Sarcoidosis: a state of the art review from the Thoracic Society of Australia and New Zealand

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Sarcoidosis is a systemic granulomatous disease of unknown aetiology, primarily affecting the lungs and lymphatic systems, although any organ may be involved. The presentation may be an incidental finding on chest radiology, or due to symptoms, most commonly cough or breathlessness, or relating to involvement of other organ systems such as the eyes, skin, nervous system or heart. Löfgren syndrome (fever, erythema nodosum, bilateral hilar lymphadenopathy, polyarthritis) is a distinct acute form with a good prognosis. Sarcoidosis is diagnosed by clinical and radiological findings and demonstration of non-caseating granulomas on biopsy, with exclusion of other causes. Differential diagnoses include tuberculosis, lymphoma and other causes of lung fibrosis. Few randomised, controlled studies indicate the appropriate treatment, despite increased knowledge of the immunopathological and genetic features. The management of sarcoidosis can be challenging, despite new developments in diagnostic techniques and biological agents for treatment. Here, we discuss developments in the understanding of its pathology, diagnosis and management.

For this narrative review, we searched PubMed for original papers and review articles published between 1999 and 2017 to formulate an evidence-based overview of sarcoidosis. This article is a summary of an educational resource provided by the Thoracic Society of Australia and New Zealand, available online at https://www.thoracic.org.au.

Summary

- Sarcoidosis is a systemic disease of unknown aetiology, characterised by non-caseating granulomatous inflammation. It most commonly manifests in the lungs and intrathoracic lymph nodes but can affect any organ.
- This summary of an educational resource provided by the Thoracic Society of Australia and New Zealand outlines the current understanding of sarcoidosis and highlights the need for further research.
- Our knowledge of the aetiology and immunopathogenesis of sarcoidosis remains incomplete.
- The enigma of sarcoidosis lies in its immunological paradox of type 1 T helper cell-dominated local inflammation co-existing with T regulatory-induced peripheral anergy.
- Although specific aetiological agents have not been identified, mounting evidence suggests that environmental and microbial antigens may trigger sarcoidosis.
- Genome-wide association studies have identified candidate genes conferring susceptibility and gene expression analyses have provided insights into cytokine dysregulation leading to inflammation.
- Sarcoidosis remains a diagnosis of exclusion based on histological evidence of non-caseating granulomas with compatible clinical and radiological findings.
- In recent years, endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal lymph nodes has facilitated the diagnosis, and whole body positron emission tomography scanning has improved localisation of disease.
- No single biomarker is adequately sensitive and specific for detecting and monitoring disease activity.
- Most patients do not require treatment; when indicated, corticosteroids remain the initial standard of care, despite their adverse side effect profile.
- Other drugs with fewer side effects may be a better long term choice (eg, methotrexate, hydroxychloroquine, azathioprine, mycophenolate), while tumour necrosis factor-α inhibitors are a treatment option for patients with refractory disease.

Epidemiology

Racial, demographic and ethnic variations in clinical manifestations of sarcoidosis exist. Sarcoidosis affects people of all ages regardless of race and ethnicity, with peak incidence among people aged 20–39 years, and is thought to be more common in rural communities.[1,2] In Australia, the prevalence is estimated to be 4.4–6.3 per 100 000 population.[3]

Aetiology and pathogenesis: recent advances

The aetiology of sarcoidosis remains uncertain; however, there is improved understanding of its genetic factors, environmental associations, putative antigens and immunopathogenesis, and it probably results from the exposure of genetically susceptible individuals to specific environmental agents.[4,5]

Genetic factors

Familial clustering of disease, increased concordance in monozygotic twins and racial differences suggest that genetic factors are important in sarcoidosis pathogenesis, presentation and outcomes.[6] The African American population has the highest incidence, with more severe and chronic disease.[1] Human leucocyte antigen genotypes confer susceptibility and subtypes of sarcoidosis,[7] particularly a polymorphism in the butyrophilin-like 2 receptor gene.[6,7] Associations with certain disease subtypes and within populations exist, indicating that susceptibility to sarcoidosis is complex and polygenic in nature.

Mycobacteria and other putative antigens

Microbial nucleic acid analyses suggest that mycobacteria and perhaps propionibacteria play a role in the pathogenesis of sarcoidosis, with a 9- to 19-fold higher incidence in histopathological samples compared with controls, including immune responses against some microbe-derived antigens.[8-10] Intracellular persistence of such bacterial antigens and failure to clear non-degradable antigen–protein complexes in patients with certain genotypes may explain chronic sarcoidosis.[11]

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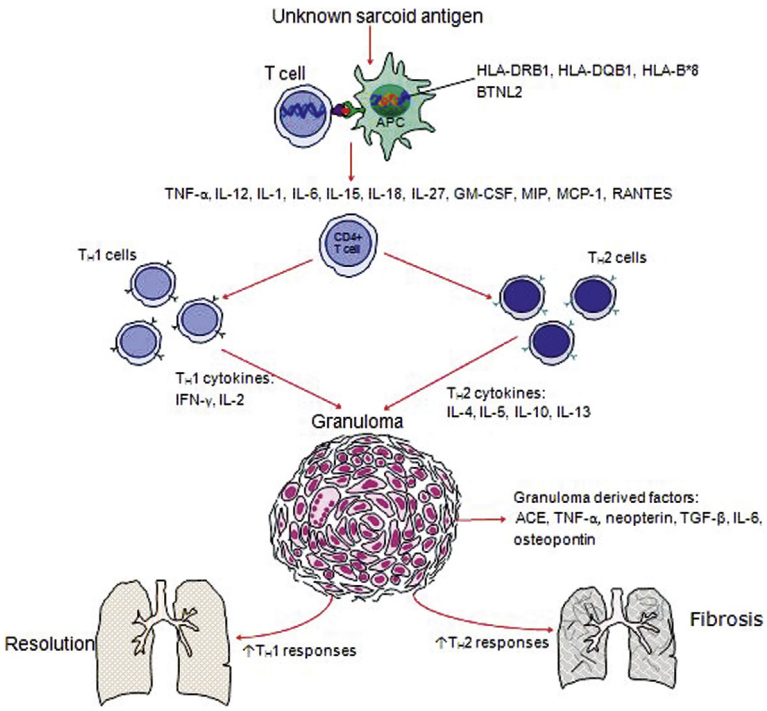
1 Overview of the hypothesised immunopathogenesis of sarcoidosis*



ACE = angiotensin-converting enzyme; GM-CSF = granulocyte-macrophage colony-stimulating factor; HLA = human leucocyte antigen; IFN = interferon; IL = interleukin; MCP = monocyte chemo-attractant protein; MIP = macrophage inflammatory protein; RANTES = regulated on activation, normal T cell expressed and secreted; TGF = transforming growth factor; T_H = T helper; TNF = tumour necrosis factor. The inciting agent may be cleared leaving behind an undegradable antigen or it may cause a cross-reacting response with a self-antigen with strong evidence for HLA and BTNL2 alleles contributing to susceptibility. The processed antigen is presented by HLA molecules on antigen-presenting cells to sarcoid antigen-specific T cells, which express restricted Vα and Vβ regions of the T cell receptor. Ligation of co-stimulatory signals such as CD80 and CD86 on the APC binding to CD28 on the T cell is required for full T cell activation. This leads to release of a variety of cytokines and chemokines activating CD4+ T cells to become active T_H1 cells that secrete IL-2 and IFN-γ that drives granulomatous inflammation yet promotes resolution. Contributions of T_H2 cells and macrophage-derived cytokines, namely TGF-β, lead to development of fibrosis and chronic disease. * Diagram modified from Iannuzzietal[2] and reproduced with permission from Ahmadzai.[6] ◆

Immunological features

Initially, an antigenic peptide is presented to the T cell receptor on naive T cells via human leucocyte antigen class II molecules on antigen-presenting cells, resulting in activation with subsequent clonal proliferation and T helper (Th)1 polarisation with release of cytokines and chemokines. Th1 cells and macrophages stimulate monocytes to form non-caseating granulomas which may persist or regress. Fibrosis is an alternative outcome through a transition from a Th1 to a Th2 cytokine profile, with Th1 cytokines being important in promoting granulomatous inflammation and inhibiting fibrosis (Box 1).[2,6]

Unlike normal CD4+:CD8+T cell ratios of 2:1 in healthy controls, most patients with sarcoidosis have elevated ratios ranging from 3.5:1 to 15:1 at sites of inflammation.[6] The Th1-dominated inflammation at the site of disease is associated elsewhere with peripheral immunological anergy, characterised by T cell lymphopenia and reduced delayed-type hypersensitivity to common recall antigens.[11] This may be explained by systemic proliferation of T regulatory cells, which suppress cell-mediated immunity in the periphery but not locally at sites of disease.[12,13] Recently, Th17 cell responses associated with autoimmunity and defence against extracellular pathogens have been identified, including increased interleukin-17, interferon-γ and interleukin-23R expression by CD4+ T cells in lung, peripheral blood and lymph node biopsies of patients.[14,15]

Diagnostic procedures

A compatible clinical–radiological presentation with histopathology showing non-caseating granulomas is diagnostic of sarcoidosis. Serum angiotensin-converting enzyme (ACE) is an indicator of the total granuloma burden but has modest sensitivity and specificity, and is elevated in other granulomatous conditions, making it of limited utility in diagnosis and monitoring.[16] Other markers have yet to prove themselves superior to ACE,[17] which in turn is influenced by ACE polymorphisms and the use of ACE inhibitors.[16] Hypercalcaemia and hypercalciuria should be investigated as part of the diagnostic work-up and may be confounded by concomitant vitamin D and calcium supplementation. Serum 1,25-hydroxyvitamin D_3 levels are also elevated while serum 25-hydroxyvitamin D_3 levels may be low, leading to the erroneous diagnosis of vitamin D deficiency.[16,18]

Biopsy

Non-caseating granulomas on tissue biopsy and exclusion of other causes of granulomatous inflammation are required for diagnosis.[19] A biopsy is unnecessary in Löfgren syndrome and difficult in neurosarcoidosis.

Pulmonary function tests

Abnormal pulmonary function tests occur in about 20% of patients with mild disease, increasing to 40–70% with more advanced disease.[1] Obstructive and restrictive abnormalities may occur, with functional impairment occurring with decreased forced vital capacity and diffusing capacity,[1,20] although these may improve.[21] Airway hyper-responsiveness (increased sensitivity to an inhaled agent) is common[21] but pre- and post-bronchodilator spirometry may not show a significant change, unlike in asthma.

Radiological investigations

Chest x-ray and abdominal ultrasound provide cost-effective initial investigations. Bilateral hilar lymphadenopathy is often found incidentally, and other mediastinal lymphadenopathy and upper zone intrapulmonary abnormalities may be identified. Abdominal adenopathy as well as splenic abnormalities (such as nodular spleen or enlargement) can be seen on ultrasound. There is no consensus on whether interval chest x-ray or low dose high resolution computed tomography (CT) scanning is more appropriate for surveillance.[22] An initial CT scan of the chest can assess the lung parenchyma and lymph nodes (which may calcify) and provide useful information about the liver and spleen. It can demonstrate classic parenchymal findings of nodules clustered along the bronchovascular bundles, interlobular septa and subpleural regions considered by some to be diagnostic of sarcoidosis. Nodules vary from a few in a subpleural distribution to profuse micronodules in a primarily upper lobe distribution; larger nodules may coalesce while small nodules may surround larger

lesions.[23] Ground glass opacification may represent profuse small nodules beyond the resolution of the CT scan. In many patients with less marked disease, resolution may occur on CT; however, in a minority, reticular opacities develop, often with an upper lobe distribution and sometimes honeycombing. If the disease progresses to fibrosis, patchy reticular changes and dense opacification become more evident in an upper zone perihilar distribution extending to the apices. Eventually, the distortion may result in traction bronchiectasis, cavity formation and the risk of aspergillomata.[23] Bronchial abnormalities are relatively common, with nodular wall thickening and sometimes endobronchial lesions. Small airway obstruction by active disease or fibrosis can lead to gas trapping seen on expiratory views.

Parenchymal disease evident on CT scanning correlates with pulmonary function tests more than chest x-ray,[24] and an integrated functional and morphologic staging system for sarcoidosis might allow a more confident assessment of treatment response.[25] Cardiac enlargement can be seen on chest imaging, suggesting cardiac sarcoidosis or pulmonary hypertension, which in turn may be evident with right ventricular hypertrophy or enlargement of the pulmonary outflow tract.

Nuclear imaging

Nuclear medicine studies have been used to identify features of sarcoidosis and sites of disease suitable for a confirmatory biopsy, and to determine the involvement of particular organs. Sarcoidosis classically appears on gallium-67 scanning as panda and lambda signs, where salivary glands, conjunctivae and nasal passages create the impression of the facial characteristics of a panda, and mediastinal and hilar lymph nodes represent the Greek letter lambda. Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scanning has largely replaced gallium-67 scanning and has been shown to be effective[26] in identifying disease activity in sarcoidosis. However, both procedures rely on pattern recognition. ^{18}F-FDG has greater availability as it is used extensively in oncology, involves a lower radiation dose, provides better resolution, and is able to co-register scans with CT imaging.[6] Currently, ^{18}F-FDG PET is not reimbursed for sarcoidosis by national medical programs.

Bronchoscopy, bronchoalveolar lavage analysis and endobronchial ultrasound fine needle aspiration

Bronchoscopy is helpful for diagnosis and excluding other diagnoses — a transbronchial biopsy has a diagnostic yield of 70–85% and endobronchial biopsy may also demonstrate non-caseating granulomas even if radiology results are normal.[27] Transbronchial biopsy has a higher rate of obtaining granulomas, at the risk of bleeding and pneumothorax.[27,28] Bronchoalveolar lavage (BAL) fluid analysis can demonstrate a lymphocytosis with elevated ratios of CD4+:CD8+ cells, typically > 3.5:1, in the absence of other causes.[6] BAL T lymphocyte subset analysis can identify sarcoid alveolitis and greater basal activation of BAL CD4+ T cells compared with peripheral blood lymphocytes, indicative of compartmentalisation of the immune response.[29]

The high diagnostic yield of endobronchial ultrasound (EBUS) allows real-time ultrasound-guided transbronchial fine needle aspiration of hilar and mediastinal lymph nodes; the technique returns a yield of up 90% and has largely replaced surgical biopsy.[28,30] The choice of EBUS fine needle aspiration or bronchoscopy with transbronchial biopsy will depend on the anatomical location of lesions and whether EBUS fine needle aspiration is locally available. Sometimes both may be required if an initial EBUS fine needle aspiration with simultaneous cytology is inconclusive, but this will require two bronchoscopes.

Magnetic resonance imaging and lumbar puncture

Gadolinium-enhanced magnetic resonance imaging (MRI) can detect sarcoid of the brain, spinal cord, meninges, skull vault and pituitary lesions. In neurosarcoidosis, cerebrospinal fluid analysis may indicate non-specific lymphocytosis and elevated protein level, while CD4+:CD8+ T cell ratios and lysozyme, β2-microglobulin and ACE levels may suggest the diagnosis.[31]

Cardiac investigations: cardiac MRI and PET

Patients with parenchymal pulmonary sarcoidosis should receive baseline electrocardiography and transthoracic echocardiography with ambulatory electrocardiography monitoring if any conduction or rhythm disturbance is detected. Electrophysiological studies are helpful to investigate patients with syncope or dysrhythmias but cannot exclude the development of granulomatous infiltration and myocardial fibrosis.[2,32] Unexplained bundle branch, heart block or frequent ventricular ectopics indicate that other investigations are required to exclude ischaemic heart disease or cardiomyopathy. Evaluation for cardiac sarcoidosis by cardiac MRI, ^{18}F-FDG PET, or technetium-99m plus sestamibi–thallium-201 scan or gallium-67 scan should be performed depending on local availability.[33,34] Delayed contrast-enhanced cardiac MRI may detect sarcoid-related cardiac damage and could be useful in patients on anti-inflammatory treatments that reduce FDG uptake.[35] Nuclear medicine scans, particularly with special ^{18}F-FDG PET protocols, may indicate increased uptake indicating cardiac inflammation associated with decreased myocardial function.[36,37] Oncology-related ^{18}F-FDG PET protocols are less useful, as glucose is avidly taken up by the normal cardiac muscle. Mantini and colleagues provide a practical guide, with the choice between PET and cardiac MRI being made based on local availability, although the investigations are not mutually exclusive.[37] Endomyocardial biopsy is usually not performed as the disease has a patchy distribution.

Management of sarcoidosis

Some specialised centres for management exist, but most patients are managed according to the principal organ system involved. Respiratory physicians are able to appropriate biopsy samples, but the mode of referral will be dictated by the main symptoms and organ involvement. Ocular and rheumatological symptoms are the other main presentations.

Indications for treatment

The decision to treat is guided by the aim of improving the patient's symptoms and preventing organ damage, complications and disease progression. Ocular sarcoidosis must be treated as it may cause permanent vision loss. Sarcoid hypercalciuria requires treatment to prevent impaired renal function from nephrocalcinosis and renal calculi.[1,2,6] Significant neurological and cardiac disease warrants treatment usually over a prolonged period, measured in years. Pulmonary hypertension is rare but prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase-5 inhibitors may help.[38] Pharmacological agents and a pacemaker or implantable cardiac defibrillator may be indicated for atrioventricular block, dysrhythmias and heart failure.

2 Criteria for initiating corticosteroid therapy in patients with sarcoidosis*

- Progressive symptomatic pulmonary disease
- Asymptomatic pulmonary disease with persistent infiltrates or progressive loss of lung function
- Cardiac disease
- Neurological disease
- Eye disease not responding to topical therapy
- Symptomatic hypercalcaemia
- Other symptomatic/progressive extrapulmonary disease

* American Thoracic Society, European Respiratory Society and World Association of Sarcoidosis and other Granulomatous Disorders.[1] ◆

Corticosteroids

Corticosteroids have traditionally been used in acute and chronic sarcoidosis, but there are no trials to indicate the appropriate dose or duration. Although effective in gaining disease control, they may be supplemented or replaced by drugs such as methotrexate, hydroxychloroquine or azathioprine, particularly if significant steroid side effects have developed. Rheumatologists tend to use these drugs at an earlier stage to control systemic symptoms. Corticosteroids remain the recommended first line therapy for pulmonary forms of the disease,[39] but methotrexate and azathioprine are also used. It is important to note that treatment acts only to suppress and not to cure sarcoidosis, as relapses are frequent. Corticosteroids do not necessarily prevent disease progression or development of pulmonary fibrosis in all patients. The 1999 international statement on sarcoidosis suggested a list of criteria for the initiation of corticosteroid therapy (Box 2).[1]

Australian therapeutic guidelines (https://tgldcdp.tg.org.au/etgcomplete) recommend a daily dose of 0.5 mg/kg/day of oral prednisolone for 4 weeks, with subsequent tapering or increase according to clinical and radiological response in individual patients, although this is not based on clinical trials. A protracted course is needed in patients who relapse after ceasing treatment, and if a response is observed by 3 months, the course should continue for at least 12 months.[39-46] Pulmonary sarcoidosis can be very responsive, unlike neurosarcoidosis.[40-42] Cutaneous and ocular sarcoidosis may respond to topical steroid-containing creams or eye drops.[42] Inhaled corticosteroids may be sufficient to control cough, although a meta-analysis showed no clear benefit.[43-45] Regular ophthalmological review is advisable for glaucoma or cataracts as well as sarcoid eye disease.[42] Non-steroidal anti-inflammatory drugs and hydroxychloroquine may be useful in Löfgren syndrome for relief of arthralgia and myalgia.[47]

Immunosuppressive agents

Several immunosuppressive drugs are used as corticosteroid-sparing agents for long term treatment and to reduce steroid-related side effects[40] but are contraindicated in pregnancy, breastfeeding and before conception. Risks of infections and the long term risk of malignancy need to be discussed with the patient. Box 3 provides a summary of pharmacological treatments for sarcoidosis, including the levels of evidence for the use of different pharmacological agents.[43-60]

Methotrexate, an inhibitor of folic acid metabolism, is the most widely used corticosteroid-sparing agent used. It has a relatively low side effect profile, with 50–70% of patients responding and about 25% weaned off corticosteroids.[48] Side effects include nausea, malaise, leukopenia, hepatotoxicity, pneumonitis and an increased risk of opportunistic infections. Concomitant folic acid supplement should be given.[40] Recently, multinational evidence-based recommendations have been developed.[49]

Azathioprine has a similar response rate but involves the risk of skin neoplasia. It has a greater inhibitory effect on cell-mediated immunity than on humoral immunity; however, no randomised controlled clinical trials have been performed.[40,50,51] Levels of thiopurine methyltransferase should be measured for dose adjustment.[61] Mycophenolate can be an effective treatment for neurosarcoidosis and cutaneous sarcoidosis, but data on its efficacy for other forms of sarcoidosis are limited.[52,53] Likewise, some but not all studies[54,55] have found leflunomide to be as effective as methotrexate in treating both pulmonary and extra-pulmonary sarcoidosis, and it may have less hepato- and pulmonary toxicity. Cyclophosphamide is considered toxic and is usually reserved for life-threatening neurological and ocular sarcoidosis that has become refractory to corticosteroids and other agents.[40,42]

Tumour necrosis factor-α inhibitors and other monoclonal antibodies

Logically, such agents should be beneficial, because the development of granulomas is thought to be dependent upon the cytokine

3 Pharmacological treatment for pulmonary sarcoidosis

Intervention	Level of evidence*	Comment
Inhaled corticosteroids	A	Conflicting results from a small number of trials but essentially ineffective for control of pulmonary disease; may be effective for cough symptom control[43-45]
Oral corticosteroids	B	No robust placebo-controlled RCT; one non-randomised trial[46]
(Hydroxy) chloroquine	B	One small RCT in pulmonary disease; may be useful as a steroid-sparing agent[47]
Methotrexate	A	Steroid-sparing agent: one small RCT in pulmonary disease[48] and several case series in extra-pulmonary disease[49]
Azathioprine	B	Steroid sparing[50,51]
Mycophenolate	C	Steroid sparing[52,53]
Leflunomide	B	Steroid sparing[54,55]
Infliximab	A	Two RCTs demonstrating small effect in pulmonary disease; underpowered to demonstrate effect on extra-pulmonary manifestations[56,57]
Adalimumab	B	One small RCT in skin disease and case series pulmonary disease; lower rates of immunogenicity and allergy symptoms[58-60]

RCT = randomised controlled trial. * Level A: at least one double-blind, placebo-controlled trial with positive results with one or more case series supporting the results. Level B: majority of case series showing positive results. Level C: case series with mixed reports of effectiveness, or only a small number of cases reported. Levels of evidence as proposed by Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 2006; 129: 174-181. ◆

tumour necrosis factor-α. Overall, tumour necrosis factor-α inhibitors (eg, infliximab, adalimumab) have modest, beneficial effects; however, cost, side effects and limited effect discourage their use and these agents are used only after other agents have failed.[56] Studies to date are limited to a few placebo-controlled trials.[56-60] Other diseases should be excluded that could be activated with tumour necrosis factor-α suppression (eg, multiple sclerosis, tuberculosis). Infliximab may slightly increase vital capacity in patients with active, symptomatic stage 4 disease and may be helpful for patients with refractory neurosarcoidosis; however, randomised controlled trials are required.[62-65] Other agents such as anti-CD20 (rituximab) have yet to be studied in a controlled manner, but logically, an intervention that targets CD4 cells or the Th1 (and perhaps Th17) pathways would be of potential benefit. Problems include cost and availability.

Lung and other organ transplantation

Refractory and severe end-stage pulmonary sarcoidosis is an indication for consideration of lung transplantation. The subsequent immunosuppression usually protects the patient from disease recurrence, which has nonetheless been described in the donor organ.[2]

Prognosis

Overall, the prognosis for sarcoidosis is good, with more than 70% of patients eventually showing no evidence of disease activity, although residual changes may be seen on pulmonary radiology. A minority develop long term disease, which may prove difficult to manage, with later development of lupus pernio and other complications.

Future directions

Despite advances in our knowledge of sarcoidosis, the exact aetiology and immunopathogenesis of the disease remain ill-defined, and probably represent a reaction to several different antigens in a genetically susceptible host. It remains a diagnosis of exclusion with non-caseating granulomas on biopsy. Endobronchial ultrasound has aided diagnosis and whole body PET scanning has advanced disease localisation, but it would be ideal if the diagnosis could be made using non-invasive methods such as biomarkers that will be useful also for monitoring. There is also a need to improve the currently available treatments and to design new therapies with better efficacy and fewer side effects, especially if long term treatment is required. Better collaborative networks and a multidisciplinary approach would aid such important clinical research and trials.

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1 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), adapted by the ATS Board of Directors and by the ERS Executive Committee. *Am J Respir Crit Care Med* 1999; 160: 736-755.

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