document on the role of 18F-FDG PET/CT in cardiac sarcoid detection and therapy monitoring. J Nucl Cardiol 2017;24:1741-58.
96. Hamzeh N, Steelman DA, Sauver WH, Judson MA. Pathophysiology and clinical management of cardiac sarcoidosis. Nat Rev Cardiol 2015;12:278-88.
97. Ungrasert P, Crowson CS, Matteson EL. Characteristics and long-term outcome of neurosarcoidosis: A population-based study from 1976-2013. Neuroepidemiology 2017;48:87-94.
98. Ehrhart IC, Parker PE, Weidner WJ, Dabney JM, Scott JB, Haddy FJ. Coronary vascular and myocardial responses to carotid body stimulation in the dog. Am J Physiol 1975;229:754-60.
99. Chareonthaitawee P, Beanlands RS, Chen W, Dorbala S, Miller EJ, Murthy VL, et al. Joint SNMMI-ASN expert consensus document on the role of 18F-FDG PET/CT in cardiac sarcoid detection and therapy monitoring. J Nucl Cardiol 2017;24:1741-58.
100. Hamzeh N, Steelman DA, Sauver WH, Judson MA. Pathophysiology and clinical management of cardiac sarcoidosis. Nat Rev Cardiol 2015;12:278-88.
101. Ungrasert P, Crowson CS, Matteson EL. Characteristics and long-term outcome of neurosarcoidosis: A population-based study from 1976-2013. Neuroepidemiology 2017;48:87-94.
102. Krumholz A, Stern BJ, Stern EG. Clinical implications of seizures in newly diagnosed autoimmune disease. Medicine (Baltimore) 2013;92:451-77.