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Editorial

Sarcoidosis: From Granulomatous Inflammation to Precision, Multidisciplinary Care

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Abstract

Background: Sarcoidosis is a heterogeneous, multisystem inflammatory disorder characterised by non-caseating epithelioid cell granulomas. Although pulmonary involvement is predominant, manifestations range from asymptomatic bilateral hilar lymphadenopathy to progressive pulmonary fibrosis, cardiac arrhythmias, neurological disability and potentially life-threatening complications.

Discussion: Despite advances in genetics, immunology, and imaging, sarcoidosis remains incompletely understood, with a limited set of biomarkers for predicting disease progression. Diagnosis requires compatible clinical findings, histological evidence when appropriate, and exclusion of other likely conditions. Management should be tailored according to symptoms, organs involved, risk of irreversible damage and treatment toxicity. Glucocorticoids remain a mainstay in the treatment, while steroid-sparing agents and biological therapies offer additional options. However, evidence remains limited for several extrapulmonary manifestations and long-term patient-centred outcomes.

Conclusion: Sarcoidosis should be approached as a spectrum of biologically distinct phenotypes. Multidisciplinary collaboration, risk-adapted treatment, and patient-reported outcomes are essential to advancing personalised care.

Keywords: *Sarcoidosis; Pulmonary Sarcoidosis; Immunomodulation; Extrapulmonary Manifestations; Granulomatous Inflammation; Multidisciplinary Care; Precision Medicine*

Introduction

Though sarcoidosis was first discovered and described in 1869 by the British surgeon and dermatologist Dr. Jonathan Hutchinson in London, it still remains a challenging condition mainly because its aetiology, course of progression, and optimal treatment are incompletely understood. Characterised by non-caseating granulomas, it can affect virtually any organ, particularly the lungs and intrathoracic lymph nodes [1]. Its course ranges from spontaneous resolution to chronic inflammation, irreversible organ dysfunction, and premature mortality.

This variable course of disease progression complicates diagnosis and treatment. Some patients require observation, whereas others need prolonged immunosuppression. Importantly, radiological abnormalities do not necessarily directly correspond to symptoms, functional impairment, or prognosis. Effective care must therefore identify patients at risk of progression and balance organ preservation against treatment-related harm.

Epidemiology and pathobiology

Sarcoidosis occurs worldwide, although incidence, presentation, and outcomes vary across populations because of genetic susceptibility, environmental exposures, demographic characteristics, and healthcare access [1,2]. It commonly presents during early or middle adulthood.

Current evidence suggests that genetically susceptible individuals develop dysregulated immune responses to unidentified environmental or microbial antigens. Familial aggregation, immune-regulatory gene associations, and occupational studies support genetic and environmental contributions, although no universal causative antigen has been established [1,2].

Granuloma formation involves antigen-presenting cells, macrophages, and activated T lymphocytes. Inflammatory mediators, namely, tumour necrosis factor and interferon-γ contribute to macrophage activation and granuloma maintenance [1]. In some patients, inflammation subsides while in others persistent immune activation promotes fibrosis and permanent damage.

These divergent outcomes suggest that sarcoidosis comprises biologically distinct inflammatory phenotypes. Identifying these endotypes could improve prognostication and enable mechanism-directed treatment.

Diagnosis: Clinical judgement is crucial

Diagnosis requires a compatible presentation and histological evidence of non-caseating (non-necrotizing) granulomas with exclusion of other likely causes [3]. Tuberculosis, fungal infections, occupational exposures, malignancy-associated reactions, and drug-related conditions have similar findings and are necessary differential diagnoses. Excluding infection is crucial before immunosuppression can be commenced in places where tuberculosis and endemic fungal diseases are widely prevalent.

Biopsy is not always necessary. A typical presentation such as Löfgren syndrome, may support the clinical diagnosis, while selected patients with asymptomatic bilateral hilar lymphadenopathy can undergo surveillance when diagnostic confidence is high [3]. When sampling is required, endobronchial ultrasound-guided lymph-node biopsy is useful.

Normally, assessment includes clinical history, physical examination, chest radiography, pulmonary function testing, total blood count, renal function, calcium, and liver function tests. The American Thoracic Society (ATS) recommends baseline electrocardiography for patients with extracardiac sarcoidosis, even without cardiac symptoms [3]. Further investigations should reflect clinical suspicion and the consequences of missing organ involvement.

Serum angiotensin-converting enzyme and soluble interleukin-2 receptor may provide supplementary information but cannot independently establish or exclude sarcoidosis. Diagnosis consequently depends on a combination of clinical, radiological, pathological, and microbiological findings.

Multisystem disease and risk stratification

Pulmonary involvement predominates, but sarcoidosis can affect the heart, nervous system, eyes, skin, kidneys, liver, and musculoskeletal system [1,4]. Pulmonary diseases ranges from asymptomatic bilateral hilar lymphadenopathy to pulmonary fibrosis, airflow obstruction, and pulmonary hypertension, which may be responsible for the consequent morbidity and mortality. Serial assessment of clinical symptoms and signs, pulmonary functions, and radiographic imaging help identify progression, although no individual finding adequately captures disease activity [5].

Cardiac sarcoidosis is particularly concerning because conduction abnormalities, ventricular arrhythmias, and ventricular dysfunction may precede recognition of systemic disease. Syncope, unexplained palpitations, or increasing breathlessness require urgent assessment.

Electrocardiography, echocardiography, cardiac magnetic resonance imaging, and fluorodeoxyglucose positron-emission tomography provide complementary information [3,5].

Neurological manifestations include cranial neuropathy, meningitis, myelopathy, and pituitary dysfunction. Ocular inflammation can threaten vision, while renal complications may arise from granulomatous inflammation or abnormal calcium metabolism [1,3].

The World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) organ assessment instrument supports systematic evaluation of organ involvement [4]. Nevertheless, identifying disease does not automatically justify treatment. Intervention depends on symptoms, progression, and the likelihood of irreversible damage. Even apparently limited disease may require urgent treatment when vital organs are threatened.

Treatment: Balancing potential benefits and harms

Treatment aims to improve quality of life by preserving organ function, relieving significant symptoms, and preventing death [5]. Observation is usually the appropriate course for many patients with mild disease and no significant organ dysfunction. Follow-up should depend on the clinical phenotype and disease trajectory.

Systemic glucocorticoids remain an important initial treatment for selected symptomatic or progressive cases. However, prolonged exposure increases risks of diabetes, hypertension, osteoporosis, infection, weight gain, and neuropsychiatric complications.

European Respiratory Society (ERS) guidelines support glucocorticoids for selected patients with pulmonary disease at substantial risk of mortality or permanent disability. Methotrexate may be considered when disease persists despite glucocorticoids or their adverse effects become unacceptable [5]. Other steroid-sparing agents, include azathioprine, mycophenolate mofetil, and leflunomide. They may be used depending on organ involvement, contraindications, and treatment response.

Tumour necrosis factor inhibitors, particularly infliximab, can be considered in selected refractory cases. Their efficacy varies, and infection risks require careful assessment [1,5].

Evidence remains limited for several extrapulmonary manifestations. Nevertheless, cardiac or neurological disease may require prompt treatment because delays can cause irreversible injury. Multidisciplinary decisions should reflect organ-specific risks rather than follow a uniform treatment sequence.

Treatment success extends beyond radiological improvement. Persistent symptoms may reflect irreversible damage, treatment toxicity, deconditioning, sleep disturbance, depression, or comorbidities rather than active inflammation. Distinguishing these contributors is essential before escalating immunosuppression.

Fatigue and quality of life

Fatigue is a frequent and debilitating manifestation that may persist despite apparently inactive disease. Breathlessness, sleep disturbance, mood changes, pain and cognitive difficulties further impair day-to-day functioning and social interaction [1,5].

Assessment should therefore extend beyond imaging and physiological measurements to include patient-reported symptoms, functional limitations, treatment burden, and personal choices. Management should therefore also include sleep assessment, rehabilitation, appropriate exercise, psychological support, and treatment of comorbidities.

Shared decision-making helps align treatment with patients' preferences and realistic expectations. Persistent fatigue should not automatically prompt intensified immunosuppression without evidence of ongoing inflammation.

International priorities and future directions

Progress towards precision medicine requires international prospective cohorts that clarify the natural history of different phenotypes. Harmonised registries could reduce inconsistencies arising from variable diagnostic criteria, referral patterns, outcome measures, and healthcare access.

Research should identify biomarkers distinguishing active inflammation from established fibrosis and predicting treatment response. Integrating clinical data with genomic, transcriptomic, proteomic imaging may reveal actionable disease subgroups. They combine high-throughput molecular profiling with spatial visualization to map genes, RNA transcripts, and proteins directly within tissue architecture and cells.

Clinical trials should prioritise organ preservation, reduced glucocorticoid exposure, fatigue, physical functioning, quality of life, and long-term safety. International collaboration is particularly important for recruiting sufficient participants with rare, severe manifestations.

Equitable progress also requires addressing disparities in diagnostic capacity, specialist access, and treatment availability. Recommendations developed in high-income settings may not translate directly to regions where infectious granulomatous diseases are prevalent or advanced imaging is unavailable. Locally appropriate pathways and international partnerships are therefore essential.

Conclusion

Sarcoidosis is a clinically complex disorder which is characterised by variable progression, multisystem involvement, uncertain aetiology, and imperfect biomarkers. Uniform diagnostic and therapeutic strategies cannot adequately address this diverse set of characteristics.

Effective management requires assessing organ involvement, irreversible damage risk, potential spontaneous improvement, and treatment toxicity. Multidisciplinary collaboration, longitudinal reassessment, and meaningful patient participation remain central to care.

Future research must connect biological mechanisms with clinical phenotypes and treatment responses. Until precision approaches become established, individualised, risk-adapted management remains fundamental to improving outcomes.

Bibliography

1. Grunewald J., *et al.* "Sarcoidosis". *Nature Reviews Disease Primers* 5.1 (2019): 45.
2. Iannuzzi MC., *et al.* "Sarcoidosis". *New England Journal of Medicine* 357.21 (2007): 2153-2165.
3. Crouser ED., *et al.* "Diagnosis and Detection of Sarcoidosis: An Official American Thoracic Society Clinical Practice Guideline". *American Journal of Respiratory and Critical Care Medicine* 201.8 (2020): e26-e51.
4. Judson MA., *et al.* "The WASOG Sarcoidosis Organ Assessment Instrument: An Update of a Previous Clinical Tool". *Sarcoidosis Vasculitis and Diffuse Lung Diseases* 31.1 (2014): 19-27.
5. Baughman RP., *et al.* "ERS Clinical Practice Guidelines on Treatment of Sarcoidosis". *European Respiratory Journal* 58.6 (2021): 2004079.

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