



## REVIEW ARTICLE

# SARCOIDOSIS; A DISEASE OF MANY CLINICAL FACES

By

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## INTRODUCTION

Sarcoidosis is a chronic, multiorgan inflammatory disorder of unknown etiology, characterized by non-caseating granulomas, that primarily affects the lungs and the lymphatics. The diagnosis is "established when the clinico-radiological findings are supported by histological evidence of non-caseating epithelioid granulomas". The cause of the disorder remains unknown. Currently, the consensus view is that sarcoidosis results from exposure of genetically susceptible hosts to - as yet unidentified - environmental agents that trigger a Th1-type cellular immune response with granuloma formation.

The majority of patients recover spontaneously. Some features of sarcoidosis such as lupus pernio, neurologic involvement, bone cysts, and pulmonary fibrosis predict a more chronic course, with a low rate of remission. Approximately one-third of patients suffer a more persistent and progressive disease requiring prolonged treatment with corticosteroids and occasionally with one or

more second-line drugs such as azathioprine.

**Clinical features:** The lung is the organ most commonly involved but almost any organ in the body may be affected. Ethnicity appears to have some effect on the distribution and severity of disease.

**Lung:** Respiratory symptoms are relatively uncommon even in radiologically extensive disease and include dyspnoea, vague central chest discomfort, and cough. Digital clubbing is rare and is usually associated with chronic, widespread pulmonary fibrosis. Chest auscultation is often normal, whereas advanced fibrosis may produce changes consistent with this process (i.e., end-inspiratory crackles).

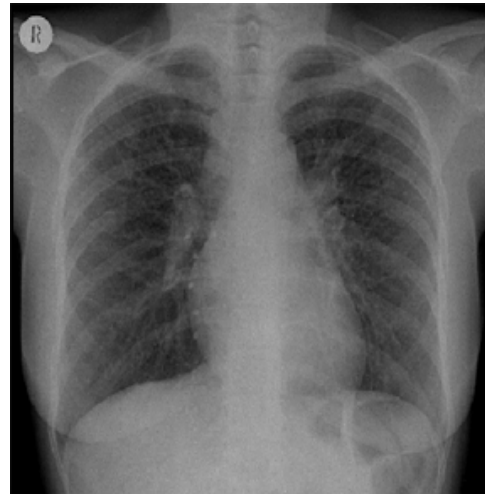
Chest radiography is abnormal in 90 to 95% of patients during the course of the disease, and is atypical in up to 30%. Pulmonary infiltration is almost always bilateral, with nodular shadowing distributed throughout all lung fields but slightly more pronounced in the midzones. More dense

infiltration leads to reticulonodular shadowing, nodular opacities, and fibrotic change of strand-like linear opacities that may radiate from the hilum and be associated with vascular distortion and upward displacement of the hila and fissures. Chest radiography is traditionally classified using

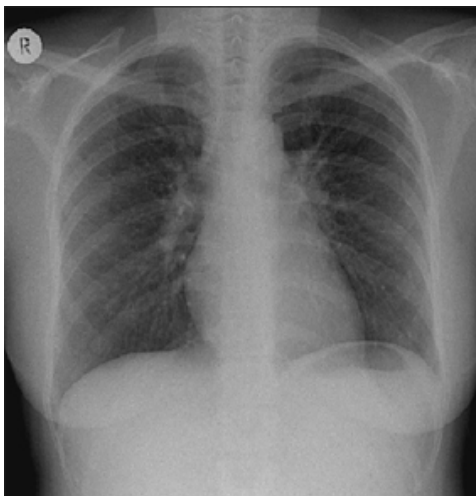
the Scadding classification of pattern. Examples are shown in (Fig. 1). Computed tomography is not required as a routine but should be performed if the chest radiograph is unusual, or to assess the pattern of disease and/or progression. A typical CT is shown in (Fig. 2).



(Stage 1)



(Stage 2)

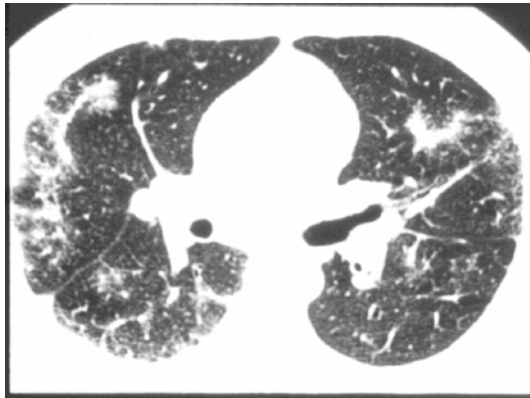


(Stage 3)



(Stage 4)

*Fig 1. Chest radiographic staging based on radiographic pattern.*



**Fig 2. Typical CT features of sarcoidosis showing multiple nodules, many of which are peripheral or along lymphatic drainage routes including bronchovascular bundles and interlobular septa.**

**Upper Respiratory Tract:** Sarcoidosis of the upper respiratory tract is a relatively uncommon condition and is seen in up to 6% of patients. Symptoms include nasal stuffiness or blockage, nasal crusting; nasal discharge, which may be blood stained, and laryngeal disease. Upper respiratory tract destruction may occur resulting in nasal septal perforation, collapse of the bridge of the nose and palate perforations. Sicca manifestations may be also present. Local treatment of nasal symptoms may include nasal douche with an alkaline solution for relief of retained secretions and crusting, followed by betamethasone nasal drops. Systemic disease dictates the need for systemic steroids.

**Heart:** Cardiac disease may remain asymptomatic until the fatal arrhythmia occurs. Rhythm disturbances include ventricular and supra ventricular arrhythmias and atrioventricular (AV) nodal block including complete heart block (CHB). All patients should therefore have an ECG at presentation. If this is abnormal in any way or if there are symptoms suggestive of dysrhythmia, then further investigation is needed.

The diagnosis of cardiac disease is troublesome as endomyocardial biopsy, although providing diagnostic certainty, has major sampling problems due to the inhomogeneous distribution of the disease. Magnetic Resonance Imaging (MRI) is emerging as a useful non invasive measure being

able to identify infiltrative lesions and also to provide an index of ventricular function. Radionuclide methodologies have not yet been fully developed but a combination of Rubidium (Rb)-82 perfusion imaging and 18F-2-fluoro-deoxyglucose PET scanning may hold promise. Myocardial scintigraphy with thallium 201 can identify segmental contraction abnormalities. In contrast to the pattern seen in coronary artery disease, it demonstrates resting perfusion defects that resolve with exercise. 24-hour Holter monitoring and exercise stress testing increases the diagnostic yield of resting 12-lead electrocardiography.

Whereas heart failure and dysrhythmias should be treated as normal, corticosteroids are the mainstay of anti-inflammatory treatment of myocardial sarcoidosis. Automatic implantable cardioverting defibrillators have been used for malignant arrhythmias. Cardiac transplantation should be considered for the treatment of congestive cardiac failure, malignant arrhythmia, and cor pulmonale.

**Skin: The different patterns of skin disease that occur in sarcoidosis include:**

- Erythema nodosum -tender warm raised nodular swelling over the anterior aspects of the lower legs and less frequently upper legs, buttocks, and arms. Initially bright red, the lesion evolves through a dusky red to a bruised appearance. The condition persists between 1 and 6 weeks and regresses spontaneously or with control of the underlying disease process.
- Lupus pernio is the most easily recognizable form of cutaneous sarcoidosis, typically forming purplish papules or plaques that involve the nose, cheeks, lips, ears, eyelids.
- Granulomatous scar infiltration
- Plaque lesions
- Nail dystrophy
- Maculo-papular rash
- Areas of hypo- or hyperpigmentation
- Subcutaneous nodules.

**Nervous system:** Clinically evident neurosarcoidosis is found in less than 10% of total cases. The diagnosis of neurosarcoidosis is clear when disease is known to be present in other organs but it may prove elusive when neurologic signs occur in isolation. Virtually any manifestation may occur including:

- Central nervous system (CNS) involvement
- Meningitis
- Cranial nerve palsies, especially the seventh
- Peripheral neuropathy
- Myopathy
- Multiple neurologic manifestations.

The use of Gadolinium-enhanced MRI has greatly facilitated diagnosis in neurosarcoidosis and is now the investigation of choice for CNS disease. MRI appearances, however, are protean and non specific and may mimic infections, tumours, and demyelinating diseases, particularly multiple sclerosis. Definitive histological diagnosis is needed to be sure but this is often impracticable.

**Eyes:** Ocular sarcoidosis affects up to 25% of patients at some stage of chronic disease and is potentially sight threatening. Manifestations include:

- uveitis
- granulomatous conjunctivitis
- dryness of the eyes
- pain and diplopia due to orbital granulomata.

Uveitis is the most serious presentation and may occur as the primary manifestation of disease, and may affect the entire uveal tract (iris, ciliary body, and choroid), but most frequently the anterior segment, commonly presenting as an acute process that may resolve spontaneously or with topical corticosteroid therapy. Systemic corticosteroids and immunosuppression may be required in more severe disease. Chronic uveitis, particularly when associated with posterior synechiae and raised intraocular pressure, has a markedly poorer visual outcome. Nodular granulomatous involvement of the conjunctiva may be amenable to biopsy and is useful diagnostically. Untreated ocular sarcoidosis can lead to cataract, glaucoma or even blindness,

making a careful examination of the eye mandatory in all patients

**Lymphoreticular system:** The reported frequency of hepatic sarcoidosis ranges widely depending on the method of detection, with biopsies revealing granulomas in 50-80% of cases. Mild elevations of transaminases or alkaline phosphatase are also common, but such findings are rarely of clinical importance and, usually, therapy is not indicated. Progressive cirrhosis and portal hypertension can occur but rarely. Nonetheless patients whose liver function tests are abnormal need these tests to be monitored to resolution.

Patients with splenic sarcoidosis are usually asymptomatic, although left upper quadrant pain and constitutional symptoms may occur. Splenic sarcoidosis may cause hypersplenism resulting in anaemia, leucopenia and thrombocytopenia. Splenomegaly is usually homogeneous, but multiple low-attenuating nodular lesions are occasionally seen and easily mistaken for lymphoma, metastases, or infections such as tuberculosis.

Approximately a third of sarcoidosis patients have palpable peripheral nodes, particularly of the cervical and scalene groups. The nodes are classically firm, non-tender and non-ulcerating. However, isolated granulomatous inflammation in a peripheral lymph node is not diagnostic of sarcoidosis as it may simply represent a "sarcoid-like" reaction from inflammatory disease or malignancy.

**Musculoskeletal system:** Non specific arthralgia occurs in 25% of patients, but a deforming arthritis is less common. Acute sarcoid arthritis is commonly self-limiting, and occurs in 1 to 4% of patients. The acute disease manifests as a migratory polyarthropathy typically affecting the ankles but also knees, wrists, and elbows. When associated with bilateral hilar lymphadenopathy (BHL) and fever, the diagnosis is Lofgren's syndrome.

Chronic sarcoid arthritis has a joint distribution similar to the acute form (i.e., ankles, knees, wrists,

and elbows) but may also affect the metacarpophalangeal and interphalangeal joints.

Myopathies can occur; they tend to be chronic and are more common in women. A steroid-induced myopathy is the main differential, and muscle biopsies may reveal non-caseating granulomas.

Sarcoid bone disease primarily takes the form of bone cysts and has been described in bones of the hands, feet, nose, skull, vertebrae, and pelvis. These cysts are generally asymptomatic and may be seen in the hands and feet in up to 5% of patients. These cysts may become symptomatic as a dactylitis in which the finger may become reddened, swollen, and tender over the affected bone or joint.

**Kidneys:** Renal involvement is an unusual but difficult complication of sarcoidosis. Primary glomerular disease is uncommon but membranous, membrano-proliferative, and mesangiocapillary glomerulonephritis have been described.

Renal sarcoidosis is usually asymptomatic and is generally discovered by routine creatinine and calcium estimations. Urinalysis may reveal minimal proteinuria, few white cells and granular casts.

Response to corticosteroid therapy is generally prompt and gratifying.

**Calcium Metabolism:** Hypercalciuria is seen in almost a third of patients with sarcoidosis, and hypercalcaemia is seen in approximately 10%. Hypercalciuria can be present without hypercalcaemia, but the reverse is not true. Persistent severe hypercalciuria (with or without hypercalcaemia) represents a mandatory indication for treatment. Thus, assessment of both serum calcium and 24-hour urinary calcium excretion is mandatory in all new presentations of sarcoidosis.

Hypercalciuria appears to result purely from elevated renal calcium filtration and not from an independent effect of vitamin D on the kidney. Treatment with corticosteroids leads to rapid normalization of serum and urinary calcium

concentrations in the majority of cases, often within 3 to 5 days. In those unresponsive to corticosteroids or intolerant of their side effects, chloroquine, hydroxychloroquine, or ketoconazole offer effective and relatively safe alternatives when used with appropriate supervision. Drug therapy should be linked to dietary modification that reduced intake of vitamin D and calcium-rich foods.

**Constitutional symptoms:** Fever, weight loss, fatigue, and malaise are seen in roughly 30% of patients with sarcoidosis. The fever is usually low grade, although temperature elevations of 39-40° C may be seen. Fatigue, when present, can be quite disabling. Weight loss and night sweats can also occur. Constitutional symptoms are more common in Blacks than in Whites or Asian patients.

**Pregnancy:** Unlike other interstitial lung diseases, sarcoidosis has a significant incidence during the reproductive years. Pregnancy, however, appears to have little effect on the long-term course of the disease in the majority of patients. The disease often remits during pregnancy but may relapse postpartum.

**Investigation Algorithm:** Our current approach to all patients at first presentation involves a series of routine screening tests Table 1. To identify occult disease and the severity of organ involvement. Histological confirmation of the diagnosis should be obtained whenever possible. If organs are inaccessible to biopsy then the diagnostic investigation algorithm should be tailored to the manner of presentation. <sup>(67)</sup>Gallium scanning can be helpful in identifying subclinical disease (in a typical pattern that would support a diagnosis of sarcoidosis) in patients who present with disease compatible with sarcoidosis but for whom biopsy is not possible. Specialist ophthalmologic review is recommended for all patients at diagnosis to ensure a thorough visual evaluation.

**Table 1. Routine Screening Tests for Evaluation of New Presentations of Sarcoidosis.**

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- Posteroanterior chest radiography
  - Pulmonary function tests: spirometry and DL<sub>CO</sub>
  - Peripheral blood counts
  - Serum chemistries: calcium, liver enzymes, renal function
  - Urine analysis
  - ECG
  - Routine ophthalmologic examination
  - Tuberculin skin test
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**TREATMENT:** There has been considerable debate over the place of treatment, particularly corticosteroids, in sarcoidosis. There is no dispute that severe symptoms or involvement of vital organs such as the eyes, central nervous system, or the heart require therapy, and that corticosteroids are the most effective treatment option.

However, there is less agreement about the role of corticosteroids in pulmonary sarcoidosis. The main issues revolve around the therapeutic ratio in acute and chronic disease. The natural inclination in these circumstances is to withhold treatment until there are symptoms, but by this stage there may be considerable, irreversible lung injury that treatment will not help, leaving the patient with symptoms. Patients with progressive deterioration in lung function and pulmonary infiltrates should be offered treatment with corticosteroids. Patients who are likely to require long-term treatment with corticosteroids, or who have progressive disease despite corticosteroid treatment, should have second-line agents introduced.

**CORTICOSTEROIDS:** Corticosteroids have formed the mainstay of treatment in sarcoidosis for over 30 years, and their use in this disease has been critically re-evaluated. The efficacy of long-term corticosteroids is disputed. There have been few studies designed to address this issue in a prospective trial. The study of the British Thoracic Society of sarcoidosis treatment attempted to overcome this design problem by tailoring treatment to response and tapering the dosage of

treatment while ensuring that response was maintained. The study concluded that long-term corticosteroids conferred a functional advantage as assessed by a change in vital capacity (VC). A meta-analysis reviewing the use of corticosteroids in pulmonary sarcoidosis has recently been published by the Cochrane group. Five trials involving 516 patients were deemed suitable for inclusion. Outcomes were symptoms, chest radiograph changes, lung function, and global scores (combination of all three outcomes). Their conclusion was that "oral steroids improved the chest x-ray score, symptoms and spirometry over 6-24 months, but there is little evidence of an improvement in lung function. There are no data beyond two years to indicate whether oral corticosteroids have any modifying effect on long-term disease progression. Oral corticosteroids are indicated for patients with Stage II and III disease with moderate-severe or progressive symptoms or CXR changes."

In most cases, a period of observation for 6 to 12 months while monitoring CXR, spirometry, and gas transfer is indicated to allow for spontaneous resolution. In our practice, progressive or unimproved disease is then treated. A starting dose of 20-40 mg of prednisolone for 4 weeks is appropriate for most patients. Dosage may be tapered to 10 to 15 mg over 2 months, titrated to improvement in clinical state, CXR, and pulmonary function test (PFT). The aim is to achieve the lowest effective alternate-day dose possible. Treatment for acute disease is usually necessary for 12 to 18 months, although 6- to 12-month courses of therapy are occasionally effective. Relapse of disease, as evoked by a recurrence of symptoms or the development of new pulmonary infiltrates, is common after stopping corticosteroids, with up to 36% of patients relapsing. Relapses do not always occur immediately on withdrawal of corticosteroids, with 20% of relapses occurring more than 1 year after cessation of steroid treatment and 10% beyond 2 years. Alternate-day therapy is as effective as daily therapy and delivers the same weekly dose but may cause fewer corticosteroid-related side effects. Patient selection is important,

as this strategy may hinder compliance.

Corticosteroid therapy for extrathoracic disease is better defined and is indicated for all disease that impairs or threatens organ function. Doses are typically larger than in pulmonary disease and may be as high as 60 to 80 mg per day; medication is frequently taken for longer periods than in pulmonary disease. Features such as asymptomatic glandular involvement, minor elevation of liver function tests (LFTs), and fatigue may not require treatment or may not respond to therapy, and therefore corticosteroid therapy should be avoided. The decision to treat with long-term corticosteroids should be based on the anticipated therapeutic ratio, which may require an initial trial period followed by a concerted effort to achieve the minimum effective dose.

Topical corticosteroids for ocular involvement, topical and intralesional corticosteroids for skin and laryngeal involvement, and intravenous pulsed methylprednisolone have all found some usefulness in chronic disease and may replace the need for oral prednisolone in some patients.

**INHALED CORTICOSTEROIDS:** Given the bronchocentric nature of sarcoidosis, inhalation seems a logical route for corticosteroid delivery. Studies of inhaled therapy have in general not clarified their place in the disease. The most likely applications are for cough due to endobronchial disease.

**ALTERNATE IMMUNOSUPPRESSIVE AGENTS:** A wide variety of agents has been assessed for their value as potential anti-inflammatory agents or as steroid-sparing agents and is summarized below.

- **Hydroxychloroquine:** The antimalarial chloroquine is recognized as a treatment in cutaneous sarcoidosis. It has some suppressive effect on pulmonary disease, particularly airway disease and has an adjunctive benefit for the treatment of hypercalcemia. Patients started on antimalarials require regular

ophthalmic assessment, as long-term use may be associated with retinopathy and blindness. Hydroxychloroquine is less likely to be associated with ocular toxicity than chloroquine.

- **Methotrexate:** The antimetabolite folate antagonist methotrexate has been used for both pulmonary and extrathoracic disease with both corticosteroid-sparing and primary immunosuppressive intent. It appears to be the most promising alternative to corticosteroids in the treatment of cutaneous sarcoidosis. In this regard, methotrexate has induced some regression of disfiguring skin lesions when used in treatment of resistant lupus pernio and cutaneous sarcoidosis.

Hypersensitivity reactions can occur in up to 5% of patients treated with methotrexate; thus, in patients on methotrexate lung function monitoring is of particular importance. Hepatotoxicity is, however, the main adverse event associated with long-term use of methotrexate. Guidelines have been established to inform treatment. Liver function tests should be performed prior to starting treatment, and repeated thereafter at 4 to 6 week intervals together with full blood counts.

- **Azathioprine:** There is little published data on the use of this agent in sarcoidosis. The role of azathioprine as a steroid-sparing agent in pulmonary disease has some support and is the author's first choice as a corticosteroid sparing agent for pulmonary disease, especially disease that is more fibrotic. Liver function tests should be performed prior to starting treatment, and repeated thereafter at 4 to 6 week intervals together with full blood counts. Mycophenolate mofetil is a reasonable alternative if azathioprine cannot be tolerated.
- **Chlorambucil:** This drug still appears in some text books as a treatment option. However, the long-term effects of this agent on gonadal function are of concern, as are its teratogenesis and the appearance of secondary leukemias.

Myelosuppression is the most common toxicity and leads to thrombocytopenia and leukopenia. At present it is not recommended.

- **Cyclosporin A:** Theoretically, cyclosporin A is a logical and attractive agent for use in sarcoidosis due to its potent IL-2 inhibition, suppression of T-lymphocyte proliferation, and reduction of monocyte chemotactic factor expression. Despite apparent in vitro benefit, this has not been translated into clinical efficacy and it is used rarely if at all.
- **Ketoconazole:** Ketoconazole, the imidazole-derivative antifungal, has significant activity in inhibition of the cytochrome P-450 complex and may inhibit synthesis of 1,25-dihydroxyvitamin D3 and other steroid hormones in patients with sarcoidosis with both normal and elevated calcium levels. It should be considered in patients with hypercalcemia when simpler measures are of no benefit or if too high doses of corticosteroids are needed.
- **TNF- $\alpha$  Blockade:** There is good scientific logic to use TNF blocking strategies in sarcoidosis. This cytokine is secreted in increased amounts in this disease, especially when there is evidence of disease activity. Drugs that block TNF include pentoxifylline, thalidomide and the TNF monoclonal antibody infliximab.

Of these, infliximab has been evaluated most comprehensively in a large multicenter, randomized, double-blind, placebo-controlled study including 138 patients with pulmonary sarcoidosis. Patients in the combined infliximab groups (3 and 5 mg/kg) had a modest increase from baseline to week 24 in forced vital capacity (FVC) compared with no change in placebo-treated patients. Post hoc analyses identified two groups of patients that might potentially benefit from infliximab: those with multiorgan, extrapulmonary disease and those with more "active" disease. In a second study it was concluded that infliximab may improve VC in patients with active pulmonary disease

resistant to steroids. However, three patients in these series had serious adverse events and one died of acute renal failure and pulmonary embolus. Preliminary results suggest that infliximab may be effective and safe especially in cutaneous sarcoidosis, whereas its routine use cannot be endorsed in pulmonary sarcoidosis.

- **Thalidomide** has been shown to be effective in chronic cutaneous sarcoidosis but has a significant side effect profile including teratogenicity, somnolence and peripheral neuropathy. Its use should therefore be cautious and only in experienced hands.

**TRANSPLANTATION:** Sarcoidosis has proved amenable to transplantation, especially for lung and cardiac disease when disease in other organs is not severe.

#### MANAGEMENT STRATEGIES: A SUMMARY

**Treatment Algorithm:** A summary of the authors' approaches to treatment for the various manifestations of sarcoidosis is shown in Tables 2. & 3 and in several reviews.

**Table 2. Treatment Strategies for Pulmonary Sarcoidosis.**

Stage	Treatment
I	Corticosteroids are generally not indicated for stage I disease. NSAIDs are first-line therapy for fever and arthralgia
II	Asymptomatic patients may be observed and treatment decisions based on deterioration in PFT and CXR. Corticosteroids are indicated in symptomatic disease for control of symptoms and titrated to maintain response.
III	No treatment is required for asymptomatic patients with stable, good lung function. Corticosteroids are indicated dependent on change in PFT/CXR indices and for symptomatic disease and are titrated to effect.
IV	Fibrosis is unlikely to be affected by corticosteroid therapy; however, decision to treat is made if disease is progressive indicating ongoing activity

**Table 3. Treatment Approach for Non-Pulmonary Sarcoidosis.**

Clinical Features	First Line	Second Line
Fevers; Night sweats; Arthralgia; Löfgren's syndrome	Observation and nonsteroidals	Steroids for severe or recalcitrant symptoms
Ocular	Ophthalmologic assessment	Topical cycloplegics Topical steroids Systemic steroids Immunosuppression
Upper respiratory tract	Nasal alkaline douche	Topical steroids Systemic steroids Hydroxychloroquine Methotrexate
Cardiac	Systemic steroids	Permanent pacemaker Antiarrhythmics Automatic implantable cardiac defibrillator Heart transplant
Skin	Systemic steroids	Topical treatment Methotrexate Hydroxychloroquine
Liver and spleen	Systemic steroids	Immunosuppression
Neurosarcoidosis	Systemic steroids	Immunosuppression ? Shunt
Hypercalcemia/ hypercalciuria	Low calcium diet	Low vitamin D diet Avoid sunlight Systemic steroids Hydroxychloroquine Ketoconazole
Renal	Systemic steroids	Immunosuppression

### CONCLUSION

In conclusion, sarcoidosis is a disease - and likely a group of distinct diseases - that presents with variable clinical faces. Investigation needs to be meticulous and treatment geared to the organ of involvement, disease pattern and severity of disease.

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