

Review article

Pulmonary sarcoidosis

Sarcoidosis is a multisystemic disease of unknown aetiology characterized by the formation of immune granulomas in involved organs. It is a worldwide disease that mainly affects 25–40 years old people with a lifetime incidence rate of 0.85–2.4%. Multiple clinical phenotypes are observed according to presentation, involved organs, disease duration and severity. Sarcoidosis primarily affects the lungs and the lymphatic system. The prevailing pathogenic hypothesis is that various antigens could promote sarcoidosis in genetically susceptible hosts, both these factors modulating the incidence and the clinical phenotype of sarcoidosis. So far, environmental agents have been suspected, including possible mycobacteria and propionibacteria. Interferon- γ , tumour necrosis factor (TNF)- α , interleukin (IL)-12 and IL-18 play a critical role in driving the Th1 commitment in the course of granulomatous process. Evolution of sarcoidosis is often marked by spontaneous resolution within 12–36 months, but can be severe because of chronic cases with pulmonary fibrosis or involving other organs, including heart, central nervous system and eyes. Mortality, ranging between 0.5 and 5%, is most often related to pulmonary fibrosis. Corticosteroids can reverse the granulomatous process, but are only suspensive, and their long-term benefit remains under question. Corticosteroids are recommended when sarcoidosis shows unfavourable clinical tolerance and evolution. Alternative and corticosteroid-sparing therapies are of increased interest in difficult cases, while targeted new drugs such as anti-TNF- α are still under investigation.

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Sarcoidosis is a multisystemic disorder of unknown aetiology usually affecting the respiratory tract and characterized by the formation of immune granulomas in involved organs (1, 2, 3). Many arguments converge on the prevailing hypothesis that various antigens may promote sarcoidosis in genetically susceptible hosts, which may account for the diversity of disease expression. This hypothesis is strongly supported by several data on the pathogeny of granuloma formation, including time and space-related clusters (4), tracing case contacts (5, 6), familial transmission (7) and correlations between human leucocyte antigens (HLA) and other polymorphisms and the incidence or phenotype of sarcoidosis (3, 8, 9).

Sarcoidosis is a worldwide disease with a lifetime incidence rate of 0.85–2.4% (9), but generally affects 25–40 years old people (10–12). The clinical phenotype of sarcoidosis can be extremely diverse in terms of presentation, involved organs, duration and severity (1, 10, 13). Lung involvement is present in 86–92% of cases according to chest X-ray, alone or in association with extrapulmonary localizations in about 50% of cases (10, 13–15). In at least half of cases, sarcoidosis follows a benign course with spontaneous resolution within less than 12–36 months (10, 13, 15). However, the disease can be severe. Severity can result from various mechanisms. It

can be due to the localization of granulomatous lesions in particularly vulnerable organs such as central nervous system, heart, eye, kidney or larynx. It can also be the consequence of the unusual abundance of granulomas in the lung, leading to subacute respiratory insufficiency. Pulmonary fibrosis develops in chronic forms of the disease and is actually the most frequent severe manifestation in Western Europe and North America, accounting for main morbidity and most of the deaths caused by sarcoidosis (10–12, 16, 17). Last, sarcoidosis can induce abnormal metabolism of vitamin D3 within granulomatous lesions and hypercalcaemia (18). Mortality attributable to sarcoidosis is estimated between 0.5 and 5% (12, 19). Although this proportion may seem low, it is clinically relevant for a not so uncommon disease affecting relatively young people.

These heterogeneous, sometimes conflicting aspects of sarcoidosis explain why, besides diagnosis, the major concern for clinicians is to determine prognosis and to offer the best therapeutic option (13). The mainstay of sarcoidosis treatment has been systemic corticosteroids for many years but several points need to be underlined. First, corticosteroid therapy is not 'curative' but purely 'suspensive' and a relapse of the disease can be observed in case of premature interruption. Secondly,

corticosteroids suppress the granuloma formation and reverse consecutive clinical, radiographical, functional and biological manifestations (13). However, they do not affect established fibrotic lesions. Moreover, there is uncertainty regarding the effects of therapy on the natural history of the disease, particularly on preventing the development of fibrosis in chronic cases (13). Last, there is usually a threshold dose of corticosteroids that allows a control of granuloma formation. Immunosuppressive agents have been introduced either as sparing or alternative drugs to corticosteroid therapy, mainly to reduce the awkward side-effects of corticosteroids in chronically treated patients (13). The better understanding of sarcoidosis pathogeny made possible the development of attractive novel therapies targeted on different steps of granulomatous process. Among them, interest has been recently taken in drugs inhibiting tumour necrosis factor (TNF)- α , a corner-stone cytokine of sarcoidosis (20).

The aim of the current review is to summarize our knowledge on this complex disease, sarcoidosis, focusing on the new data concerning pathogeny, clinical phenotypes and therapy.

Pathogeny of sarcoidosis

It is now well established that sarcoidosis is a granulomatous disorder resulting from an uncontrolled cell-mediated immune reaction characterized by the presence of typical granulomas at the sites of the disease (10, 13, 21). Although the aetiology of sarcoidosis remains unknown, important advances in the pathogeny of this disorder have been made recently, leading to a better understanding of the mechanisms of granuloma formation and allowing a better approach to individual or environmental factors linked to the occurrence of the disease.

Morphology of sarcoid granulomas

Sarcoid granulomas are immune granulomas resulting from a specific cell-mediated immune response to an antigenic agent (Fig. 1). They are made of 'epithelioid cells', so called because of their resemblance with epithelial cells in light microscopy, and T lymphocytes (Fig. 2) (21). Epithelioid cells represent an activated form of macrophages. Their monocytic origin has been clearly established, and electron microscopy has demonstrated characteristics of secretory cells. Immune granulomas are complex structures, typically composed of a central follicle made of tightly packed epithelioid cells and T lymphocytes surrounded by a ring of fibroblasts, and a peripheral loose area rich in lymphocytes (Fig. 2). CD4⁺ T lymphocytes predominate within the follicle, whereas CD8⁺ T lymphocytes and B lymphocytes are present mainly in the peripheral area. Early fibrotic changes are sometimes present at the periphery of the granuloma (Fig. 1).

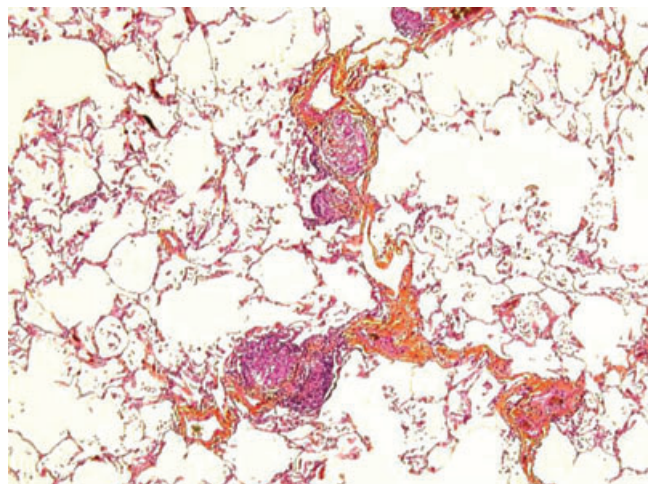


Figure 1. Scattered well-demarcated non-necrotizing granulomas along an interlobular septa that characterize sarcoidosis. Mild fibrotic changes are seen at the periphery of the granulomas (HES $\times 20$).

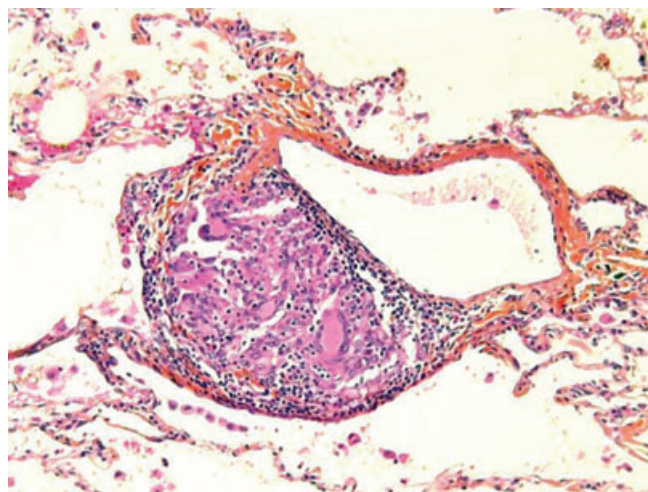


Figure 2. Peri-vascular sarcoid granuloma typically composed of central epithelioid and giant cells surrounded by a ring of lymphocytes (HES $\times 200$).

Formation of sarcoid granulomas

Animal models have proved useful to study the kinetics of granuloma formation (21). Immune granulomas may be initiated by infectious, inorganic and organic agents. Monocytes/macrophages are the first cells to be recruited to the site of a developing granuloma. If the antigenic agent responsible for their recruitment is not totally or slowly degraded, they accumulate and progressively mature into epithelioid cells. Simultaneously, T lymphocytes infiltrate into these cell aggregates which organize into compact granulomas. The interactions between these two cell types play a central role in the early development

of the granuloma. The antigenic substances responsible for the recruitment of macrophages are internalized, processed and presented to specific T lymphocytes in association with class II major histocompatibility complex (MHC) molecules. Antigenic presentation stimulates T cells to proliferate and accumulate via the production of interleukin (IL)-2. Activated lymphocytes release a number of lymphokines that in turn activate macrophages. Both cell types in turn release several mediators that amplify the cell immune response by recruiting other T lymphocytes and monocytes which aggregate and differentiate, forming a granuloma.

Immune granulomas are dynamic structures that evolve over time. The periphery of the granulomas is an area of transit where freshly recruited monocytes are continually entering. They then penetrate the central follicle where they differentiate into epithelioid cells forming subdivisions each centred by lymphocytes and monocytes (22). After their stay within the follicle, epithelioid cells leave the granuloma via the peripheral zone and are eliminated in the surrounding structures. Sarcoid granulomas may persist several months or years, but they usually resolve, sometimes leading to a small fibrous scar.

Sarcoid macrophages and T lymphocytes

It is now well established that a specific cell-mediated immune response against a yet unidentified antigen is associated with granuloma formation in sarcoid patients. As expected for a cell-mediated reaction, sarcoidosis is characterized by the accumulation of activated monocytes/macrophages and CD4⁺ T lymphocytes at all sites of disease activity (10, 13, 21, 23, 24). In the lung, this accumulation in both air spaces and interstitium (alveolitis) precedes and accompany the development of granulomas (25). As cells of the lower respiratory tract are easily recoverable by bronchoalveolar lavage (BAL), the alveolitis from patients with pulmonary sarcoidosis has been extensively studied (reviewed in refs 21, 23, 24). Alveolar macrophages (AM) from sarcoid patients have been shown to express a phenotype of recently recruited monocytes, including molecules involved in leucocyte-endothelial cell recognition. Sarcoid AM are metabolically active. Their phagocytic capacities are increased. They produce more metalloproteinases, oxygen and nitrogen free radicals, angiotensin-converting enzyme, and lysosome than normal AM. They express IL-2 receptor (CD25), and transferrin receptor (CD71) as do proliferating cells stimulated by growth factors. They actively incorporate gallium-67, possibly via transferrin receptor (26), and highly bind somatostatin analogues (27). They also express M-CSF and GM-CSF receptors, involved in macrophage proliferation, and proliferate at a higher rate than normal AM. They express at their surface larger amounts of class II MHC molecules and different adhesion molecules necessary for interactions

with T cells, and they have been shown to be more potent antigen presenting cells than normal AM. Epithelioid cells themselves, which strongly express B7 and CD40 co-stimulatory molecules, do have the capability to fully activate T cells (28). Finally, sarcoid AM produce numerous cytokines and chemokines involved in granulomatous responses.

T lymphocytes from sarcoid patients are also activated (21, 23, 24). The majority of these cells are CD4⁺ T cells expressing a T 'memory' cell phenotype and the α/β T-cell receptor (TCR). They express IL-2 receptor at their surface and are able to proliferate *in vitro* in response to IL-2. They also express transferrin receptor, class II MHC molecules, the very late activation antigen (VLA-1), and the ligand for B7 costimulatory molecules (CD28) (28) together with various adhesion molecules necessary for interactions with macrophages. They spontaneously release interferon (IFN)- γ , IL-2 and numerous other cytokines and chemokines involved in granuloma formation and maintenance. In this regard, as mentioned above, if IL-2 plays a critical role in the local proliferation of lymphocytes during the granulomatous response, other cytokines, such as IL-15, may be involved in this process (23, 24). Interleukin-15 is known to influence T-cell proliferation and recruitment, and this cytokine is expressed by AM from sarcoid patients. Furthermore, since IL-15 inhibits T-cell apoptosis, this factor could favour the persistence of the granulomatous process.

Cytokines and sarcoid granulomas

Numerous cytokines and other mediators are produced by both activated macrophages and T lymphocytes during granulomatous responses, favouring granuloma formation and maintenance (reviewed in refs 21, 23, 24, 29). The cytokine pattern in lesions and LBA from patients with sarcoidosis have been shown to be of the Th1 phenotype. Through the production of Th1 cytokines, sarcoid T cells favour the organization of the local inflammatory response into granulomas. Sarcoid T cells express elevated levels of IL-2 and IFN- γ . Interleukin-2 acts as a local growth factor for T cells, whereas IFN- γ enhances the accessory and cytotoxic functions of local macrophages, increases the cytotoxic function of T cells, and regulates the secretion of other lymphokines. A number of data suggest that IFN- γ and cytokines such as TNF- α , IL-12 and IL-18 play a critical role in driving the Th1 commitment during the granulomatous process. Experiences in mice defective in IFN- γ or TNF- α activities, or both, indicate that these cytokines are essential for the induction and maintenance of granulomas. Interleukin-12 and IL-18 also are important for the induction of Th1 responses. Both cytokines are known to induce IFN- γ production and to enhance T-cell cytotoxicity. They are increased in the lungs of patients with sarcoidosis and synergistically stimulate IFN- γ production by sarcoid BAL cells. Moreover, sarcoid macrophages,

unlike normal AM, spontaneously produce high levels of IL-12, and sarcoid T lymphocytes express the functional chain of the IL-12 receptor known to signal the Th1 differentiation. Various other cytokines are produced at sites of disease activity, among which GM-CSF and LT- β seem to be important for the formation of granulomas (30). Very recently, data have been reported which support a possible role for IL-27 in human granulomatous disorders characterized by a Th1 response (31). Finally, several chemokines, including MIP-1, 3, MCP-1, RANTES, IP-10, IL-16 and osteopontin, are produced in sarcoid lesions suggesting they play a role in the pathogenesis of sarcoidosis by favouring the migration and accumulation of monocytes and T cells at the sites of the disease (24).

Aetiology of sarcoidosis

The aetiology of sarcoidosis remains unknown and is not easy to clarify because of its heterogeneous clinical course, the influence of ethnic and genetic factors, and its resemblance to other granulomatoses of various known causes. Currently, the disease is viewed as the consequence of a chronic immunological response associating a genetic susceptibility and specific environmental factors.

Genetic susceptibility

Genetic factors are clearly involved in the occurrence of sarcoidosis, as suggested by the highly variable prevalence and incidence of the disease in individuals from different ethnic and racial groups, and by the existence of familial forms with a higher risk of disease in family members than in the general population (32, 33). As the sarcoid granulomatous process is mediated by activated macrophages and CD4⁺ T cells, genetic predisposition could be related to the regulation of the immunological response, to antigen presentation/processing, or to the function of T cells. In this regard, numerous studies have emphasized associations between HLA class II alleles and sarcoidosis in patients of different racial or ethnic groups. Varying associations have been observed, depending on the populations studied (32, 33). Whereas several alleles have been identified that confer susceptibility to the disease (HLA-DR3, 5, 8, 9, 11, 12, 14, 15, 17, HLA-DPB1, HLA-DQB1), others seem to be protective (HLA-DR1, DR4). Very recently, it has been suggested that the influence of HLA class I alleles on sarcoidosis could be more pronounced than previously thought, and that both class I and class II molecules should be relevant to evaluate in sarcoidosis patients (8).

Other genes have been targeted because of their known expression in the course of the disease (32, 33). For instance, it has been suggested that the polymorphism of genes encoding IL-1 α , TNF- α , CC chemokine receptor 2

and 5, angiotensin-converting enzyme, vitamin D receptor, natural resistance-associated macrophage protein (NRAMP gene), or transporters associated with antigen processing (TAP genes) could play a role in sarcoidosis susceptibility. From these studies, it has been suggested that different haplotypes could be associated with different forms of the disease. In this respect, a strong association between CCR2 polymorphisms and Löfgren's syndrome has been recently reported, suggesting a prominent role for this receptor in acute forms of sarcoidosis (9).

Finally, genetic alterations such as microsatellite instability or loss of heterozygosity have been shown in some patients with pulmonary sarcoidosis (34). Such genetic alterations, known to be important stages in cancerogenesis, could help explain the higher risk to develop cancer following sarcoidosis (35).

Environmental factors

Several lines of evidence support the idea that sarcoidosis results from exposure to specific environmental agents (23, 32, 33). For instance, the existence of seasonal variations in disease presentation and of geographical and occupational clusterings suggest that a communicable environmental factor might be the triggering agent. Other more direct arguments supporting the idea of a transmissible agent are provided by the occurrence of cutaneous granulomas following intradermal inoculation with pretreated sarcoid tissue in the course of the Kveim-Siltzbach test (36), and by the occurrence of granulomas in the lungs of heart or bone marrow transplanted patients from donors with a history of sarcoidosis (37, 38). Furthermore, immune granulomas may be initiated by various agents, including infectious agents (mycobacteria, parasites and fungi), inorganic agents (beryllium, zirconium and aluminium) and organic particles. All these substances are internalized by macrophages, all share a low biodegradability or the capacity to persist within macrophages, and all act as antigens. Inorganic particles which are not immunogenic, such as silica, may also accumulate and persist within macrophages, but they do not induce the formation of immune granulomas.

Research aiming at identifying the potential triggers of the sarcoid reaction focused these last years on TCR repertoire, to identify specific antigens, and on the detection of mycobacteria.

Sarcoid T-cell receptor repertoire

T-cell receptors are heterodimeric glycoproteins generated by rearrangements of variable (V), diversity (D), joining (J) and constant (C) region gene segments. These highly diverse molecules constitute the TCR repertoire and play a central role in antigen recognition and in antigen-specific T-cell activation (39). In theory, if sarcoidosis is a disease triggered by specific antigens, an

oligoclonal expansion of specific T cells activated by these antigens might be present at the sites of the disease. Restricted usage of V α or V β segments of TCR consistent with oligoclonality has been reported in different studies (23). However, only a limited number of T-cell clones using preferentially some V α or V β segments have been detected, associated with an overall polyclonal expansion of T cells using all the known V gene segments. These findings suggest that sarcoid alveolitis results from two distinct processes, a local clonal expansion of T cells, and an apparently nonspecific accumulation of T cells that use an extremely diverse V repertoire. It is likely that, once the granulomatous response is triggered by specific T cells, other T cells are recruited and nonspecifically activated via the inflammatory cascade that develops at the sites of the lesions.

Sarcoidosis and mycobacteria

Pathological similarities between sarcoidosis and mycobacterial infections such as pulmonary tuberculosis have led for a long time to suspect the role of mycobacteria in the aetiology of sarcoidosis. However, the attempt to detect or to isolate mycobacteria in sarcoid tissues using conventional microbiological techniques failed to support this possibility. More recently, the development of sensitive molecular approaches, such as polymerase chain reaction (PCR), allowing the identification of mycobacterial DNA, has strongly stimulated this field of research. Numerous specific molecular studies have been reported in the last decade, but results are contradictory (33). The majority of studies, even those using the most sensitive PCR techniques, failed to detect mycobacterial DNA, including *Mycobacterium tuberculosis* DNA, or detected these molecules in relatively few patients. These findings do not support a pathogenetic role of mycobacteria in sarcoidosis. However, as discussed elsewhere (40), caution must be exercised in the interpretation of these data, as false-positive results can be linked to DNA or PCR product contamination, while the sensitivity of the techniques can be implicated in the absence of positive response.

While the role of mycobacteria in sarcoidosis aetiology remains a matter of debate, the role of other bacteria has been investigated. Recently, a study from a large series of Japanese and European (Italy, Germany and England) sarcoid patients demonstrated that high copy numbers of propionibacterial DNA, either from *P. acnes* or *P. granulosum*, were found in tissues from all but two patients (41). Another study performed in Greece also reported the presence of *P. granulosum* in a significant proportion of patients with sarcoidosis (42). In addition, the detection of *P. acnes* DNA in BAL cells was found to be significantly more common in Japanese sarcoid patients (43). Last, clear evidence of the contribution of indigenous *P. acnes* to the formation of granulomatous lesions in mice lung has been reported very recently (44).

These findings make propionibacteria better candidates than mycobacteria for an aetiological role in sarcoidosis. Further studies are needed, however, to demonstrate they do play a role in triggering sarcoid granulomatous response.

Epidemiology

The incidence, the course of sarcoidosis and the involved organs vary according to sex, age, race, previous cases in relatives, HLA and other polymorphisms, and smoking habit (1, 7–9, 11, 12, 14, 45). The incidence of sarcoidosis is estimated between 15.3 and 21.7/100 000 according to sex and series (11, 12). The female/male ratio is between 1.2 and 1.5/1 (1, 2, 12, 14). About 70% of cases are 25–40 years old at presentation (1, 2, 46) while 30% are over 50 years of age (14). Sarcoidosis is rare in childhood (2, 46). The mean age at onset is respectively lower and higher than 40 years in men and women. In a Scandinavian series a peak incidence between 25 and 35 years was found in both sexes and a second lower but broader peak between 45 and 65 years of age in women (12). However, such a second peak was not observed in the ACCESS study from United States (14). Sarcoidosis incidence is four times higher in black than in white individuals (11). The increased risk in relatives primarily concerns the siblings of the index cases with sarcoidosis reaching the odd ratio of 5.8 (7). The role of genetic and environmental factors have been discussed in the 'Aetiology' section. Acute onset with erythema nodosum is more often seen in young European women with particular genetic haplotypes (1, 2, 8, 9), while extrathoracic localizations are more frequent in black subjects (Tables 1 and 2).

Table 1. Symptoms of patients with sarcoidosis at presentation

Clinical manifestations	Frequency			References
	Global (%)	Factors of increase	Factors of decrease	
Respiratory symptoms	30	Blacks	Whites	(1, 46)
Dry cough	30			
Dyspnoea at exertion	28			
Chest pain	15			
Extrathoracic localizations	50	Blacks	Whites	(1, 14, 16, 46)
Acute uveitis	7–25			
Peripheral lymphadenopathy	15–37			
Skin lesions	4–12			
Erythema nodosum	4–33	Women Whites	Men Blacks	(1, 2, 14, 17)
		Age <40 years	Japanese	
Constitutional symptoms	30–43	Blacks	Whites	(46, 13, 51)
Fatigue	27			
Weight loss	28			
Fever	10–17			
Fortuitous chest X-ray	8–60	Whites	Blacks	(15, 46)

Table 2. Extrathoracic localizations of sarcoidosis

Localization	Frequency		Severity			References
	Global (%)	Factors of increase	Local	General	Chronicity	
Peripheral lymph nodes	15–37	Blacks, age <40 years				(1, 14)
Skin except lupus pernio	16–32	Blacks				(1, 14)
Lupus pernio		Blacks, Puerto-Ricans	++	+	+++	
Eyes	12–75	Blacks, women				(1, 13, 14, 51)
Chronic uveitis		Japanese	++			
Liver	11.5	Blacks			++	(2)
Spleen	5–12				++	(1, 2, 14)
Nervous system	4.6–5.1	Women	++	++	++	(14, 46)
Parotid glands	3.9–6.1					(1, 14, 46)
Heart	2.5–5.1	Japanese, Blacks	++	++++	++	(2, 14, 46)
Nose, larynx	3–3.5	Blacks	+++	++	+++	(14, 46)
Kidney	0.7		++			(14)
Bones	0.5–4		++		++	(1, 14, 46)
Muscles	0.4–1.4	Women, menopause	++			(14, 46)

Clinical expression of sarcoidosis

Symptoms at presentation

The symptoms at presentation are diverse and their respective incidence depends on epidemiological factors. Their incidence and favouring factors are shown on Table 1. The most frequent manifestations include (i) respiratory symptoms, (ii) extrathoracic localizations, (iii) constitutional symptoms and (iv) erythema nodosum. These are isolated or associated. Chronic dry cough is the most frequent respiratory symptom. Chronic dyspnoea is rare and usually associated with advanced pulmonary fibrotic lesions at presentation (12, 16). Extrathoracic localizations affect mainly peripheral lymph nodes, eyes or skin. Constitutional symptoms include fatigue which can be very disabling, weight loss, or fever (46). Erythema nodosum or acute uveitis can pinpoint the onset of sarcoidosis. Erythema nodosum is most seen in young European white women and is usually associated with bilateral intrathoracic lymphadenopathies defining Löfgren's syndrome. Finally, fortuitous discovery of an abnormal chest X-ray in asymptomatic patients remains a nonuncommon circumstance of discovery (15).

Intrathoracic manifestations

Detailed occupational and environmental history is usually unremarkable. An exposure to beryllium dusts and to drugs inducing sarcoid-like granulomatosis must be excluded. Physical examination of the chest is normal in most patients. Crackles are heard in less than 20% of cases and digital clubbing is extremely rare (15). Chest X-ray still remains a corner-stone tool for diagnosis (15, 46–49), prognosis (1, 2, 12, 13) and follow-up (13, 50, 51). Chest X-ray is abnormal in 86–92% of cases. Radiographic staging of sarcoidosis is based on the presence of hilar/mediastinal lymphadenopathies and/or lung infiltration without or with fibrosis (13). The definition of the

four radiographic stages as well as their respective frequency at presentation and outcome are indicated in Table 3. Lymphadenopathies are typically hilar, bilateral, symmetrical and noncompressive. An associated involvement of right paratracheal and aortic-pulmonic window lymph nodes is common (70–76%) contrasting with the low frequency of subcarinal (21%) and anterior mediastinal (16%) involvement (48). Parenchymal infiltration in stage II and III consists typically in a diffuse micronodular or reticulomicronodular pattern with predominance for the middle and the upper parts of the lungs (15). Stage IV is characterized by coarse linear opacities associated with retraction of the lung and often bullae usually predominant in the upper lobes. Many unusual and often confusing radiographic features have also been described (52).

Pulmonary function is part of the routine investigation of sarcoidosis (13). The main typical abnormalities are decreased volumes and TLCO (15, 53). Although airway dysfunction is very frequent using very sensitive tests, low FEV₁/VC is accordingly encountered in less than a third of cases. Low TLCO reflects a tight decrease of membrane component of diffusing capacity and is highly predictive of desaturation at exercise (54). Abnormalities of pulmonary function tend to be more frequent and marked from stage I to stage IV with an overlap between stages (16). Low FEV₁/VC is often associated with chronic dyspnoea, stage IV and worse prognosis (16, 17, 55).

Fiberoptic bronchoscopy is very useful in obtaining mucosal and transbronchial biopsied granulomas with a sensitivity of 57–88% and minimal morbidity (13, 15, 49). In some cases, it allows visualizing macroscopic bronchial nodules, and exceptionally stenosis, showing infiltrating or pseudo-tumoral lesions generally located at the lobar or segmental levels (56). Moreover, it makes possible the recovering of immune effector cells by BAL. Lymphocytosis in BAL is observed in 80% of cases with a variable

Table 3. Chest X-ray staging of sarcoidosis

Chest X-ray stage	Involvement		Frequency at presentation (%)	Spontaneous remission (%)	References
	Nodes	Lungs			
Stage 0	Absent	Absent	8–16		(1, 14)
Stage I	Present	Absent	25–65	55–90	(1, 2, 13, 15, 51)
Stage II	Present	Present	14–49	40–70	(1, 2, 15, 51)
Stage III	Absent	Present without fibrosis	9.8	10–20	(13, 15)
Stage IV	Absent	Present with fibrosis	5.4	0	(14, 15)

CD4+/CD8+ T lymphocyte ratio. A result >3.5 is found in only half cases but has a positive and negative predictive value for the diagnosis of sarcoidosis of respectively 76 and 85% (57). Neutrophils count can be also increased in cases with pulmonary fibrosis.

Thorax computed tomography (CT) demonstrates lymphadenopathy and pulmonary infiltration with a better accuracy than radiography (15, 58, 59). High resolution CT (HR-CT) allows a good evaluation of elementary pulmonary lesions and their anatomical relationship with normal lung structures. Typical pulmonary lesions are diffuse micronodules located at peribroncho-vascular, subpleural and septal perilobular spaces with a lymphangitic distribution and a predominance for the middle and upper parts of the lungs (Fig. 3) (15). Various other atypical features of HR-CT have also been described (Figs 4 and 5) (58, 59). Of clinical relevance, HR-CT can reliably distinguish inflammatory lesions likely to reverse under therapy from irreversible lesions (60, 61). For stage IV, several fibrotic patterns have been identified by means of HR-CT (Fig. 6) (62, 63). Computed tomography is not always indispensable in sarcoidosis, particularly in the typical stage I (15, 47, 48)

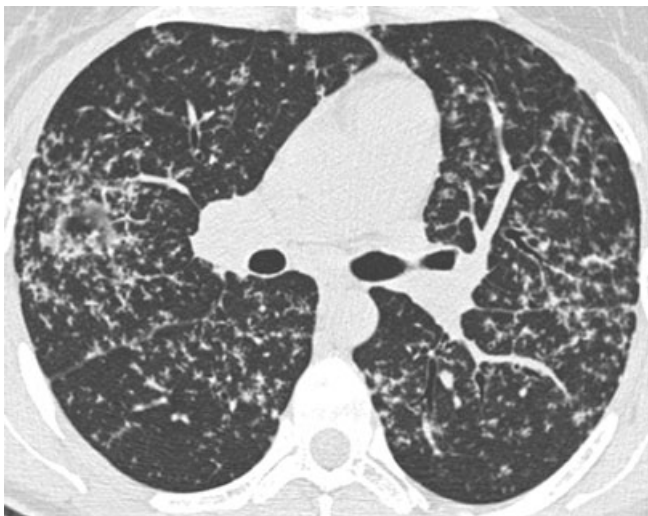


Figure 3. High resolution computed tomography typical features of pulmonary sarcoidosis. The micronodules predominate along the peribroncho-vascular cuffs and in subpleural regions drawing a characteristic lymphatic distribution.

but has been shown to reinforce the probability of sarcoidosis in cases with pulmonary infiltration on chest X-ray (64). The HR-CT provides a valuable aid in several situations like uncertain diagnosis, unexplained respiratory symptoms, atypical radiographic signs and complications such as pulmonary fibrosis, frankly impaired pulmonary function, pulmonary hypertension and aspergilloma (15).

Extrathoracic manifestations

The frequency, severity, and prognostic value of extrathoracic localizations and factors influencing them are shown on Table 2. Some localizations are relatively frequent such as peripheral lymphadenopathy, eyes and skin. Some others can be severe and must be primarily taken into account for treatment, including heart, central nervous system, eye lesions unresponsive to local treatment, larynx or kidney. Lupus pernio can be very unpleasant. Most localizations are evidenced at presentation or during the first year of observation. However, in some cases, a delay of several years may be observed between the onset of the disease and the involvement of some organs such as heart, central nervous system, muscle and bone.

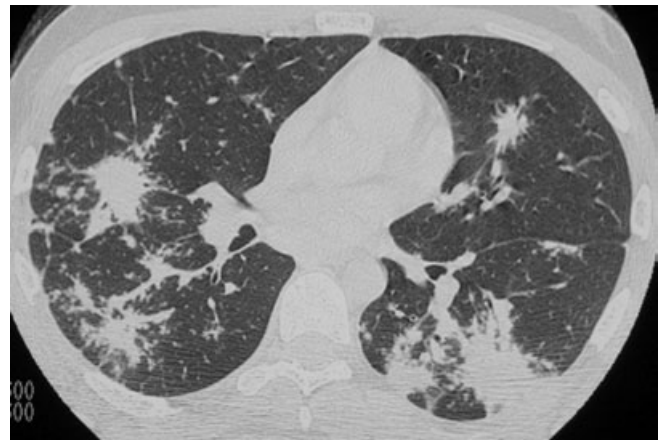


Figure 4. Example of high resolution computed tomography unusual features of pulmonary sarcoidosis: alveolar pattern. The alveolar consolidations have irregular outlines and are surrounded by micronodules with a lymphatic distribution.

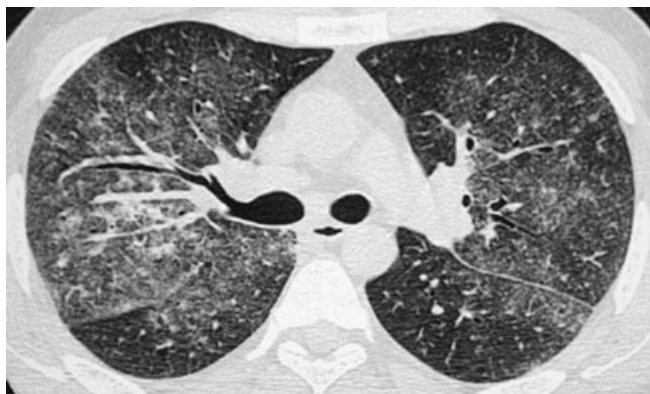


Figure 5. Example of high resolution computed tomography unusual features of pulmonary sarcoidosis: ground-glass pattern. The ground-glass attenuation is extensive but has a heterogenous distribution.

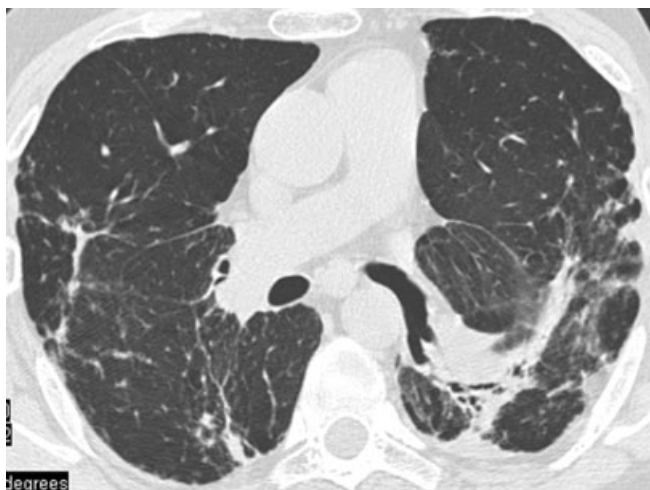


Figure 6. The most frequent high resolution computed tomography pattern of fibrotic pulmonary sarcoidosis with a proximal bronchial and fissure distortion.

Biologic manifestations

Hypercalcaemia is seen in <5% of cases and is mainly encountered in men over 40 years (14). Hypercalciuria is seen in more than 40% of cases. An increase of serum angiotensin converting enzyme (SACE) is linked with disease activity and dissemination. However, its diagnostic and prognostic value is limited. The SACE dosage can be helpful for the monitoring of therapy as it decreases under corticosteroids, and re-increases in relapses (51). Polyclonal hypergammaglobulinaemia is present in the range of 20–80% of cases, while hypogammaglobulinaemia is atypical and should make reconsider the diagnosis of sarcoidosis (1, 13, 49). Hepatic tests, particularly alkaline phosphatase, are abnormal in 20% of cases (1, 2, 13). Increased serum creatinine level can reflect renal

involvement. Lymphopenia is common but other cell blood anomalies such as neutropenia or auto-immune haemolytic anaemia and/or thrombopenia appear very unfrequent.

Diagnosis

Because of the lack of specific test and the diversity of clinical expression, the diagnosis of sarcoidosis relies on the conjunction of three different criteria (13): (i) a typical or compatible clinico-radiographical presentation, (ii) the histologic demonstration of noncaseating granulomas on biopsy specimens and (iii) the exclusion of all possible alternative diagnosis.

Clinico-radiographical presentation is often typical, particularly in stage I asymptomatic patients with normal physical examination, or when extrathoracic localizations are associated with intrathoracic. Löfgren's syndrome is highly suggestive. In case of less characteristic presentation, other arguments can be supportive such as typical findings on HR-CT, CD4⁺ T lymphocytosis in BAL, SACE level twice higher than the upper normal limit or abnormal calcium metabolism.

Most recommended sites for histologic confirmation are mucosal or lung transbronchial biopsy specimens through fiberoptic bronchoscopy (13, 15, 49). Biopsy can be readily obtained from skin lesions, peripheral lymphadenopathy or conjunctival nodules. Lip biopsy of salivary glands can be helpful. Lung and lymph node biopsy through video-assisted thoracic surgery and biopsy of mediastinal nodes through mediastinoscopy are rarely necessary (15, 49). Other biopsies can be guided on the basis of clinical presentation. When noninvasive biopsies are unproductive in the context of typical clinico-radiographic settings, when the disease appears mild, or when a spontaneous remission seems likely, immediate histologic support may not be required. In symptomatic or worsening cases, histologic confirmation is always necessary before treatment initiation. Sometimes, even when sarcoidosis has been confirmed, the biopsy of some localizations is justified to avoid confusion with an associated disease.

Mycobacterial infections, histoplasmosis and other fungal infections must be excluded. Chronic beryllium disease is easily supported by detailed occupational history and abnormal lymphocyte proliferative response to beryllium (10). Granulomatosis induced by IFN α and β or intravesical BCG therapy can be very similar to sarcoidosis, but is recognized without difficulty (65). Loco-regional granulomatous reactions in case of breast or lung carcinoma and lymphomas are also easy to distinguish from sarcoidosis. Granulomatosis associated with common variable immunodeficiency is a very rare condition that can mimic sarcoidosis, but this affection is remarkable for the existence of iterative previous bacterial infections and low serum immunoglobulin levels (66).

Prognosis and evolution

The evolution of sarcoidosis varies according to disease duration, involved organs and severity. Sarcoidosis is most often a time-limited disease that lasts for 12–36 months in half cases and for < 5 years in many others. A minority of patients will experience a longer disease, sometimes for multiple decades. Interestingly, subsequent relapse is very unfrequent when remission occurred without treatment or when remission persisted for at least 3 years after removal of any treatment. Serial survey is absolutely necessary until recovery is strengthened in order to appreciate improvement, stabilization or progression of the disease. Response under treatment must be evaluated in the months following its initiation and during tapering therapy.

The most severe and frequent complication is the development of pulmonary fibrosis which can be easily detected on chest X-ray. It is usually a late manifestation after years of evolution but sarcoidosis is sometimes revealed at this advancement stage of the disease. Pulmonary fibrosis is usually associated with chronic dyspnoea and frank impairment of pulmonary function, including decrease of volumes and TLCO and very often of FEV₁/VC. Abnormal haematosiis at rest and exercise must be searched as well as pulmonary hypertension. The severity and the aspect of pulmonary fibrosis vary from one case to the other. Pulmonary fibrosis can be constituted of several different patterns which are best assessed by HR-CT: central peribronchovascular distortion, the most frequent (Fig. 4), honeycombing lesions predominating in the upper lobes and hilo-peripheral linear opacities (62, 63). In many cases, active pulmonary lesions are associated with fibrosis but their relative contribution to pulmonary function impairment is generally secondary. Pulmonary fibrosis is the main cause of respiratory failure and mortality in sarcoidosis.

Airway obstruction can be rarely severe in sarcoidosis (67). Several mechanisms can be incriminated: apart bronchial distortion related to pulmonary fibrosis, this complication can also result from the direct localization of sarcoid lesions on airways, or more seldom from an extrinsic compression by hilar or mediastinal lymphadenopathy. Sarcoid bronchial lesions are predominantly located in the distal bronchi, but they can also be present as infiltrative or pseudo-tumoral stenosis particularly at the lobar or segmental level (56). In such proximal stenosis, patients can feel breathless and have wheezing. In case of airway obstruction because of bronchial involvement, the response to corticosteroid therapy depends on the respective contribution of granulomatous and fibrotic lesions.

Pulmonary hypertension is a rare but severe manifestation that usually occurs in end-stage fibrotic cases (68). It is associated with a poor vital prognosis and is mostly unresponsive to medical treatment. However, pulmonary hypertension can also exceptionally present as an early

primary manifestation of sarcoidosis and improve with steroid therapy (69).

Mycetomas develop in bullous lesions and are generally encountered in African-Americans with advanced pulmonary fibrosis (15, 49). Patients with mycetomas exhibit an increased risk of death caused by either severe bleeding or underlying fibrotic respiratory insufficiency. Nevertheless, prolonged survival without serious haemoptysis remains possible (49). Although mycetoma is the main cause, many other mechanisms can provoke haemoptysis in the course of sarcoidosis.

The concept of clinical phenotypes

The diversity of sarcoidosis phenotype is often linked to epidemiologic factors and, interestingly, as shown by recent studies, to genotype (70). Sarcoidosis can be considered as mild or severe. Interestingly, mild and severe phenotypes do not seem to evolve from one to the other. Mild cases are usually characterized by absent or discrete symptoms, stage I, erythema nodosum or acute uveitis and rapid spontaneous resolution within 12–36 months. By contrast, severe cases are often characterized by prolonged evolution, evidence of stage III or IV, frankly impaired pulmonary function, and some extrathoracic localizations such as heart, central nervous system, eyes, muscles, rhino-sinus, larynx or kidney.

Treatment

Not all patients with sarcoidosis need systemic therapy. Between 30 and 70% of patients never require therapy (49, 71–74). In the other cases a treatment is necessary, either at the onset of the disease or during follow-up because of various consequences (49, 71–74). Some crucial questions provide a helpful clinical framework for treatment strategy. Whether and when to initiate systemic corticosteroids? What is the optimal dose and duration of corticosteroids? When to propose an alternative treatment to corticosteroids?

Whether and when to initiate systemic corticosteroids?

There are no firm guidelines regarding either whether or when to start systemic corticosteroids in sarcoidosis as there are only few randomized controlled trials (75–80). Ideally, patients with recent sarcoidosis should be initially observed without any treatment. Yet, according to ATS/ERS/WASOG statement, there are several severe conditions in which systemic therapy should always be offered rightaway (13). These include cardiac, neurological, renal, ocular sarcoidosis not responding to topical therapy and malignant hypercalcaemia (13). Incapacitating general symptoms may exceptionally lead to short-course corticosteroid therapy.

For pulmonary disease, systemic therapy is recommended in patients with stage II or III who are symptomatic or who disclose significant physiologic impairment or progressive disease (deterioration in serial pulmonary function tests and/or chest radiographs) (3, 10, 13, 81, 82). Conversely, it is clearly not indicated in stage I. In case of Lofgr n syndrome, fever and arthralgia are generally relieved with nonsteroidal anti-inflammatory drugs or colchicine. Systemic therapy in asymptomatic patients with stage II or III remains more controversial. A reference study supports its use in patients with persistent lung infiltration for at least 6 months (72). A recent study suggests that even patients with newly detected pulmonary stage II or III and normal lung function may take advantage from immediate treatment with oral prednisolone for 3 months followed by inhaled budesonide for 15 months (79). Stage IV with advanced pulmonary fibrosis is usually poorly or not at all affected by systemic therapy. However, a trial of therapy to identify residual inflammation is warranted particularly in patients with persistent signs of activity.

An outstanding meta-analysis has recently clarified the real role of corticosteroids in pulmonary sarcoidosis (82). This review led to the conclusion that oral corticosteroid therapy ameliorates the chest radiograph in patients with stage II and III after 6–24 months. It also weakly improves FVC and DLCO (mean increase of 4.2 and 5.7% of predicted value respectively) (82). While the short-term benefit of systemic corticosteroids is undeniable, there is continued debate about its role in ultimately altering the long-term course of the disease. Some authors have suggested that the risk for relapse may be more important in patients treated with corticosteroids (73) and that this treatment may be strikingly associated with a higher mortality (19, 83). However, this rather reflects the widespread use of corticosteroids in serious and chronic sarcoidosis than the negative impact of therapy.

What is the optimal dose and duration of corticosteroids?

This issue has never been accurately studied. For pulmonary sarcoidosis, protocols suggest the initial dose of 20–40 mg daily of prednisone or its equivalent on alternate days (13, 84). Higher dosage may be necessary to control cardiac and neurologic involvement. After 1–3 months therapy, patient should be evaluated for response (13, 84). In case of positive response, posology is gradually and slowly tapered under cover of close monitoring (13, 84).

A common problem with therapeutic management of sarcoidosis is the risk of recurrence after reduction or discontinuation of therapy, which occurs in 20–70% of cases (49, 71, 73). In order to elude unnecessary adverse events, physicians should take a great care in establishing the minimal efficient dose for each patient, which usually varies between 5 and 20 mg daily of prednisone. As a general rule, therapy should be maintained for at least

12 months (13). Yet, duration of therapy should also be individualized. Indeed, there is a sub-group of patients with chronic sarcoidosis who do not recover after 2–5 years. These patients often experience repeated relapses and may require long-term, low-dose therapy during years (2, 49). Conversely, some patients with mild and recent forms of the disease may only need 3–6 months therapy (13).

Alternative drugs to systemic corticosteroids

The dose and the side-effects of main drugs used in sarcoidosis are summarized in Table 4. Their mechanism of action is wide, as indicated in Table 4. There is increasing evidence that TNF- α plays a critical role in sarcoidosis pathogeny. The TNF- α polymorphisms seem to correlate with disease phenotype (85, 86). Tumour necrosis factor- α is released at high levels by AM from patients with active sarcoidosis (87, 88). Of clinical relevance, these levels decrease after successful treatment of sarcoid patients with corticosteroids (89), methotrexate (89) and azathioprine (90). Moreover, several studies suggest that elevated expression of TNF- α by AM is a marker of bad prognosis and is predictive for persistent disease (91–93). Taken together these observations support the attractive concept that the inhibition of TNF- α may be a key target for therapy, particularly in chronic refractory disease.

Inhaled corticosteroids. The delivery of corticosteroids by the inhaled route is appealing in pulmonary sarcoidosis without extrapulmonary involvement. There are five main randomized controlled trials evaluating high doses of inhaled corticosteroids in adults (78, 94–97) including budesonide (78, 96, 97) or fluticasone propionate (94, 95). Inhaled corticosteroids were employed either after oral corticosteroids (78, 94, 95) or alone (96, 97). In all the studies but one, inhaled therapy did not significantly change objective symptom scores, physiological measures and chest radiography in comparison with placebo. In one study sequential therapy with 3 months of oral prednisone followed by 15 months of budesonide resulted in a significant but very mild improvement of DLCO at 18 months in patients with recent stage II or III (78). Inhaled corticosteroids may subjectively ameliorate symptoms.

Antimalarial agents. Antimalarial drugs include choroquine and hydroxychloroquine. Most data on the effect of antimalarial drugs for pulmonary involvement are old except one recent study (98). In this placebo-controlled trial, patients with symptomatic chronic pulmonary sarcoidosis initially received chloroquine for 6 months and were then randomized to either a maintenance or to an observation group. At 6 months chloroquine resulted in a significant improvement of respiratory symptoms, FEV1, FVC, DLCO and ACE. During monitoring

Table 4. Mechanism of action, dose and side-effects of the main drugs used in sarcoidosis

Drugs	Main mechanism of action	Usual dose	Main side-effects	Remarks	References
Corticosteroids	Broad-spectrum anti-inflammatory effect	Prednisone: 20–40 mg/day initially, 5–10 mg/day for maintenance therapy	Obesity, diabetes, hypertension, osteoporosis...	Most successful and rapidly effective drug First-line therapy for severe sarcoidosis	(3, 13, 81, 82, 150)
Antimalarial agents*	Inhibit antigen presentation	Hydroxychloroquine: 200–400 mg/day orally	Nausea, retinal toxicity	Useful for mild hypercalcemia and skin disease Corticosteroid sparing agent Delayed effect	(3, 13, 81, 98–100, 150)
Methotrexate	Inhibits TNF- α production from macrophages	10–15 mg/week orally or IM	Nausea, hepato-toxicity†, neutropenia, hypersensitivity pneumonitis	Second-line therapy for cortico-resistant disease Corticosteroid sparing agent Delayed effect	(3, 13, 81, 102–104, 113, 150)
Azathioprine	Inhibits lymphocyte proliferation	50–150 mg/day orally	Nausea, neutropenia‡, hepato-toxicity	Similar comments than with methotrexate but less published data	(3, 13, 81, 90, 116, 117, 150)
Cyclophosphamide	Inhibits lymphocyte proliferation	50–150 mg/day orally or 500–1500 mg every 2–4 weeks IV pulse	Neutropenia, nausea, cystitis, carcinogenic	Potentially severe side-effects limiting its use May be useful for refractory neuro-sarcoidosis	(3, 13, 81, 110, 111, 120, 150)
Pentoxifylline	Inhibits TNF- α production from macrophages	400–1200 mg/day orally	Nausea	Only one study for acute pulmonary disease	(137, 150)
Thalidomide	Inhibits IL-12 and TNF- α production from mononuclear cells	50–200 mg/day orally	Teratogenic, sleepiness, peripheral polyneuropathy, bradycardia, hypothyroiditis, venous thrombo-embolism	Useful for lupus pernio and severe skin disease Unknown efficacy for other manifestations	(3, 81, 122–125, 150)
TNF- α inhibitors§	Infliximab: chimeric humanized monoclonal antibody against TNF- α Etanercept: human soluble TNF- α receptor dimeric fusion protein	Infliximab: 5 mg/kg week 0, week 2 and then every 6–8 weeks IV Etanercept: 25 mg twice weekly SC	Increased risk for infection, particularly tuberculosis, allergic reaction to infusion, carcinogenic ?	Rapid effect Potentially severe side-effects Very few published data about effectiveness and optimal dosage in sarcoidosis May be useful for chronic and refractory cases Possibly not yet known side-effects	(3, 81, 20, 127–136, 150)

* Hydroxychloroquine is preferred to chloroquine because of the lower risk for ocular toxicity.

† Some authors recommend to perform a liver biopsy after a cumulative dose of 1 to 2 g.

‡ A small percentage of the population has methyl-transferase deficiency and may develop severe pancytopenia because azathioprine is not correctly metabolized. This sensitivity to azathioprine will be recognized by initiating the drug at the low dose of 50 mg daily and by closely monitoring complete blood count especially within the first month.

§ Doses of infliximab and etanercept are those used in rheumatoid arthritis and Crohn's disease.

IL, interleukin; TNF- α , tumour necrosis factor alpha; IM, intramuscular; IV, intravenous; SC, sub-cutaneous.

control subjects showed a significantly faster decline in FEV1 and DLCO than patients under chloroquine but not in FVC. Treated patients had fewer relapses but the difference did not reach the level of significance (98).

Antimalarial drugs are recognized to be the treatment of choice for mild and isolated cutaneous lesions with an effect appearing within 4–12 weeks of therapy (99). Chloroquine has also been helpful for hypercalcaemia (100). Some authors have reported that choroquine and hydroxylchloroquine may be useful in selected patients with neurological sarcoidosis (101). Yet, hydroxylchloroquine is probably substantially less effective than methotrexate or azathioprine in sarcoidosis so that it should not be given for severe sarcoidosis.

Methotrexate. Methotrexate has been the most extensively used among cytotoxics. Although no prospective placebo-controlled study, this drug has usually been reserved for chronic sarcoidosis (81, 102–104). Lower and Baughman have published their experience of 50 patients with chronic sarcoidosis treated with methotrexate, 10 mg orally per week for at least 2 years (104). About 66% of patients had objective improvement in one or more organ (47% for lung involvement). In addition, 25 of 30 patients on corticosteroids at the time of starting methotrexate were able to be totally weaned or reduce their dose of corticosteroids after 6 months therapy (104). Similar results have been noted in several other uncontrolled studies (102). Response rates depend on involved organ but methotrexate can be effective in pulmonary and most extra-pulmonary manifestations, particularly skin lesions (104–106) including lupus pernio, ophthalmic (104, 105, 107–109), nervous system (104, 110, 111) and musculoskeletal sarcoidosis (104, 112).

In a double blind randomized trial vs placebo, methotrexate has demonstrated efficiency after 6 months therapy as a corticosteroids sparing drug in patients with acute pulmonary sarcoidosis (113). However, the effect of methotrexate is quite delayed, which limits its use in acute sarcoidosis except if a prolonged course of the disease is anticipated. In such a context, methotrexate may be initiated with corticosteroids, particularly if there is a relative contraindication to corticosteroids.

Methotrexate-induced hepatotoxicity is a dose-dependent phenomenon occurring in about 10% of patients with sarcoidosis treated for more than 2 years (114). The reliability of serial liver function tests to detect the early reversible hepatotoxicity has been the subject of controversy and some guidelines recommend a liver biopsy after every 1–2 g of cumulative therapy (115). A recent study has demonstrated that in sarcoidosis abnormal liver function tests were not predictive of hepatotoxicity because of hepatic involvement as a result of sarcoidosis. Conversely, more than half of the patients with hepatotoxicity had no elevated transaminases (114). These findings suggest that systematic biopsy remains the most

important part of screening for methotrexate-induced hepatotoxicity in sarcoidosis (114).

Azathioprine. Published data of azathioprine are much fewer than methotrexate. Azathioprine has clearly proved benefit as a corticosteroid sparing agent in open studies with a small number of patients (90, 116, 117). The efficacy of azathioprine as a second-line treatment in cortico-resistant patients is less sure, but has been emphasized in refractory neurosarcoidosis (111).

Other immunosuppressive agents. Most of reports with other immunosuppressive agents are anecdotal or disappointing. Although efficient in sarcoidosis (118), chlorambucil has been abandoned by most physicians because of the risk of lymphoproliferative disease with this drug. Several uncontrolled studies have conceded some variable effectiveness to cyclosporine in sarcoidosis. However, the only randomized controlled trial comparing a combined therapy with cyclosporine and prednisone with prednisone alone has shown an increased prevalence of serious adverse effects and no between-group differences in terms of efficacy (119). Cyclophosphamide has been occasionally offered in refractory disease with interesting results in cortico-resistant neurosarcoidosis (110, 111, 120).

Initially indicated in the prevention of organ transplant rejection, the use of mycophenolate mofetil has been rapidly expanded for the treatment of auto-immune and inflammatory diseases. In a recent publication, five patients with sarcoidosis have been successfully treated with this drug as an adjunctive therapy to corticosteroids (121). All these patients had systemic sarcoidosis with skin and sinonasal involvement and failed to respond or were intolerant to several previous standard regimens (121). The advantage of mycophenolate mofetil in comparison with other immunosuppressive medications is its safe profile, but controlled studies are needed in sarcoidosis.

Thalidomide. Thalidomide has demonstrated efficacy for chronic cutaneous sarcoidosis unresponsive to prior therapy in several small uncontrolled series (122–125). A recent open-label study on 14 patients suggests that this drug may be particularly helpful in lupus pernio, a chronic and disfiguring skin lesion of the face which is notoriously known to be a difficult therapeutic issue (125). The benefit of thalidomide is usually observed between 50 and 100 mg/day but an increasing of the dose until 200 mg/day is sometimes required. The onset of the drug action is fairly rapid as a partial or complete regression of cutaneous lesions is achieved within 1–2 months for most patients. The response requires 5 months therapy in rare cases (122, 125). This medication may be efficient in sinonasal (125) and muscle involvement of the disease (126), but its effect on pulmonary disease is unclear (125). Yet, the side-effects of thalidomide can be extremely serious.

Specific TNF- α inhibitors. As noted above, TNF- α is an attractive target for sarcoidosis treatment. The TNF- α inhibitors include infliximab and etanercept. These molecules are currently used in the clinical setting of rheumatoid arthritis and active Crohn's disease. They have also led to a dramatic improvement in small series or several case reports with refractory chronic sarcoidosis affecting various organs (20, 127–135). Yet, these promising data have been recently contradicted by a prospective open-label phase-2 trial with etanercept (136). In this study, patients with stage II or III progressive pulmonary disease and no extrapulmonary organ involvement received etanercept, 25 mg subcutaneously twice weekly for 12 months, as the sole therapy. The study was stopped after the enrolment of 17 patients because of excessive treatment failures. Of these patients, five improved, one withdrew from the study and 11 deteriorated according to pulmonary function parameters, Chest X-ray or dyspnoea scale (136). Interestingly, the basal level of total TNF- α or TNF- α bioactivity in serum or BAL fluid, or released from cultured AM could not predict the subset of patients who had favourable response. Two patients experienced localized intestinal lymphoma and nasopharyngeal extramedullary plasmacytoma (136). These discarding results may be explained by a dominant effect of anti-TNF- α in chronic and resistant forms of sarcoidosis. Given the potential toxicity and expense of anti-TNF- α therapies, controlled studies are needed to clearly identify the patients who may profit from these novel agents.

Other treatments. There is only one open-label trial on the effect of Pentoxifylline in sarcoidosis (137). Yet, most included patients had acute mild or moderate disease so that the true responsivity of Pentoxifylline for the observed amelioration could not be ascertained. Minocycline and doxycycline have demonstrated efficiency for skin lesions in one open-label trial (138).

When to propose an alternative treatment to corticosteroids? It is generally agreed that systemic corticosteroids are the most successful, rapid and dependable agents in sarcoidosis, so that they are still first-line therapy for pulmonary sarcoidosis and disease involving vital organs (3, 13, 81). Yet, the awareness of corticosteroids side-effects has led to rethink the therapeutic approach of sarcoidosis. A corticosteroid-sparing treatment should be employed in patients with chronic sarcoidosis when the threshold level to control the disease exceeds 10 mg daily of prednisone or its equivalent on alternate days. The conventional sparing agents are hydroxychloroquine, methotrexate or azathioprine (3, 13, 81).

While other drugs than corticosteroids are clearly of value in selected patients, their place in the therapeutic strategy of sarcoidosis has never been accurately delineated. The opportunity of an alternative option to corticosteroids should be discussed in several circumstances including contra-indication or occurrence of side-effects

under corticosteroids, cortico-resistance and involvement of specific organs (3, 13, 81).

Patients failing to respond after 3 months of corticosteroids therapy are unlikely to respond to a more prolonged course of treatment (13). After exclusion of noncompliance, inadequate dosage, irreversible fibrotic disease and exposition to beryllium, these patients are considered to have authentically cortico-resistant sarcoidosis, which is very rare (13). Corticosteroids should then be changed for second line-therapy. On the basis of safety and efficacy, methotrexate and azathioprine are preferred by most physicians (3, 13, 81). Thalidomide, mycophenolate mofetil and infliximab should be reserved for refractory cases, ideally as part of controlled trials.

Some drugs should be specifically favoured rather than corticosteroids according to the manifestation of sarcoidosis: for example, hydroxychloroquine or tetracycline for mild dermatologic sarcoidosis, thalidomide for extensive or disfiguring cutaneous lesions particularly lupus pernio, hydroxychloroquine or ketoconazole for mild hypercalcaemia...

Treatment of associated conditions or complications. Seeing the frequency of hypercalcaemia and hypercalcuria, currently available agents for the prevention of glucocorticoid-induced osteoporosis may not be safe in sarcoidosis. Yet, there is also some recent evidence that corticosteroid-naïve subjects with sarcoidosis may have a greater incidence of osteopenia than the general population (139). There are only few studies specifically addressing the management of glucocorticoid-induced osteoporosis in sarcoidosis. The recently published recommendations should be largely followed (140) with some minor modifications to accommodate the young age of many patients and the disturbances in calcium metabolism unique to sarcoidosis. Vitamin D should be avoided as it can cause hypercalcaemia. Calcium supplementation may be given to patients without hypercalciuria. Among bisphosphonates alendronate should be preferred to cyclical etidronate as available data on sarcoidosis only concern this medication (141). A measure of serum calcium and 24-h urinary calcium excretion should be performed before and soon after initiating any treatment.

Various symptomatic treatments may be helpful in sarcoidosis in addition to specific therapy: for example diet low in calcium and avoidance of sunlight exposure in case of hypercalcaemia, supplemental oxygen for hypoxemia at rest or exercise, cardiac drugs, implantable pacemakers or cardioverter-defibrillator for symptomatic cardiac involvement, hormonal substitution in case of hypothalamic-pituitary sarcoidosis, anti-epileptic agents... Corticosteroids may be ineffective in endobronchial stenosis because of sarcoidosis (142), which sometimes necessitate mechanical dilatation (142, 143).

Mycetomas represent a difficult therapeutic problem because antifungal therapy has never clearly proved efficacy in such a context and surgery is risky in patients with usually underlying end-stage pulmonary fibrosis (15, 49). Bronchial artery embolization can be effective for haemoptysis.

Organ transplantation should not be denied in sarcoidosis despite several specific problems raised by this disease. Lung, liver and heart transplantation have been successfully performed in patients with end-stage refractory sarcoidosis with good results, not significantly different from those obtained for other disorders (144–147). Medical therapy must have been exhausted and the extent and severity of the disease must have been carefully evaluated before candidates are selected for transplantation (144, 145). The presence of mycetomas is considered as a relative or absolute contra-indication according to the transplant centre (148). Sarcoidosis is the most common disease to recur in the allograft after lung transplantation with a frequency reaching 35% of cases (149), but the disease is usually mild and controlled by post-transplantation immunosuppression (146). Transplantation in patients with sarcoidosis has been

associated by some authors with higher-than-normal rates of rejection.

Conclusion

Sarcoidosis is a frequent but many-faceted disease that still raises diagnostic and therapeutic challenges. Our better understanding of sarcoidosis pathogeny will certainly provide the development of selective treatments with cytokine-targeted effects, particularly against TNF- α . Another searching pathway may be combination therapies that would act at several levels of disease pathogeny. Future directions will also probably focus on the links between the genotype and phenotype profiles of the disease.

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