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Sarcoidosis

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Abstract | Sarcoidosis is an inflammatory disorder of unknown cause that is characterized by granuloma formation in affected organs, most often in the lungs. Patients frequently suffer from cough, shortness of breath, chest pain and pronounced fatigue and are at risk of developing lung fibrosis or irreversible damage to other organs. The disease develops in genetically predisposed individuals with exposure to an as-yet unknown antigen. Genetic factors affect not only the risk of developing sarcoidosis but also the disease course, which is highly variable and difficult to predict. The typical T cell accumulation, local T cell immune response and granuloma formation in the lungs indicate that the inflammatory response in sarcoidosis is induced by specific antigens, possibly including self-antigens, which is consistent with an autoimmune involvement. Diagnosis can be challenging for clinicians because of the potential for almost any organ to be affected. As the aetiology of sarcoidosis is unknown, no specific treatment and no pathognomic markers exist. Thus, improved biomarkers to determine disease activity and to identify patients at risk of developing fibrosis are needed. Corticosteroids still constitute the first-line treatment, but new treatment strategies, including those targeting quality-of-life issues, are being evaluated and should yield appropriate, personalized and more effective treatments.

Sarcoidosis is an inflammatory disease characterized by the presence of granulomas (abnormal lumps of inflammatory cells) in virtually any organ, although the lung is the most common site. Consequently, sarcoidosis has many different clinical phenotypes (distinct clinical presentations that result from a combination of genetic variants and/or the influence of environmental factors), and the disease course can vary — many patients recover, even without treatment, whereas others develop chronic inflammation and fibrosis. Löfgren syndrome is a well-characterized acute form of sarcoidosis in which patients at disease onset usually have fever, bilateral ankle arthritis (typically in men) and/or erythema nodosum (typically in women) and bilateral hilar lymphadenopathy on chest radiography[1,2]. Sarcoidosis often substantially affects quality of life (QOL), decreases work ability and increases mortality.

The incidence is highly variable and depends on sex, age and ethnicity. The seasonal and geographic variation in incidence indicates an influence of unknown agents, possibly including microorganisms, environmental factors and/or inorganic materials, which trigger inflammation in genetically predisposed individuals. Genetic factors clearly have an important role in the aetiology of sarcoidosis, as disease risk is considerably higher in first-degree relatives of patients with sarcoidosis. Human leukocyte antigen (HLA) alleles and variants of other genes, such as *TNF*, may also be associated with the disease course and predict the prognosis.

Sarcoidosis is characterized by the accumulation of activated T helper cells in the lungs and the formation of non-necrotizing epithelioid cell granulomas, which suggests that a specific antigen or antigens trigger an immune reaction. In a subgroup of patients, the accumulated T cells in the lungs express identical T cell receptors (TCRs), which suggests that these patients were exposed to an identical antigen. Microorganisms or their non-degradable remnants (for example, *Mycobacterium tuberculosis* or *Cutibacterium acnes* (formerly *Propionibacterium acnes*)) might act as triggers, albeit in different ways. For example, molecular mimicry (similarity between microorganismal and human proteins) may cause autoimmune reactions that contribute to sarcoidosis. The autoimmune hypothesis is supported by the detection of vimentin-directed TCRs and anti-vimentin antibodies in patients with sarcoidosis and by reports of cross reactivity of human antibodies with mycobacterial and human heat shock proteins (HSPs)[3].

New techniques, such as ^{18}fluor-fluorodeoxyglucose-PET (^{18}F-FDG-PET) and cardiac MRI, are being developed to improve diagnosis and to evaluate disease activity. As we gradually learn more about antigen exposure, genetic predisposition and immune responses,

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we are certainly entering a new era of personalized and hopefully more effective treatment of sarcoidosis.

In this Primer, we discuss new and important findings about the epidemiology of sarcoidosis, as well as immune abnormalities and genetic influences that are considered to be important in the pathophysiology of sarcoidosis. Furthermore, we discuss methods for screening and diagnosis of sarcoidosis, some of the different clinical phenotypes of the disease, how to manage them and which patients to treat. Last, we discuss how QOL in patients with sarcoidosis seems to be more severely affected than previously thought.

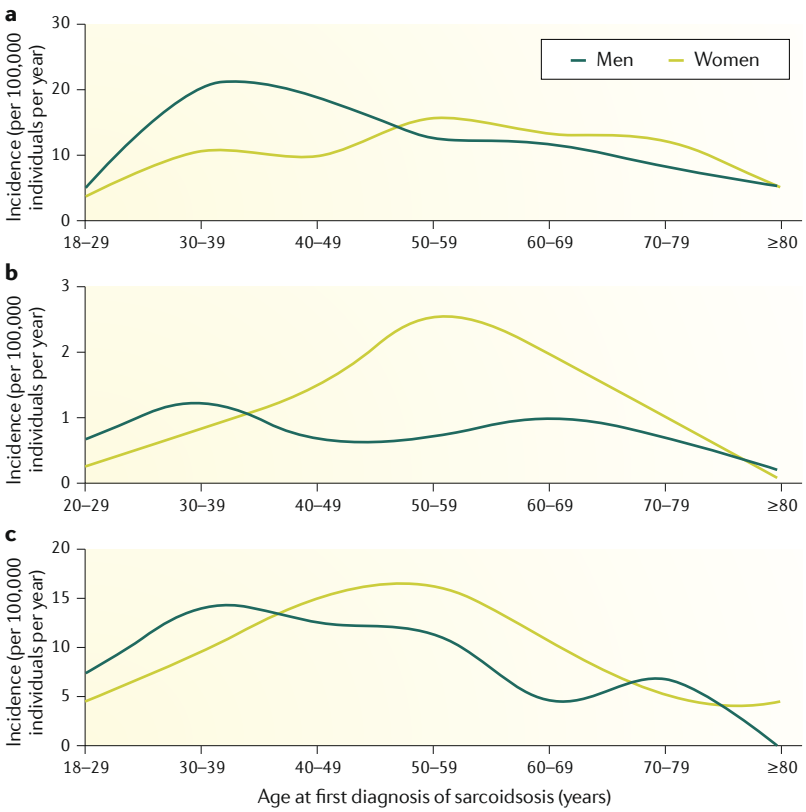

Fig. 1 | **Incidence of sarcoidosis.** Graph of sarcoidosis incidence per 100,000 individuals per year by age at diagnosis in (part **a**) Sweden[5] (2003–2012, *n* = 8,395), (part **b**) Korea[12] (2009–2015, *n* = 2,981) and (part **c**) Olmsted County, Minneapolis, MN, USA[48] (1946–2013, *n* = 448).

Epidemiology

Incidence and prevalence

The incidence and prevalence of sarcoidosis and its clinical presentation vary greatly across geographical regions and between the sexes and different ethnicities and age groups[4]. The incidence of sarcoidosis is highest in Scandinavian countries (11–24 cases per 100,000 individuals per year)[5–7] and among African Americans (18–71 cases per 100,000 individuals per year)[8–10] and lowest in Asian countries (1 case per 100,000 individuals per year)[11,12]. Within countries, the distribution of sarcoidosis varies by geographical region[8,10,13,14], and some studies have found that the prevalence is higher in less densely populated areas[5,15]. The average age of onset is 40–55 years of age, with a younger peak age at diagnosis in men (30–50 years of age) than in women (50–60 years of age), a pattern that is confirmed by several reports in different regions (FIG. 1). Between 45% and 60% of incident cases occur in women[16].

The clinical manifestations of sarcoidosis vary depending on patient characteristics. Low income and financial barriers to care are associated with more severe disease at diagnosis[17]. African Americans have more severe disease at diagnosis and are more likely to have advanced pulmonary involvement or multiple organ involvement[4,18,19] than individuals of other ethnicities.

Löfgren syndrome has the highest reported incidence in white individuals and is rarely diagnosed in black or Asian individuals. In Sweden, Löfgren syndrome comprises about one-third of all sarcoidosis cases, and patients usually have the *HLADRB1*03* (HLA-DR3) allele and have a good prognosis, with remission in 70–80% of these patients[20].

Risk factors

Genetic factors. Genetic susceptibility is an important component of disease risk, as demonstrated by genome-wide association studies[21,22] with the HLA class II alleles, several non-HLA genes and familial aggregation studies[23–25]. Having a family member with the disease is associated with a 2–4-fold increased risk of developing sarcoidosis[24,25], and the risk increases as the number of affected relatives increases[24]. A study involving twins from Denmark and Finland reported concordance rates of 0.148 in monozygotic twins and 0.012 in dizygotic twins[26]. The heritability of sarcoidosis (the proportion of a population's phenotypic variance that is attributable to genetic variation) is estimated to be 39–70%[24,26,27].

Environmental and lifestyle factors. In addition to genetic risk factors, non-genetic or environmental factors are also associated with sarcoidosis. The ACCESS study in the USA investigated environmental and occupational factors retrospectively via questionnaire[28] and identified multiple environmental exposures that are associated with sarcoidosis, including mouldy environments, occupational exposure to insecticides and agricultural employment. Other occupations have been implicated as risk factors, including iron foundry workers (from exposure to silica dust)[29] and firefighters[30,31]. In addition, rescue workers from the World Trade Center

Table 1 | **Radiographic types of sarcoidosis**

Radiographic type	Radiographic characteristics	Prognosis
0	No visible findings	Not applicable
I	Bilateral hilar lymphadenopathy	Spontaneous resolution in most cases
II	Bilateral hilar lymphadenopathy and parenchymal infiltration	Spontaneous resolution possible
III	Parenchymal infiltration without hilar adenopathy in regular chest radiography	Spontaneous resolution in rare cases
IV	Advanced fibrosis with evidence of honeycombing bronchiectasis, hilar retraction, bulla and cysts	Permanent organ damage

Based on classification of thoracic disease in REF.[150].

disaster were shown to be at risk of developing a 'sarcoidosis-like pulmonary disease' that includes the formation of non-necrotizing epithelioid granulomas[32–34]. An infectious agent may trigger sarcoidosis, and several studies observed an increased prevalence of microorganism DNA and protein antigens in samples from patients with sarcoidosis, although all of these studies were cross-sectional[35]. Together, many studies suggest that inhaled environmental factors, such as microbial bioaerosols, and possibly inorganic materials, may induce sarcoidosis.

Smoking has consistently been associated with a decreased risk of sarcoidosis, possibly owing to the immunomodulatory effects of nicotine[28,36–38]. However, all but one of these studies collected smoking status at the time of a sarcoidosis diagnosis, which may have introduced reverse causation bias (the disease causing people to stop smoking and/or report to be non-smokers). However, in a study in which smoking data were collected before diagnosis and were thus unaffected by this bias, ever smoking was associated with 50% lower risk of sarcoidosis[36]. In this study, nicotine-containing smokeless tobacco was not associated with risk reduction, suggesting that a component of cigarette smoke other than nicotine exerts a protective role[36].

In two large cohort studies of women in the USA, obesity and weight gain were associated with increased risk of sarcoidosis[39,40]. In the Black Women's Health Study (n = 59,000), obesity was associated with a 40% increased risk of sarcoidosis, and in the Nurses' Health Study II (predominately white women; n = 116,430), obesity was associated with 70% increased risk. Both of these studies reported a relationship between a higher body mass index at 18 years of age and increased sarcoidosis incidence in later life[39,40]. These findings add to the growing body of literature on the relationship between obesity and immune-mediated disorders[41].

In the Black Women's Health Study, markers of higher endogenous oestrogen (such as later age at menopause, later age at first birth and having a more recent birth) were associated with a decreased risk of sarcoidosis[42]. The observation that women are more often diagnosed with sarcoidosis later in life (50–60 years of age; FIG. 1) than men may be due to hormonal changes around the time of menopause.

Comorbidities and mortality

Epidemiological studies show that sarcoidosis is not a benign disease for many patients but instead that they suffer from a high burden of the disease[43] and show excess mortality[44–47]. The global sarcoidosis mortality is 9–14 cases per 1,000 person-years and 5-year survival is 93–95%[44–48]. Mortality risk is increased by 60% in Sweden[46], 70% in Korea[45], 2-fold in the UK[44] and 2.4-fold in black American women[47]. Mortality is higher in individuals with more severe disease at diagnosis, as shown in a French study of patients with stage IV sarcoidosis (HR 3.6)[49] (see below and TABLE 1 for staging of sarcoidosis). In a population-based study from Sweden, starting treatment around the time of diagnosis was used as a proxy for disease severity and was associated with greater than twofold higher risk of death (HR 2.34; FIG. 2). Some studies have observed an increased relative risk (RR) of death in men compared with women with sarcoidosis[37,44,45].

Sarcoidosis is associated with increased risk of infection (HR 2.13; further increased in patients on immunosuppressive treatment)[50], congestive heart failure (HR 1.7–2.7)[51,52], cerebrovascular accident (HR 3.3)[52], venous thromboembolism (HR 2–4)[53,54] and autoimmune disease (specifically, autoimmune thyroiditis (HR 1.3), Sjogren syndrome (HR 11.6), ankylosing spondylitis (HR 3.8) and systemic lupus erythematosus (HR 3.0)[55]). In a systematic review and meta-analysis of 16 studies, sarcoidosis was associated with an increased risk of haematological cancers (RR 1.92), skin cancers (RR 2.00), upper digestive cancer (RR 1.73), kidney cancer (RR 1.55), liver cancer (RR 1.79) and colorectal cancer (RR 1.33)[56]. Few studies have addressed the role of glucocorticoids and other immunosuppressive treatments in causing sarcoidosis comorbidities. Teasing apart disease activity and the effects of treatment (and thus adjusting for confounding by indication) is challenging, especially when disease activity measures are not available.

Mechanisms/pathogenesis

The pathological hallmark of sarcoidosis is the presence of compact, epithelioid, non-necrotizing granulomas with varying degrees of lymphocytic inflammation[57]. The sarcoidosis-type granuloma alone is never diagnostic of sarcoidosis, as these lesions occur in multiple other diseases, such as cancer (near tumours), infectious granulomatous diseases, chronic beryllium disease (CBD) and inflammatory responses to inorganic foreign material, such as talc or zirconium[57]. Studies suggest that sarcoidosis probably results from exposure to an unknown antigen or antigens in genetically predisposed individuals. As patients with Löfgren syndrome share a specific genetic background (HLA-DR3), distinct clinical features and a specific, local immune response, this phenotype might be useful to elucidate the cause of sarcoidosis. However, despite extensive research, the aetiology of sarcoidosis remains unknown. Most researchers agree that genetic factors, an environmental exposure and a seemingly dysregulated immune system characterized by an exaggerated T helper 1 (T_H1) immune response are involved in causing sarcoidosis.

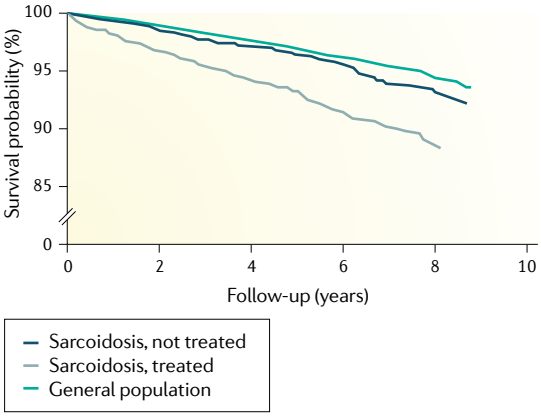

Fig. 2 | **Survival in sarcoidosis.** Graph of survival probability after follow-up[46] showing decreased probability of survival in patients who are in need of treatment compared with patients who do not need treatment and the general population. Adapted from REF.[46], CC-BY-4.0 https://creativecommons.org/licenses/by/4.0/.

Immunological hallmarks

In the 1960s and early 1970s, clinical observations of peripheral blood lymphopenia and cutaneous anergy (no delayed hypersensitivity skin reaction to antigens such as purified protein derivative (PPD)) in most patients suggested that sarcoidosis was the result of a T cell deficiency. However, the advent of flexible bronchoscopy and bronchoalveolar lavage (BAL) in the late 1970s led to the discovery of greatly expanded populations of lymphocytes in the lungs and affected tissues of patients with pulmonary sarcoidosis. Subsequent studies over the next >40 years reported that this expanded lymphocyte population comprised predominantly CD4-positive ($CD4^+$) T helper cells, which may differentiate into T_H1 and $T_H17.1$ effector cells that produce IFNγ and T_H17 cells that produce IL-17 (REFS[58–60]). Pro-inflammatory cytokines, such as tumour necrosis factor (TNF), IL-12, IL-18 and IL-6, and regulatory cytokines, such as transforming growth factor-β (TGFβ) and IL-10, are also upregulated in affected tissues. A highly exaggerated, polarized T_H1 cell and $T_H17.1$ cell-mediated inflammatory response and reduced expression of cytotoxic T lymphocyte antigen 4 (CTLA4) on BAL fluid and mediastinal lymph node cells, especially in patients with non-Löfgren syndrome sarcoidosis, are seen in sarcoidosis[58,61,62]. The role of T_H17 cells in sarcoidosis inflammation is less well defined, but these cells may be important in determining clinical phenotype, as higher T_H17 cell abundance has been associated with Löfgren syndrome[62,63]. The exaggerated effector T cell responses are associated with regulatory T (T_{reg}) cell and invariant natural killer T cell (iNKT cell) deficiencies in number and function[57,64,65]. Whether these deficient T_{reg} cell responses are primary or secondary to local persistent antigenic stimulation remains unclear (FIG. 3). Most interestingly, inhalation of vasoactive intestinal peptide (VIP) can correct T_{reg} cell dysfunction in patients with sarcoidosis[66].

Further evidence for an exaggerated T_H1 and $T_H17.1$ immune response includes the upregulation of the T_H1 transcription factors TBX21 and signal transducer and activator of transcription 1 (STAT1) and of IFNγ-inducible chemokines and chemokine receptors. IFNγ is key for the activation of the Janus kinase (JAK)–STAT signalling pathway, and STAT1-dependent transcripts are characteristically found in the transcriptome of blood cells, lung tissues and lymph nodes of patients with sarcoidosis[67–70]. The STAT3 signalling pathway is important in T_H17 cell differentiation and probably has a role in sarcoidosis pathology and fibrosis[71]. Inhibitors of JAK–STAT signalling are now used with promising results for the treatment of patients with refractory clinical phenotypes[72,73].

A pivotal role for $CD4^+$ T cells in granuloma formation is supported by the observation that HIV infection and subsequent $CD4^+$ lymphopenia leads to remission of sarcoidosis[74]. By contrast, in HIV-positive patients treated with highly active anti-retroviral therapy (HAART), who thereby recover $CD4^+$ T cell counts to >200 μl^{-1}, a sarcoidosis-like granulomatous disorder or recurrent sarcoidosis may develop as part of an immune reconstitution syndrome[75,76]. However, at present, it is not possible to establish whether these patients develop sarcoidosis because of increased T_H1-driven inflammation due to increased production of cytokines, such as IL-2, IFNγ, IL-12, IL-18 and TNF (as part of an immune reconstitution syndrome).

Innate immune responses are crucial in the pathogenesis of sarcoidosis but are less well studied than adaptive immunity. Presumably, the agents that trigger sarcoidosis stimulate macrophages and dendritic cells to respond in a pathological way, which results in sarcoidosis-type granulomas depending on genetic, epigenetic and environmental factors (FIG. 3). Major histocompatibility complex (MHC) expression is upregulated in these cells, and they produce cytokines that determine the type of adaptive immune response. Activated macrophages can transform into epithelioid cells that can coalesce into multinucleated giant cells. Furthermore, sarcoidosis is associated with activation of the metabolic checkpoint kinase mechanistic target of rapamycin complex 1 (mTORC1), which induces this differentiation step and mediates granuloma persistence in progressive disease[77]. A role for innate immune signalling pathways, including those mediated by Toll-like receptors (TLRs), NOD-like receptors (NLRs), HSPs and receptor for advanced glycation end products (RAGE), is supported by genetic and immunological studies[78–80]. Chronic cytokine stimulation can result in fibrosis in granulomas, typically in a circumferential pattern initially but coalescing thereafter, which alters organ structure and function[57].

Increased accumulation of serum amyloid A (SAA) proteins by resident macrophages and subsequent local aggregation of SAA in granulomas was proposed to promote feedforward amplification of T_H1 immune responses to local tissue antigens in sarcoidosis[81,82]. Given the lack of clinical or microbiological evidence for an active replicating infection in granulomas, this mechanism provides an alternative explanation for the chronic, slowly progressive inflammation in untreated sarcoidosis (FIG. 3). SAA is a highly induced, acute phase reaction protein and its upregulation is not specific to

sarcoidosis but occurs in many diseases, such as AA amyloidosis, tuberculosis, rheumatoid arthritis (RA) and sepsis, although SAA might have different mechanistic roles in these diseases.

Immune cells in the lungs differ considerably from those in blood; for example, they usually express higher levels of markers of activation[83,84]. Furthermore, the expression of several immune-regulating factors differs between patients with Löfgren syndrome and those with other forms of sarcoidosis[85]. For example, studies have reported higher expression of inducible co-stimulator (ICOS)[86] and production of IL-10 (REF.[87]) in T_{reg} cells from patients with Löfgren syndrome than from those with other forms of sarcoidosis, suggesting that the immune response is more self-restrictive in patients with Löfgren syndrome. Conversely, a shift towards a purely effector-driven immune response seems to occur in other forms of sarcoidosis, exemplified by a reduction in T cell immunoglobulin mucin domain (TIM) molecules, which might disrupt the normal regulation of T_H1 responses[88].

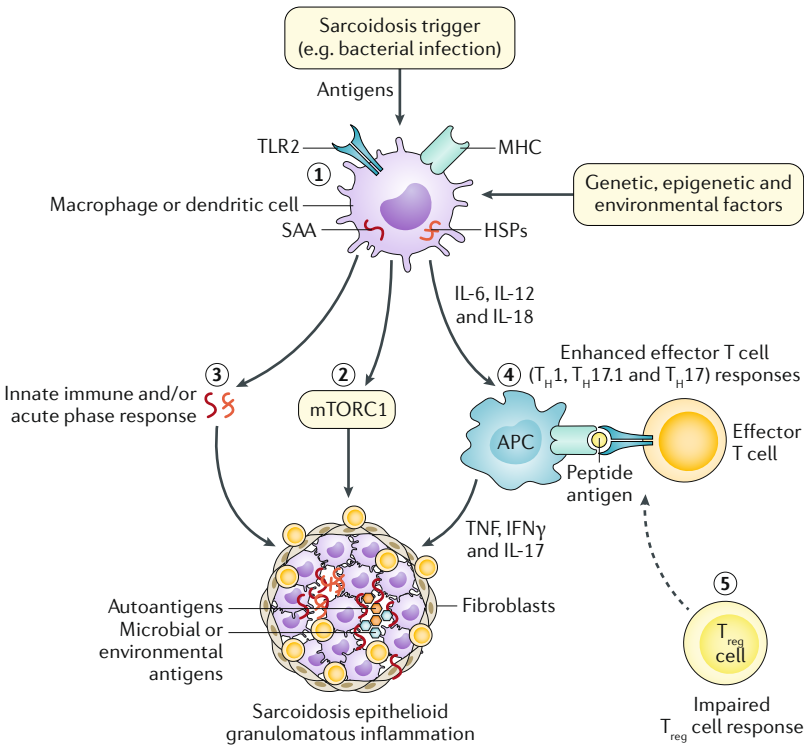

Fig. 3 | **Immunological features of granuloma formation in sarcoidosis.** Sarcoidosis is triggered by environmental agents, primarily mycobacterial infections. Genetic, epigenetic and environmental factors interact with environmental triggers to result in the following: innate immune activation of macrophages and dendritic cells, which have upregulated major histocompatibility complex (MHC) expression and express cytokines that direct the phenotype of the adaptive immune response (step 1); upregulation of the mechanistic target of rapamycin complex 1 (mTORC1) pathway leading to differentiation of epithelioid cells (activated macrophages that resemble epithelial cells) and changes in metabolic and immune pathways (step 2); upregulation of serum amyloid A (SAA) and heat shock proteins (HSPs) as part of an acute phase response (step 3), followed by SAA aggregation in granulomas, which promotes enhanced effector T cell responses, in part through innate immune receptors, such as Toll-like receptor 2 (TLR2); an enhanced T cell response to pathogenic tissue antigens, which in the presence of IL-12, IL-18, IL-6 and transforming growth factor-β (TGFβ) promotes polarization of T helper 1 (T_H1), T_H17 and $T_H17.1$ responses in affected sites (step 4); and an impaired regulatory T (T_{reg}) cell response (dashed arrow; step 5) allows enhanced local effector T cell responses to tissue antigens to persist, resulting in chronic sarcoidosis. APC, antigen-presenting cell; TNF, tumour necrosis factor.

Antigens

Sarcoidosis-specific antigens. The accumulation of T_H cells in the lungs, due to local recruitment of T cells in response to foreign or self-antigens, and the formation of non-necrotizing granulomas, which is an immune mechanism to isolate a potentially non-degradable antigen, are both classical features of sarcoidosis (FIG. 4). However, granuloma formation could also function as a trap for infectious agents, such as *Mycobacteria* spp., as the granulomatous environment itself is 'sticky' and could confine infected cells that may contribute to a prolonged immune response and possibly account for the presence of bacterial remnants without clinical signs of infection[89]. Regardless, granulomas are believed to initiate chronic inflammation and (pulmonary) fibrosis. Identifying the factors that determine whether granulomas persist (and lead to fibrosis) or resolve is of substantial interest (FIG. 5).

T cells that accumulate in the lungs of patients with sarcoidosis express a restricted set of variable (V) gene segments of the TCR, such as β-chain variable segment 8 (TRBV8) and α-chain variable segment 2.3 (TRAV2.3)[90,91]. In patients with Löfgren syndrome in particular, these TRAV2.3$^+$ T cells are extremely abundant (15–35% of all BAL fluid T_H cells)[92], and there is an association between their abundance and a good prognosis[93]. Furthermore, BAL fluid from the lungs of HLA-DR3$^+$ patients with sarcoidosis contains T_H cells with TRAV2.3 and TRBV22 (REF.[94]), which are highly clonal and with identical nucleotide sequences in different patients[95,96]. Consequently, T_H cells with specific TCR pairings and identical sequences might recognize disease-specific antigenic peptides that are presented by specific HLA molecules. Consistent with this idea, a number of antigens, including possible self-antigens such as peptides derived from ATP synthase, lysyl-tRNA synthetase and vimentin, have been identified in BAL samples from HLA-DR3$^+$ patients with sarcoidosis[97,98].

In the 1940s, Nickerson and Kveim reported that 3–6 weeks after intradermal injection of an insoluble homogenate of sarcoidosis lymph node tissue, delayed formation of a cutaneous nodule containing granulomas occurred[99]. Injection of the Kveim–Siltzbach reagent, which was prepared from spleen tissue of affected patients with sarcoidosis, showed that 70–80% of untreated patients worldwide, but not individuals with non-sarcoidosis-related diseases or healthy individuals, developed a granulomatous skin reaction[100]. This test was used in some centres as a diagnostic skin test until the 1990s, when it was discontinued owing to the risk of transferring infections. However, the use of this mixture of undefined, granuloma-derived, non-degradable proteins for diagnostic purposes suggests that unknown components of the Kveim–Siltzbach reagent are involved in the disease process and can serve as an in vivo experimental model of sarcoidosis granulomatous inflammation[101–103].

Vimentin. The intermediate filament protein vimentin is an important constituent of the cytoskeleton, is expressed predominantly by mesenchymal cells[104] and is secreted by activated macrophages[105], which are abundant in sarcoidosis granulomas. Vimentin has been eluted from HLA-DR molecules on cells in BAL samples from patients with sarcoidosis, especially those with Löfgren syndrome[98,106]. Identical TCR sequences were identified in T cells from BAL samples from different patients, strongly indicating that the immune response in these patients is triggered by the same antigen. Structural modelling of these TCR sequences with the HLA-DR3 protein sequences revealed an ideal fit of a vimentin carboxy-terminal peptide in the peptide-binding cleft, including connections with all four HLA binding pockets, implicating vimentin as a potential autoantigen in sarcoidosis. Furthermore, vimentin peptides stimulate IFNγ production by T cells derived from HLA-DR3$^+$ patients with sarcoidosis[107]. Interestingly, vimentin in the Kveim–Siltzbach reagent promotes IFNγ production by T cells[102].

In addition, vimentin-specific antibodies were identified in the BAL fluid of patients with sarcoidosis, especially HLA-DR3$^+$ patients. These anti-vimentin antibodies preferentially bind to the carboxy-terminal end of vimentin, whereas antibodies from healthy individuals preferentially bind to the amino-terminal end[108]. There was also a correlation between the percentage of TRAV2.3$^+$TRBV22$^+$CD4$^+$ T cells in BAL fluid and the production of specific anti-vimentin antibodies, which is consistent with recognition of the vimentin peptide by TRAV2.3$^+$TRBV22$^+$CD4$^+$ T cells when presented by HLA-DR3 molecules[95,108]. Vimentin is also implicated as a self-antigen in other autoimmune disorders, such as RA[109] and systemic lupus erythematosis[110], in which the titre of anti-vimentin antibodies correlates with disease severity[110]. Future investigations should elucidate the role of vimentin in sarcoidosis aetiology; for example, molecular mimicry after an infection or an environmental exposure might drive anti-vimentin reactivity[111].

Environmental non-microbial factors. There are multiple reports of 'immunotherapy-induced sarcoidosis' in individuals treated with immune-stimulating agents or biologics, such as IFNα (in malignancy or chronic hepatitis C virus infection), IFNγ (in psoriasis) and immune checkpoint inhibitors, including anti-CTLA4, anti-PD1 and anti-PDL1 antibodies and BRAF inhibitors (TABLE 2). The histopathology of the sarcoidosis-like granulomatous disease in these individuals is identical to that in sarcoidosis[112–117]. However, consensus is lacking about whether these cases represent sarcoidosis or sarcoidosis-like drug reactions[118]. Reduced expression of CTLA4 on CD4$^+$ T cells in patients with sarcoidosis, especially in those with non-Löfgren syndrome forms of the disease, has been reported[119]. Retained CTLA4 and PD1 expression in HLA-DR3$^+$ patients with Löfgren syndrome, who are known to have a particularly good prognosis, is consistent with the central importance of the balance between immune activation and regulation in sarcoidosis inflammation. In addition, blockade of the PD1 pathway restores the proliferative capacity of CD4$^+$ T cells from patients with sarcoidosis[120]. To control the immune response to persistent tissue self-antigens, PD1 could be upregulated in sarcoidosis, as occurs in CBD, a granulomatous pneumonitis caused by inhalation of beryllium, which is often misdiagnosed as sarcoidosis[121,122]. Thus, downregulating peripheral tolerance using anti-CTLA4 or anti-PD1 antibodies may propagate sarcoidosis inflammation, regardless of antigen specificity[123–127]. As sarcoidosis-like drug reactions occur in only a small percentage of patients who receive these therapies, it is likely that a second trigger initiates granuloma formation. Biological therapies, such as anti-TNF agents (etanercept, infliximab and adalimumab), have rarely been associated with new onset of recurrent sarcoidosis (or sarcoidosis-like reactions). Whether these agents are causally linked to the occurrence of a dysregulated immune response or are ineffective in preventing the natural onset of sarcoidosis remains unclear[118].

Infections

Microorganisms may trigger specific immune responses against distinct microbial and self-antigens, such as occurs in rheumatic fever, in which a group A *Streptococcus* infection through molecular mimicry generates an autoimmune response against joints, skin and heart[128]. Several reports of seasonal variation in the incidence of sarcoidosis support the involvement of microorganisms in the pathogenesis of sarcoidosis, given

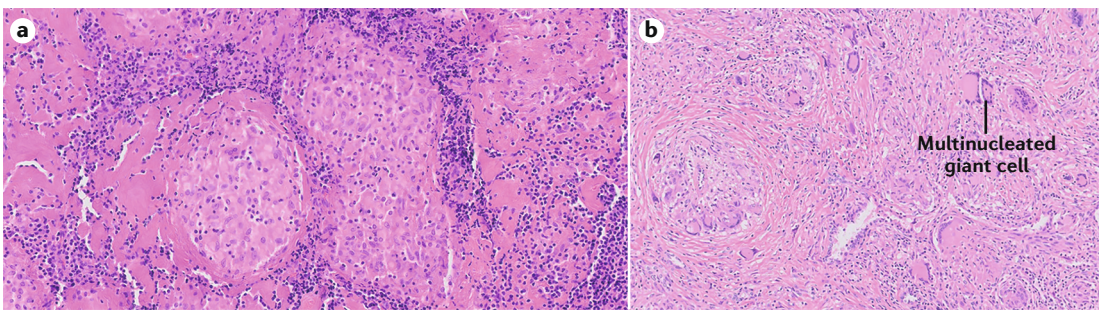

Fig. 4 | **Histology of lymph node and granuloma in sarcoidosis. a** | Biopsy specimen taken from an enlarged mediastinal lymph node showing non-necrotizing granulomas in a patient with radiographic type I sarcoidosis on chest radiograph. Magnification 200×. **b** | Specimen from a consolidated mass in the lung of a patient with pulmonary sarcoidosis, showing non-necrotizing granulomas with multinucleated giant cells. Magnification ×100. Biopsy samples in both panels are stained with haematoxylin and eosin. Images in parts **a** and **b** courtesy of C. A. Seldenrijk, St Antonius Hospital, Netherlands.

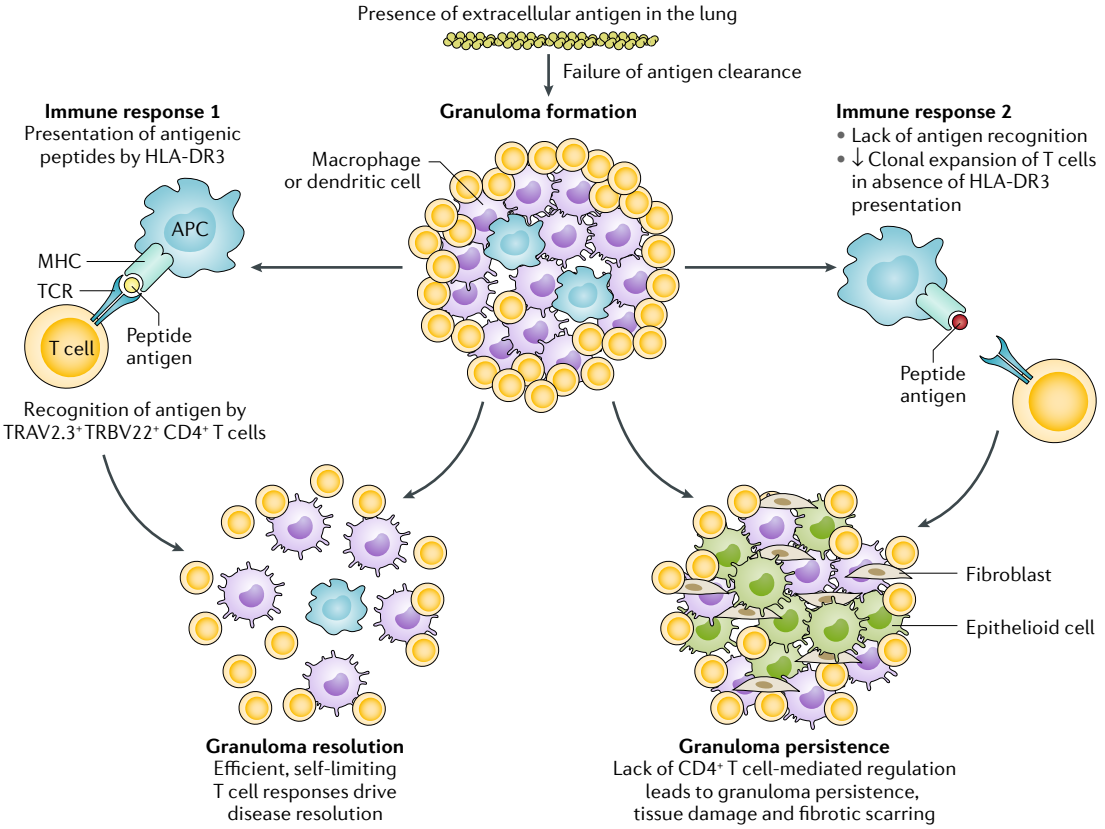

Fig. 5 | **Granuloma resolution or progression in sarcoidosis.** Exposure to an unknown antigen or antigens leads to either resolution or progression. Granuloma resolution (immune response 1) occurs when peptide antigens are presented by human leukocyte antigen (HLA)-DR3 molecules on dendritic cells or macrophages and recognized by a specific T cell receptor (TCR) β-chain variable segment 8 (TRBV8) and α-chain variable 2.3 (TRAV2.3) and CD4-positive (TRAV2.3$^+$TRBV22$^+$CD4$^+$) T cells. An efficient immune response is generated that involves the production of a large range of cytokines, and the antigen is eliminated and the granuloma resolves. Conversely, granuloma progression (immune response 2) occurs if antigen recognition is not efficient, possibly because other peptides are displayed by HLA molecules other than *HLADRB1*03* (HLA-DR3) or T cells are not capable of generating efficient T cell clones. Consequently, granulomas continue to grow and the disease persists. APC, antigen-presenting cell; MHC, major histocompatibility complex.

seasonal changes in environmental exposures[20,129–131]. Furthermore, rare case reports indicate that sarcoidosis can be transferred to recipients of transplanted bone marrow cells from donors with the disease, suggesting that these donor cells can transmit the disease[132].

Owing to similarities in clinical features and histopathology between tuberculosis and sarcoidosis and to the formation of granulomas in both diseases, *M. tuberculosis* is the most studied microorganism in relation to sarcoidosis. Accordingly, a meta-analysis estimated that mycobacteria are 10–20 times more likely to be detected in samples from patients with sarcoidosis than in those from healthy individuals[133]. Another meta-analysis of 58 studies that included 6,000 patients found that *M. tuberculosis* infection was associated with sarcoidosis, as was *C. acnes*, whereas *Borrelia* spp., human herpesvirus 8 and *Chlamydia pneumoniae* were not[35].

However, the presence of bacterial or viral remnants in patients alone is not evidence that these infectious agents have a causative role in the disease. Consistent observations worldwide of repeated failure to detect microorganisms in granulomatous tissues from patients with sarcoidosis by histological staining or culture, even after years of treatment with immunosuppressive drugs, argue against direct involvement of active replicating microorganisms in sarcoidosis pathogenesis[81]. However, microorganisms may still be involved in the aetiology of sarcoidosis as a trigger, as mycobacterial remnants are detected in the tissues of patients with sarcoidosis, in particular an intracellular protein, mycobacterial catalase–peroxidase (KatG), which could be a target of the adaptive immune response[81,82,134,135]. Other candidate mycobacterial antigens include early-secreted antigenic target of 6 kDa (ESAT6), superoxide dismutase and HSPs[3,78,136,137]. *C. acnes* proteins and nucleic acids were identified in patients' samples in several studies from Japan, and immune responses to *C. acnes* antigens differ between patients with sarcoidosis and control individuals; however, the significant frequency of immune responses in control individuals, in keeping with a commensal organism, provides some uncertainty about the role of *C. acnes* in different populations of patients with sarcoidosis[138,139].

In summary, the order of events in sarcoidosis pathogenesis is conceptualized as follows: exposure to antigen, which initiates an innate immune response; interaction

Table 2 | **Drugs or therapies that cause sarcoidosis**[a]

Agent or therapy	Examples	Type of agent or therapy
Biological response modifiers		
Cytokines	IFNα, IFNγ, IFNβ and IL-2	Recombinant protein
Immune checkpoint inhibitors	Anti-CTLA4, anti-PD1 or anti-PDL1 antibodies	Monoclonal antibody
Immune reconstitution	Bone marrow transplantation	Donor cells
Anti-retroviral therapy in patients with HIV	HAART (such as lamivudine, stavudine and indinavir or zidovudine, lamivudine and efavirenz)	Drug
Cancer chemotherapy after immune recovery	R-CHOP or paclitaxel and carboplatin or doxorubicin, cyclophosphamide and paclitaxel	Chemotherapeutic agent
Biologics		
Anti-TNF therapies	Etanercept, infliximab and adalimumab	Monoclonal antibody
BRAF inhibitors	Vemurafenib, dabrafenib and encorafenib	Small molecule

CTLA4, cytotoxic T lymphocyte antigen 4; HAART, highly active anti-retroviral therapy; PD1, programmed cell death 1; PDL1, programmed cell death 1 ligand 1; R-CHOP, combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; TNF, tumour necrosis factor. [a]Or a sarcoidosis-like drug reaction[118].

between antigen-presenting cells and local T cells, which causes loss of tolerance to commensals and autoantigens; antigen recognition by local T cells and recruitment of more T_H cells; triggering of pro-inflammatory cytokine production, which favours an IFNγ T_H1 and $T_H17.1$ response; activation of B cells and development of a humoral response; a dysregulated immune response that aids in the initiation and maintenance of granuloma formation (FIG. 4); and progression of granulomas to chronic inflammation and fibrosis or granuloma resolution in some patients (FIG. 5).

Diagnosis, screening and prevention

Clinical symptoms

Sarcoidosis has a wide range of clinical symptoms that are related to the multisystem nature of the disease, with variable organ involvement and burden of granulomas. Symptoms that are related to a specific organ involvement are numerous. The most encountered symptoms in pulmonary sarcoidosis and forms with other organ involvements in clinical practice are summarized in TABLE 3.

Of note, many symptoms are not caused by granulomas in a specific location but result from their release of mediators. Important examples include hypercalcaemia (which occurs in ~10% of patients) and/or hypercalcuria (which occurs in ~40% of patients), which result from the uncontrolled synthesis of calcitriol (the metabolically active form of vitamin D_3) by activated macrophages[140]. Calcitriol increases the gastrointestinal absorption of calcium and stimulates osteoclast-mediated bone resorption, resulting in increased serum and/or urine calcium levels.

Fatigue is another common symptom that is not usually related to specific organ involvement. Many patients suffer from debilitating fatigue without extensive and/or life-threatening organ involvement. Even patients with a history of sarcoidosis who seem to be in remission may still suffer from debilitating fatigue. If other causes of fatigue are excluded, this is often referred to as post-sarcoidosis fatigue syndrome[141]. A number of factors are associated with post-sarcoidosis fatigue syndrome, such as altered cytokine production (especially T_H2 cytokines), certain personality characteristics in combination with high levels of psychological distress and decreased ACTH and cortisol levels, lower night sleeping time, depression and reduced exercise capacity[141–145]. However, at present, the cause and mechanism of this fatigue syndrome in patients with sarcoidosis remains largely unresolved.

Clinical presentation

Clinically, sarcoidosis can be classified in many different ways, such as by type of onset, by natural history and by organ involvement. Furthermore, a few characteristic combinations of presenting symptoms exist that have been named eponymously.

The onset of sarcoidosis can be either acute or gradual, but sometimes symptom-free sarcoidosis can be discovered unexpectedly in a routine medical examination. In most patients, the onset of symptoms is gradual, although this differs considerably between ethnic groups. For example, disease onset is typically acute in Scandinavian populations, with symptoms such as fever, erythema nodosum (inflammation of subcutaneous adipose tissue) and/or ankle arthritis. However, acute onset with epileptic seizure, cranial neuropathy or cardiac arrest can also be the initial presenting symptom.

The natural history of sarcoidosis includes self-limiting, chronic but stable or chronic and progressive disease. In 50% of patients, disease resolves spontaneously within 2 years and in many others it does so within 5 years, whereas remission is much less likely after 5 years[146]. Last, the disease can be classified according to major organ involvement — pulmonary sarcoidosis, cardiac sarcoidosis and neurosarcoidosis are the most severe clinical presentations. This classification is especially important for risk stratification, as sarcoidosis-associated mortality is 20–25% when only these organs are involved[147]. Overall mortality due to sarcoidosis is much lower, although it is significantly higher than in the general population[46,146].

Sarcoidosis syndromes. A few clinical presentations have such distinct symptoms that they have been recognized as syndromes. For example, the clinical presentation of Löfgren syndrome is highly suggestive, therefore biopsy is usually not considered necessary for histological confirmation of a diagnosis[146]. Patients with Löfgren syndrome have a distinct combination of genetic, immunological and environmental features (for example, association of disease onset with spring months) that has been regularly reported by different scientists around the world[20,85,129–131]. Therefore, Löfgren syndrome is consistently considered the best-established phenotype of sarcoidosis[85]. Heerfordt syndrome is an extremely rare sarcoidosis syndrome characterized by uveitis, enlargement of the parotid and submaxillary salivary glands and paresis of the cranial nerves

(especially the seventh nerve)[148] and is only sporadically seen, even in larger sarcoidosis centres.

Pulmonary sarcoidosis. The lungs and mediastinal lymph nodes are the organs most commonly affected in patients with sarcoidosis (in 80–90%). Traditionally, intrathoracic involvement has been staged on the basis of chest radiograph features (first described by John Scadding around 1950), and this staging was later shown to have prognostic value[149,150] (TABLE 1). Although still in use, this staging has important limitations. First, inter-observer variability is poor, especially between stages with parenchymal involvement. Second, the stages suggest a relation with disease severity and/or order in which sarcoidosis may evolve. However, this is far from true, as a patient presenting with stage I might seem to have mild disease but instead might suffer from severe extrapulmonary involvement. Furthermore, although stage I on a chest radiograph is associated with high probability of resolution of intrathoracic lymphadenopathy after 1–2 years, it may nevertheless evolve towards severe pulmonary fibrosis thereafter in a minority of patients. Thus, the term radiographic type should be used.

Pulmonary sarcoidosis can be complicated by fibrosis, which can be mild and clinically non-relevant but can also be progressive and life threatening. Different patterns of fibrosis have been described from high-resolution CT (HRCT) scans, including bronchial distortion, linear pattern and cystic lung disease, which can be accompanied by honeycombing[151].

Cardiac sarcoidosis. Clinically evident cardiac involvement has been noted in at least 2–7% of patients with sarcoidosis[152], whereas occult involvement of the myocardium is probably much higher (>20%)[153–155]. Cardiac sarcoidosis may occur in the absence of pulmonary or systemic involvement. Given the potential mortality associated with cardiac sarcoidosis, early diagnosis and treatment are crucial and may be lifesaving. Most deaths in patients with cardiac sarcoidosis are due to ventricular arrhythmias, high-degree heart blocks or progressive heart failure due to massive granulomatous infiltration and/or fibrosis of the myocardium[153–155].

Currently, gadolinium-enhanced cardiac MRI is the best test to determine the presence and extent of cardiac involvement[18]. ^{18}F-FDG-PET can be helpful to determine the extent of granulomatous inflammation of the cardiac involvement (FIG. 6). The yield of myocardial biopsy samples is low, although this might improve with the arrival of new guiding imaging technologies.

Neurosarcoidosis. Neurological involvement occurs in 4–10% of patients with sarcoidosis[156]. The clinical and imaging features of neurosarcoidosis and its functional consequences vary widely, depending largely on the anatomic distribution of the disease. In order of frequency, the most common anatomic sites of symptomatic involvement are the cranial nerves, the meninges, the brain parenchyma, the spinal cord and its coverings, the hypothalamo-neurohypophyseal system, the dura and peripheral nerves[156]. Detection of hypothalamo-neurohypophyseal involvement can be especially challenging, as it may cause various endocrinopathies, including hyperprolactinaemia, decreased levels of testosterone, follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH) and diabetes insipidus, and MRI of the hypophysis does not always show abnormalities[157].

In 2002, small-fibre neuropathy (decreased intra-epidermal nerve fibre density) was recognized as a nongranulomatous parasarcoidosis syndrome[158]. Presentations include painful hyperesthesia or hypoesthesia and/or dysautonomia (such as cardiac sympathetic dysfunction). This syndrome and sarcoidosis-associated fatigue, depression and cognitive impairment are often classified as 'parasarcoidosis' syndromes. Parasarcoidosis syndromes are poorly understood and can be very difficult to treat, as symptoms such as pain and fatigue persist for a long time in many of these patients, even after disease remission.

Other organ involvements and clinical phenomena. Aside from the manifestations of sarcoidosis mentioned above, almost any other organ or tissue can be directly affected by granulomas (FIG. 7). The reported prevalence of organ involvements varies widely across the world. Important factors for this variability are local work-up and type of diagnostics, referral settings and ethnicity of the patients. For example, uveitis is fairly common in black and Asian patients with sarcoidosis (10–30% prevalence)[146]. Skin involvement occurs in up to 15% of patients, most commonly in black individuals. Interestingly, tattoos predispose to granuloma formation[159]. Facial lupus pernio, although not a health risk to patients, can be very embarrassing and lead to substantial psychosocial problems; however, it is often associated with severe sinus sarcoidosis, which is a health risk. Furthermore, a number of clinical phenomena are linked to paracrine activity of the granuloma (described below). Last, various autoimmune disorders can occur in sarcoidosis, such as vitiligo, pernicious

Table 3 | **Common organ involvements and symptoms in sarcoidosis**

Affected organ	Examples of related symptoms	Prevalence of organ involvement (%)[a]
Lung	Cough, dyspnoea, wheezing and stridor	89–99
Skin	Lupus pernio, papules, nodules, plaques and infiltrated scars and tattoos	16–32
Eyes	Painful and/or red eye and vision loss	5–23
Liver	Abdominal pain and elevated liver functions	12–20
Lymph nodes	Peripheral lymphadenopathy	13–15
Spleen	Abdominal pain	5–10
Nervous system	Facial palsy, fatigue (for example, pituitary insufficiency), gait disturbance, headache, hearing loss, numbness or paraesthesia, seizure, trigeminal neuralgia, vertigo, visual loss and weakness and/or paresis	3–9
Heart	Conductance disturbances, arrhythmias, dyspnoea, fatigue (for example, cardiomyopathy) and syncope	2–5

[a]Prevalence data are from REF.[280].

anaemia and autoimmune thyroidosis[160], although they are considered comorbidities rather than manifestations of sarcoidosis.

Diagnosis

Diagnosis of sarcoidosis traditionally depends on a combination of compatible clinical findings, histological evidence of non-necrotizing granulomas and exclusion of other diseases with a similar histological or clinical picture[161] (FIG. 8). Some differential diagnoses that need to be considered are listed in TABLE 4. In general, a multidisciplinary team approach is required to obtain a confident diagnosis and proper multisystemic assessment of sarcoidosis[162] as there is no simple diagnostic test, diagnosis is complex because more than one organ is usually involved and symptoms are not one-to-one attributable to a specific organ involvement in many patients.

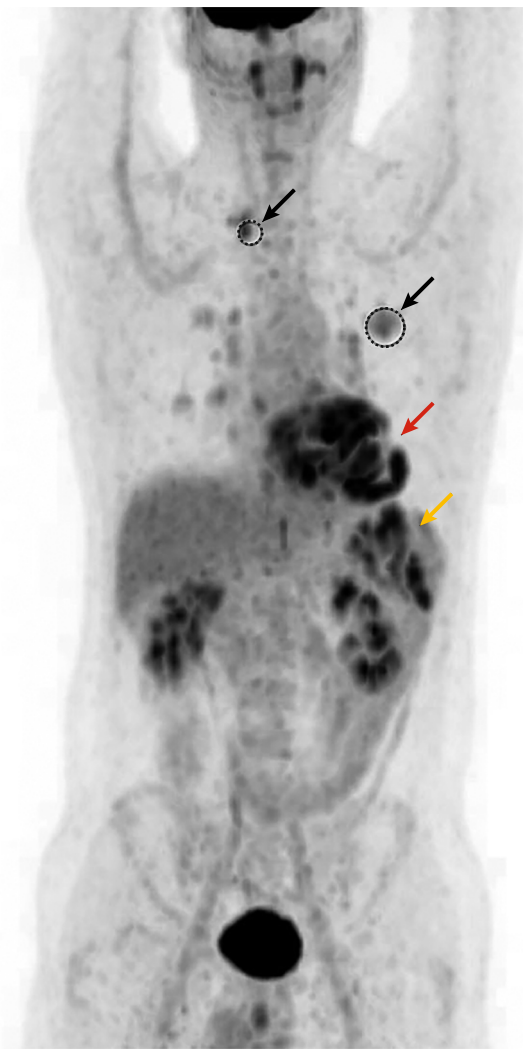

Fig. 6 | **Whole body ^{18}F-FDG-PET scan of a patient with sarcoidosis.** ^{18}Fluor-fluorodeoxyglucose-PET (^{18}F-FDG-PET) image showing pulmonary (black arrows), cardiac (red arrow) and spleen (yellow arrow) localization of inflammatory lesions due to sarcoidosis. Image courtesy of R. G. M. Keijsers, St Antonius Hospital, Netherlands.

Cases in which the disease seems to affect only one organ, despite the multisystemic nature of sarcoidosis, are challenging (for example, lupus pernio or cardiac sarcoidosis)[163]. Furthermore, the number of affected organs may change over time, requiring the right awareness (vigilance at regular checks during follow-up visits by patients), especially if new symptoms arise. Consequently, renewed diagnostic assessment is indicated during follow-up.

A diagnosis of sarcoidosis is made on the first physician visit in only 15% of cases[164]. Often, a high number of physicians are consulted and visits are made before a diagnosis is attained. Increased awareness and knowledge of the disease, up-to-date guidelines and centralization of care in clinics with acknowledged multidisciplinary teams might reduce this delay. FIGURE 8 provides a concise and stepwise approach for the diagnosis and multisystemic assessment of sarcoidosis.

Laboratory tests. Various laboratory tests are important to consider in the diagnosis of sarcoidosis. Although whole blood count and liver and kidney function assessment are important in screening for involvement of a specific organ, they do not have diagnostic value. An increase in serum and/or urine calcium levels, IgG and active vitamin D can be indicative for sarcoidosis, but their diagnostic value is poor.

Serum levels of angiotensin-converting enzyme (ACE) and soluble IL-2 receptor (sIL-2R) can be raised in a substantial proportion of patients, but the diagnostic value of these tests is low. ACE levels indicate the granuloma burden, and a change in ACE levels within or above the normal range reflects the dynamics of granuloma burden[165]. In Sweden, HLA-typing for different *HLADRB1* alleles is carried out because of their association with the natural history of disease — HLA-DR3 is associated with self-limiting disease and *HLADRB1*15* with chronic disease[166].

Skin tests. An interesting clinical phenomenon in patients with active disease is 'peripheral anergy', which leads to patients previously exposed to *M. tuberculosis* testing negative in the PPD skin test. Although this observation has been used as supportive evidence for a diagnosis, this is no longer standard practice.

Radiological imaging. Although conventional chest radiography can reveal features that are suggestive of sarcoidosis and/or its complications, HRCT is the leading imaging modality for definitive assessment of pulmonary involvement. For patients presenting with symptoms of Löfgren syndrome, only a chest radiograph and observing the course of the disease is diagnostic. However, in most other patients with suspected sarcoidosis, HRCT may reveal features that are very supportive of a diagnosis, such as the bronchovascular beading sign (FIG. 9). In addition, HRCT is best for visualizing the extent of parenchymal involvement and for revealing secondary complications, such as fibrosis, an aspergilloma (mycetoma or fungal mass) and/or features of pulmonary hypertension[167]. The extent of fibrosis revealed by HRCT, in combination with lung

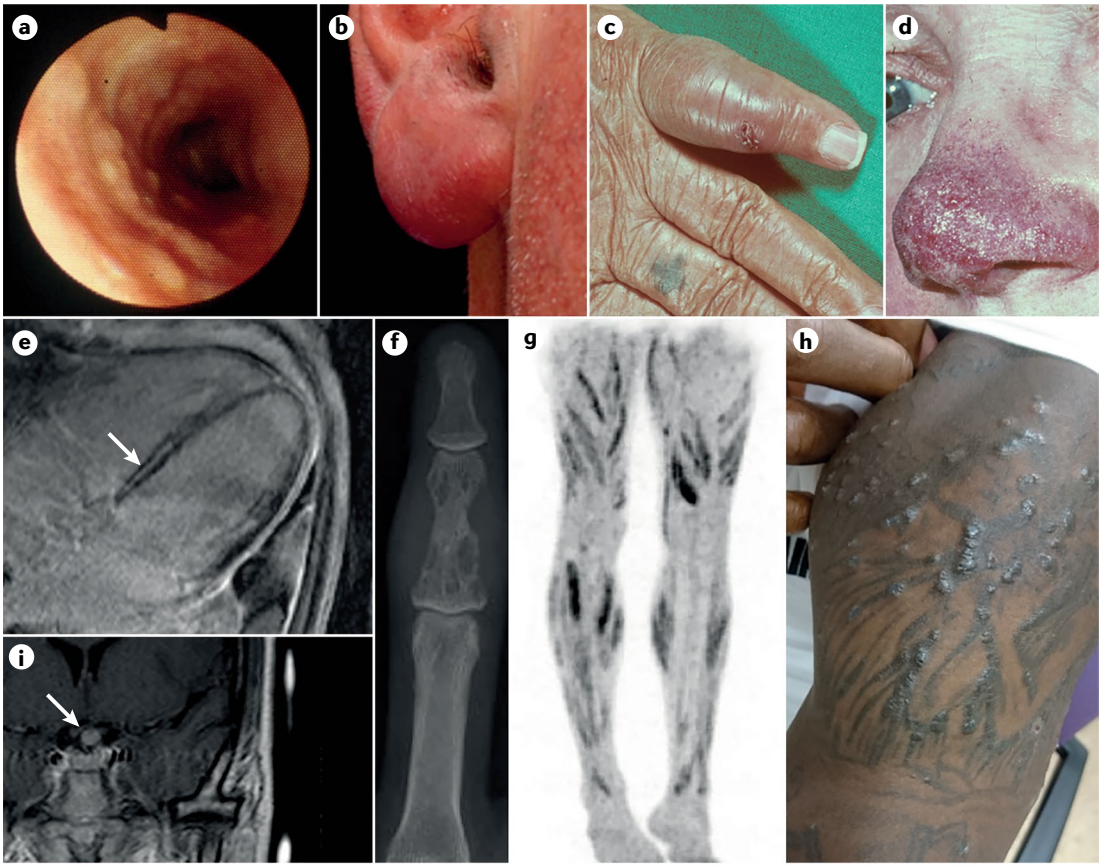

Fig. 7 | **Extrapulmonary manifestations of sarcoidosis. a** | Endobronchial cobblestones (a nodular appearance of the tracheal wall mucosa). **b** | Diffuse reddish swelling of the earlobe due to skin localization of sarcoidosis granulomas. **c** | Sarcoid dactylitis (classical Perthes–Jüngling disease associated with sarcoidosis) causing cystic lesions in the hand bones. **d** | Lupus pernio (a chronic hardened red lesion of the skin). **e** | Cardiac sarcoidosis with midmyocardial delayed enhancement (arrow) on MRI. **f** | Radiography scan of the finger of a patient with sarcoid dactylitis. **g** | Skeletal muscle involvement, visualized on fluorodeoxyglucose-PET scan of the lower limbs. **h** | Sarcoidal reaction with nodular thickening of the skin at the site of tattooing in a patient with pulmonary sarcoidosis. **i** | MRI scan showing a neurosarcoidosis lesion (arrow) to the left and caudally of the optic chiasma.

function parameters, provides important prognostic information[168].

Echography and/or CT imaging of the abdomen and especially cardiac and brain MRI are indispensable for the diagnosis of some major organ involvement in sarcoidosis, for example, when other clinical findings (such as impaired liver function tests) and/or symptoms (such as epileptic insult) are suggestive of involvement of one of these organs. Echocardiography is particularly useful for monitoring left ventricular function in cardiac sarcoidosis and screening for pulmonary hypertension in pulmonary sarcoidosis[154].

Nuclear imaging. ^{18}F-FDG-PET has considerable diagnostic value for detecting occult inflammatory lesions, especially in pulmonary and cardiac sarcoidosis (FIG. 6). In cardiac sarcoidosis, a high-fat and low-carbohydrate diet should precede ^{18}F-FDG-PET for optimal sensitivity[169]. In pulmonary sarcoidosis, a high maximum standardized uptake value (SUVmax) on ^{18}F-FDG-PET at initiation of infliximab treatment can predict clinically relevant lung function improvement[170]. In suspected cardiac sarcoidosis, ^{18}F-FDG-PET in combination with cardiac MRI is now considered the imaging modality of choice in most centres worldwide[171]. Despite growing interest in ^{18}F-FDG-PET in the past decade and an expanding list of indications for which it provides diagnostic value, its fairly high radiation burden and cost require careful balancing of benefits and drawbacks[172].

Bronchoscopy. Bronchoscopy is an important diagnostic option, as it may show 'cobble stones', the typical feature of endobronchial localization of granulomas. Bronchial biopsy is a simple, safe method for histological confirmation of a diagnosis. Even without visual abnormalities, there is ~20% chance of finding non-necrotizing granulomas in a biopsy sample[173]. BAL may also provide supportive evidence for a diagnosis and help to exclude other causes. In combination with compatible clinical features, lymphocytosis in BAL fluid, with an increased $CD4^+$ T cell/$CD8^+$ T cell ratio (>3.5) or a decreased $CD4^+CD103^+$ T cell/$CD4^+$ T cell ratio (<0.2), also supports a diagnosis of sarcoidosis[174].

Endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA) and conventional

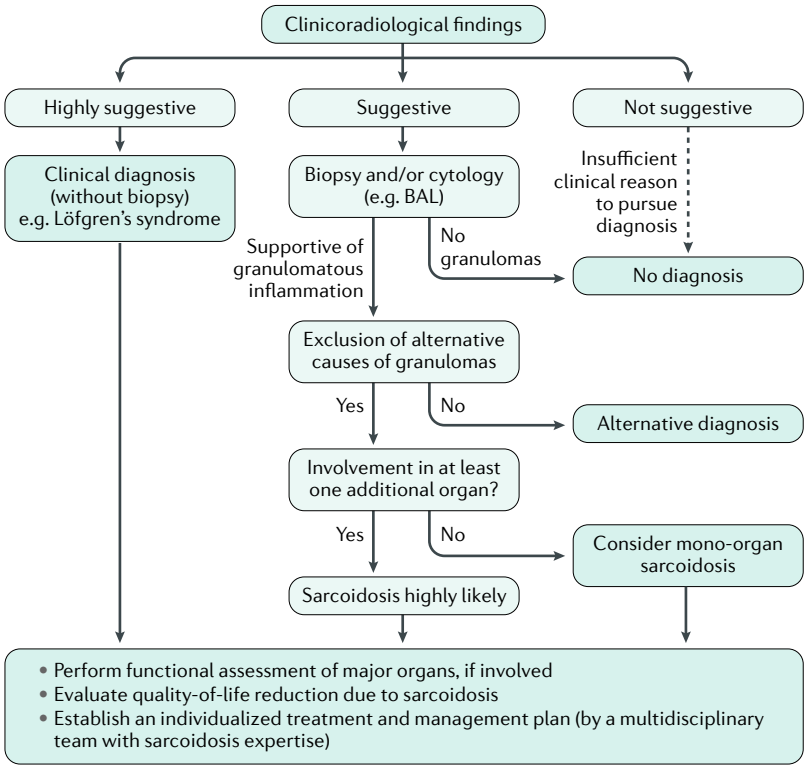

Fig. 8 | **Proposed algorithm for diagnosing sarcoidosis.** A proposed algorithm based on expert opinion. Diagnosis usually depends on a combination of compatible clinical findings, histological evidence of non-necrotizing granulomas (for example, in transbronchial biopsy samples or ultrasonography-guided transbronchial needle aspiration (EBUS-TNA) of mediastinal lymph nodes) and exclusion of alternative causes of granulomas that result in a similar histological or clinical pattern. Bronchoalveolar lavage (BAL) with a typically increased CD4-positive ($CD4^+$) T cell/$CD8^+$ T cell ratio is supportive of a sarcoidosis diagnosis. Adapted with permission from REF.[279], Elsevier.

TBNA can help to exclude other causes of mediastinal and/or hilar lymphadenopathy, such as malignancy (especially lymphoma) or infection[175], and provide a high yield (up to 80%) in the hands of experienced physicians[176]. EBUS-TBNA has a 27% higher diagnostic yield to detect granulomas than bronchoscopy with transbronchial lung biopsy[176].

Extrapulmonary biopsy. As almost any organ or tissue can be involved, there are many other potential sites for biopsy and/or cytological evaluation to confirm diagnosis, the choice of which depends on the clinical presentation, the likelihood of extrapulmonary involvement and local experience and resources. For example, minor salivary gland biopsy is undertaken in some clinics whereas others have shown the usefulness of conjunctiva biopsy. As mentioned earlier, ^{18}F-FDG-PET has specific value in detecting occult sites of disease.

Pulmonary function testing. Although not diagnostic for sarcoidosis, pulmonary function testing is extremely important for estimating the severity of pulmonary involvement and for monitoring disease natural history or response to treatment. All three types of ventilatory defect (obstruction, restriction and mixed obstruction and restriction) exist in pulmonary sarcoidosis, with or without impairment of gas exchange or the diffusion capacity of the lung for carbon monoxide (DLCO). Therefore, spirometry (especially forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1)), plethysmography (especially total lung capacity (TLC)) and DLCO measurement are most commonly used in clinical practice.

Management

After diagnosis, it is important to assess the disease extent, severity and activity in affected organs; screen for subclinical organ involvement that can jeopardize organ function and/or become life threatening or for other potentially harmful disease manifestations, such as hypercalcaemia; and determine whether therapy is needed and how to monitor the patient.

Sarcoidosis affects multiple areas, including physiological functioning of organs and QOL (fatigue and reduced mental health), with each being considered for therapeutic intervention. The natural course of the disease is highly variable and can range from spontaneous resolution, which is quite common, to recalcitrant disease that requires lung, heart or liver transplantation. Organ manifestations differ widely across studies owing to ethnic differences between study populations and often asymptomatic organ involvement that is not detected by all diagnostic routines. However, pulmonary manifestations account for most morbidity, health-care use and mortality. This heterogeneity makes it difficult to compare studies but could be compensated for by the use of phenotype and outcome scores, which is becoming more commonplace in clinical studies[177–179]. Treatment decisions, which are aimed at remission and symptom relief, must be individualized throughout the course of the disease, balancing therapeutic benefits and potential adverse effects (FIG. 10). Symptoms caused by inflammation need to be distinguished from those caused by permanent, non-progressing defects. Symptoms caused by inflammation are usually treated with corticosteroids. Patients with symptoms caused by permanent defects but not by inflammatory processes require specific therapy and support, such as supplementary oxygen in respiratory insufficiency, desmopressin treatment of diabetes insipidus or implantable cardioverter–defibrillator (ICD) device therapy for ventricular arrhythmias.

Treatment flow

Initiation of treatment. The decision of when to initiate treatment is fraught with difficulties, as predicting disease behaviour is almost impossible, with spontaneous resolution potentially occurring even in those with advanced disease. Thus, a decision has to be taken whether to watch and wait for spontaneous resolution or whether pharmacological therapy is needed (FIG. 10). Follow-up in a watch and wait approach needs to gauge organ function over time, most often pulmonary function, to identify progressing disease early enough to be able to prevent harm by initiating timely pharmacological therapy. Mandatory indications for anti-inflammatory therapy include progressive impairment

of pulmonary function, major radiographic progression (such as development of cavities or fibrosis), arrhythmias, high-degree heart blocks, cardiomyopathy, congestive heart failure, pulmonary hypertension, ophthalmological manifestations, central and peripheral nervous system manifestations, meningitis, diabetes insipidus, disfiguring or obstructive lymph nodes, lupus pernio, hepatic involvement with pronounced liver abnormalities, splenomegaly with thrombopenia, renal involvement and hypercalcaemia. Of note, anti-inflammatory therapy is warranted only when it can be confirmed that inflammation causes the symptoms; for example, advanced fibrotic disease may cause pulmonary hypertension without ongoing inflammation, which obviates the need for corticosteroids. As sarcoidosis is not disabling in most patients, treatment may be delayed in favour of careful monitoring to allow spontaneous remission to take place, which occurs in ~50% of patients, with a wide variation in remission rates between ethnicities[146]. Although corticosteroids may be necessary in patients with highly symptomatic disease, these drugs can be avoided by using NSAIDs to relieve symptoms in some cases of highly symptomatic, acute disease without mandatory indications for corticosteroid therapy[146,180,181].

Fatigue, sleep disturbances and cognitive failure are common manifestations of sarcoidosis (in up to 70% of patients) and can be measured and monitored by validated scales, are independent of inflammatory disease activity and may persist after remission, reducing QOL and creating a therapeutic problem[182].

Table 4 | **Differential diagnoses for sarcoidosis**

Differential diagnosis	Example	Test or assessment
Bacterial infections	Mycobacterium	• Culture • Antigen or antibody detection methods
Fungal infections	Aspergillosis	• Culture • Antigen or antibody detection methods
Systemic vasculitis	Granulomatosis with polyangiitis (GPA)[a]	• Detection of ANCA • Analysis of urinary sediment • Nasal and oral assessment
IgG4-related disease	Pulmonary inflammatory pseudotumours	• Measurement of serum IgG4 level • IgG4 immunohistochemistry of biopsy samples
Exposure-induced sarcoid-like lesions	• Silicosis • Berylliosis • Hypersensitivity pneumonitis	• Extrapulmonary organ assessment (especially for silicosis; usually by FDG-PET scanning) • Assessment of birefringent crystals in silicosis (for example, in BAL fluid or lung or lymph node tissue) • BeLPT • Precipitin test in hypersensitivity pneumonitis
Drug-induced granulomas	Immunotherapy-induced granulomas	• Compatible drug exposure • Timeline with symptoms
Haematological malignancies	Lymphomas	• Cytological assessment • Histological assessment
Sarcoid-like lesions due to other diseases	• Cancer • Common variable immunodeficiency	• Cytological assessment • Histological assessment • Major organ assessment for sarcoidosis (for example, by FDG-PET scanning) • Measurement of serum immunoglobulins

ANCA, anti-neutrophil cytoplasmic antibodies; BAL, bronchoalveolar lavage; BeLPT, beryllium lymphocyte proliferation test; FDG-PET, fluorodeoxyglucose-PET. [a]Previously known as Wegener granulomatosis.

Monitoring treatment. The therapeutic aim needs to be communicated to the patient to identify an unequivocal end of therapy, as corticosteroids may cause secondary adrenal insufficiency with symptoms that are also seen in chronic sarcoidosis. In these cases, an ACTH test is helpful to differentiate sarcoidosis symptoms from those of Addison disease (primary adrenal insufficiency).

In the therapy-tapering phase, constitutional symptoms may arise from corticosteroid-induced myopathy, which must be differentiated from sarcoidosis muscle involvement[183,184]. MRI or ^{18}F-FDG-PET and/or CT are the measures of choice to distinguish these possibilities[184]. Timely detection of symptoms and organ malfunction heralding relapse is important to ensure early treatment.

These rules apply to all manifestations of sarcoidosis, although gauging inflammatory disease processes in isolated myocardial sarcoidosis and neurosarcoidosis is extremely difficult and in most cases imaging approaches are the only available tools to guide therapy and follow-up[154,185,186]. In multisystem disease, pulmonary changes usually occur in parallel with those in other organs, such as the heart and central nervous system (CNS). However, for CNS treatment, it has to be kept in mind that, unlike corticosteroids, many second-line drugs do not pass the blood–brain barrier (although they can during inflammation). In cardiac sarcoidosis, unrecognized disease activity may cause life-threatening events and, therefore, monitoring needs to include imaging of inflammatory processes.

Relapse. In chronic sarcoidosis, relapses after terminating corticosteroid monotherapy are frequently observed. Corticosteroid therapy may then be repeated, preferably in combination with immunosuppressants. For example, in an induction phase of 8–12 weeks, a higher dose of prednisolone is tapered from 0.5 mg per kg (body weight) daily to a maintenance dose of 5–10 mg daily and the immunosuppressant is given in a constant dose. If effective and well tolerated, this therapy should last about 2 years[180,187,188].

Available treatments

The lack of approved drugs tested in randomized controlled trials hampers development of standardized treatment protocols in sarcoidosis. Treatment trials are difficult to design owing to heterogeneity in disease severity, presentation and natural history. Until conclusive evidence-based guidelines are established, interim reliance on consensus expert experience (Delphi technique) is considered to be useful[181].

Glucocorticoids. Glucocorticoids are considered central to initiation of anti-inflammatory therapy in sarcoidosis but lack randomized-controlled-trial-based demonstration of long-term benefits, such as prevention of pulmonary fibrosis. However, observational studies

of glucocorticoid therapy have demonstrated either stabilization or improvement in patients with evidence of deterioration[180,189,190]. A general rule is that deterioration that threatens any organ function warrants treatment intervention (FIG. 10).

BAL might be performed, and its differential cytology provides some hints about prognosis. A high $CD4^+$ T cell/$CD8^+$ T cell ratio (>3.5) is most frequently associated with spontaneous remission and a follow-up might be sufficient; however, an elevated percentage of neutrophils indicates progressive disease that requires frequent monitoring when a clear indication for therapy is not present[191–193]. Serological parameters, although non-specific and non-diagnostic, may indicate granuloma burden (ACE), T cell activation (sIL-2 receptor) and monocyte activation (neopterin)[165,193]. An increase in these parameters demonstrates ongoing inflammation and a decrease indicates remission. Of note, none of these parameters is cardinal for the decision to initiate or terminate therapy but they guide the frequency of monitoring.

Oral glucocorticoids are the initial first-line therapy in symptomatic patients (who are identified as outlined in FIG. 10). Inhaled corticosteroids cannot be used as a substitute or for sparing a systemic dose[146,180,194]. Treatment is often initiated with 0.5–0.75 mg prednisolone per kg (body weight) daily for 4 weeks and tapered by 10 mg per 4 weeks, depending on disease response. In most cases, therapy can be terminated after 6–12 months when patients are asymptomatic and pulmonary function has improved, but refractory disease may require up to 24 months. Whether a low-dose maintenance therapy for 6–12 months is of any benefit remains controversial, given the adverse effects of corticosteroids, such as weight gain, diabetes, infections, fluid retention, muscle weakness, glaucoma, cataracts, insomnia, mood swings, personality changes, osteoporosis and osteonecrosis of the femoral head. Given the adverse effects of corticosteroids and the lack of dose-finding studies, lower starting doses and faster tapering protocols could be used and seem to be equally effective in case series[60,195].

Hypercalcaemia occurs in ~5–10% of patients with sarcoidosis[196]; therefore, bisphosphonates should be used for prevention[197,198].

Glucocorticoid-sparing regimens. If glucocorticoids do not control the disease, intolerable adverse effects develop or immediate relapse occurs, then immunosuppressants can be used as corticosteroid-sparing agents. Azathioprine[188] and methotrexate[187] are frequently used, with mycophenolate mofetil and leflunomide as common alternatives; however, cyclosporine demonstrated no benefit[180]. In severe cases, after failure of these therapies, cyclophosphamide can be considered. Immunosuppressants have a pivotal role in the treatment of corticosteroid-resistant disease; however, observational medicine demonstrates that a small dose of corticosteroids is mandatory, although there are occasional reports of successful treatment with immunosuppressants in the absence of corticosteroids[199]. Injectable corticotropin was approved for sarcoidosis treatment by the US FDA in the 1950s but has had only limited use as a corticosteroid-sparing agent[200].

Targeted treatment. An improved understanding of the immunopathogenesis of sarcoidosis has led to the use of mechanism-based therapeutic approaches. Analyses of the cytokine network in sarcoidosis revealed that TNF is a pivotal mediator in recalcitrant sarcoidosis and therefore is a potential therapeutic target[201]. Thalidomide and lenalidomide inhibit TNF production as an off-target effect and have shown some therapeutic benefit in case series[202] and case reports[203], mostly for cutaneous manifestations. Pentoxifylline, a TNF-suppressing drug[204], has demonstrated corticoid-sparing effects in a randomized controlled trial[205], and a related phosphodiesterase inhibitor, roflumilast, is being tested in a clinical trial (NCT01830959).

Nicotine has numerous anti-inflammatory effects through its binding to the α7-subunit of nicotinic acetylcholine receptors, and in smokers, a lower frequency of autoimmune disorders, including sarcoidosis, is observed[206]. Therefore, the efficacy of nicotine as an anti-inflammatory therapy for sarcoidosis[207] is being tested in a clinical trial (NCT00701207).

Anti-cytokine monoclonal antibodies are a more precise way to manipulate the cytokine network[208]. Infliximab[209] and golimumab[210] were evaluated as sarcoidosis therapies in phase II trials. However, because infliximab treatment resulted in only a small (albeit significant) improvement in vital capacity, the trial sponsor did not proceed to phase III. Post hoc analyses indicate that a stratification according to serum TNF levels might have yielded more positive results[211] and that infliximab is more effective in treating extrapulmonary sarcoidosis[212]. Nevertheless, infliximab and the humanized alternative adalimumab are well established as off-label third-line therapy[208] and are predominantly used

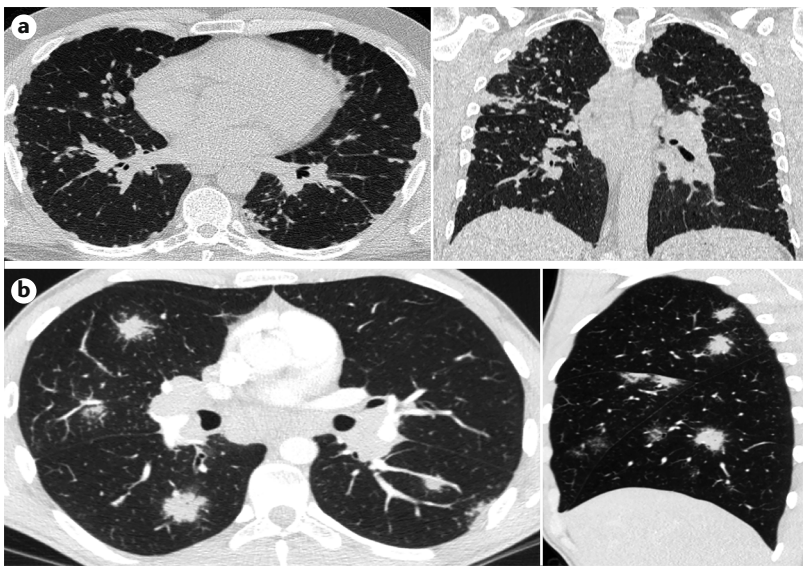

Fig. 9 | **High-resolution CT imaging of pulmonary sarcoidosis. a** | 'String of beads' appearance of peribronchovascular nodules in a patient with sarcoidosis. **b** | 'Galaxy' appearance of granulomas in a patient with sarcoidosis. Images courtesy of H. W. van Es, St Antonius Hospital, Netherlands.

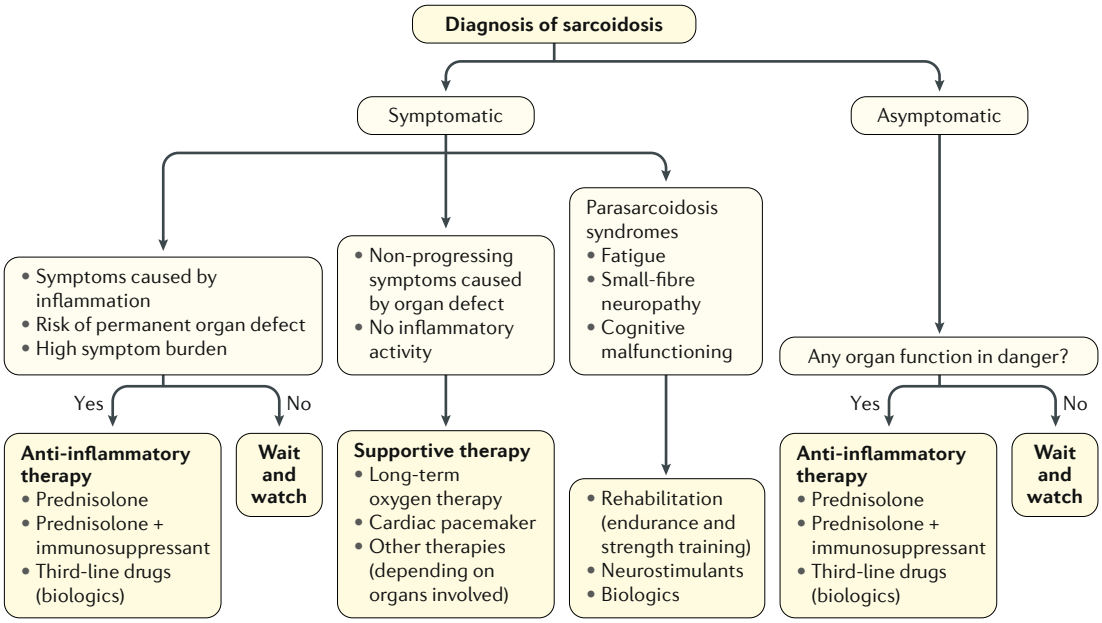

Fig. 10 | **Proposed algorithm for choice of therapy or disease monitoring in sarcoidosis.** A proposed algorithm based on expert opinion. In patients with symptomatic disease, it is important to distinguish symptoms caused by inflammation from those caused by permanent, non-progressing defects, as treatments differ. Corticosteroids (such as prednisolone) are first-line therapy for treatment of symptoms caused by inflammation, whereas symptoms caused by permanent defects require supportive therapy that depends on organ involvement, such as supplementary oxygen in respiratory insufficiency or a cardiac pacemaker for ventricular arrhythmias. As the disease course is difficult to predict (and spontaneous resolution can occur, even in advanced cases), whether to watch and wait or begin pharmacological therapy is a difficult choice that is informed by periodically assessing organ function to ensure timely pharmacological therapy to prevent permanent organ damage.

for treating extrapulmonary disease, although prolonged therapy seems to be necessary[213].

The complexity and redundancy in the cytokine network, underpowered trial designs and insufficient end points may explain the disappointingly small therapeutic effect of anti-TNF monoclonal antibodies. Furthermore, many biological drugs (including infliximab and adalimumab) may themselves induce autoimmune diseases, such as interstitial lung diseases and even sarcoidosis[214]. Aside from aberrant production of cytokines, such as TNF, IL-17, IFNγ and many others[59], the imbalance of T_H17 cells and T_{reg} cells and the disturbed signal transduction pathways in these cells are pivotal pathophysiological mechanisms that need to be addressed by pharmacological studies[61,77,215]. Interestingly, reduced expression of CTLA4 in sarcoidosis causes a T_H17 cell hyperreactivity that could be sensitive to downregulation by the CTLA4–IgG fusion protein abatacept[119], which is being evaluated in a currently recruiting phase II trial in patients with treatment-resistant sarcoidosis (DRKS00011660).

Other treatments. An ICD device should be placed in patients with cardiac sarcoidosis who have serious ventricular arrhythmias or decreased left ventricular function.

Although randomized trials of therapeutics are lacking, corticosteroids (alone or combined with additional immunosuppressive agents) remain the mainstay of therapy.

Serial transthoracic echocardiography and ^{18}F-FDG-PET are most used to evaluate the effect of corticosteroids and/or immunosuppressive agents, although the appropriate use of ^{18}F-FDG-PET has not been ascertained (FIG. 6).

The pathogenesis of parasarcoidosis syndromes, such as fatigue, small-fibre neuropathy and cognitive impairment, is elusive, and they are difficult to treat. Neurostimulants and anti-TNF biologics showed positive effects in treating fatigue and small-fibre neuropathy[182]. Furthermore, pharmacological activation of the innate repair receptor (a heterodimer comprising the erythropoietin receptor and CD131) using new agonists is emerging as a treatment for small-fibre neuropathy[216]. Rehabilitation is another approach for treating these syndromes that should not be underestimated[217], although the data are minimal.

In rare cases, heart or liver transplantation may be indicated. Lung transplantation should be considered in end-stage pulmonary disease and in particular in those with pulmonary hypertension[218]. Sarcoidosis-associated pulmonary hypertension (SAPH) is multifactorial, heralds an unfavourable prognosis and has no approved treatment. A double blind, placebo-controlled study demonstrates that the endothelin receptor antagonist bosentan improves haemodynamics, as is seen in other pulmonary hypertension WHO groups treated with this drug, suggesting that a trial of these drugs may be considered in persistently dyspnoeic patients with SAPH who are diagnosed by right heart catheterization[219].

Quality of life

Health-related QOL (HRQOL) is rarely a primary end point in clinical trials but may be the single outcome that is most reflective of patient priorities. HRQOL is a multidimensional concept that indicates the extent to which a patient's health condition (and treatment) impairs physical and psychological ease to interface with important areas of life activity, such as making a living, engaging with loved ones and pursuing life's interests[220].

The Bio-Psycho-Social Model of Health[221] recognizes that physical, social and psychological health are inextricably inter-influential and are favourably or negatively influenced by qualities intrinsic to the patient or environment, including an individual's adaptability and coping behaviour, disease duration, cultivation of self-management strategies, family support, financial resources and assistive aids, devices or techniques that improve physical, mental or emotional function or decrease physical or medication symptoms[221].

Symptom burden

The core components of HRQOL (that is, physical, emotional, functional and social well-being) are augmented or diminished by various factors, which are discussed below.

Physical symptoms. Owing to the multi-organ involvement in sarcoidosis, the disease is associated with reversible symptoms (that is, active disease that is treatable) and irreversible symptoms (related to inactive disease or damage) and adverse effects of treatment[222,223] (FIG. 8; TABLE 2). Another category relates to symptoms that result from irreversible biological damage but that could still be improved, such as with increasing physical conditioning or education in dyspnoea and cough. Treating symptoms with targeted pharmacological and non-pharmacological interventions[224,225] can augment function and increase medication tolerability.

Fatigue is the most prevalent symptom[226] and comprises cognitive, emotional, motivational, physical and muscular aspects[227]. Fatigue is driven by multiple influences, including inflammatory and/or cytokine, mitochondrial, hormonal, hypothalamic, vascular, neurological and psychological mechanisms, and often correlates with inflammatory disease activity[228,229]. Sarcoidosis-related fatigue correlates with both sarcoidosis-specific and generic measures of HRQOL[220,226,230–233].

Impaired sleep and sleep-disordered breathing are highly prevalent in sarcoidosis[234–237] and result in escalating fatigue, depression, anxiety, and cognitive and physical impairments[234–236]. Sleep disorders worsen with increasing dyspnea[234] and with glucocorticoid treatment[237].

Psychological symptoms. Sarcoidosis has serious psychological effects on patients and their families, resulting in high rates of anxiety, depression and isolation in patients[226,233,238,239] and family members[226]. Severity of disease, respiratory symptoms, multi-organ involvement and unpredictable disease course correlate with severity of depression[233,238,239], which erodes emotional well-being[233]. Patients desire better attention to the psychological effects of the disease, patient education and shared decision-making[226,233,239,240]. Furthermore, treatment with glucocorticoids can trigger and/or intensify depression, anxiety, sleep disorders or psychosis[241], as well as physical changes, such as weight gain, cushingoid features, acne and striae, which diminish self-esteem.

Chronic illness may cause greater distress in loved ones than in patients[226,242,243], possibly exacerbating patient stress. Patients may minimize symptoms to preserve their independence and self-identity and to protect loved ones from the emotional pain and anxiety caused by witnessing hardship[244].

Participation

Work life. Work ability (that is, productivity) is a robust example of bio-psycho-social convergence in sarcoidosis. The societal burden of sarcoidosis-related work absenteeism averages 30 days per year, a high level that persists for at least 5 years from diagnosis[43,245–247]. Sarcoidosis-related work absenteeism corresponds to 8% of income lost annually[245], which is compounded by other disease-related costs, including work absenteeism of family members, travel and other treatment costs that are not covered by insurance.

External factors, such as disposable income and savings, workplace policies and co-worker attitudes[248], hierarchical position, supportive relationships and even climate[249], influence work-associated HRQOL. Educational innovations for patients, families and employers on preventive health strategies, potential financial changes, workplace policies (such as work-from-home and sick-day-donation programmes[250]) and operational tactics (such as consolidating clinical visits and testing and home-based health care[251–254]) reduce absenteeism, co-pay and travel costs.

Family and social life. As in other diseases[255–257], fatigue, dyspnoea, pain, physical deconditioning and psychological effects in sarcoidosis probably diminish HRQOL, family and social relations and seeking and maintaining intimate relationships[226,244,258,259].

Assessing HRQOL

Disease registries and government and commercial medical databases estimate crude aspects of disease burden, whereas patient-reported outcome measures (PROMs) convey finer group and individual HRQOL, epidemiological and clinical data. Disease-specific measures include the Sarcoidosis Health Questionnaire (SHQ)[260], King's Sarcoidosis Questionnaire (KSQ)[261] and the Sarcoidosis Assessment Tool (SAT)[262]. The Fatigue Assessment Scale (FAS) was developed for and validated in patients with sarcoidosis[263]. Generic measures, such as the 36-item Short Form Health Survey (SF-36), EuroQol Group 5-dimension questionnaire (EQ-5D) and PROMIS, enable group comparisons of HRQOL across diseases.

Strategies to enhance HRQOL

Strategies that target symptom burden, physical impairment, adaptations to home and work participation and

financial management can enhance HRQOL. Clinician-communicated recognition of patient and family suffering can motivate patient-driven modifications, such as nutrition, smoking cessation, exercise and medication adherence[264,265]. Prevention of sarcoidosis and treatment-related complications[266,267] and wellness interventions[224,268] protect HRQOL status.

Outlook

Mechanisms

Candidate antigens. Using various 'omics' techniques, we anticipate the identification of additional 'candidate antigens'. Functional aspects of these antigens must be investigated thoroughly to improve our understanding of their role in T cell accumulation in the lung and in granuloma formation. These studies might reveal key components of the inflammatory reaction in sarcoidosis and lead to the identification of new targets for immunotherapy.

Immune response. Research focus has been mostly on T cells, partly because they typically accumulate in the lungs, where the disease is most likely initiated. New insights into T cell biology have revealed that T cell subtypes, such as T_H17 cells and $T_H17.1$ cells, are also involved in the inflammation in sarcoidosis[61]. The role of these hybrid cells, as well as that of T_{reg} cells, NKT cells and NK cells, also requires further investigation[111]. There is increasing interest in B cells and antibody production, especially in relation to clinical parameters and T cell responses, but other immune cell types should not be overlooked. In the search for disease-specific antigens and immunological mechanisms, collaborative efforts to simultaneously study the function and interaction of multiple immune cell types might clarify immune processes in sarcoidosis.

Granuloma formation. Granuloma formation and why granulomas spontaneously resolve or persist (leading to fibrosis) are of increasing interest. An understanding of the factors that drive granuloma resolution or persistence should enable development of specific treatments that target these factors.

Patient stratification

The use of large administrative health data sets and longer follow-up to investigate the epidemiology of sarcoidosis, including risk factors and outcomes, will advance our understanding of the disease, enable the identification of subgroups of patients who are at the highest risk of poor outcomes and elucidate the overall burden of disease.

We anticipate that the 'sarcoidosis' diagnostic category includes several disease entities with distinct phenotypic characteristics and molecular signatures (thus the term 'sarcoidoses') and that the mechanisms underlying phenotypes involving specific organs, such as cardiac sarcoidosis or neurosarcoidosis, will be revealed. Research is ongoing to determine which clinical presentations of sarcoidosis result from a distinct combination of genetic variants, phenotypic traits and/or environmental factors[146,269]. In a large European study, >2,000 patients with sarcoidosis were phenotyped in depth, and multiple correspondence analysis and clustering identified five new phenotypic categories (abdominal organ involvement, ocular–cardiac–cutaneous–CNS involvement, musculoskeletal–cutaneous involvement, pulmonary and intrathoracic lymph node involvement, and dominant extrapulmonary involvement)[152] and a search for genetic signatures of these phenotypes is in progress. Additional studies are needed to determine the clinical relevance of these categories. Furthermore, a microbiome and genomic study of sarcoidosis[270] evaluated the molecular basis of novel phenotypes in sarcoidosis and is expected to provide further insight into disease heterogeneity.

The identification of new biomarkers is sorely needed to improve diagnosis and prediction of disease course. Mass cytometry is one of many new techniques that will be useful for improving our understanding of sarcoidosis pathology, by enabling multiparameter analyses of the expression of >30 unique markers of specific immune cells, such as T cells[271]. Evaluation of disease activity using PET–CT should enable selection of patients who are suitable for specific therapies, such as immune therapy using anti-TNF antibodies.

Aside from HLA variants that are associated with disease course, variants in many other genes are associated with increased risk of disease and are in genomic regions that are important for immune system function[272]. Mapping these genes may reveal immune pathways that are key for inflammation in sarcoidosis and lead to the identification of targets for immunotherapy. The MESARGEN initiative is collecting samples from clinically well-characterized patients in several cohorts worldwide. Large-scale omics analysis of these samples will enable researchers to decipher the genetic architecture of sarcoidosis and its clinical phenotypes, thereby enabling the discovery of diagnostic and prognostic biomarkers of disease for use in the clinic and the development of personalized medicine[273].

Management

An improved understanding of all aspects of the immune response in sarcoidosis is needed, as the diverse range of immune cell types and factors involved in the pathogenesis of sarcoidosis are potential therapeutic targets. In the case of immune cell types, autoantigen-specific T cells are an obvious target. In parallel to the well-founded interest in T cells, B cells are also being targeted for the treatment of recalcitrant pulmonary and extrapulmonary sarcoidosis, such as successful rituximab therapy in two case series[274,275].

Immune factors and antigens are also potential therapeutic targets. For example, JAK inhibitors are effective in treating other chronic inflammatory disorders and broadly suppress signalling by cytokines, including those involved in inflammation in sarcoidosis[68]. Two case reports showed positive responses with JAK inhibitors in patients with pulmonary or cutaneous sarcoidosis after multiple relapses following tapering off immunosuppressants[72,73]. Furthermore, to target potential mycobacterial involvement in sarcoidosis, oral antimycobacterial therapy (concomitant levofloxacin,

ethambutol, azithromycin and rifampin (the CLEAR regimen)) is being tested for the treatment of chronic pulmonary sarcoidosis in a currently recruiting phase II trial (NCT02024555). Targeting the production of SAA (for example, by reducing the levels of cytokines such as IL-6, TNF or IL-1, which control SAA production by macrophages) should reduce aggregation and improve clearance of SAA. Immune checkpoint inhibition requires caution until we learn more about it.

Measuring QOL

Sarcoidosis is a pleiotropic disease, therefore, aside from organ impairment, patients with sarcoidosis experience cough, fatigue, depression and perception of cognitive dysfunction that do not necessarily correlate with classical measures of disease activity and usually do not improve with treatment of sarcoidosis-associated inflammation[234]. Thus, study end points of pulmonary function do not reflect all the needs of patients; consequently, sarcoidosis experts recommend the inclusion of new study end points that gauge QOL. For cough, electronic monitors and questionnaires have been developed; these questionnaires have been translated and validated in many languages, thereby enabling international studies[276]. Inhaled VIP increases the number of T_{reg} cells in BAL samples and dampens cough in patients with sarcoidosis[66], and given the limited therapeutic options for cough in patients with sarcoidosis[277], a study with cough reduction by VIP inhalation as an end point is planned. Questionnaires that cover multiple dimensions of QOL, such as KSQ[261], have been developed, translated and validated in numerous languages and will enable future pharmacological studies with QOL parameters as end points[278].

An important goal in sarcoidosis research is the identification of disease-triggering antigens that might be novel therapeutic targets, but, for now, improved disease management with more personalized treatments and a greater number of available treatment strategies will offer benefit to patients. As new disease mechanisms are identified, the conventional diagnosis of sarcoidosis will be replaced by a diagnosis based on aetiology.

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Competing interests
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