PRIMEVIEW

SARCOIDOSIS

nature REVIEWS DISEASE PRIMERS

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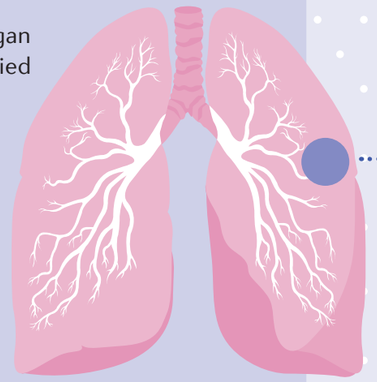
Sarcoidosis is an inflammatory disorder that occurs in genetically susceptible individuals exposed to an unknown antigen. The disease involves granuloma formation in affected organs, which can lead to fibrosis and irreversible organ damage. The lungs are most commonly affected (in ≥90% of cases), although cardiac, brain, skin and eye involvement also occurs.

DIAGNOSIS



Sarcoidosis is a multiorgan disorder with highly varied symptoms that may not always be attributable to the specific organ involved. No simple diagnostic test exists, and a confident diagnosis usually requires a complete multi-system assessment by a multidisciplinary team, as only 15% of patients are correctly diagnosed at first presentation. Diagnosis generally relies on compatible clinical symptoms, histological and/or radiological evidence of non-necrotizing granulomas and exclusion of differential diagnoses.

Imaging methods, such as PET, MRI and high-resolution CT, are useful to detect granulomas and assess disease extent. For extrapulmonary involvement, biopsy is a simple, safe method for histological confirmation of a diagnosis. Laboratory tests are useful to detect organ involvement but do not have diagnostic value.

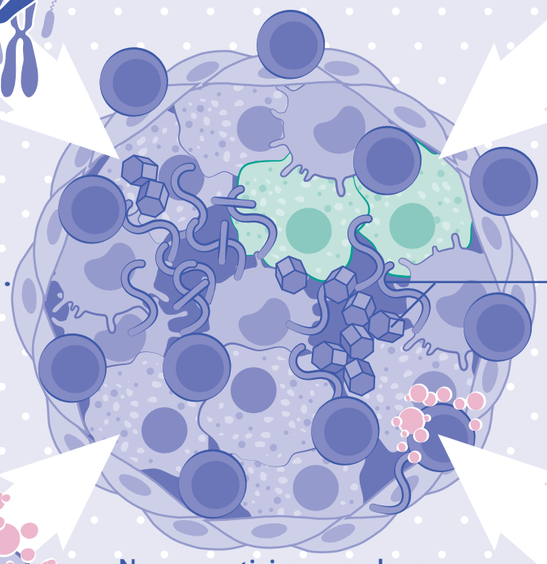
The natural history includes self-limiting, chronic but stable, or chronic and progressive disease.

PATHOPHYSIOLOGY

Sarcoidosis is triggered by unknown environmental agents interacting with genetic, epigenetic and environmental factors

Genetic, environmental (such as infectious agents) and lifestyle factors (such as obesity) all contribute to risk of the disease

Macrophages differentiate into epithelioid cells via mTORC1 upregulation, contributing to granuloma formation



Antigens

Non-necrotizing granuloma

Cytokine

An innate immune response is initiated in which macrophages or dendritic cells are activated and release cytokines that regulate adaptive immunity

An exaggerated T helper 1 cell response occurs and cytokine levels are increased in granulomas

EPIDEMIOLOGY

The prevalence and incidence of sarcoidosis varies substantially by region, sex, ethnicity and age of onset. The incidence is highest in Scandinavia and amongst African-Americans and is lowest in Asia. The average age of onset is 40–50 years of age, but the peak of diagnosis occurs at a younger age in men than in women (30–50 years versus 50–60 years of age).

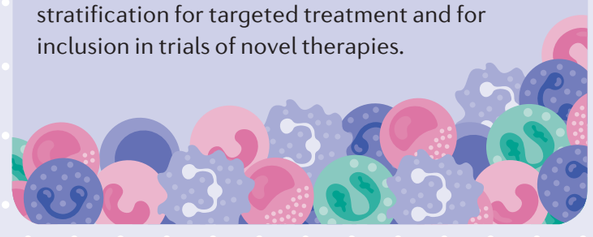
Löfgren syndrome, an acute form of sarcoidosis, comprises about one-third of cases in Sweden and incidence is much higher in white individuals than in black or Asian individuals.

MANAGEMENT

Deciding when and whether to initiate treatment is difficult, owing to the unpredictable disease course (even advanced disease can resolve spontaneously) and heterogeneity of disease severity and presentation. Inflammation is usually treated with corticosteroids, whereas specific therapies are required for permanent defects, such as supplemental oxygen for respiratory insufficiency or desmospressin treatment for diabetes insipidus. Distinguishing between symptoms caused by inflammation and those caused by permanent, non-progressing defects is crucial to ensure targeted treatment. Tapering is important to avoid adverse effects of pharmacological therapy but requires careful monitoring of disease activity to prevent harm.

OUTLOOK

As the aetiology of sarcoidosis is unknown, efforts to identify antigens that initiate inflammation are needed and various ‘omics’ technologies should prove useful. Furthermore, a better understanding of the involvement of immune cells (both innate and adaptive), the interactions between them and the inflammatory mediators they produce in granuloma formation, resolution and/or persistence will be crucial for identifying new biomarkers to improve diagnosis and prognosis and new therapeutic targets. Dissecting the unique combinations of genetic variants, phenotypic traits and environmental factors that produce distinct clinical presentations will enable better patient stratification for targeted treatment and for inclusion in trials of novel therapies.



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