REVIEW ARTICLE

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Challenges of Sarcoidosis and Its Management

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Sarcoidosis is an inflammatory, multisystemic disease of unknown cause with a wide range of clinical manifestations. The disorder can affect virtually any organ in the body — predominantly the lungs, lymphatic system, skin, or eyes or a combination of these sites — and is characterized by the formation of noncaseating granulomas. The first description of sarcoidosis is attributed to Jonathan Hutchinson, a surgeon and dermatologist practicing in London in the late 1800s, who identified patients with unusual skin lesions. The systemic manifestations of the disease were recognized in the decades around the end of the 19th century. Despite the efforts of several generations of researchers, our understanding of the disease mechanisms and general epidemiology of sarcoidosis remains limited.[1] The clinical presentation of sarcoidosis depends on the intensity and duration of the inflammation and the organs involved. It is thought that a dysregulated immune response against certain environmental antigens results in sustained granulomatous inflammation and failure to clear the offending antigens.[1,2]

The prevalence and presentation of sarcoidosis are variable. The triggering antigen is likely to vary according to race or ethnic group, geographic location, and individual genetic background.[1] The prognosis is also highly variable, ranging from spontaneous resolution to chronic inflammation complicated by fibrosis or associated irreversible organ failure or both. Sarcoidosis adversely affects the lives of patients and their families. Disease severity, coexisting conditions, and quality of life are influenced by social status, race or ethnic group, sex, and income.[3,4] The cause remains elusive, and pathognomonic markers and disease-specific treatments are lacking. Given the unpredictable clinical course and uncertainty about adequate treatment approaches, the management of sarcoidosis remains challenging.[5,6] A recent report provides an excellent summary of current concepts concerning the epidemiology, pathogenesis, and treatment of sarcoidosis.[1] This review extends the discussion to consider unresolved clinical and research challenges and related opportunities to improve the care of patients with sarcoidosis.

Epidemiologic Features

Sarcoidosis occurs throughout the world, affecting all races and ethnic groups and both sexes, with a slight predominance among women. It can affect people of all ages but mostly develops in young and middle-aged adults. The incidence has been reported to peak at 30 to 50 years of age in men and at 50 to 60 years of age in women.[7] Some data suggest that the age at onset is increasing. A family history of the disease increases the risk; for persons with one affected first-degree relative, the risk is increased by a factor of 3.7.[7] The true prevalence remains unknown because

Table 1. Selected Adverse and Favorable Prognostic Factors in Sarcoidosis.*

Variable	Adverse Prognostic Factors†	Favorable Prognostic Factors
Demographic characteristics	Age ≥40 yr at onset[10] Black race[11] Black race and female sex Lower income[4,11]	Age <40 yr at onset[10]
Pulmonary involvement[12,13]	Scadding stage III (absence of lymphadenopathy) or stage IV (signs of fibrosis) on chest radiography‡ Severe dyspnea or hypoxemia with minimal exertion at presentation[13] Clinically significant lung functional impairment Pulmonary hypertension[13]	Asymptomatic Scadding stage I or II (presence of lymphadenopathy) on chest radiography‡
Bronchoalveolar lavage fluid	Neutrophilia at presentation[14] Elevated metalloproteinases (MMP12)	Lymphocytosis without increased eosinophils or neutrophils or both[15] Increased CD4:CD8 ratio[15]
Extrapulmonary involvement	Lupus pernio: nasal mucosal involvement[10] Vitiligo Chronic uveitis[10] Cardiac involvement Hepatomegaly Splenomegaly Neurologic involvement Osseous involvement[10] Hypercalcemia[10] Nephrolithiasis or nephrocalcinosis[10] Small-fiber neuropathy–associated symptoms[16,17]	Acute inflammatory manifestations (e.g., Löfgren's syndrome: acute onset with fever, erythema nodosum, bilateral ankle arthritis, and bilateral hilar lymphadenopathy)[1] Isolated cranial-nerve palsy
Requirement for treatment	Risk of disease progression and organ failure or death[12]	No risk of disease progression or organ failure
Associated genetic variants§	*HLA-DRB1*14*, *HLA-DRB1*15+*[1] Presence of a *TNF-α* rs1800629 G/A variant allele¶ Presence of a *BTNL2* rs2076530 G/A variant allele[18]¶ Presence of an *ANXA11* rs1049550 C/T variant allele	*HLA-DRB1*03+*, *HLA-DQB1*0201* Absence of a *TNF-α* variant allele Absence of a *BTNL2* variant allele Absence of an *ANXA11* variant allele

* See References Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, for additional references pertaining to this table.

† An adverse prognosis indicates a severe course, the need for prolonged treatment, the risk of organ damage, and in some cases, the risk of death. The genetic risk factors presented here may not be applicable to all populations.

‡ According to the Scadding radiographic staging system for pulmonary sarcoidosis, stage 0 is characterized by normal chest radiographic findings, stage I by bilateral hilar lymphadenopathy, stage II by bilateral hilar lymphadenopathy and parenchymal abnormalities, stage III by parenchymal abnormalities without bilateral hilar lymphadenopathy, and stage IV by advanced lung fibrosis.

§ *HLA* variants vary among patients of different ethnic origins. *ANXA11* denotes annexin A11, *BTNL2* butyrophilin-like protein 2, and *TNF-α* tumor necrosis factor alpha.

¶ The presence of this variant allele may depend on associations with *HLA-DRB1** alleles.

the epidemiologic assessment of sarcoidosis and its manifestations is hampered by the lack of a consistent case definition; by a lack of diagnostic sensitivity; by variations in diagnostic methods, in access of patients to health care, and in the regional distribution of subphenotypes; and by seasonal variations, among other factors.[8,9] However, the available evidence indicates that the prevalence and incidence of sarcoidosis and associated mortality vary according to factors including race or ethnic group, the intensity and duration of disease-associated environmental exposure, individual genetic background, and geographic location (Table 1).

ENVIRONMENTAL AND GENETIC FEATURES

The development of sarcoidosis requires both a genetic predisposition and environmental and sometimes occupational exposure to unknown substances or microbial antigens. It is generally accepted that a dysregulated immune response against one or more disease-promoting antigens results in an inflammatory process to eliminate the offending antigen.[1] Multiple occupations and environmental exposures are associated with sarcoidosis, including exposure to moldy environments, occupational exposure to insecticides,

agricultural employment, metalworking, firefighting, exposure to inorganic dust, exposure to silica dust, and the handling of building supplies (as indicated by cases of sarcoidosis in rescue workers at the World Trade Center).[19] The role of genetic factors in sarcoidosis is supported by familial clustering of cases and by the variation in the manifestations and course of disease across racial and ethnic groups. The importance of interactions between the environment and genetic factors is underscored by a study identifying certain gene variants on chromosome 6 that substantially increased the risk of sarcoidosis in persons exposed to pesticides, as compared with unexposed persons.[18] Furthermore, the combination of certain gene variants and smoking substantially increases the risk of disease.[20] Genetic factors identified in genomewide association studies affect not only the risk that the disease will develop but also the course of the disease and the organs involved.[1] However, gene association studies have limitations, including the identification of genes with no apparent biologic relevance to sarcoidosis.

PATHOPHYSIOLOGICAL CHARACTERISTICS

PATHOGENESIS

As mentioned previously, the histologic hallmark of sarcoidosis — granulomatous inflammation — is thought to be a dysregulated antigenic response to unknown environmental exposures in a genetically susceptible person. Loci that house genes involved in antigen presentation (e.g., loci in the HLA class II region and the butyrophilin-like 2 gene [*BTNL2*]) are linked to the development of sarcoidosis and to certain disease phenotypes (Table 1). Subclinical inflammation begins with activation of membrane-bound pattern-recognition receptors (e.g., toll-like receptors). When stimulated, macrophages and other innate immune cells promote transcription factors, resulting in the production of cytokines (Fig. 1).[1,21-27]

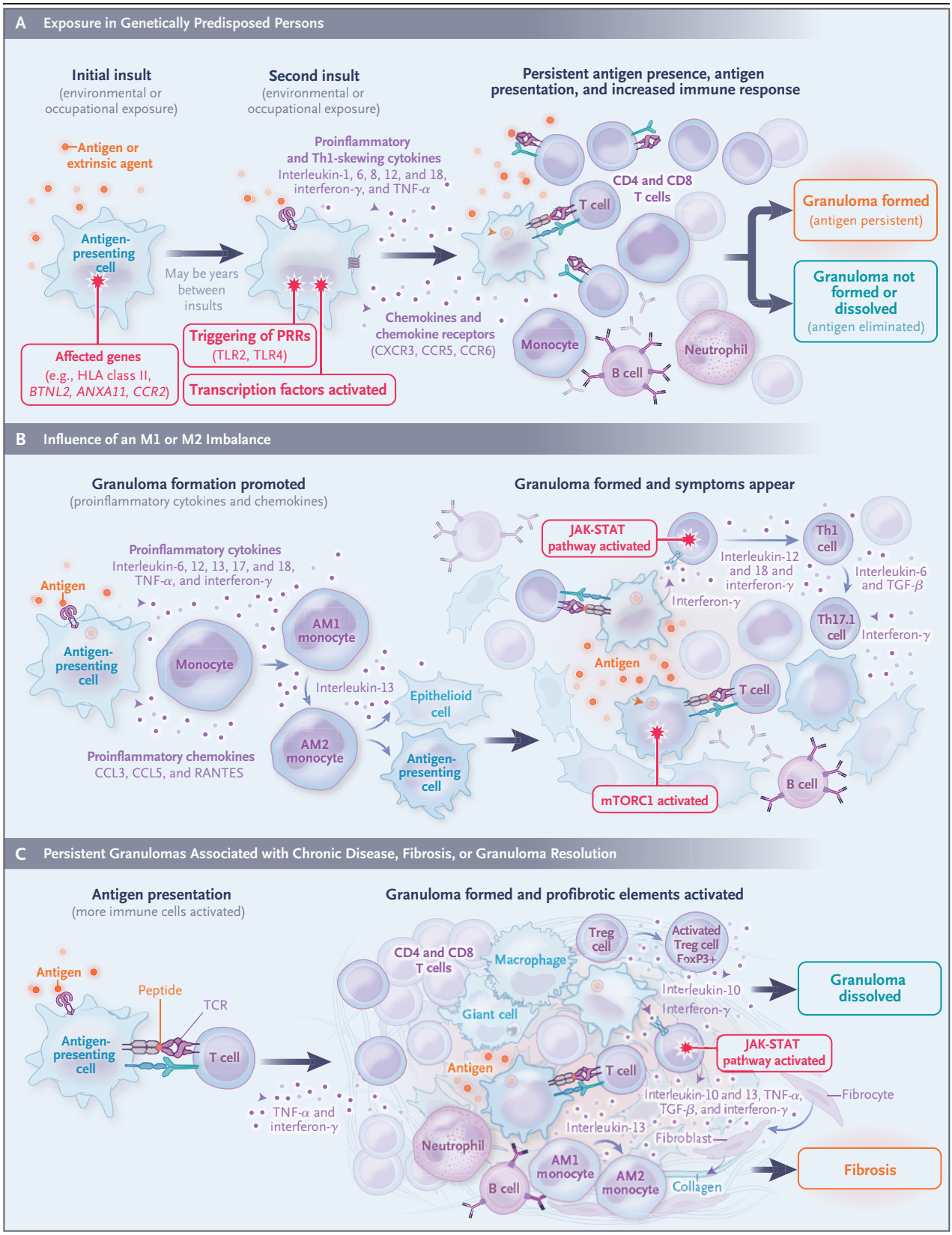
"Classically" activated macrophages are regarded as drivers of the inflammatory process (proinflammatory M1 type) associated with granuloma formation. Cytokines can also promote CD4+ helper T cells and sometimes their differentiation into type 17 helper T (Th17) cells.[1] Professional antigen-presenting cells (e.g., dendritic cells) are also activated to generate and display antigen peptides, which are recognized

Figure 1 (facing page). Immunologic Cascade Causing Granuloma Formation in Sarcoidosis, with Resolution or Persistence in Genetically Predisposed Persons.

Panel A shows the immunologic cascade during granuloma formation. The early phase of an innate immune response is the result of genetic, epigenetic, and environmental factors interacting with environmental or occupational triggers (e.g., exposure to antigens such as microorganisms) or other extrinsic agents in the context of an "initial insult" that are capable of triggering membrane-bound pattern-recognition receptors (PRRs), such as toll-like receptors (TLRs).[21] Persons with a specific genetic background (e.g., certain *HLA* alleles) have a predisposition to a dysfunctional immune response, with the formation of granulomas. A second insult (which may take years to occur) might be required to boost and sustain the immune response. Each exposure is followed by stimulation of transcription factors, resulting in the production of cytokines and the expression of chemokine receptors and chemokines. This process will also attract immune cells of an adaptive immune response, such as CD4+ and CD8+ T cells, to the site of insult. The immune response can eventually eliminate the inciting antigen, after which the response shuts down. Alternatively, if the antigen persists, formation of nonnecrotizing epithelioid-cell granulomas ensues.[1]

In a second phase, shown in Panel B, interleukin-13 promotes the AM2 (alveolar macrophage 2) phenotype, monocytes differentiate into epithelioid cells and antigen-presenting cells, and mammalian target of rapamycin complex (mTORC1) is activated, further promoting and sustaining granuloma formation.[22,23] Cytokines, especially interferon-γ, will activate the Janus kinase (JAK) and signal transducer and activator of transcription (JAK-STAT) pathway, which could be blocked therapeutically.[1] Through so-called T-cell plasticity, helper T cells can, under the influence of interleukin-12, interleukin-18, and interferon-γ, differentiate into classical type 1 helper T (Th1) cells, producing interferon-γ, tumor necrosis factor α (TNF-α), and interleukin-2 and providing protection against microorganisms.[1] Adding transforming growth factor beta (TGF-β) and interleukin-6 to helper T cells will stimulate expression of type 17 helper T (Th17) cells and production of various interleukins in the pulmonary environment. Whereas interleukin-23 initiates a more proinflammatory process with the production of granulocyte–macrophage colony-stimulating factor (GM-CSF), the absence of interleukin-23 can induce Th17 cells to take on a more regulatory role, producing interleukin-10. In the lungs, however, the Th17.1 phenotype production of interferon-γ appears to predominate.[24]

Panel C shows the processes through which granulomas either persist, resulting in chronic disease and fibrosis, or resolve. Specific antigens are presented in the form of peptides by HLA molecules on antigen-presenting cells. T cells expressing a T-cell receptor for antigen (TCR) that recognizes the HLA–peptide complex will be further stimulated, activating other immune effector cells. *HLA-DRB1**03–positive (DR3-positive) persons have large T-cell populations expressing alpha-chain variable 2.3 (AV2.3) in the lungs, suggesting recognition of specific antigens there. Granulomas consist of a core of activated and highly differentiated epithelioid cells, structurally well formed and typically nonnecrotizing. They are situated along lymphatic routes and characteristically contain intracellular bodies (Schaumann's bodies) and multinucleated giant cells.[24] Cytokines interferon-γ and TNF-α in particular promote the formation of granulomas that are surrounded by a ring of lymphocytes, primarily CD4+ T cells, but also some CD8+ T cells, as well as B cells. The complex fibrotic process includes the release of cytokines such as TNF-α, interferon-γ, or both; a transfer of monocytes as promoted by interleukin-13; and the release of other fibrosis-stimulating cytokines such as TGF-β and interleukin-10.[25] Fibrocytes, which circulate in the blood, can differentiate into fibroblasts and release collagen and other substances that promote the development of fibrosis.[26] FoxP3-expressing regulatory T (Treg) cells could, on activation, aid in the resolution of granulomas, but they are dysfunctional.[22] The role of Th17 cells and subtypes in the resolution and maintenance of granulomatous inflammation is probably tissue-specific and warrants further studies.[1] *ANXA11* denotes annexin A11, and *BTNL2* butyrophilin-like 2.



by T cells that use their antigen receptor. These interactions result in a specific adaptive immune response with different qualities depending on, for example, the surrounding milieu and directed against the offending antigen.[28]

ALVEOLAR MACROPHAGES

Granulomas often resolve spontaneously, but in some patients they persist and function as a nidus for the development of fibrosis, a process that probably depends on the nature of the offending antigen.[24] Interleukin-13 stimulates polarization toward M2-type activated macrophages (which are antiinflammatory and proangiogenic and promote type 2 helper T [Th2] cell function) that are reported to influence early granuloma formation.[29] In addition, M2 can promote fibrosis (e.g., by recruiting and differentiating fibrocytes and through differentiation into fibrocyte-like cells expressing collagen [fibroblasts]).[30] The neutrophilic component of the inflammation, including mediators such as collagenase, oxidant radicals, and proteases, can also contribute to alveolar-wall injury in sarcoidosis and to the evolution toward pulmonary fibrosis.[14,15,31,32] Tissue-resident macrophages in the liver (Kupffer cells) or microglia in the brain originate from progenitor cells. Although not as effective as dendritic cells, these macrophages can also function as antigen-presenting cells. After activation, they begin to differentiate into histiocytes and epithelioid cells, forming the core of the granuloma.[33]

T CELLS

In sarcoidosis, the accumulation of activated helper T cells in the lungs, which promotes the formation of nonnecrotizing epithelioid-cell granulomas, suggests that specific antigens trigger an immune reaction. Sarcoidosis has been characterized as an archetypal type 1 helper T (Th1) cell–driven disease, with helper T cells in bronchoalveolar lavage fluid (BALF) expressing high levels of interferon-γ, interleukin-2, and tumor necrosis factor α (TNF-α)[34]; with high levels of the Th1-skewing cytokines interleukin-12 and interleukin-18 in BALF; and with increased expression of Th1-associated chemokine receptors CXCR3 and CCR5.[35] Activation of alveolar T lymphocytes is a characteristic feature of sarcoidosis, as reflected by increased expression of typical activation markers on the cell surface, such as HLA-DR, but also by the release of specific mediators (interleukin-2 and interferon-γ). The exaggerated Th1/Th17-oriented immune response in sarcoidosis includes up-regulation of Th1-specific transcription factor (T-box tran-

Figure 2 (facing page). Clinical and Diagnostic Features That Are Helpful in the Diagnosis and Follow-up of Sarcoidosis.

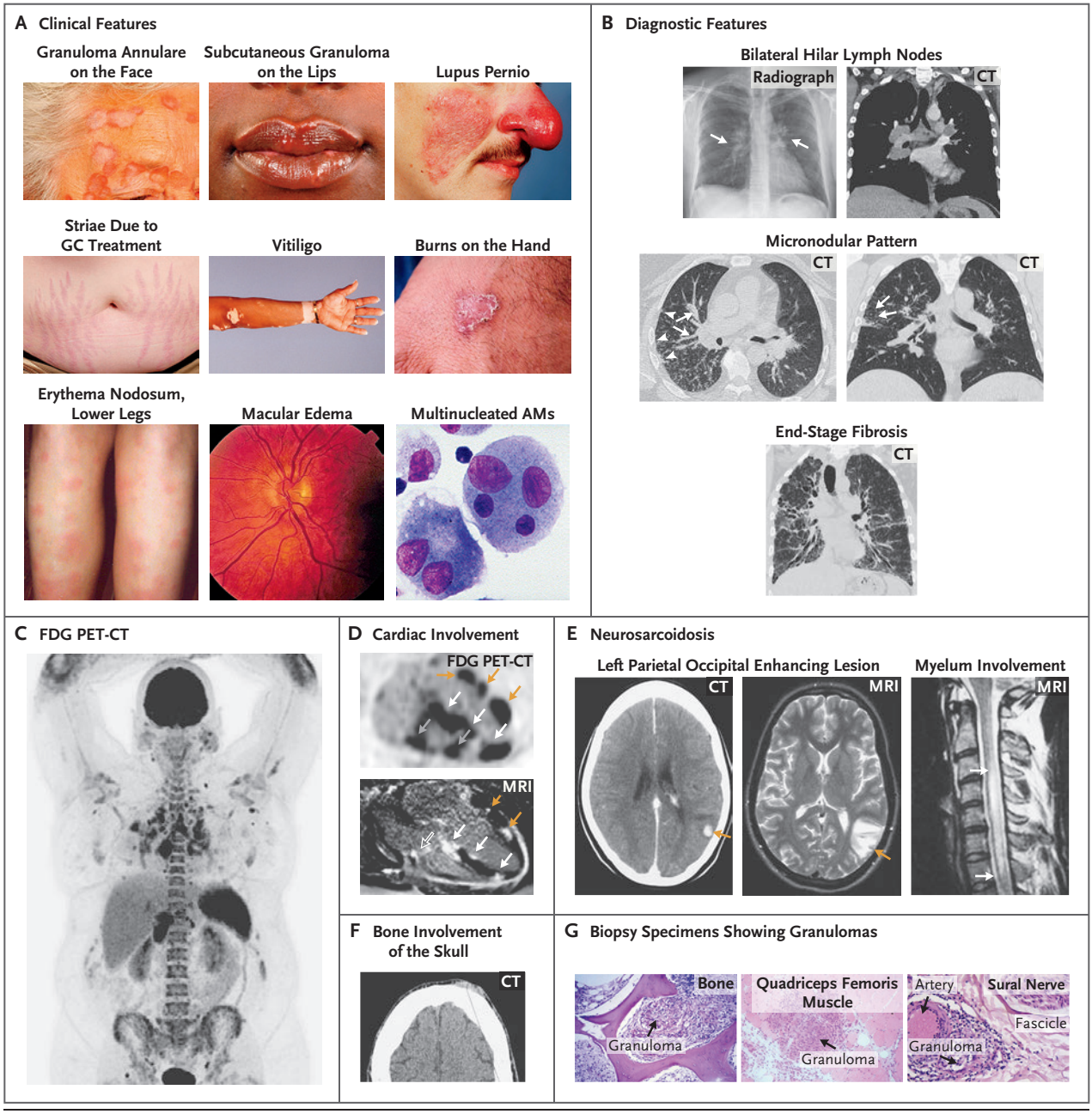
Panel A shows skin lesions associated with sarcoidosis, including burns on the hand of a patient who did not feel the difference between hot and cold water because of small-fiber neuropathy; macular edema, a rather common eye manifestation in sarcoidosis; and multinucleated alveolar macrophages (AMs, stained with May–Grünwald Giemsa), which can be found in bronchoalveolar lavage fluid (BALF) from patients with sarcoidosis.[15]

High-resolution computed tomography (HRCT) is superior to chest radiography and is more sensitive in assessing the extent of the disease. Panel B shows a chest radiograph of bilateral hilar lymph nodes (upper left image, arrows), which are better seen on coronal CT (upper right image). In the second pair of images, the left image shows a CT scan of micronodules in the peribronchovascular interstitium (arrows) and in the subpleural interstitium (arrowheads) and the right image shows micronodules in the interlobular septa (arrows), which suggest a perilymphatic distribution. The bottom image shows end-stage fibrosis with extensive deformation of the lungs, axial traction bronchiectasis, and honeycombing. Some CT features may discriminate between active lung inflammation and fibrosis. Typical inflammatory findings on HRCT include a bilateral distribution of micronodules, perilymphatic and bronchocentric distribution, perihilar ground-glass opacities, and varying degrees of fibrosis.[56,57]

Positron-emission tomography (PET) and CT with ^{18}F-fluorodeoxyglucose (FDG PET-CT) is a sensitive method for assessing inflammatory activity and the extent of disease in sarcoidosis. In Panel C, FDG PET-CT reveals extensive hypermetabolic lymphadenopathy (cervical, supraclavicular, axillary, mediastinal, abdominal, and inguinal), as well as high activity in the lung parenchyma, spleen, and bone marrow; heterogeneous activity in the parotids is more pronounced on the left. FDG PET-CT is especially useful in patients with unexplained symptoms that have no connection with already known organ involvement, in patients with persistent symptoms without serologic signs of inflammatory activity, and in patients with radiologic signs of fibrosis in whom the presence of inflammation is uncertain, as well as for the detection of a suitable location for biopsy and for the detection of active cardiac sarcoidosis.[58] Panel D shows an FDG PET-CT scan of the heart, with focal areas of inflammatory activity in the left ventricle (orange arrows), intermediate wall (white arrows), and right ventricle wall (gray arrows). Localization is similar on magnetic resonance imaging (MRI); an MRI scan obtained after contrast administration shows late gadolinium enhancement with increased signal intensity or contrast enhancement in the side wall of the left ventricle (orange arrows), partition wall (white arrows), and right ventricle wall (the left-most arrow).

In Panel E, CT and MRI scans obtained after contrast administration show a left parietal occipital enhancing lesion (orange arrows); the image on the right shows myelum involvement (between the two arrows) on gadolinium-enhanced MRI, which is the imaging study of choice for the diagnosis of neurosarcoidosis.

Panel F shows bone involvement. Panel G (hematoxylin and eosin stain) shows histologic images of granulomas; a biopsy is indicated when possible for detection of granulomas, but it is not always possible to obtain representative biopsy material.[52] GC denotes glucocorticoid.



scription factor 21 [TBX21]), which in turn controls the Janus kinase and signal transducer and activator of transcription (STAT) pathways and the Th1 hallmark cytokine, interferon-γ. Accordingly, STAT-dependent transcripts are abundant in the transcriptome of blood cells, lung tissues, and lymph nodes in patients with sarcoidosis.[36,37]

Through T-cell plasticity, CD4+ T cells can differentiate into other (related) functional T-cell subtypes. In a milieu with elevated levels of macrophage-derived interleukin-1 and interleukin-6, CD4+ T cells can differentiate into Th17 and Th17.1 cells, with high production of interleukin-17 and interferon-γ, respectively.[23] Ramstein et al. described a marked increase of Th17.1 cells in sarcoidosis, and they proposed that Th17.1 cells might be the predominant producers of interferon-γ in pulmonary sarcoidosis.[16]

Another part of the immune response is interference with the ability of memory T lymphocytes to recall antigens. In sarcoidosis, however, dampening of the immune response by regulatory T cells appears to be dysfunctional and is accompanied by an exaggerated adaptive immune response.[28,37] Thus, according to current concepts, the disturbed adaptive immune response in sarcoidosis contributes to the pathogenesis of the disorder.[1]

T-CELL ANTIGENS

In many patients with sarcoidosis, CD4+ T cells accumulating in the lung preferentially express certain T-cell receptor variable gene segments, suggesting recognition of specific antigens.[34] A number of potential autoantigens were identified in HLA molecules of BALF cells from HLA-DR3–positive patients with sarcoidosis (e.g., peptides derived from ATP synthase, lysyl–transfer RNA synthetase, and vimentin).[38] Hypothetically, these T cells are recruited to the lungs because they recognize disease-specific antigenic peptides presented by the HLA-DRB1*03+ molecules expressed on the surface of local antigen-presenting cells. Furthermore, T-cell stimulation tests have suggested a role for vimentin, a constituent of the cytoskeleton that is secreted during cellular activation and that can function as an autoantigen in rheumatoid arthritis.[39] Positive evolutionary selection driven by infections may also play a role, as suggested by a study showing that HLA genotypes conferring a predisposition to sarcoidosis have enhanced binding to tuberculosis antigens and provide protection against tuberculosis.[40] Similarly, *Cutibacterium acnes* has been proposed as an etiologic agent, given the increased frequency of genetic material in sarcoidosis granulomas as compared with control granulomas, as well as a similar exaggerated immune response to cutibacterium in sarcoidosis T cells as compared with normal T cells.[41]

PATHWAYS TO BE EXPLORED

It was assumed that B cells, as well as Th2- and Th17-like cells — the most effective cell type in supporting B-cell activity, particularly in autoantibody production, including specific vimentin recognition — may be involved in the development of sarcoidosis and several other autoimmune conditions. These results provided new evidence of autoimmune mechanisms and an important role of humoral immune responses in sarcoidosis.[42] Furthermore, sarcoidosis appears to be associated with activation of the metabolic checkpoint kinase mammalian target of rapamycin complex 1 (mTORC1), which can be involved in the granulomatous process by activating macrophages and their differentiation into epithelioid cells (which tend to aggregate) and multinuclear giant cells. A disturbed autophagy process that normally eliminates antigens will further stimulate granuloma formation.[23] Thus, growing knowledge about newer pathophysiological pathways, such as mTORC1 and dysfunctional autophagy and activation of the nucleotide-binding oligomerization domain–like receptor protein 3 (NLRP3) inflammasome, may guide the development of new therapeutic targets.[43]

CLINICAL PRESENTATION, COURSE, AND PROGNOSIS

The presentation of patients with sarcoidosis is highly variable, with many clinical phenotypes. Although virtually any organ can be affected by this chameleon-like, multisystemic disease, the lungs are usually involved, with symptoms such as cough, shortness of breath, chest pain, and most commonly, pronounced fatigue.[1,8] Clinical symptoms vary widely, depending on which organs are affected.[6] Apart from organ-related symptoms, patients with sarcoidosis, like patients with chronic diseases in general, often have a wide spectrum of systemic, nonspecific symptoms, which are not related to a single organ and cannot be explained by the granulomas but are likely to be caused by the systemic release of inflammatory mediators (e.g., TNF-α) and are difficult to verify. Nonspecific symptoms of sarcoidosis such as fatigue, exercise limitations, cognitive impairment, and symptoms associated with small-fiber neuropathy have a great effect on well-being and quality of life.[3,17,44-47]

The clinical manifestations of the disease can generally be classified according to activity or severity (e.g., organ dysfunction) or both. Active sarcoidosis does not necessarily indicate a progressive course, a fatal prognosis, or the need for treatment. Moreover, the absence of evidence

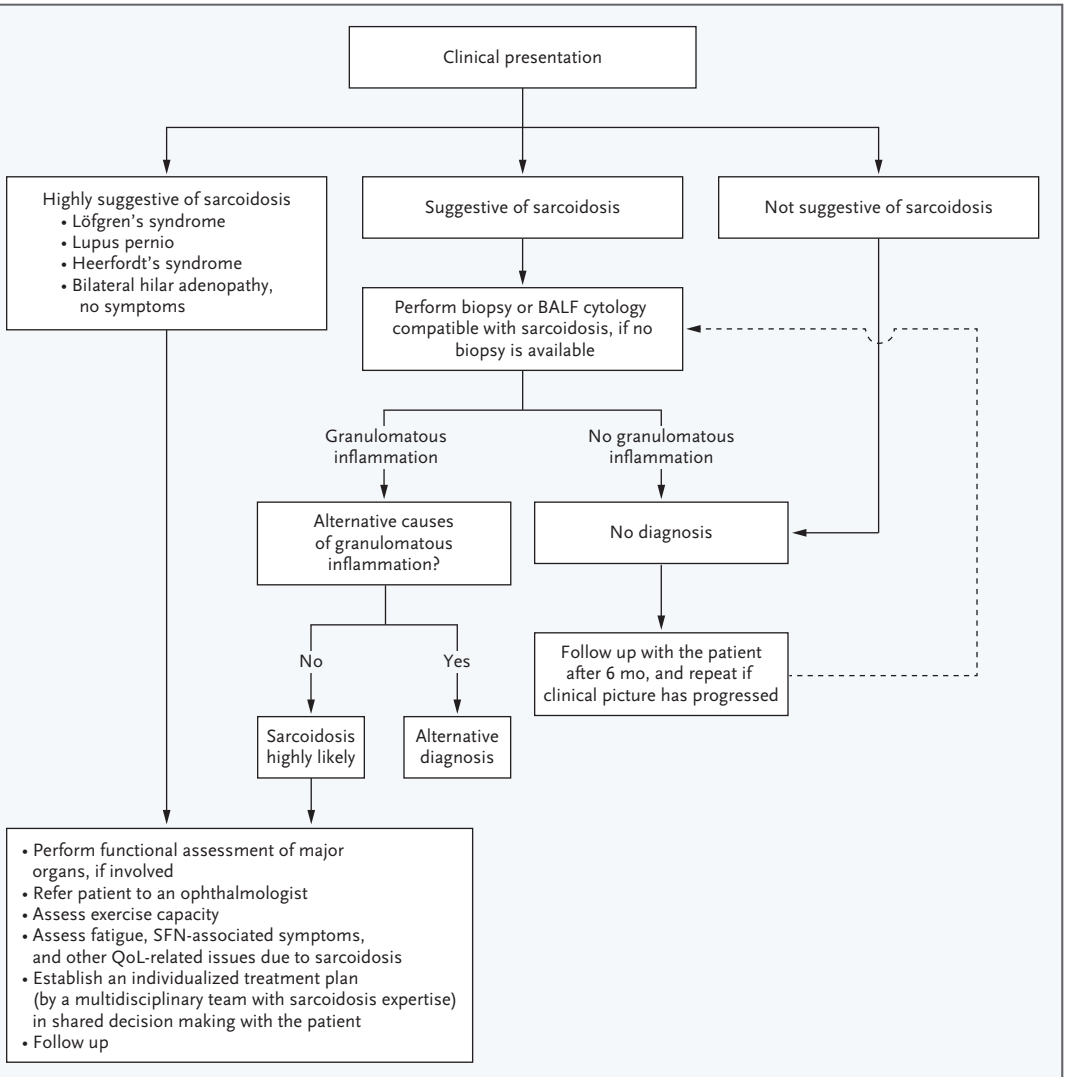


Figure 3. Proposed Algorithm for Diagnosing Sarcoidosis.

A simple algorithm for the diagnosis of sarcoidosis is not feasible, in view of the many faces of sarcoidosis. The proposed algorithm is based on expert opinion[1] and the evidence-based diagnostic pathway provided by the American Thoracic Society.[52] The diagnosis usually depends on a combination of compatible clinical findings, histologic evidence of nonnecrotizing granulomas (e.g., in transbronchial biopsy samples or ultrasonography-guided transbronchial needle aspiration of mediastinal lymph nodes), and the ruling out of alternative causes of granulomas that result in a similar histologic or clinical pattern.[1,52] BALF with an increased ratio of CD4+ T cells to CD8+ T cells supports the diagnosis. However, there is no single cell type in BALF that appears to be predictive of sarcoidosis,[15] although certain T cells have been found to be highly specific for Löfgren's syndrome.[60] Nevertheless, BALF analysis can be very helpful in the differential diagnosis. An elevated total cell count and a predominance of lymphocytes, together with nearly normal percentages of eosinophils and polymorphonuclear neutrophils and the absence of plasma cells, distinguish sarcoidosis from the most common interstitial lung diseases (extrinsic allergic alveolitis, nonspecific interstitial pneumonia, and idiopathic pulmonary fibrosis).[15] Assessment of organ involvement is very important.[1,46,52] FDG PET-CT is a sensitive method for assessing inflammatory activity and the extent of disease in sarcoidosis. FDG PET-CT is especially useful in the case of unexplained symptoms without any connection to known organ involvement.[58] Attention should also be paid to nonspecific organ-related symptoms (e.g., fatigue, everyday cognitive failure, and symptoms associated with small-fiber neuropathy [SFN]), since they can substantially influence quality of life (QoL).[3,46]

of disease activity does not rule out subclinical disease activity. Emerging evidence links the genetic risk of sarcoidosis (genotype) to the clinical manifestation and outcome (phenotype). Patients with Löfgren's syndrome have an acute clinical presentation of systemic sarcoidosis defined by the triad of erythema nodosum, bilateral hilar adenopathy, and polyarthralgia or polyarthritis, often with fever; they usually have a very good prognosis, especially those who are HLA-DRB1*03–positive.[1] More than 50% of patients with non–Löfgren's syndrome sarcoidosis will have a remission, whereas in approximately one third of patients, the disease takes a chronic course. The presence of cardiac, neurologic, renal, and progressive fibrotic pulmonary involvement with respiratory failure is associated with increased morbidity and mortality and often dictates the need for treatment.[12,48,49] Certain patient characteristics and genetic variants are prognostic (Table 1). Less than 10% of patients die from sarcoidosis; most fatal cases are due to advanced lung disease, followed by cardiac complications.[1,50] The net effect is a reported increase in the risk of death by a factor of 0.9 to 2.4.[11]

Although most patients with sarcoidosis are asymptomatic or have acute symptoms with spontaneous resolution, chronic disease develops in approximately one third of patients, waxing and waning or relentlessly progressing (if untreated) over an extended period.[51] Table 1 lists some possible adverse prognostic factors and some possible favorable prognostic factors.

DIAGNOSTIC CHALLENGES

The clinical diversity of sarcoidosis, as well as its resemblance to other, more common disorders, often leads to diagnostic uncertainty and treatment delays. Ultimately, the diagnosis of sarcoidosis is based on three major criteria: compatible clinical characteristics, identification of nonnecrotizing granulomas in one or more tissue samples, and the ruling out of other causes of granulomatous disease.[52-54] Patients most commonly present with subacute or chronic respiratory symptoms, and a diagnosis of sarcoidosis is considered on the basis of typical features on a chest radiograph or computed tomographic (CT) scan. Certain CT findings (e.g., bilateral hilar lymphadenopathy with a perilymphatic, micronodular pattern) are highly specific for sarcoidosis[55,56] (Fig. 2). Biopsy specimens obtained from the lungs or mediastinal lymph nodes provide the greatest diagnostic yield.[25,26] Surgical approaches (e.g., video-assisted thoracoscopic surgery or mediastinoscopy) reliably provide diagnostic tissue but are invasive, inconvenient, and more costly than bronchoscopic procedures. A systematic analysis of the literature showed that endobronchial ultrasound-guided transbronchial needle aspiration (TBNA) or bronchoscopy with TBNA was safe and highly effective, as well as more convenient and less expensive than mediastinoscopy.[52]

Cardiac sarcoidosis is the second leading cause of death among affected patients, after pulmonary sarcoidosis. Hence, current practice guidelines recommend routine screening for cardiac sarcoidosis in patients with newly diagnosed sarcoidosis, beginning with a history taking, physical examination, and 12-lead electrocardiogram. Patients presenting with high-risk symptoms, electrocardiographic changes (e.g., high-degree heart block[27]), or both (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) should undergo either cardiac magnetic resonance imaging (MRI) or cardiac ^{18}F-fluorodeoxyglucose positron-emission tomography and CT (FDG PET-CT) to confirm cardiac involvement on the basis of characteristic radiographic manifestations (Fig. 2). Imaging is sufficient to establish a diagnosis of cardiac sarcoidosis in most cases, obviating the need for myocardial biopsy.[59]

Awareness of other nonpulmonary manifestations of sarcoidosis may expedite management decisions.[46] Many features of sarcoidosis may aid in establishing its diagnosis and should be considered in the context of treatment (Figs. 2 and 3). Clinical manifestations that are highly predictive of sarcoidosis and preclude the need for further diagnostic testing include Löfgren's syndrome and lupus pernio (Fig. 2). In contrast, neurosarcoidosis is often a diagnostic puzzle, most commonly manifested as cranial-nerve deficits, and delays in diagnosis and treatment can lead to permanent disability. The diagnostic workup for neurosarcoidosis includes MRI of the head, cerebrospinal fluid analysis, and detection of sarcoidosis outside the nervous system.

Biomarkers should be viewed as evidence of

active inflammation, not as pathognomonic tests.[61] The serum angiotensin-converting enzyme level is elevated in 50 to 60% of patients with sarcoidosis. However, this biomarker lacks diagnostic specificity, so its use is limited to evaluating the therapeutic response.[61,62] Other biomarkers — soluble interleukin-2 receptor, C-reactive protein, serum amyloid A, and chitotriosidase — are generally useful for assessing disease activity, but FDG PET-CT is most effective for detecting tissue-specific inflammatory activity and identifying sites for diagnostic biopsies (Fig. 2).[58,61,63] Table S1 lists recommended approaches to screening and evaluation for various manifestations of sarcoidosis and sarcoidosis-associated symptoms, as well as goals of care and management strategies, in more detail.

MANAGEMENT

Management of sarcoidosis is a major clinical challenge because of the highly variable disease manifestations. The decision of whether (and, if so, when) to treat an individual patient who has sarcoidosis depends on two major factors: the risk of organ failure or death and the extent to which the patient's quality of life is impaired.[3,12,46,48,49] The decision is complex and cannot be standardized.[3,48] In most patients with sarcoidosis, the disease resolves spontaneously and does not require systemic therapy. However, for patients with severe disease, timely treatment can mitigate disease manifestations and prevent long-term complications.[48] Current treatment standards are based on low-quality evidence,[64] but experts agree that therapeutic goals should focus on suppression of inflammation-induced organ dysfunction, assessed on the basis of objective metrics (e.g., lung function), and on the avoidance of toxic effects of drugs.[1,12,48,49] However, these two measures of disease manifestations can be misleading, since many patients continue to feel unwell despite objective resolution.

A consensus statement from sarcoidosis experts endorses glucocorticoids as the primary treatment for sarcoidosis, on the basis of their efficacy and ease of use (low cost and oral administration) (Fig. 4).[64] Unfortunately, glucocorticoids are associated with a dose-dependent risk of serious adverse effects, which tend to accumulate with prolonged use.[49,69] Moreover, no discernible benefits in disease outcomes are noted with higher doses versus lower doses, particularly for maintenance therapy.[48,49] Thus, for patients requiring long-term suppression of inflammation to prevent irreversible organ damage or intolerable symptoms, early institution of glucocorticoid-sparing antisarcoidosis agents is generally recommended, either alone as first-line treatment or with a rapid reduction in glucocorticoid doses (Fig. 4).[13,49] Commonly used glucocorticoid-sparing agents for second-line treatment include methotrexate (the agent studied and prescribed most often), azathioprine, leflunomide, and mycophenolate. An alternative in this category is the antimalarial agent hydroxychloroquine, which has proved particularly useful for cutaneous disease, hypercalcemia, and some cases of neurosarcoidosis.[48]

If nonglucocorticoid antisarcoidosis agents, administered alone or in combination with glucocorticoids, are toxic or ineffective or if the disease is severe and progressive, third-line treatment with biologic agents or advanced immunomodulating agents may be considered.[12,48,49] Infliximab and adalimumab (both TNF-α inhibitors) are effective options (Fig. 4).[64] Although not yet extensively studied in sarcoidosis, biosimilar anti–TNF-α agents also seem promising.[12] Third-line alternatives, although they are associated with a risk of specific toxic effects themselves, mitigate the risks associated with glucocorticoids but present other problems and risks, including greater cost, the need to monitor patients for the toxic effects of the drugs, and the inconvenience of intramuscular or intravenous administration, as well as lack of familiarity with these agents on the part of many physicians.[49] Since immunomodulating drugs compromise antimicrobial defenses, vaccination and other measures for preventing infection are crucial in patients with sarcoidosis who are treated with these agents.[70]

The side-effect profile associated with treatments for sarcoidosis varies greatly from one patient to the next, as does the efficacy of treatments, so a simple treatment algorithm that works for all patients is not feasible. The duration of treatment depends on the individual phenotype. A small subgroup of patients with sarcoidosis requires long-term treatment to pre-

Inform the patient well and share care and decision making

Assess the need for sarcoidosis treatment repeatedly and define the target organs and symptoms

Clinical phenotypes

- **Asymptomatic; no risk of organ damage or disease progression**
- **Symptomatic or impaired QoL or both; no risk of organ damage or functional impairment**
- **Symptomatic or impaired QoL or both; risk of organ damage or functional impairment**
- **Severe danger: risk of irreversible organ damage or death**

Treatment options

- **Observation**
  No treatment indicated; encourage exercise and a healthy lifestyle
- *
- **Local treatment**
  - Lung: inhalation GCs
  - Skin: cream, ointment
  - Eye: drops, ointment
  - LS: consider NSAIDs
- *
- **First-line treatment**
  GCs; consider HCQ in severe skin lesions or hypercalcemia
- *
- **Second-line treatment**
  GCs and SSAS: MTX, AZA, MMF, or LEF; consider add-on HCQ
- *
- **Third-line treatment**
  GCs and SSAS; add-on TNF-α inhibitor

* Denotes unacceptable side effects or insufficient response

Goals of care: prevent or minimize organ damage and improve QoL

- **Disease control, no unacceptable side effects, tapering of agents**
- **Disease control, no unacceptable side effects, tapering of GCs**
- **Disease control, no unacceptable side effects, complete withdrawal of GCs and induction of SSAS agents**
- **Disease control, no unacceptable side effects, tapering of GCs, continuation of third-line treatment**

Assess for the following conditions and define treatment options

Conditions

- Fatigue
- Sleep apnea or OSAS
- Depressive symptoms
- Pain
- SFN-associated symptoms
- Cognitive failure
- Progressive pulmonary fibrosis
- Hypoxemia
- Life-threatening heart rhythm disturbances
- Sarcoidosis-associated pulmonary hypertension
- End-stage organ damage

New therapies that are under investigation

Rituximab or newer agents such as JAK2 inhibitors, tocilizumab, RCI, VIP, antifibrotics (in case of refractory fibrotic lung disease), and nicotine transdermal patches

Consider personalized treatment

Treatment options

- **Organ transplantation options**
  - Lungs
  - Heart
  - Liver
- **Supportive care**
  - Exercise, healthy lifestyle
  - Rehabilitation
  - Psychological counseling
  - Patient support groups
  - Cognitive behavioral therapy
  - Mindfulness-based therapy
  - CPAP and BiPAP
  - Supplemental oxygen
  - ICD or pacemaker
- **Pharmacologic agents not directed at granulomas**
  - Antioxidants
  - Neurostimulants
  - Antidepressants
  - Analgesics
  - Anticonvulsants
  - IVIG
  - SAPH treatment

Figure 4 (facing page). Proposed Treatment Algorithm for Sarcoidosis.

The lack of approved drugs tested in randomized, controlled trials hampers the development of standardized treatment protocols for sarcoidosis.[1,65] The care of patients with sarcoidosis should be modified on the basis of the organs involved, the associated symptoms, and the risk of irreversible organ damage or death. Some symptoms associated with sarcoidosis respond to therapies that do not directly suppress sarcoidosis granulomas.[5] A stepwise approach to therapy is generally recommended. Systemic sarcoidosis with burdensome symptoms usually responds to first-line treatment with glucocorticoids (GCs), but one needs to weigh the risk of toxic effects that are associated with long-term use against the risk of relapse.[49] The ideal dosing and duration of therapy are unknown and are likely to vary on an individual basis. A starting dose of 20 to 40 mg of prednisone or the equivalent per day, with a maximum of 0.5 mg per kilogram of body weight, is generally recommended, although patients with severe disease manifestations may initially be given much higher doses for a short period. Lower induction doses of GCs may be reasonable in less severe cases. GCs are not desirable for the management of chronic disease, since there is a dose-dependent risk of complications, including serious cardiovascular complications.[66] Thus, tapering to the lowest effective dose (or tapering to withdrawal of GCs) is an ultimate treatment goal, and GC-sparing agents should be considered. In GC-refractory cases, second-line treatment with GC-sparing drugs, referred to as steroid-sparing antisarcoidosis (SSAS) agents, is a reasonable alternative. Methotrexate (MTX) is commonly prescribed, with a starting dose of 10 to 15 mg weekly, adjusted up to 20 mg or higher if necessary and if the side-effect profile is acceptable. It is advised to combine MTX with folic acid.[67] Subcutaneous MTX is recommended in the event of gastrointestinal side effects.[49] Monoclonal antibodies targeting TNF-α, particularly infliximab and adalimumab, are recommended as third-line treatment. Concomitant use of adjunctive immunosuppressants such as MTX reduces the risk of neutralizing antibodies and increases drug efficacy. In addition to pharmacologic treatment, it is often beneficial, in terms of improving QoL, to offer counseling and encourage lifestyle changes, such as physical training for patients with fatigue or deconditioning.[68] Dietary modifications may also be beneficial, as suggested by studies indicating that antioxidants may mitigate chronic cough and reduce reliance on GCs.[31,32] AZA denotes azathioprine, BiPAP bilevel positive airway pressure, CPAP continuous positive airway pressure, HCQ hydroxychloroquine, ICD implantable cardioverter–defibrillator, IVIG intravenous immune globulin, LEF leflunomide, LS Löfgren's syndrome, MMF mycophenolate mofetil, NSAIDs nonsteroidal antiinflammatory drugs, OSAS obstructive sleep apnea syndrome, RCI repository corticotropin injection, SAPH sarcoidosis-associated pulmonary hypertension, and VIP vasoactive intestinal peptide.

vent progressive organ damage. Factors not directly related to inflammation or treatment side effects often compromise the well-being of patients with sarcoidosis. For instance, many such patients report severe, life-altering fatigue and an inability to concentrate,[46] affecting their productivity at work[71] and overall quality of life.[3,5] Patients with sarcoidosis are often deconditioned and may benefit from structured, regular exercise to reduce fatigue and improve their quality of life.[5,68,72] Sarcoidosis-associated pulmonary hypertension, chronic neuropathic pain, or dysautonomia often responds poorly to immunosuppressive therapy and may benefit from alternative treatments (e.g., antidepressant agents or dietary measures) to mitigate symptoms.[44,73] Transplantation for sarcoidosis is performed infrequently (in 3 to 5% of patients) but is effective, as reflected by a post-transplantation patient survival rate (approximately 70% at 5 years) that is similar to the rate for patients with other indications for lung transplantation (50 to 60% at 5 years).[74] The main factors associated with worse survival are older age and extensive preoperative lung fibrosis. Treatment guidelines for sarcoidosis are evolving, and health care providers are advised to consider a personalized approach based on individual variations in disease manifestations (Tables S1 and S2).

FUTURE DIRECTIONS

There is now a great need to identify (through proteomics, genetics, and epigenetics) additional key genetic components of sarcoidosis to reveal new factors that drive or resolve granuloma formation. New methods allowing in situ sequencing can localize immune transcripts within granulomas, in order to elucidate their role in progressing or nonprogressing granulomas that correlate with disease development.[1,65] Applying new techniques such as whole-exome sequencing in patient cohorts that are carefully phenotyped will improve the characterization of inflammatory pathways, identify disease markers, reveal new therapeutic targets, and encourage the investigation of new therapies (Fig. 4).[75,76] This initiative will have an important effect on clinical management. The ongoing search for specific sarcoidosis antigens, as suggested by

features of the immune response, may reveal markers of importance for pathogenesis. New concepts suggest that sarcoidosis — or subgroups or variants of sarcoidosis — is an autoimmune disease with immune reactions against self-proteins.[2] We expect to learn more about functions of T lymphocytes, their various stages of differentiation, their activation through interaction with cells of the innate immune system, and their influence on the disease outcome.

A major challenge for clinicians is to rethink and reconfigure therapeutic approaches to the disease. Treating patients with immunosuppressive drugs such as glucocorticoids, glucocorticoid-sparing antisarcoidosis agents, and anti–TNF-α agents is well accepted.[1,65] However, we need to optimize the use of pharmacotherapeutic interventions targeting phenotype-specific mechanisms in order to individualize treatment while improving the quality of life.[13] A pivotal aspect is to regularly consider how to reduce the side effects of glucocorticoids. Besides reducing glucocorticoid doses by combining them with immunosuppressive drugs, new strategies for optimizing treatment need to be explored, including lifestyle changes, physical therapy, and dietary guidance.[31,68] For instance, a flavonoid-rich diet in conjunction with glucocorticoids has been reported to increase the efficacy of glucocorticoid therapy, thereby reducing the dose required for antiinflammatory action.[31] The benefits of flavonoids and other antioxidant supplements may be related to the restoration of normal antioxidant levels in patients with sarcoidosis.[31,77]

Advancing our understanding of the pathophysiology of sarcoidosis and improving clinical care for patients will require physicians with multidisciplinary skills who are dedicated to the treatment of patients with sarcoidosis, focus on somatic as well as psychosocial aspects of the disease, and actively engage with patients to improve adherence to treatment, optimize its benefits, and reduce the risk of side effects.[5,6] Patients with sarcoidosis will benefit from the care provided by a treating physician who understands what the disease is all about and seriously considers each patient's symptoms.[46] Enhanced awareness of the special needs of patients with sarcoidosis — for instance, through patient advocacy groups — and specialized training of health care providers are necessary to provide adequate and standardized care globally for patients with sarcoidosis.[3,5,46]

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